Chapter 7

Uveitis

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INTRODUCTION

Classification

Uveitis, by strict definition, is an inflammation of the uveal tract. However, the term is now used to describe many forms of intraocular inflammation which may involve not only the uvea, but also adjacent structures. The main classifications are: (a) ***anatomical*** (Figure 7.1), (b) ***clinical*** and (c) ***aetiological***.

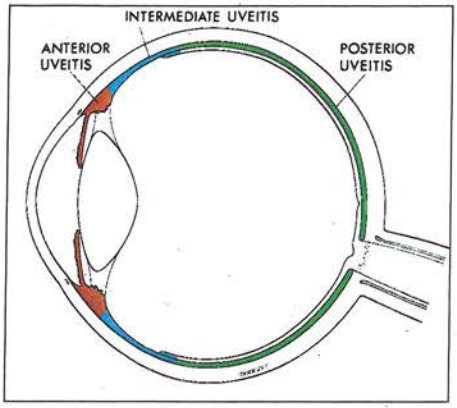


Figure 7.1 Anatomical classification of uveitis

ANATOMICAL CLASSIFICATION

1. **Anterior uveitis** is subdivided into iritis, in which the inflammation predominantly affects the iris, and iridocyclitis, in which both the iris and the anterior part of the ciliary body (pars plicata) are equally involved.
2. **Intermediate uveitis** is characterized by predominant involvement of the posterior part of the ciliary body (pars plana) and the extreme periphery of the retina and choroid.
3. **Posterior uveitis** is characterized by inflammation located behind the posterior border of the vitreous base.
4. **Panuveitis** is characterized by involvement of the entire uveal tract.

Anterior uveitis is the most common type, followed by intermediate, posterior and panuveitis.

CLINICAL CLASSIFICATION

Classified according to the mode of onset and duration, uveitis can be acute or chronic.

1. **Acute uveitis** usually has a sudden symptomatic onset and persists for 8 weeks or less. If the inflammation recurs following the initial attack, it is referred to as recurrent acute.
2. **Chronic uveitis** persists for longer than 3 months. Its onset is frequently insidious and may be asymptomatic, although occasionally acute or subacute exacerbations of inflammation may occur.

AETIOLOGICAL CLASSIFICATION

1. **Exogenous uveitis** is caused by either external injury to the uvea or invasion of micro-organisms or other agents from outside.
2. **Endogenous uveitis** is caused by micro-organisms or other agents from within the patient. The following are the main types:
   (a) ***Associated with a systemic disease*** such as sarcoidosis.
   (b) ***Infections*** with bacteria (e.g. tuberculosis), fungi (e.g. candidiasis), viruses (e.g. herpes zoster), protozoa (e.g. toxoplasmosis) or roundworms (e.g. toxocariasis).
   (c) ***Idiopathic specific uveitis entities*** are a group of unrelated disorders which are not associated with an underlying systemic disease but have special characteristics of their own warranting a separate description (e.g. Fuchs uveitis syndrome).
   (d) ***Idiopathic non-specific uveitis entities*** which do not fall into any of the above categories. They make up about 25% of all cases.

Clinical features

ANTERIOR UVEITIS

1. **Symptoms** of acute anterior uveitis include photophobia, pain, redness, decreased vision and lacrimation. In chronic anterior uveitis, however, the eye may be white and symptoms minimal, even in the presence of severe inflammation.
2. **Signs**
   (a) ***Injection*** in acute anterior uveitis is circumcorneal 'ciliary' and has a violaceous hue (Figure 7.2).
   (b) ***Keratic precipitates*** (KP) are cellular deposits on the corneal endothelium. Their characteristics and distribution may give important clues as to the probable type of uveitis. KP most commonly form in the mid and inferior zones of the cornea. However, in Fuchs uveitis syndrome, they are scattered throughout the endothelium.
   - Endothelial dusting (Figure 7.3) by many hundreds of small cells occurs in acute anterior uveitis, as well as during subacute exacerbations of chronic inflammation.
   - Medium size KP (Figure 7.4) occur in most types of acute and chronic anterior uveitis.

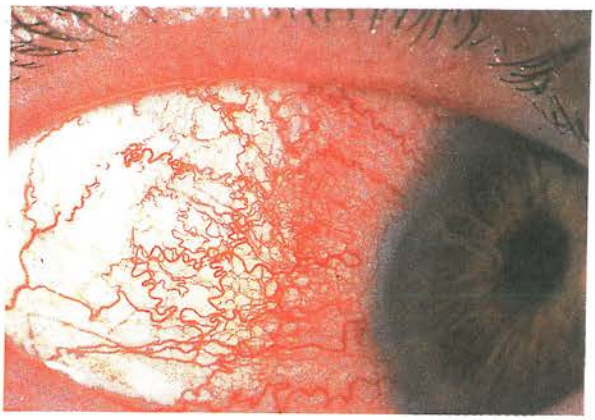


Figure 7.2 Ciliary injection in acute anterior uveitis

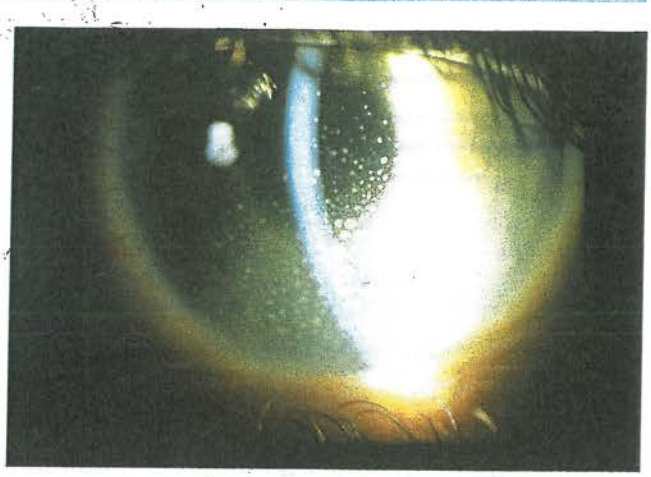


Figure 7.5 Mutton fat keratic precipitates

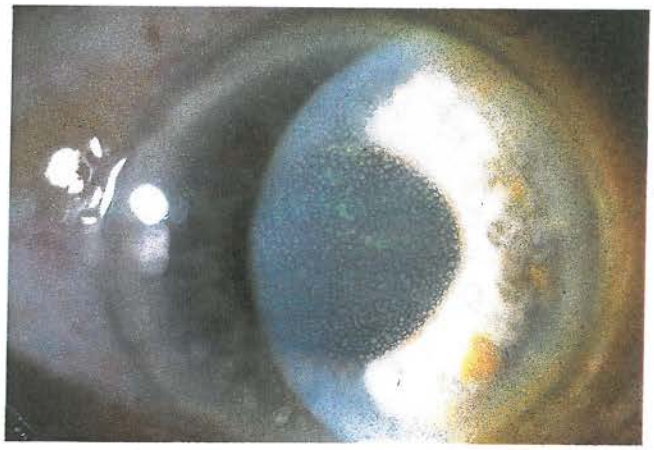


Figure 7.3 Endothelial dusting in acute anterior uveitis

Figure 7.6 Old pigmented keratic precipitates

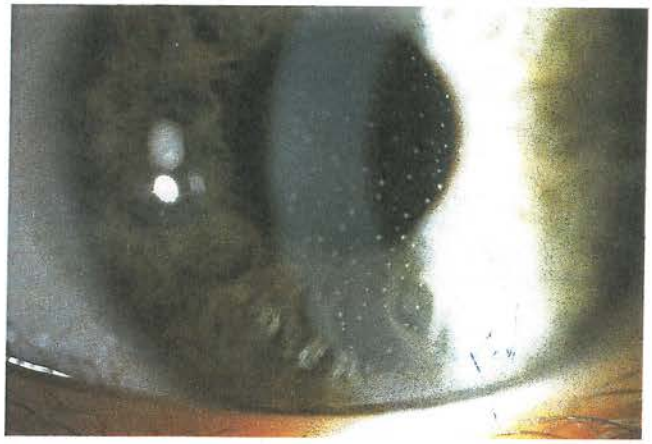


Figure 7.4 Medium size keratic precipitates

Figure 7.7 Old keratic precipitates with a 'ground-glass' appearance

- Large KP are usually of the 'mutton fat' variety and have a greasy, waxy appearance (Figure 7.5). They typically occur in granulomatous uveitis.
- Fresh KP tend to be white and round.
- Old KP are pigmented (Figure 7.6) and, if large, they develop a 'ground-glass' (hyalinized) appearance (Figure 7.7).

(c) ***Iris nodules*** are a feature of granulomatous inflammation.
- *Koeppe* nodules are small and situated at the pupillary border (Figure 7.8).
- *Busacca* nodules are less common and are located on the surface of the iris away from the pupil (Figure 7.9).

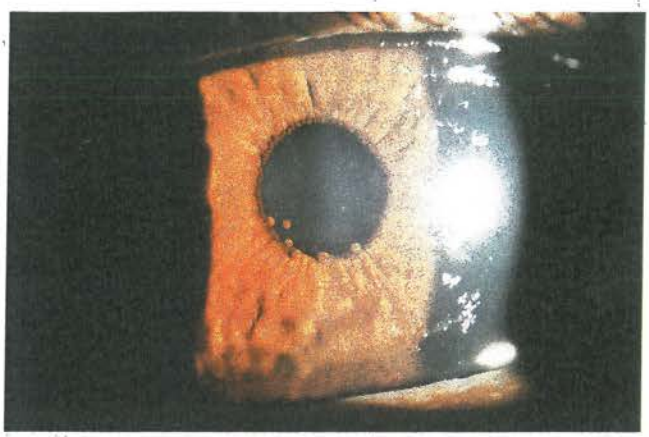


Figure 7.8 Koeppe nodules

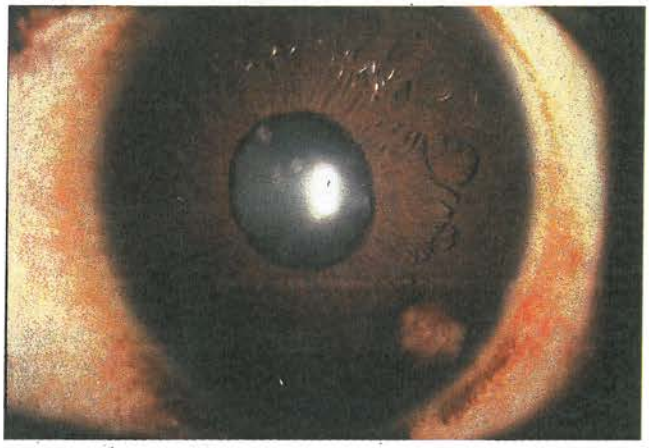


Figure 7.9 Busacca nodule

(d) ***Aqueous cells*** are indicative of active inflammation. They should be graded according to the number observed in the oblique slit beam. The light intensity and magnification of the slitlamp should be maximal and the beam 3 mm long and 1 mm wide. The number of cells should be assessed and then graded from 0 to +4 as follows:
- 5–10 cells = +1
- 11–20 cells = +2
- 21–50 cells = +3
- >50 cells = +4.
- hypopyon (Figure 7.10).

(e) ***Anterior vitreous cells*** should be compared in density with those in the aqueous. In iritis, aqueous cells far exceed the number of vitreous cells.

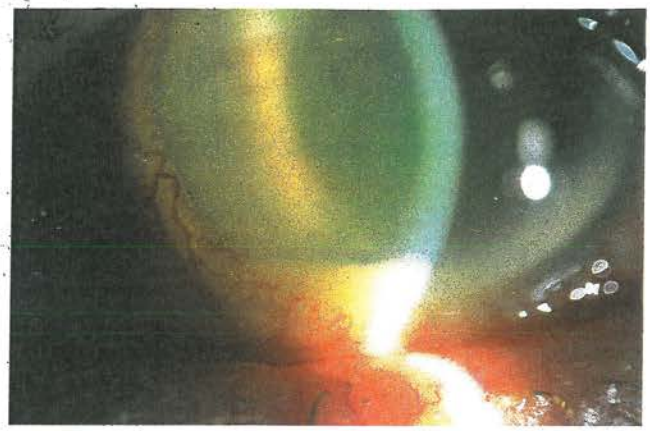


Figure 7.10 Hypopyon

(f) ***Aqueous flare*** (Figure 7.11) is the result of leakage of proteins into the aqueous humour through damaged iris blood vessels and is not necessarily indicative of active inflammation. For this reason, the presence of a flare in the absence of cells is not an indication for treatment. Aqueous flare is graded using the same setting on the slitlamp as for counting cells. The beam should be passed obliquely to the plane of the iris in order to evaluate the degree of obscuration of iris details. The flare is graded from 0 to +4 as follows:
- faint – just detectable = +1
- moderate – iris details clear = +2
- marked – iris details hazy = +3
- intense with severe fibrinous exudate = +4 (Figure 7.12).

(g) ***Posterior synechiae*** are adhesions between the anterior lens surface and the iris (Figure 7.13). They form with ease during an attack of acute anterior uveitis because the pupil is small. They may also form in eyes with moderate-to-severe chronic anterior uveitis. Posterior synechiae extending for 360° (seclusio pupillae) prevent the passage of aqueous humour from the posterior to the anterior chamber, giving rise to a forward bowing of the peripheral iris (iris bombé)

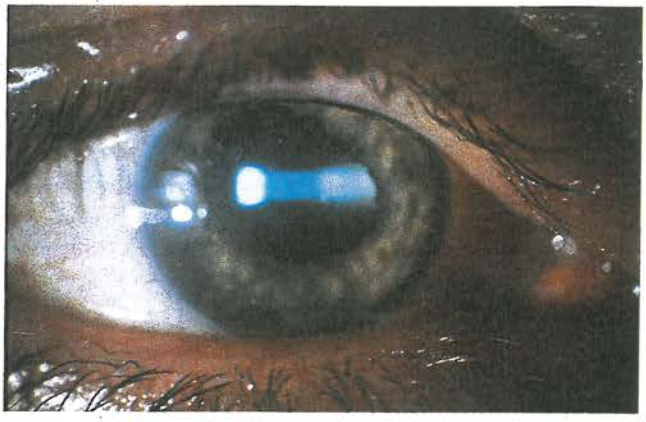


Figure 7.11 Dense flare

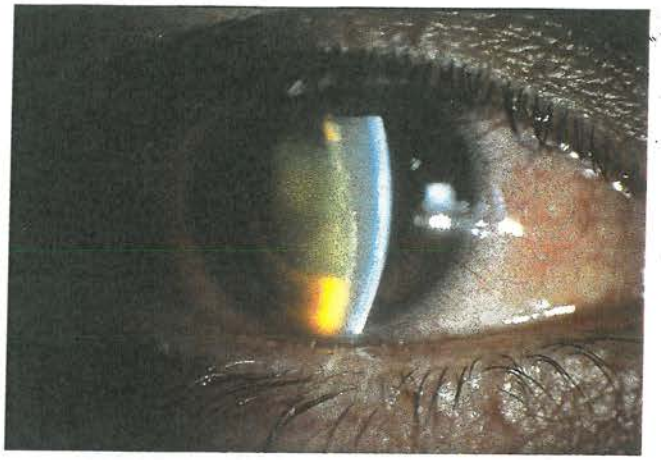


Figure 7.12 Fibrinous exudate in very severe acute anterior uveitis

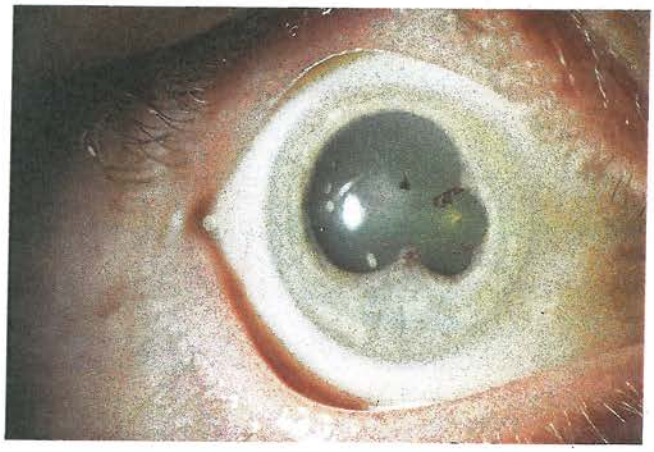


Figure 7.13 Posterior synechiae following an attack of acute anterior uveitis

(*see* Figure 6.80), which may lead to elevation of intraocular pressure secondary to closure of the angle by the peripheral iris.

INTERMEDIATE UVEITIS

1. **Symptoms** are usually floaters, although occasionally the patient presents with impairment of visual acuity caused by cystoid macular oedema.
2. **Signs**
   (a) Cellular infiltration of the vitreous (vitritis) with fewer cells in the anterior chamber.
   (b) Absence of focal inflammatory fundus lesions.

Intermediate uveitis is discussed in detail later.

POSTERIOR UVEITIS

1. **Symptoms** of posterior segment inflammation include floaters and impaired vision. A patient with a peripheral inflammatory lesion will complain of seeing floaters and may have only minimal blurring of vision. On the other hand, active choroiditis involving the fovea or papillomacular bundle will primarily cause loss of central vision, and the patient may not notice the presence of vitreous opacities.
2. **Signs**
   (a) ***Vitreous changes*** include cells, flare, opacities and, frequently, posterior vitreous detachment. In some cases the posterior hyaloid face is covered by inflammatory precipitates comparable to KP.
   (b) ***Choroiditis*** is characterized by yellow or greyish patches with reasonably well-demarcated borders (Figure 7.14). Inactive lesions appear as white well-defined areas of chorioretinal atrophy with pigmented borders (Figure 7.15). The

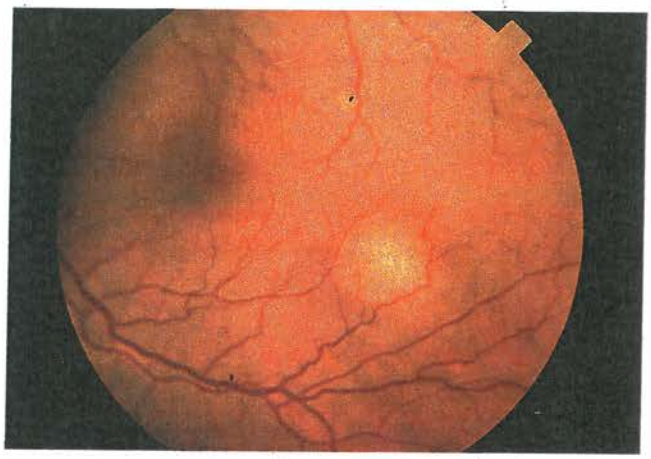


Figure 7.14 Active focal choroiditis

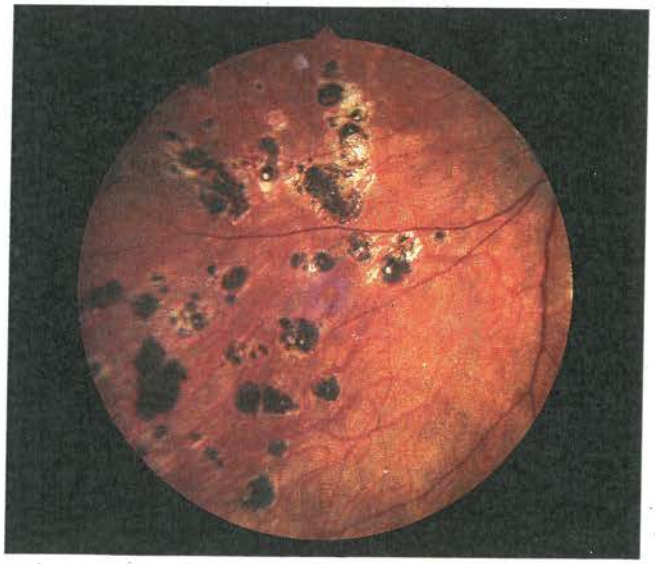


Figure 7.15 Old multifocal choroiditis

retinal blood vessels pass over the lesions undisturbed.

(c) ***Retinitis*** gives the retina a white cloudy appearance (Figure 7.16). Because the outline of the inflammatory focus is indistinct, exact demarcation between healthy and affected retina may be difficult to discern.

(d) ***Vasculitis*** is inflammation of the retinal blood vessels. The retinal veins (periphlebitis) are most frequently involved, although in some cases the arterioles (periarteritis) may be affected. Active periphlebitis is characterized by a fluffy white haziness surrounding the blood column (Figure 7.17). Involvement is patchy, with irregular extensions outside the vessel wall. Perivascular accumulation of granulomatous tissue in severe periphlebitis gives rise to 'candlewax drippings' (Figure 7.18).

The three main types of posterior uveitis are: (a) ***unifocal*** (e.g. toxoplasmosis), (b) ***multifocal*** (e.g. presumed ocular histoplasmosis) and (c) ***geographical*** (e.g. cytomegalovirus retinitis).

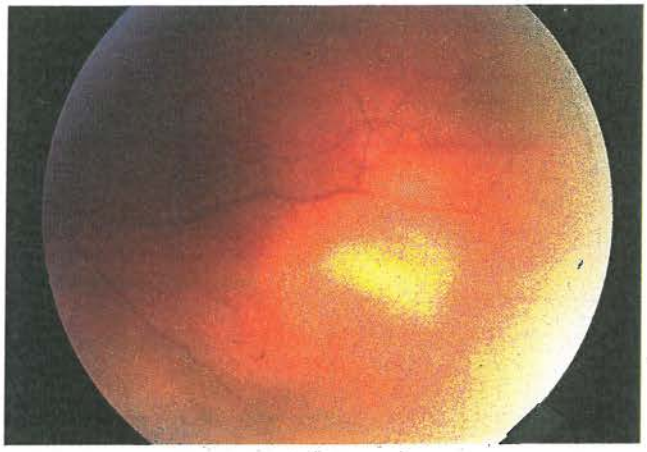


Figure 7.16 Active focal retinitis

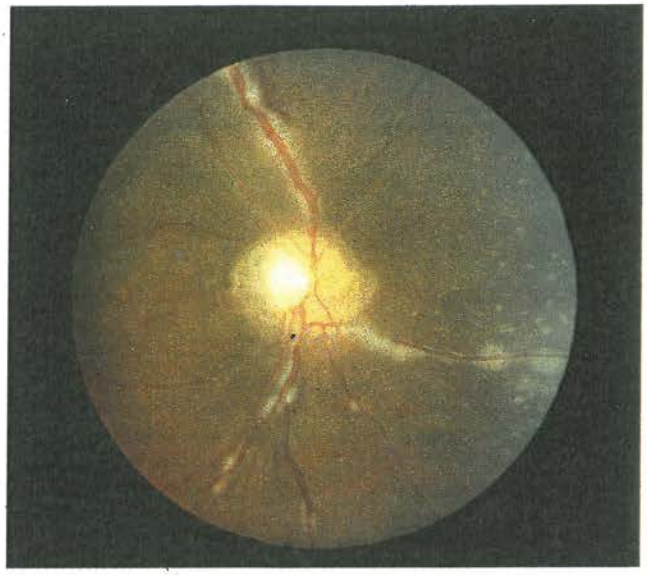


Figure 7.18 'Candlewax drippings' in severe granulomatous periphlebitis

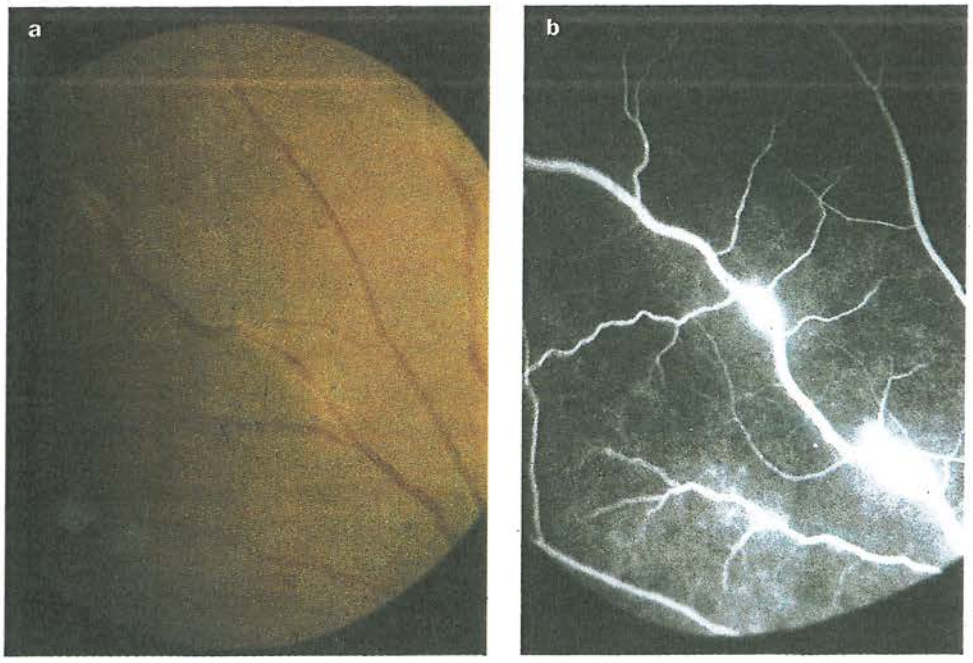


Figure 7.17 Periphlebitis. (**a**) clinical appearnce; (**b**) appearance on fluorescein angiography

UVEITIS ASSOCIATED WITH ARTHRITIS

Spondylarthropathies

INTRODUCTION

The spondylarthropathies are a cluster of overlapping forms of inflammatory arthritis that characteristically affect the spine and entheses (insertions of tendons and ligaments). The syndromes include: (a) ***ankylosing spondylitis***, (b) ***Reiter syndrome***, (c) ***psoriatic arthritis***, and (d) ***enteropathic arthritis***.

1. **Histocompatibility** antigens HLA-B27 and, to a lesser extent, HLA-CW6 are strongly associated with the spondylarthropathies but patients are seronegative for anti-immunoglobulins (rheumatoid factors).
2. **Presentation** is most frequently during young adult life and occasionally during childhood. Overall, both sexes are involved more or less equally, except for those with spinal involvement which is more common in males.
3. **Sacroiliitis** and **spondylitis** present as bilateral or unilateral discomfort in the buttocks, usually worse after inactivity but sometimes aggravated by weight bearing. Early radiological changes include juxta-articular osteoporosis and late changes are characterized by juxta-articular sclerosis and subsequent obliteration of the joint space (Figure 7.19).
4. **Enthesopathy** characteristically involves the plantar fascia, Achilles tendon insertion and the spine and pelvis. Widespread diffuse lesions in the spine or pelvis may produce stiffness and generalized discomfort.

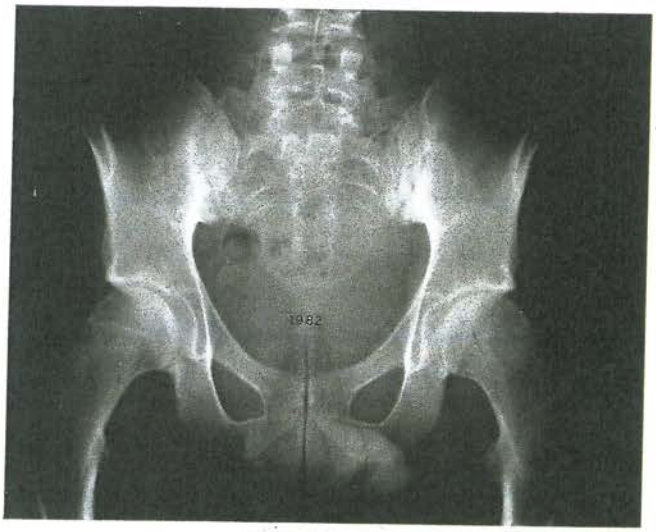


Figure 7.19 Irregular sacroiliac joints and right narrowing in a patient with sacroiliitis

5. **Inflammatory bowel disease,** which may be subclinical, is present in a substantial proportion of patients. Some patients have fully established ulcerative colitis or Crohn disease. The condition is then referered to as ***enteropathic arthritis***.
6. **Genitourinary lesions** characteristically occur in patients with Reiter syndrome.

ANKYLOSING SPONDYLITIS

Ankylosing spondylitis (AS) primarily involves the sacroiliac joints and axial skeleton. Associated inflammatory bowel disease is common but genitourinary lesions do not occur.

1. **Presentation** is usually with sacroiliitis although in some cases acute iritis is the first clinical manifestation. For this reason all young men with acute unilateral iritis should have radiographs of the sacroiliac joints irrespective of the presence or absence of low back symptoms. This is because, in early cases, the radiographs may be positive before the patient is symptomatic. The diagnosis of subclinical AS is important because appropriate therapy may prevent the development of more severe structural changes in the spine (Figures 7.20, 7.21).

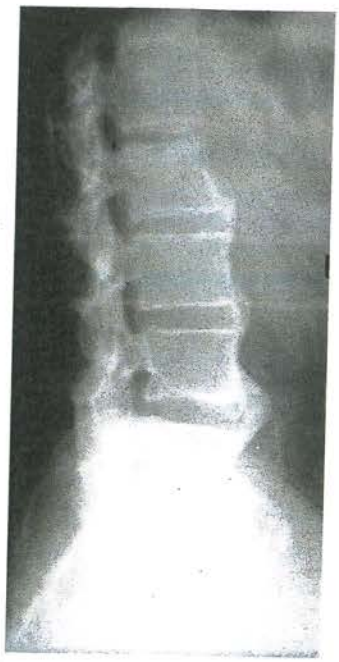


Figure 7.20 Severe spinal involvement with bony bridging by syndesmophytes in a patient with advanced ankylosing spondylitis

2. **HLA-B27** is strongly associated with AS and acute iritis. The prevalence of HLA-B27 in the UK is as follows:
   - In the general population: 8%.
   - In patients with acute iritis: about 45%.

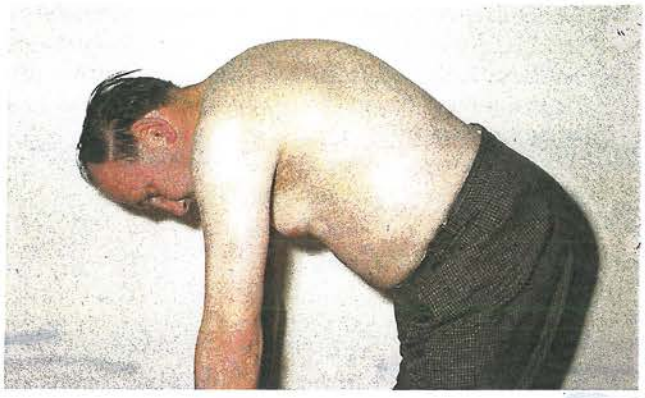


Figure 7.21 Limited spinal flexion in advanced ankylosing spondylitis

- In patients with AS: about 90%.
- In patients with both AS and acute iritis: about 95%.

The presence of HLA-B27 in a patient with early radiographic findings therefore merely confirms the diagnosis of AS.

3. **Acute iritis**, which is recurrent and non-granulomatous, occurs in 30% of patients with AS; conversely, 30% of males with acute iritis will have AS. Although both eyes are rarely involved simultaneously, either eye is frequently affected at different times. In severe cases there is a fibrinous aqueous exudate (*see* Figure 7.12). There is no correlation between the severity and activity of eye and joint involvement. Although there is a high risk that the uveitis will recur in one or other eye, the long-term visual prognosis is good and vision-threatening complications are rare. In a few patients with many recurrent attacks the inflammation eventually becomes chronic.

REITER SYNDROME

Reiter syndrome is defined as an episode of peripheral arthritis of more than one month's duration occurring in association with urethritis or cervicitis, or both. The disease affects men more frequently than women. About 70% of patients are positive for HLA-B27 and 60% of patients have associated sacroiliitis.

1. **Arthritis**, typically affecting the knees and ankles.
2. **Enthesopathy** include plantar fasciitis, Achilles tendonitis, bursitis and calcaneal periostitis. Repair by reactive bone may lead to the formation of a calcaneal spur (Figure 7.22).
3. **Extra-articular features**
   (a) Transient painless mouth ulcers (Figure 7.23).
   (b) Scaling, plaque-like, skin lesions which resemble psoriasis (keratoderma blenorrhagica) and which involve the palms and soles (Figure 7.24).

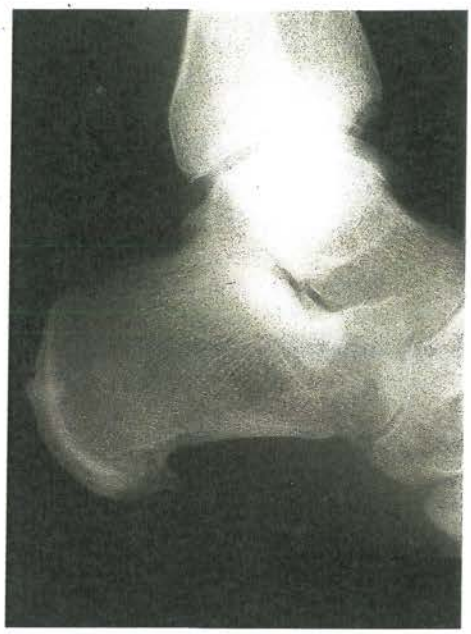


Figure 7.22 Calcaneal spur in Reiter syndrome

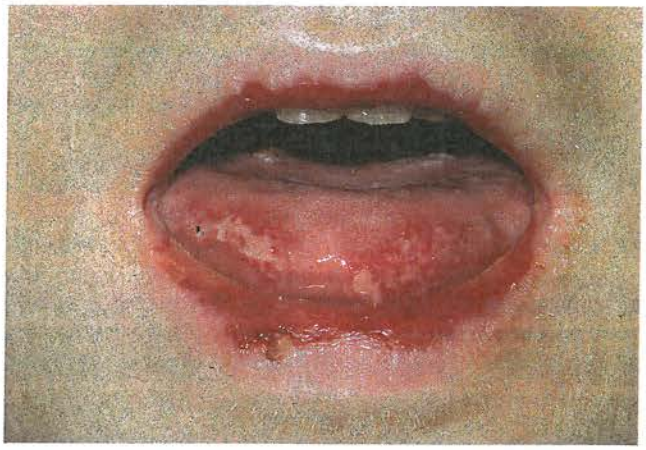


Figure 7.23 Painless tongue ulceration in Reiter syndrome

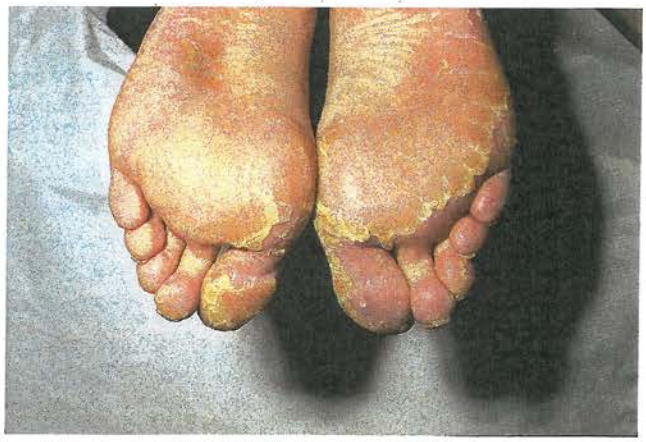


Figure 7.24 Keratoderma blenorrhagica in Reiter syndrome

(c) Painless, erythematous erosion of the glans penis (circinate balanitis, Figure 7.25).
(d) Nail changes, which are common.
(e) Aortic insufficiency, which is uncommon.

4. **Ocular features**
   (a) ***Conjunctivitis*** which is bilateral and mucopurulent is by far the most common manifestation. It usually follows the urethritis by about 2 weeks and precedes the onset of arthritis. The conjunctivitis usually resolves spontaneously within 7–10 days and does not require treatment. Cultures for bacteria are usully negative.
   (b) ***Acute iritis*** occurs in about 20% of patients, either with the first attack of Reiter syndrome or during a recurrence.
   (c) ***Keratitis*** may occur in isolation or in association with conjunctivitis. It consists of subepithelial opacities with overlying punctate epithelial lesions (Figure 7.26).

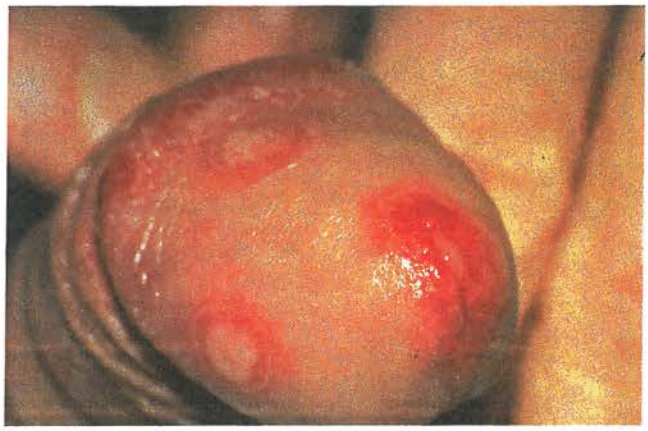


Figure 7.25 Circinate balanitis in Reiter syndrome

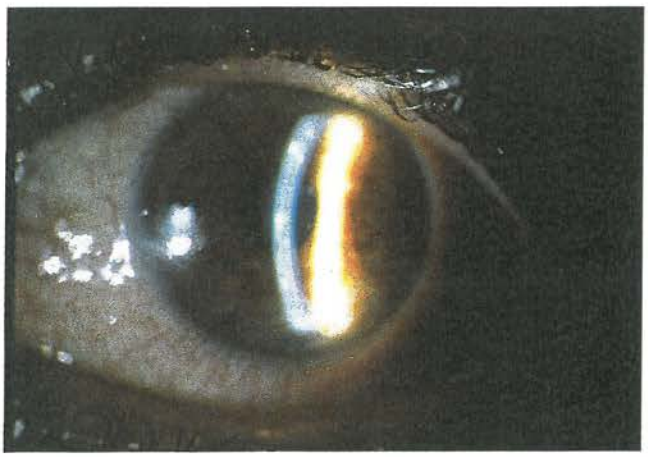


Figure 7.26 Keratitis in Reiter syndrome

PSORIATIC ARTHRITIS

Psoriatic arthritis affects about 7% of patients with psoriasis. The disease affects both sexes equally and is associated with an increased prevalence of HLA-B27 and HLA-B17.

1. **Arthritis** may have one of the following patterns:
   (a) Most common is involvement of the distal interphalangeal joints in association with nail changes (Figure 7.27).

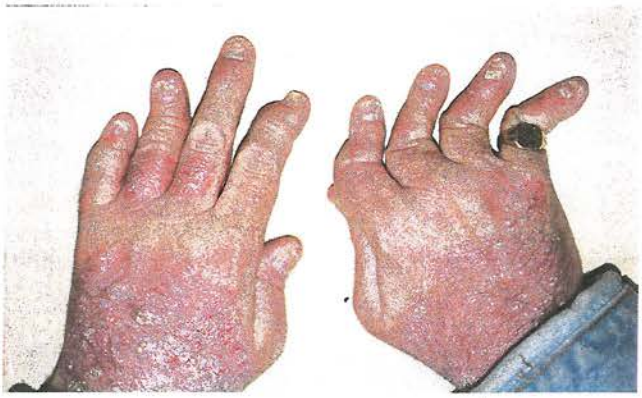


Figure 7.27 Severe involvement of the hands and nails in psoriatic arthritis

   (b) Ankylosing spondylitis, which may be associated with HLA-B27.
   (c) Pauciarticular peripheral disease.
   (d) Symmetrical peripheral involvement that mimics rheumatoid arthritis.
   (e) Arthritis mutilans affecting a few digits is rare.
2. **Nail changes**, which initially consist of pitting.
3. **Ocular features**
   (a) ***Conjunctivitis*** occurs in about 20%.
   (b) ***Acute iritis*** occurs but is less common than in AS and Reiter syndrome.
   (c) ***Keratitis*** in the form of raised corneal infiltrates just inside the limbus develops in some patients with acute iritis.
   (d) ***Secondary Sjögren syndrome*** is uncommon.

Juvenile chronic arthritis

SYSTEMIC FEATURES

Juvenile chronic arthritis (JCA) is an uncommon, idiopathic, inflammatory arthritis of at least 3 months' duration developing in children before the age of 16 years. The female:male ratio is 3:2. Patients are seronegative for IgM rheumatoid factor. In North America, JCA is frequently referred to as juvenile 'rheumatoid' arthritis.

1. **Presentation**
   Based on the onset and the extent of joint involvement during the first 6 months, the three types of presentation are as follows.
   (a) ***Pauciarticular onset JCA*** accounts for about 60% of cases. It affects girls five times as often as boys, with a peak age at onset of around 2 years. The arthritis involves four or fewer joints, most commonly the knees (Figure 7.28c), although the ankles and wrists may also be affected. Some patients in this subgroup remain pauciarticular whereas others subsequently develop a polyarthritis. About 75% of children are positive for antinuclear antibodies (ANA). *Uveitis* is common in this group and affects about 20% of children. Risk factors for uveitis are early-onset of JCA, and positive findings for ANA and HLA-DR5.
   (b) ***Polyarticular onset JCA*** accounts for a further 20% of cases. It affects girls about three times as often as boys and its onset is throughout childhood. The arthritis involves five or more joints, with both small and large joints being involved symmetrically (Figure 7.28b). About 40% of children are positive for ANA. *Uveitis* occurs in about 5% of cases. Systemic features are mild or absent and uveitis is uncommon.
   (c) ***Systemic onset JCA***, which accounts for about 20% of cases. The disease occurs with equal frequency in boys and girls and can occur at any age. Systemic features include a high remittent fever and at least one of the following features: transient maculopapular rash (Figure 7.28a), generalized lymphadenopathy, hepatosplenomegaly and serositis. Initially, arthralgia or arthritis may be absent or minimal, and only a minority of patients subsequently develop a progressive polyarthritis. The term '*Still's disease*' is now reserved for patients in this subgroup in which *uveitis* is extremely rare.

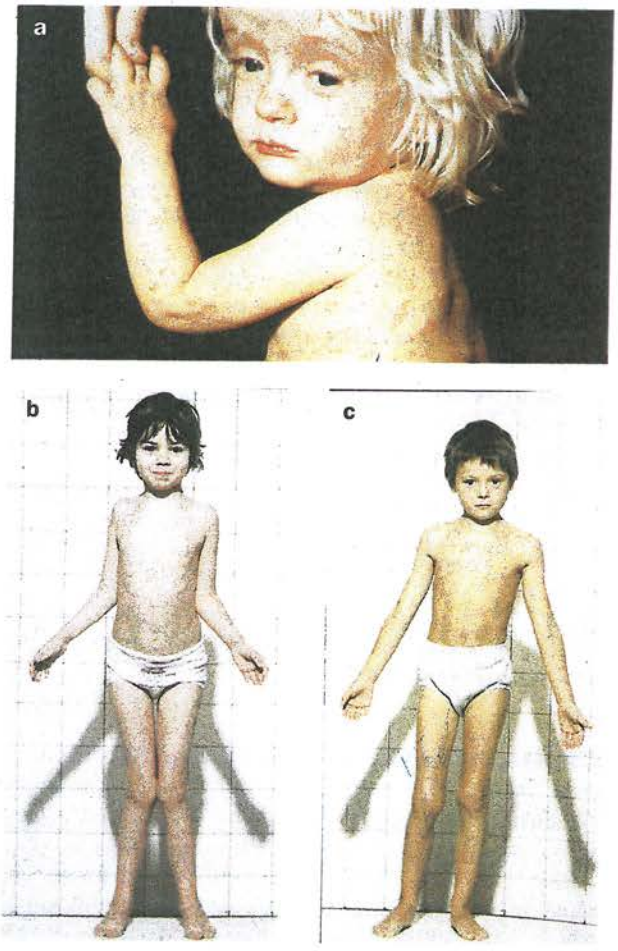


Figure 7.28 Juvenile chronic arthritis. **(a)** maculopapular rash in systemic-onset disease; **(b)** polyarticular disease; **(c)** pauciarticular disease involving only the right knee

SCREENING FOR UVEITIS

Because the onset of intraocular inflammation is invariably asymptomatic, it is extremely important for children at risk to have regular screening for at least 7 years from the onset of arthritis. The frequency of slitlamp examination is governed by the various risk factors as follows:

- Systemic onset = annual
- Polyarticular onset = every 9 months
- Polyarticular onset + ANA = every 6 months
- Pauciarticular onset = every 4 months
- Pauciarticular onset + ANA = every 3 months.

OCULAR FEATURES

Anterior uveitis in JCA is chronic, non-granulomatous and bilateral in 70% of cases. It is unusual for patients with initially unilateral uveitis to develop involvement of the second eye after more than 1 year. In those with bilateral uveitis, the severity of intraocular inflammation is usually symmetrical.

1. **Presentation** is invariably asymptomatic and the uveitis is frequently detected on routine slitlamp examination. Even during acute exacerbations with +4 cells in the aqueous humour, it is rare for patients to complain, although a few report an increase in vitreous floaters.
2. **Signs**
   (a) The eye is usually uninjected even in the presence of severe uveitis.
   (b) The KP are usually small to medium in size. During acute exacerbations, the entire corneal endothelium shows 'dusting' by many hundreds of cells, although hypopyon is very rare.
   (c) Posterior synechiae are common in eyes with longstanding undetected uveitis.

3. **The clinical course** follows one of the following patterns:
   (a) In about 10% of cases the intraocular inflammation is very mild, unassociated with keratic precipitates, never with more than +1 aqueous cells and persists for less than 12 months.
   (b) About 15% of patients have one attack of uveitis which lasts less than 4 months, with the severity of inflammation varying from +2 to +4 aqueous cells.
   (c) In 50% of cases, the uveitis is moderate to severe and persists for more than 4 months.
   (d) In 25% of cases, the intraocular inflammation is very severe, lasts for several years. In this subgroup, band keratopathy (Figure 7.29) occurs in 40% of patients, cataract (Figure 7.30) in 30%, and secondary inflammatory glaucoma in 15%.
4. **Treatment** with topical steroids, if appropriately administered, is usually effective in most patients; acute exacerbations require very frequent instillations. Those who respond poorly to topical medication may respond to periocular injections. The therapeutic value of cytotoxic agents such as chlorambucil and methotrexate is undetermined.

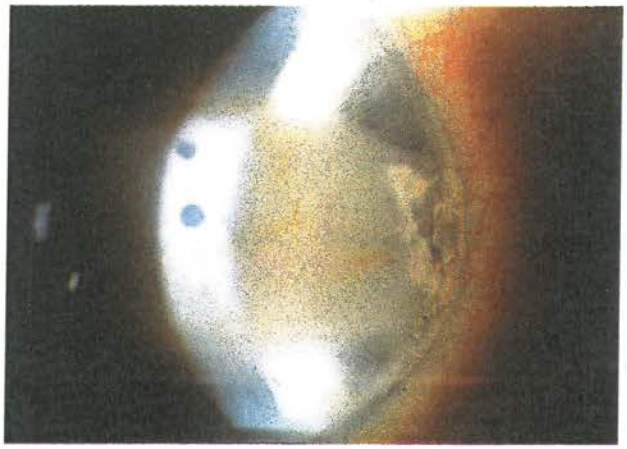


Figure 7.29 Band keratopathy secondary to chronic iridocyclitis associated with juvenile chronic arthritis

Figure 7.30 Band keratopathy and cataract secondary to chronic iridocyclitis associated with juvenile chronic arthritis

Relapsing polychondritis

SYSTEMIC FEATURES

Relapsing polychondritis is an uncommon disease characterized by recurrent inflammation of cartilage of the external ear (Figure 7.31), as well as nasal, costal, tracheal and laryngeal cartilages. The latter may lead to laryngeal obstruction. Other systemic features include a transient arthritis, fever, cardiovascular disease and anaemia. Ocular complications occur in about 60% of cases.

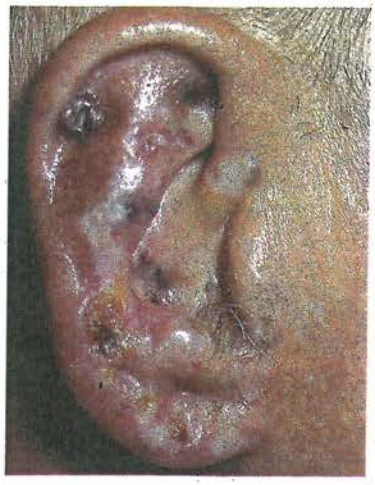


Figure 7.31 Involvement of the pinna in relapsing polychondritis

OCULAR FEATURES

1. **Anterior uveitis** occurs in 10% of cases.
2. **Episcleritis** and **scleritis** occur in 30–60% of patients.
3. **Other**, less common complications, include keratoconjunctivitis sicca, marginal corneal ulceration and exudative retinopathy.

UVEITIS IN NON-INFECTIOUS SYSTEMIC DISEASES

Sarcoidosis

PRESENTATION

Sarcoidosis is a common, idiopathic, multisystem disorder characterized by the presence of non-caseating granulomata which may affect virtually any single or combination

of organs in the body. The lungs are affected in about 90% of cases. The initial presentation may vary dramatically, and the clinical course may be acute, subacute or chronic.

1. **Acute disease** usually affects patients during the third decade. It develops over a few weeks and presents in one of the following ways:
   (a) ***Lofgren syndrome***, which is characterized by fever, erythema nodosum (Figure 7.32), bilateral hilar lymphadenopathy (Figure 7.33) and frequently arthralgia.
   (b) ***Heerfordt syndrome*** (uveoparotid fever) which is characterized by fever, parotid enlargement (Figure 7.34) and uveitis.
   (c) ***Seventh nerve palsy*** (Figure 7.35) with other neurological involvement may be present.
2. **Insidious-onset disease** typically presents during the fifth decade with fatigue, dyspnoea and arthralgia.

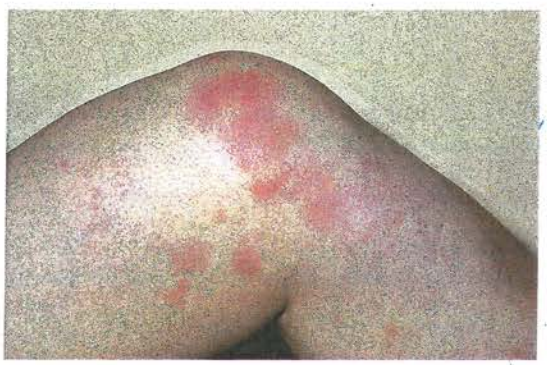


Figure 7.32 Erythema nodosum in sarcoidosis

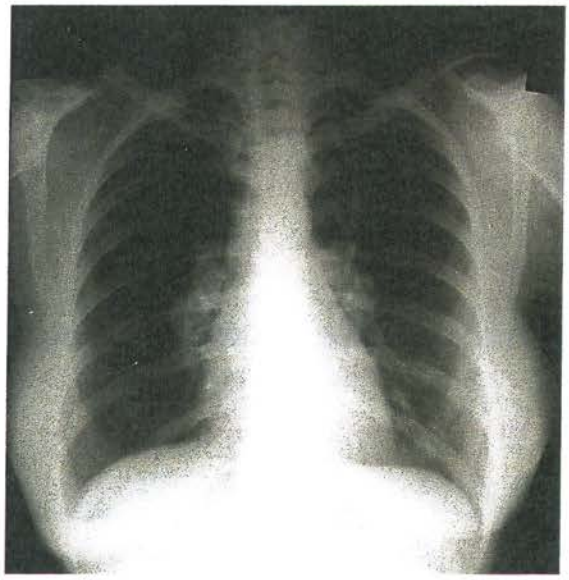


Figure 7.33 Bilateral hilar lymphadenopathy in sarcoidosis

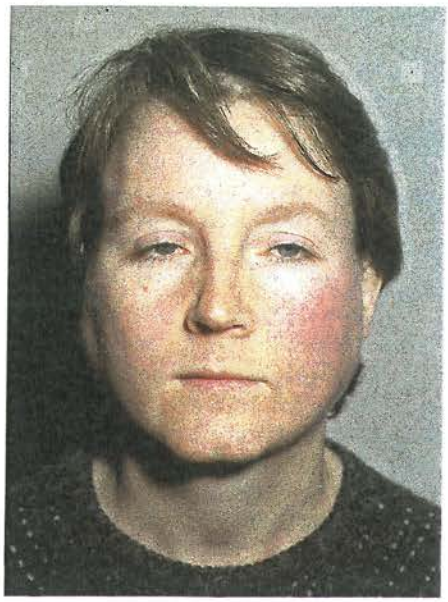


Figure 7.34 Parotid enlargement in uveoparotid fever associated with sarcoidosis

Figure 7.35 Facial palsy and cutaneous sarcoid granulomata on the nose

CLINICAL FEATURES

1. **Lung involvement** is the hallmark of the disease. Staging is based on radiological assessment of both parenchymal and lymphatic involvement as follows:
   (a) ***Stage 1*** – bilateral hilar lymphadenopathy (*see* Figure 7.33)

(b) ***Stage 2*** – bilateral hilar lymphadenopathy and reticulonodular parenchymal infiltrates (Figure 7.36).

(c) ***Stage 3*** – reticulonodular infiltrates alone (Figure 7.37).

(d) ***Stage 4*** – progressive pulmonary fibrosis with bullae formation and bronchiectasis (Figure 7.38).

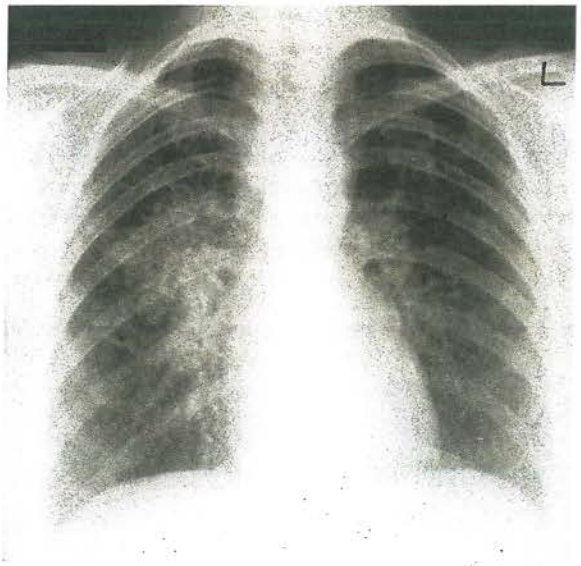


Figure 7.36 Bilateral hilar lymphadenopathy and reticulonodular parenchymal infiltrates in sarcoidosis

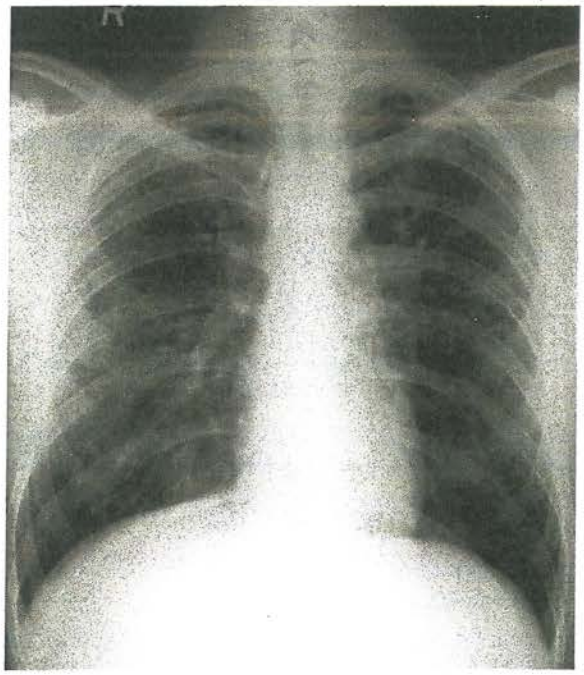


Figure 7.37 Reticulonodular parenchymal infiltrates without hilar lymphadenopathy in sarcoidosis

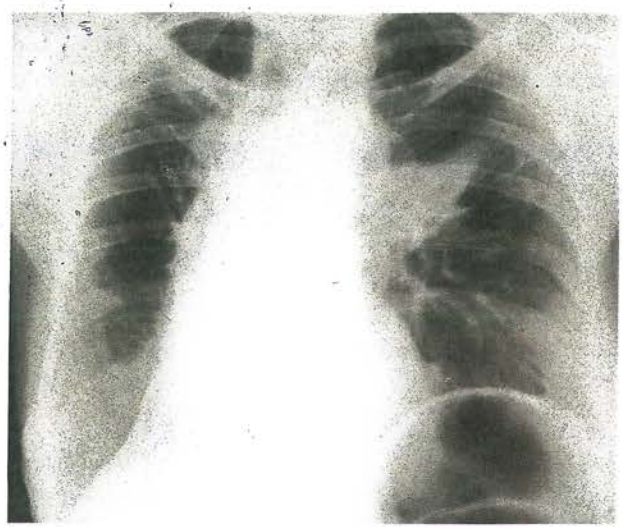


Figure 7.38 Severe pulmonary fibrosis in sarcoidosis

2. **Skin lesions**
   (a) ***Erythema nodosum*** is by far the most common. It is charcterized by red, tender nodules on the anterior surface of the legs (*see* Figure 7.32) and occasionally on the buttocks and arms.
   (b) ***Cutaneous granulomata***, which may be maculopapular, raised or nodular, may be seen on the face (Figure 7.39), buttocks and extremities.
   (c) ***Lupus pernio*** (purple lupus) is the classical cutaneous granulomatous manifestation which is characterized by chronic, indurated, purple-blue lesions (Figure 7.40).
3. **CNS lesions** occur in 5% of patients and are associated with significant morbidity and mortality.

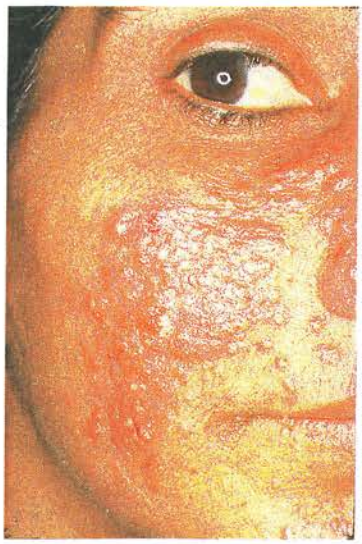


Figure 7.39 Cutaneous sarcoid granulomata

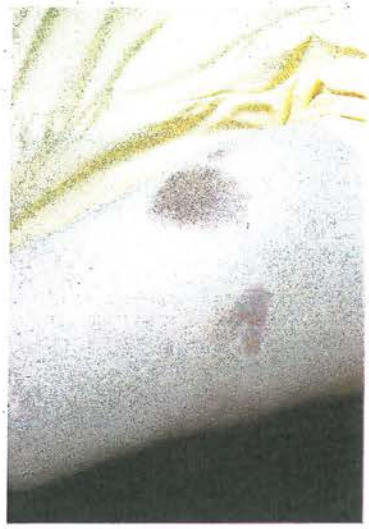


Figure 7.40 Lupus pernio

(a) ***Cranial nerve palsies***, which may affect any cranial nerve, are the most common CNS manifestation. The facial nerve is most frequently affected (*see* Figure 7.35).
(b) ***Other lesions*** include meningeal infiltration, intracranial and intraspinal granulomas, seizures and personality disturbance.

4. **Other lesions** may involve the reticuloendothelial system, liver, kidneys, bones and heart.

DIAGNOSTIC TESTS

Although the diagnosis is often easy, in some patients many of the features are missing and the following special investigations may be useful:

1. **Chest radiographs** are abnormal in over 90% of patients (*see* Figures 7.33, 7.36–38).
2. **Biopsy**
   (a) ***Lung*** biopsy is accurate in diagnosing sarcoidosis in about 90% of patients.
   (b) ***Conjunctival*** biopsy is positive in about 70% of patients irrespective of the presence of eye involvement.
   (c) ***Lacrimal gland*** biopsy by a transconjunctival route may be considered in patients with suspected sarcoidosis, particularly if the lacrimal glands are enlarged or if they demonstrate increased gallium uptake. Biopsies are positive in 25% of patients with non-enlarged glands and in 75% with enlarged glands.
3. **The Kveim–Siltzbach test** is positive in 85–90% in patients with early or active systemic disease but sensitivity decreases with chronicity.
4. **Serum angiotensin-converting enzyme** (ACE) is usually elevated in patients with active sarcoidosis and normal during remission. In patients with suspected neurosarcoid, ACE should be measured in the cerebrospinal fluid.
5. **Calcium assays** show abnormal metabolism. Hypercalciuria is common but hypercalcaemia is unusual.
6. **Gallium-67 scan** of the head, neck and thorax frequently shows increased uptake in patients with active sarcoidosis.
7. **Bronchoalveolar lavage** shows a raised proportion of activated T-helper lymphocytes.

OCULAR FEATURES

The eye is involved in about 30% of patients with systemic sarcoidosis. Ocular involvement may occur in patients with few, if any, constitutional symptoms, as well as in those with inactive systemic disease. The posterior segment is involved in about 25% of patients with ocular sarcoid and is usually associated with anterior uveitis.

1. **Anterior segment** lesions may involve the conjunctiva, episclera and, rarely, the sclera.
2. **Keratoconjunctivitis sicca** may occur as a result of lacrimal gland involvement.
3. **Anterior uveitis** is usually bilateral and may be either acute or chronic.
   (a) ***Acute iridocyclitis*** typically affects young patients with acute sarcoidosis.
   (b) ***Chronic granulomatous iridocyclitis*** (Figure 7.41) usually affects older patients with chronic lung fibrosis in whom the systemic disease may be inactive. The intraocular inflammation may be difficult to control and complications such as band keratopathy, complicated cataract and secondary glaucoma are frequent.
4. **Vitreous** changes are either in the form of diffuse vitritis or, less frequently, 'cotton ball' opacities (Figure 7.42).

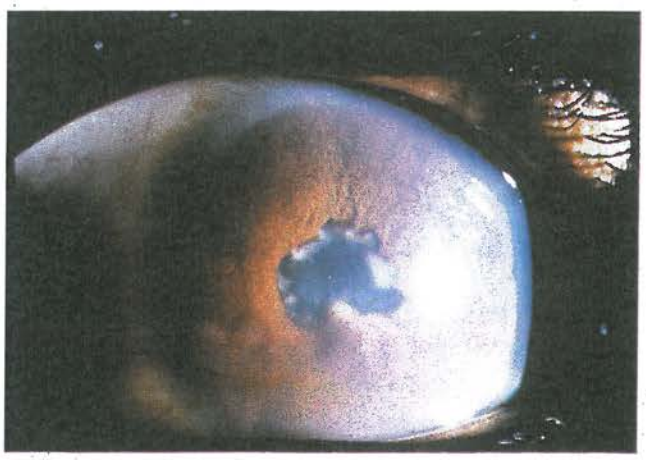


Figure 7.41 Iris nodules in chronic anterior uveitis associated with sarcoidosis

5. **Periphlebitis** is the most common feature of posterior segment sarcoidosis. It is most frequently mild (Figure 7.43), although rarely advanced periphlebitis gives rise to the characteristic perivascular 'candle-wax drippings' (Figure 7.44). Although acute lesions may resolve spontaneously or with the use of systemic steroids, vascular sheathing, once established, usually persists.
6. **Retinal** (Figure 7.45) and **preretinal granulomata** are uncommon. The latter are typically discrete, grey–white and located inferior and anterior to the equator (Landers sign, Figure 7.46).
7. **Choroidal granulomata** are common and characterized by bilateral, multiple, small, pale-yellow elevated lesions, usually most numerous inferiorly (Figure 7.47). Rarely a choroidal granuloma may be solitary and large (Figure 7.48), and may be mistaken for an amelanotic melanoma.

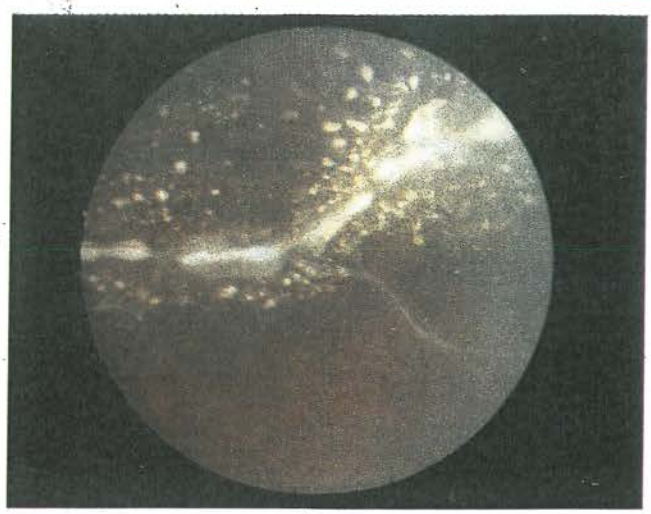


Figure 7.44 'Candlewax drippings' in severe sarcoid periphlebitis

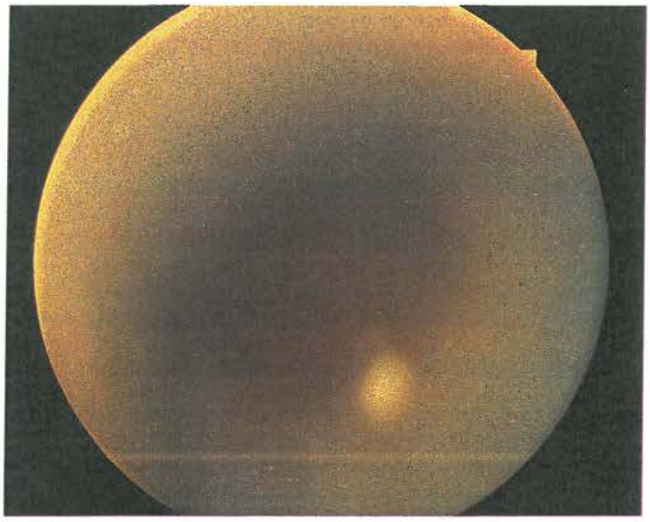


Figure 7.42 Vitreous 'cotton ball' in sarcoid uveitis

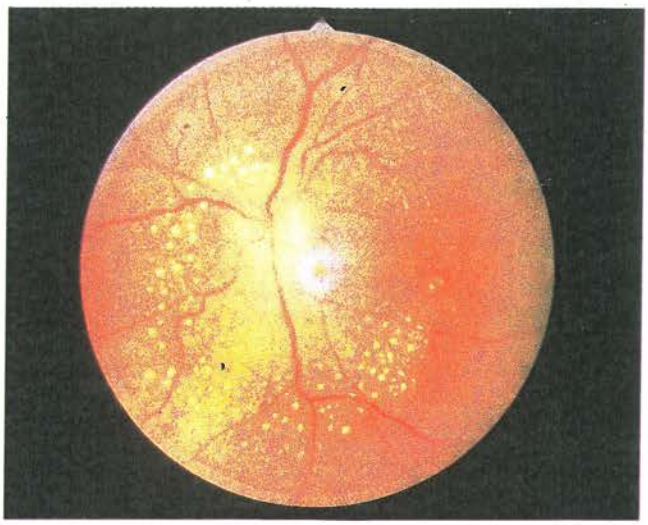


Figure 7.45 Multiple sarcoid retinal granulomata

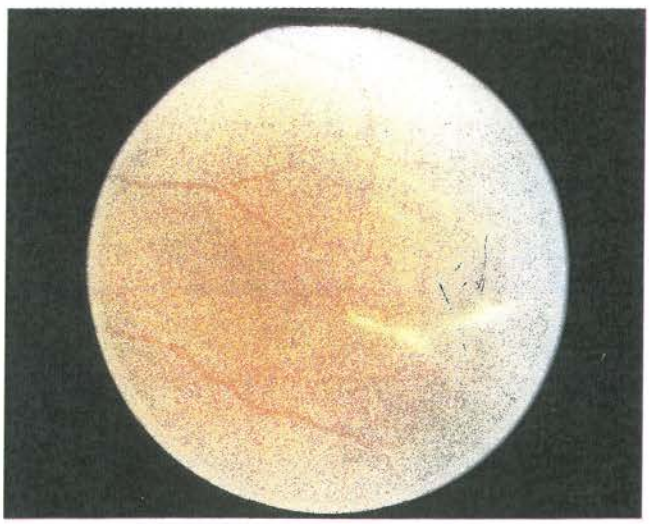


Figure 7.43 Mild retinal periphlebitis in sarcoidosis

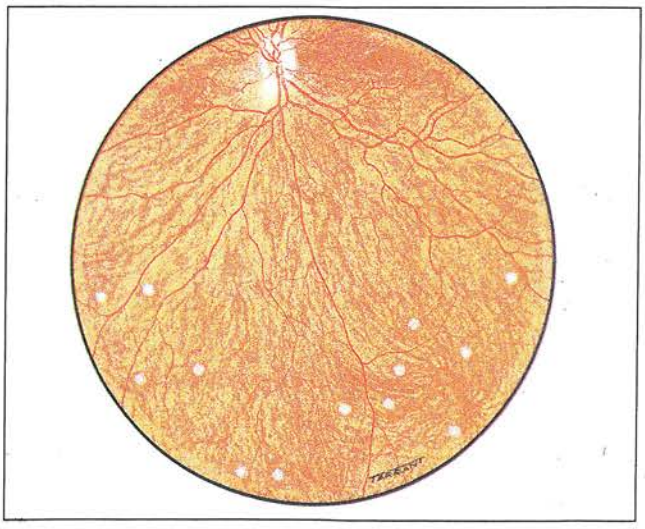


Figure 7.46 Preretinal sarcoid granulomata (Landers sign)

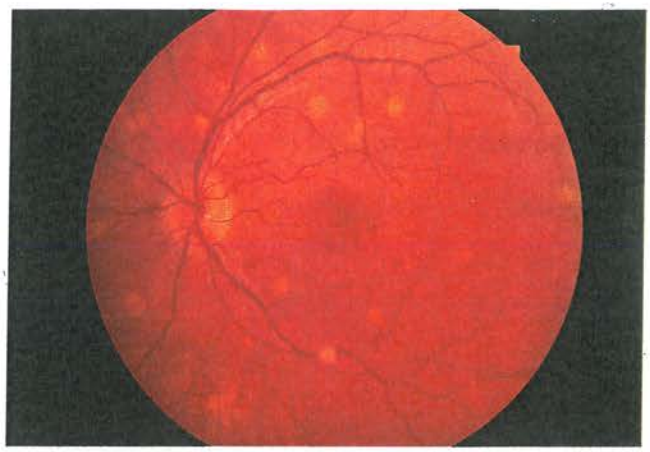


Figure 7.47 Multiple small choroidal sarcoid granulomata

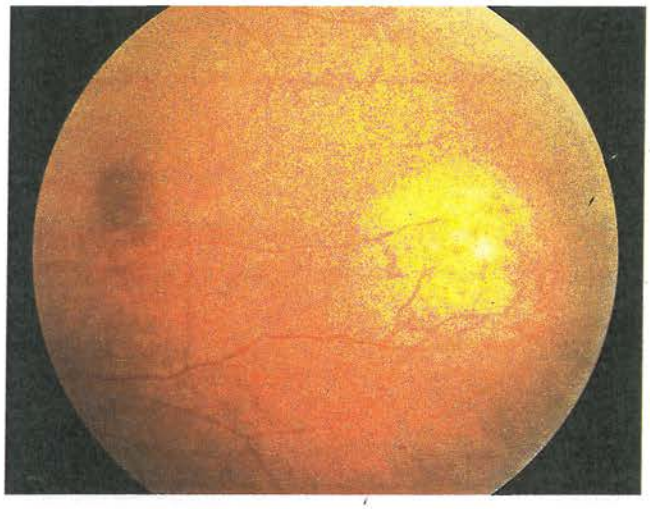


Figure 7.48 Solitary large sarcoid choroidal granuloma

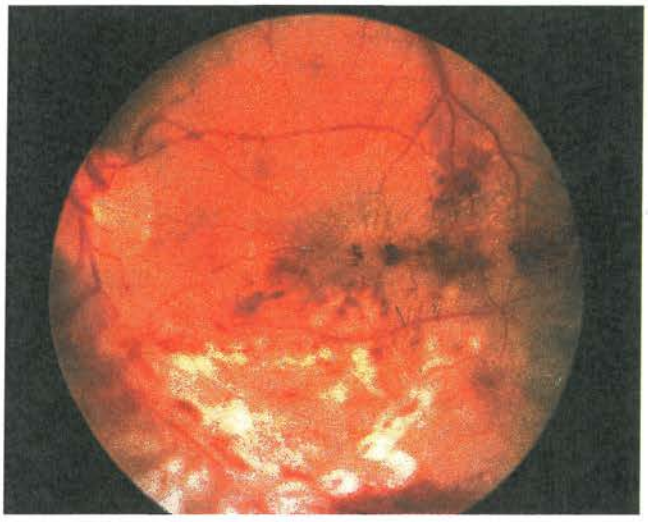


Figure 7.49 Acute sarcoid retinopathy with severe vasculitis and retinal haemorrhages

8. **Acute sarcoid retinopathy** is characterized by a combination of vitreous haze, 'candlewax drippings', retinal and pre-retinal granulomata and retinal haemorrhages (Figure 7.49).
9. **Peripheral retinal neovascularization** (Figure 7.50) may occur in association with retinal capillary drop-out on fluorescein angiography. In black patients it may be confused with sickle-cell retinopathy.
10. **Optic nerve** lesions may be of the following types:
    (a) ***Focal granulomata*** (Figure 7.51) may involve the optic nerve but do not usually affect visual acuity.
    (b) ***Papilloedema*** (Figure 7.52) is usually secondary to CNS involvement and may occur in the absence of other ocular lesions.

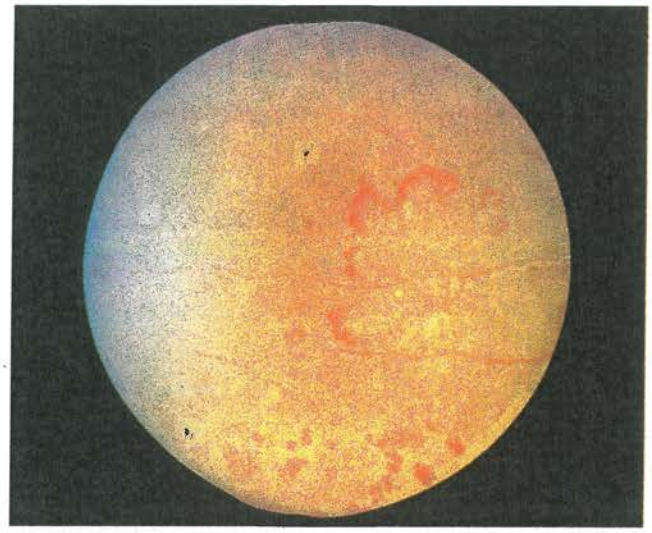


Figure 7.50 Peripheral retinal neovascularization in sarcoidosis

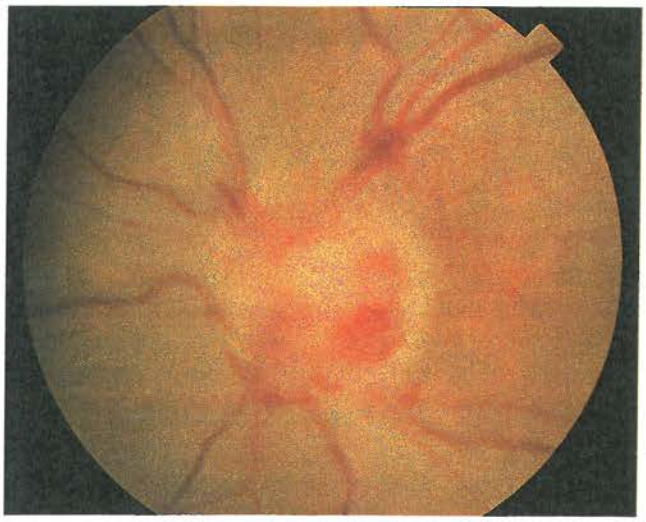


Figure 7.51 Sarcoid granuloma involving the optic nerve head

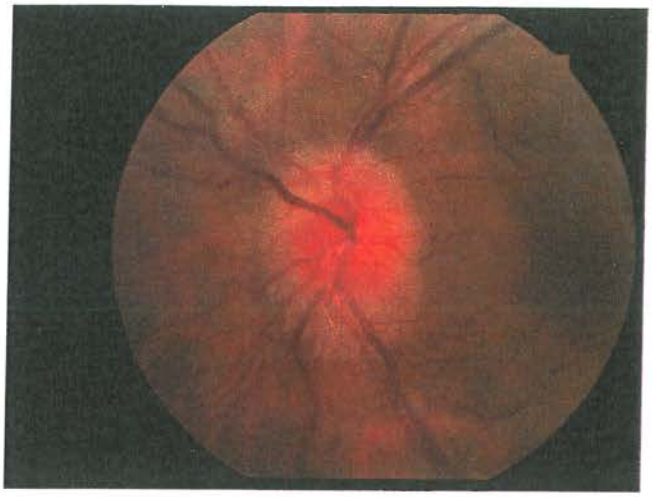


Figure 7.52 Papilloedema in neurosarcoid

(c) ***Disc neovascularization*** is an occasional complication of retinal branch vein occlusion, secondary to severe periphlebitis or, rarely, it may be associated with an optic nerve head granuloma.

(d) ***Persistent disc oedema*** of unknown cause is a frequent finding in patients with retinal or vitreous involvement.

Systemic steroid therapy may be necessary in patients with severe posterior segment disease, particularly if the optic nerve is involved.

Behçet disease

SYSTEMIC FEATURES

Behçet disease is an idiopathic, multisystem disorder which typically affects young men from the eastern Mediterranean region and Japan, but is rare in Western Europe and America. It is associated with an increased prevalence of HLA-B5.

1. **Presentation** is usually in the third and fourth decades with recurrent oral aphthous ulceration. As there are no special confirmatory tests, the diagnosis requires the presence of oral ulceration in association with two of the following: recurrent genital ulceration, skin lesions, eye involvement and a positive pathergy test.
2. **Oral ulceration** is a universal finding and a very common presenting feature. Aphthous ulcers are painful and shallow with a yellowish necrotic base. They are recurrent and tend to occur in crops, which may involve the tongue (Figure 7.53), gums, lips and buccal mucosa (Figure 7.54).

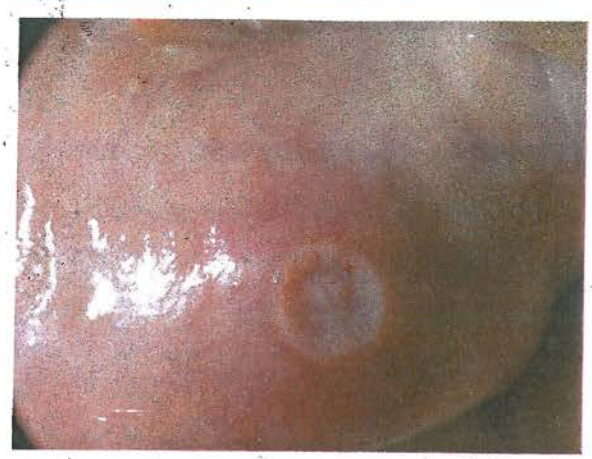


Figure 7.53 Tongue ulcer in Behçet disease

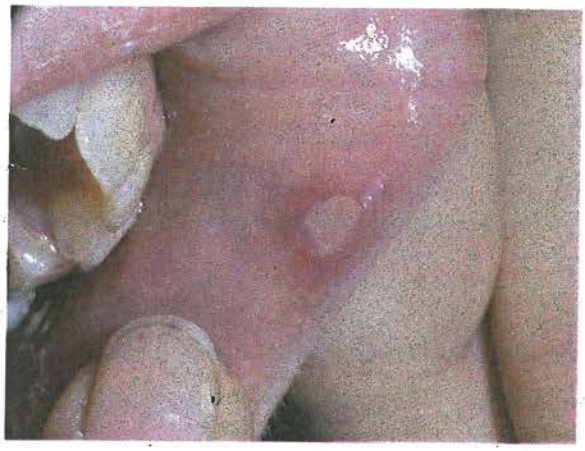


Figure 7.54 Ulcer of buccal mucosa in Behçet disease

3. **Genital ulceration** is present in about 90% of patients and is more apparent and troublesome in men (Figure 7.55) than in women.
4. **Skin lesions**
   (a) ***Erythema nodosum-like*** lesions on the anterior surface of the legs (Figure 7.56).

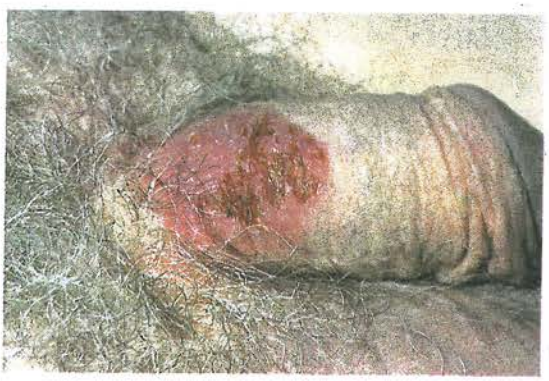


Figure 7.55 Genital ulcer in Behçet disease

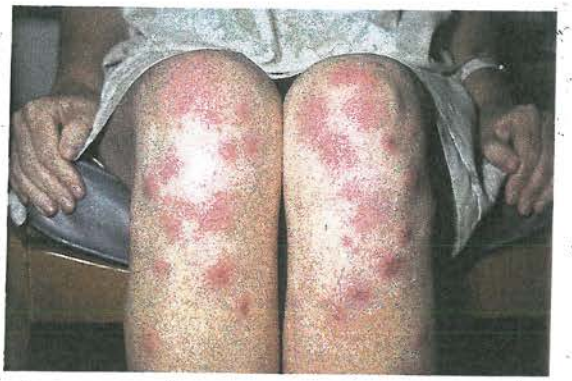


Figure 7.56 Erythema nodusum-like skin lesions in Behçet disease

(b) ***Acneiform lesions*** are common on the back and face.

(c) ***Cutaneous hypersensitivity*** is a characteristic feature. It can be tested with the 'prick' (pathergy) test, in which a pustule forms after puncture of the skin with a needle (Figure 7.57). Cutaneous hypersensitivity can also be tested by stroking the skin and demonstrating the appearance of corresponding lines (dermatographism, Figure 7.58).

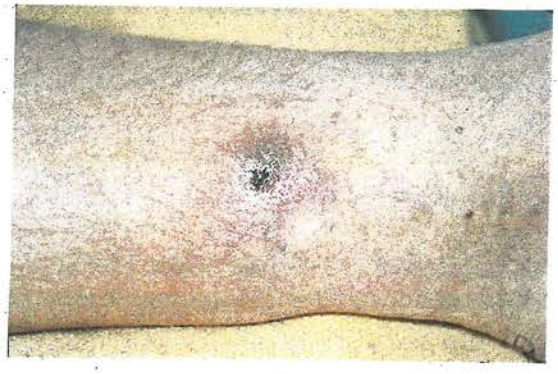


Figure 7.57 Pustule which has formed after pricking the skin in a patient with Behçet disease

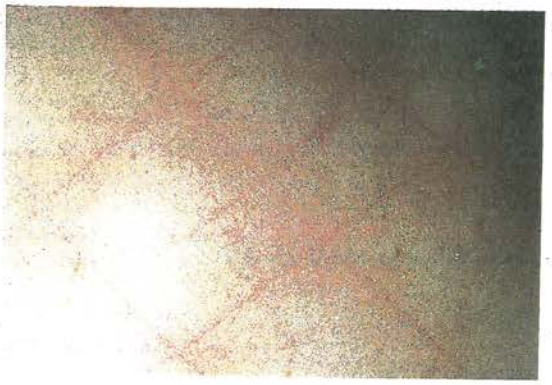


Figure 7.58 Dermatographism in Behçet disease

(d) ***Thrombophlebitis*** is less common. It usually occurs in the extremities and can be migratory.

5. **Vascular lesions** may affect vessels of all sizes.
   (a) ***Obliterative thrombophlebitis*** is the most common and can give rise to major internal venous occlusions (Figure 7.59).
   (b) ***Other vascular lesions***, which are less common but carry a poor prognosis, include arterial occlusion and aneurysm formation.
6. **Other features** include arthropathy, gastrointestinal lesions and CNS involvement.

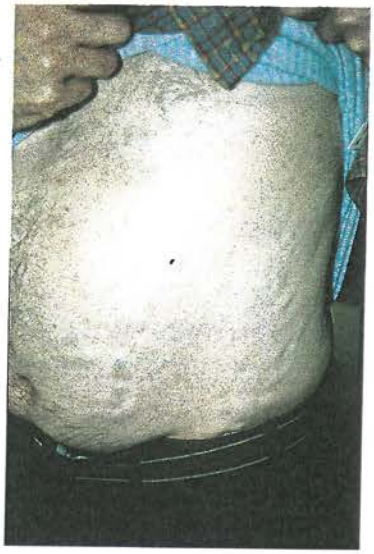


Figure 7.59 Dilated superficial veins secondary to deep obliterative thrombophlebitis in a patient with Behçet disease

OCULAR FEATURES

About 70% of patients with Behçet disease develop recurrent, bilateral, non-granulomatous, intraocular inflammation. In any individual patient, either anterior or posterior segment involvement can predominate. In patients with posterior segment involvement, the long-term visual prognosis is poor.

1. **Acute recurrent iridocyclitis** which may be associated with a transient hypopyon is common (Figure 7.60). Initially, the iridocyclitis responds well to topical steroids but it may subsequently become chronic and lead to phthisis bulbi.
2. **Retinitis** characterized by white, necrotic, superficial retinal infiltrates (Figure 7.61) may be seen during the active stage of the systemic disease. The lesions are usually transient and do not lead to scarring.
3. **Occlusive retinal periphlebitis** (Figure 7.62) is much more serious. It may result in venous occlusion (Figure 7.63) which may be complicated by secondary retinal neovascularization.

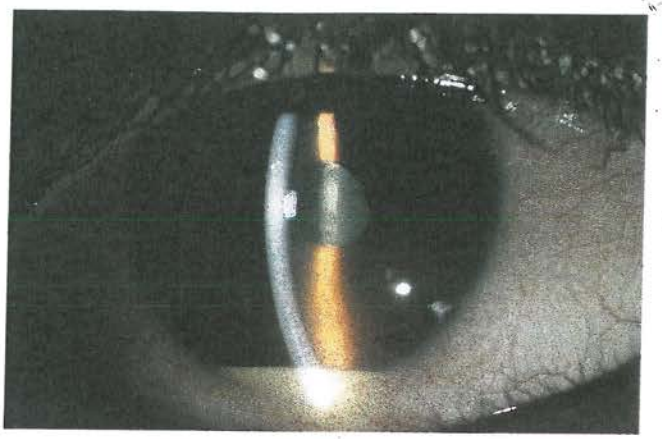


Figure 7.60 Hypopyon in Behçet disease

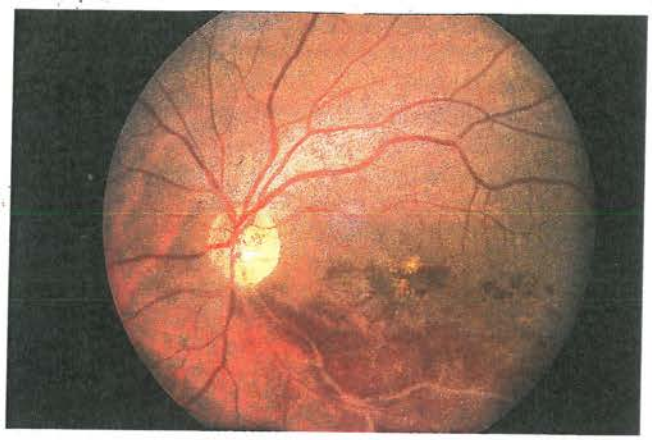


Figure 7.63 Retinal vein occlusion in Behçet disease

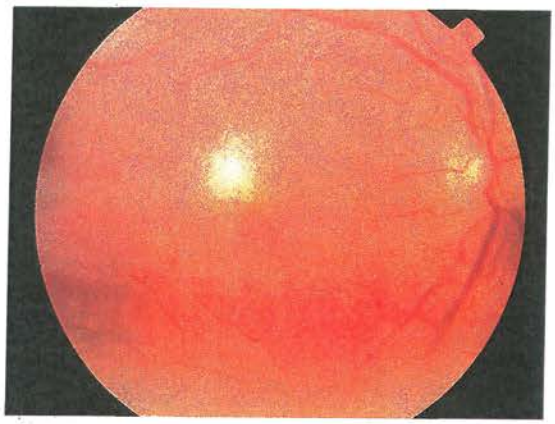


Figure 7.61 Retinal infiltrate in Behçet disease

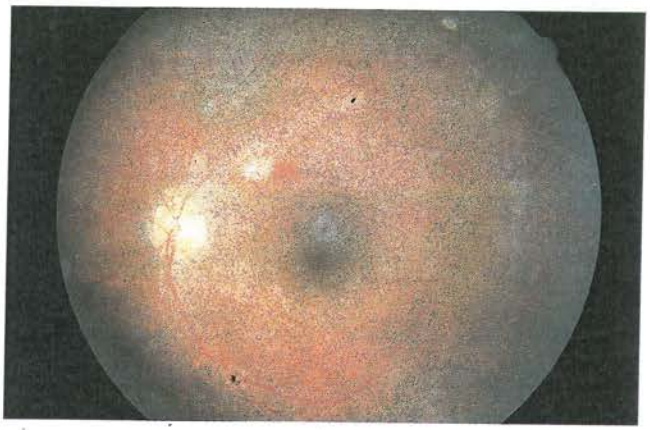


Figure 7.64 Severe retinopathy in Behçet disease

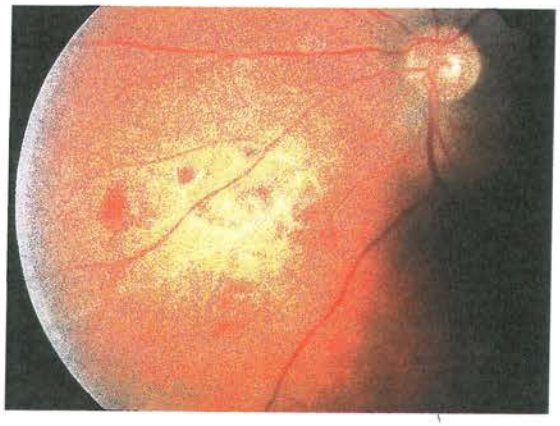


Figure 7.62 Vascular occlusion in Behçet disease

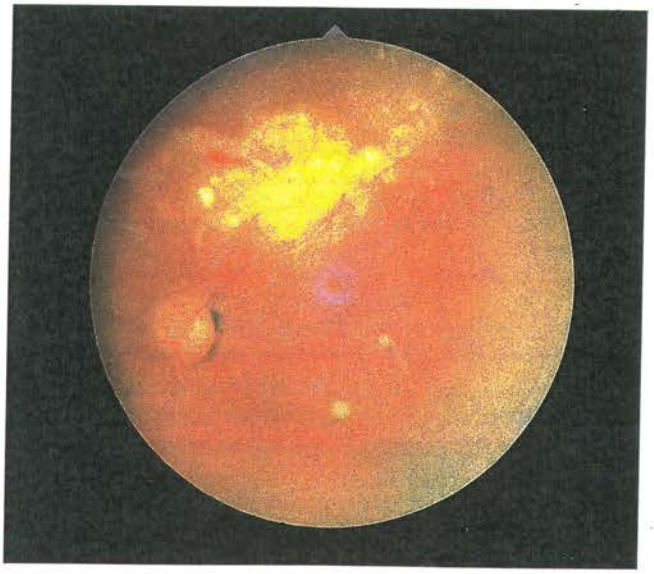


Figure 7.65 Massive retinal exudation and vascular obliteration in Behçet disease

4. **Diffuse leakage** throughout the fundus (Figure 7.64) which may give rise to diffuse retinal oedema and cystoid macular oedema. Occasionally, oedema or hyperaemia of the optic disc may be seen.

5. **Acute massive retinal exudation** involving the outer retinal layers, with associated obliteration of the overlying blood vessels (Figure 7.65), is relatively rare but serious.
6. **Vitritis**, which may be severe and persistent, is universal in eyes with uveitis.
7. **End-stage disease** is characterized by atrophic retina and optic disc, vascular attenuation and sheathing, and variable chorioretinal scarring (Figure 7.66).

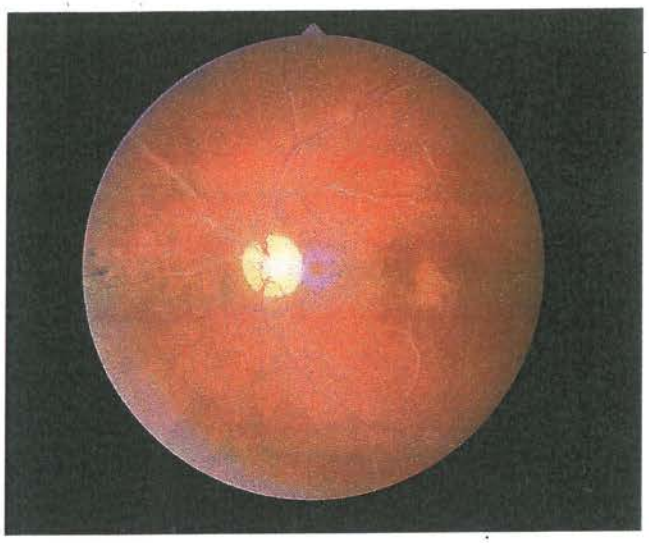


Figure 7.66 Optic atrophy and vascular occlusion in end-stage retinopathy of Behçet disease

TREATMENT OF POSTERIOR UVEITIS

1. **Systemic steroids** in high doses are usually effective initially in controlling posterior segment inflammation. Unfortunately, the lesions often subsequently become steroid resistant and require alternative therapy.
2. **Cyclosporin** is a potent immunomodulator affecting both the cellular and humoral arms of the immune response. It may be beneficial for the acute exacerbations of both eye and mucocutaneous lesions.
3. **Plasma exchange** may be useful in some cases.

Vogt–Koyanagi–Harada syndrome

The Vogt–Koyanagi–Harada (V–K–H) syndrome is an idiopathic, multisystem disorder which typically affects pigmented individuals. Japanese patients, in whom the disorder is relatively common, have an increased prevalence of HLA-DR4 and Dw15. In practice V–K–H can be subdivided into Vogt–Koyanagi syndrome, characterized mainly by skin changes and anterior uveitis, and Harada disease, in which neurological features and exudative retinal detachment predominate.

SYSTEMIC FEATURES

1. **Alopecia** (baldness) occurs in about 60% of patients and is usually confined to small areas.
2. **Poliosis** (whitening of hair) is also common and usually develops several weeks after the onset of the disease. It may sometimes surround bald areas.
3. **Vitiligo** (patches of skin depigmentation, Figure 7.67) usually follows the onset of visual symptoms by several weeks.
4. **Neurological features**
   (a) ***Meningeal involvement*** causing headache and neck stiffness, develops simultaneously with uveitis.
   (b) ***Encephalopathy*** is less frequent than meningeal involvement. It may manifest as convulsions, cranial nerve palsies and paresis.
   (c) ***Auditory symptoms*** include tinnitus, vertigo and deafness.
   (d) ***CSF lymphocytosis*** is present during the acute phase of the disorder.

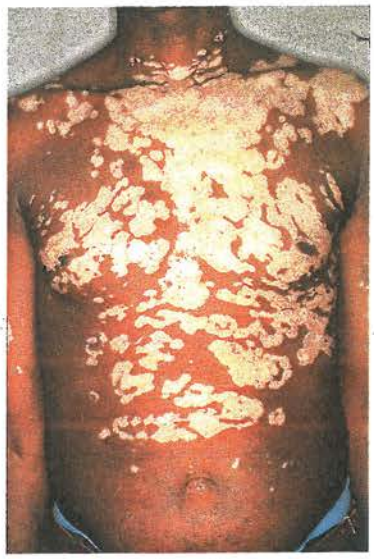


Figure 7.67 Severe vitiligo in Vogt–Koynagi–Harada syndrome

OCULAR FEATURES

1. **Chronic granulomatous iridocyclitis** is the only anterior segment finding. It runs a prolonged course and frequently leads to the formation of posterior synechiae, secondary glaucoma and cataract.
2. **Posterior segment involvement** in chronological order is as follows:
   (a) ***Multifocal choroiditis*** (Figure 7.68), which may be associated with disc hyperaemia or oedema.
   (b) ***Multifocal detachments of the sensory retina*** at the posterior pole (Figure 7.69), which with time, may become bullous.

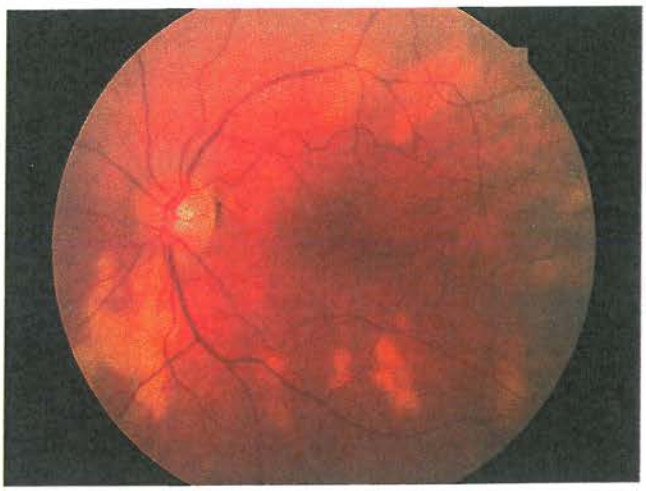


Figure 7.68 Multifocal choroiditis in Harada syndrome

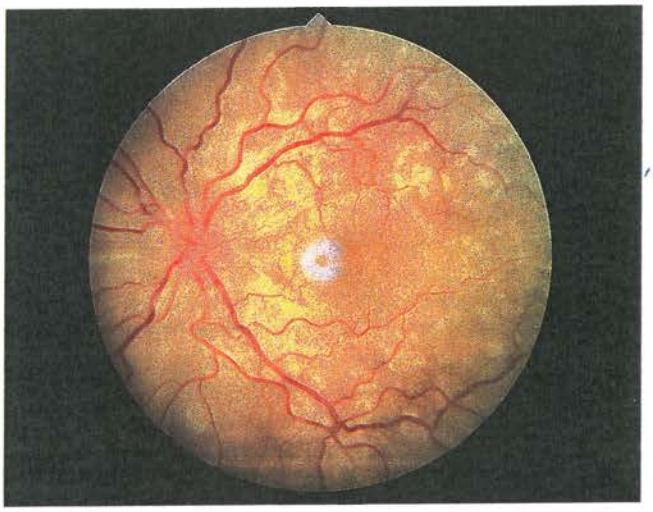


Figure 7.69 Multifocal detachments of the sensory retina in Harada syndrome

(c) ***Exudative retinal detachment***, which gradually subsides either spontaneously or with the help of systemic steroids.

(d) ***Residual lesions*** consist of mottled scars corresponding to atrophy and proliferation of the retinal pigment epithelium. Visual acuity may remain good, even with involvement of the macula.

Inflammatory bowel disease

ULCERATIVE COLITIS

1. **Clinical features**
   Ulcerative colitis (UC) is an uncommon, idiopathic, chronic, relapsing inflammatory disease, involving the rectum and extending proximally to involve part or all of the large intestine. The disease is characterized by diffuse surface ulceration of the gut mucosa with the development of crypt abscesses and pseudopolyposis (Figure 7.70). Presentation is usually in the second and third decades. Between relapses, UC is usually asymptomatic. During a relapse, the severity of diarrhoea and systemic upset depends on the extent of the disease and depth of mucosal ulceration. Patients with longstanding disease carry an increased risk of developing carcinoma of the colon.

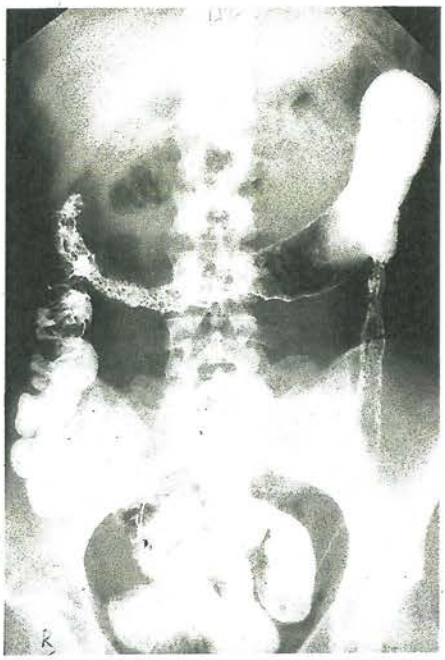


Figure 7.70 Barium enema showing widespread involvement of the colon in ulcerative colitis

2. **Extra-intestinal manifestations**
   (a) ***Skin*** – erythema nodosum and pyoderma gangrenosum (Figure 7.71).
   (b) ***Arthritis*** – large joint arthropathy, sacro-iliitis and ankylosing spondylitis. Patients with ankylosing spondylitis have an increased prevalence of HLA-B27.
   (c) ***Liver*** – sclerosing cholangitis and cholangiocarcinoma.
   (d) ***Blood vessels*** – arterial and venous thrombosis.
3. **Ocular manifestations**
   (a) ***Acute iridocyclitis*** occurs in about 5% of patients and the attacks may be synchronized with exacerbation of colitis. As expected, the incidence of uveitis is greater in those with associated ankylosing spondylitis.
   (b) ***Other manifestations***, which are uncommon, include peripheral corneal infiltrates and papillitis.

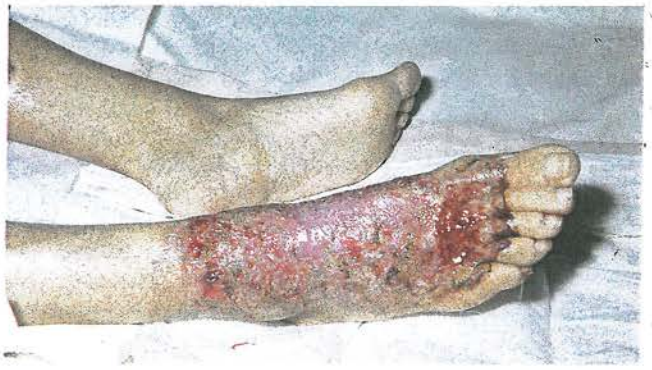


Figure 7.71 Pyoderma gangrenosum in ulcerative colitis

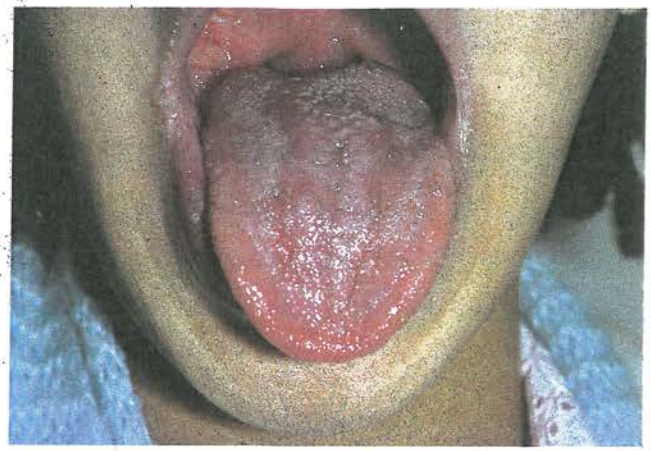


Figure 7.73 Oral involvement in Crohn disease

CROHN DISEASE

1. **Clinical features**
   Crohn disease (regional ileitis) is an idiopathic, chronic, relapsing disease characterized by multifocal non-caseating granulomatous inflammation involving the full-thickness of the bowel. Presentation is usually in the second and third decades. Unlike UC, it can involve any part of the gastrointestinal tract although its most frequent site is the ileocaecal region (Figure 7.72). In children it may even affect the mouth and tongue (Figure 7.73). Perirectal complications such as fistulae, abscesses and fissures are common.
2. **Extra-intestinal manifestations** include erythema nodosum, psoriasis, hepatitis, reactive arthritis and ankylosing spondylitis.
3. **Ocular manifestations**
   (a) ***Acute iridocyclitis*** occurs in about 3% of patients.
   (b) ***Other manifestations*** include conjunctivitis, episcleritis, scleritis, peripheral corneal infiltrates, and occasionally posterior segment inflammation.

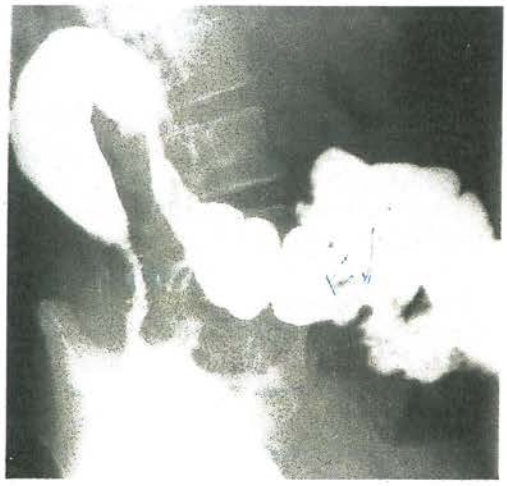


Figure 7.72 Barium enema showing showing tight strictures and 'rose thorn' ulceration in Crohn disease

WHIPPLE DISEASE

1. **Clinical features**
   Whipple disease is a very rare, idiopathic systemic disorder characterized by intestinal malabsorption and steatorrhoea. The diagnosis is usually made by jejunal biopsy which demonstrates the presence of PAS-positive intracellular granules in macrophages. Presentation is usually in the fifth decade with abdominal symptoms, fever and malaise.
2. **Extra-intestinal manifestations** include arthralgia or arthritis, skin hyperpigmentation, peripheral lymphadenopathy, hepatosplenomegaly, and occasionally neurological lesions and heart murmurs.
3. **Ocular manifestations** include chronic iridocyclitis, vitritis, posterior segment inflammation and ophthalmoplegia.

Nephritis

TUBULOINTERSTITIAL NEPHRITIS

1. **Systemic features**
   Tubulointerstitial nephritis and uveitis (TINU) is an uncommon kidney-based hypersensitivity reaction, usually to a drug such as an antibiotic or a non-steroidal anti-inflammatory agent. It most frequently affects women and children. Renal disease usually precedes the onset of uveitis. Presenting features include fatigue, weight loss, proteinuria, anaemia, hypertension and non-oliguric renal failure. The response to systemic steroid therapy is good and the condition resolves within a few months.

2. **The iridocyclitis** in TINU is usually bilateral and non-granulomatous. It responds well to topical therapy but may become recurrent.

IgA GLOMERULONEPHRITIS

1. **Systemic features**
   IgA glomerulonephritis is a common renal disease in which IgA is found in the glomerular mesangium. Presentation is usually in the third to fifth decades with recurrent macroscopic haematuria which may be associated with upper respiratory tract infection. In between attacks there is microscopic haematuria and albuminuria.
2. **Ocular manifestations** include iritis, keratoconjunctivitis and scleritis.

UVEITIS IN CHRONIC SYSTEMIC INFECTIONS

Acquired immune deficiency syndrome

INTRODUCTION

Acquired immune deficiency syndrome (AIDS) is caused by the human immunodeficiency virus (HIV) which is predominantly transmitted by sexual intercourse. Homosexual men are more commonly infected than heterosexuals. The virus may also be transmitted by contaminated blood and syringes. AIDS was initially defined as the occurrence of opportunistic infections, Kaposi sarcoma (Figure 7.74) or lymphoma, or both, in patients who are not immunosuppressed from other causes. The definition was subsequently expanded to include HIV infected patients with severe immunosuppression in the absence of opportunistic infection. Patients can be HIV positive some years before they develop the clinical manifestations of AIDS. One of the hallmarks of progressive immune deficiency is a steady decline in the absolute number of CD4+ T-lymphocytes. The life expectancy of AIDS patients has been significantly improved with the introduction of new drugs such as protease inhibitors which can be used in conjunction with anti-HIV drugs such as didanosine.

1. **Opportunistic infections in AIDS**
   (a) ***Protozoa***: *Pneumocystis carinii* pneumonia or disseminated disease, and toxoplasmosis.
   (b) ***Viruses***: cytomegalovirus (CMV) retinitis, CMV pneumonitis, CMV colitis and persistent invasive herpes virus lesions.
   (c) ***Fungi***: cryptococcosis and oesophageal candidiasis.
   (d) ***Bacteria***: atypical mycobacterial and extrapulmonary tuberculosis.
2. **Classification of ocular complications**
   Ocular complications are very common and occur in about 75% of AIDS patients. The four main categories are:
   (a) ***Retinal microangiopathy***.
   (b) ***Opportunistic infections***.
   (c) ***Tumours***.
   (d) ***Neuro-ophthalmological lesions*** associated with intracranial infections and tumours.

ANTERIOR SEGMENT COMPLICATIONS

1. **Molluscum contagiosum** in patients with AIDS is usually transmitted sexually with lesions appearing in the groin and genitalia. Lesions on the eyelids may be multiple (Figure 7.75) and when located near or on the lid margin they may give rise to follicular conjunctivitis, epithelial keratitis, sometimes accompanied by pannus.
2. **Kaposi sarcoma** occurs in about 30% of AIDS patients and after *Pneumocystis carinii* infection is the most frequent presenting feature. Overall eyelid (Figure 7.76) or conjunctival (Figure 7.77) tumours develop in about 20% of cases.

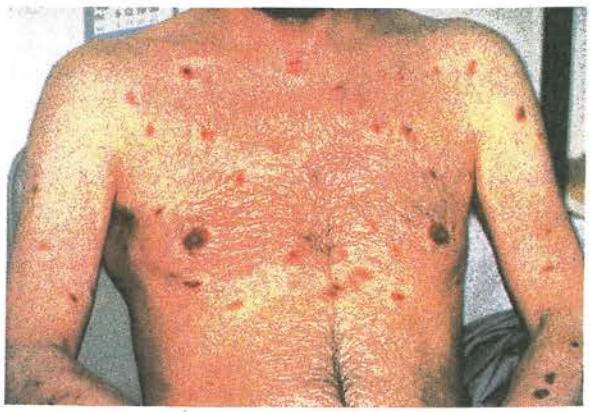


Figure 7.74 Kaposi sarcoma in AIDS

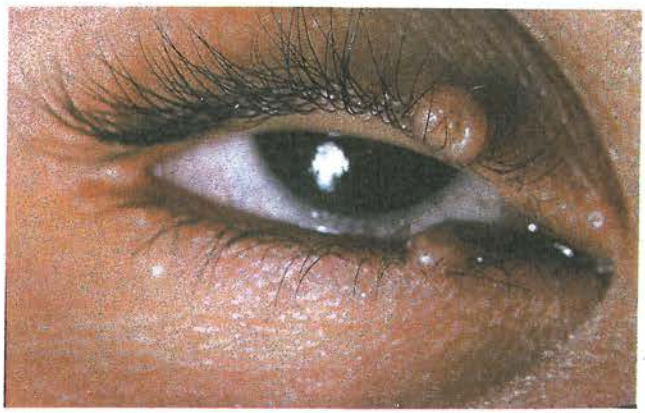


Figure 7.75 Multiple molluscum contagiosum nodules in AIDS

Figure 7.76 Kaposi sarcoma of the lower eyelid in AIDS

3. **Herpes zoster ophthalmicus** (HZO) is relatively common in AIDS and may have a more severe clinical course (Figure 7.78). The occurrence of HZO in a young person should alert the clinician as to the possibility of underlying HIV infection.
4. **Herpes simplex keratitis** tends to be more severe with more frequent recurrences in AIDS patients. The dendrites are usually located in the peripheral cornea (Figure 7.79) in contrast to the predilection for central disease in immunocompetent individuals.
5. **Microsporidial keratitis**, which is chronic and bilateral, is uncommon. It is caused by Microsporidia which are ubiquitous protozoan parasites. The keratitis is characterized by diffuse, fine-to-coarse epithelial lesions.

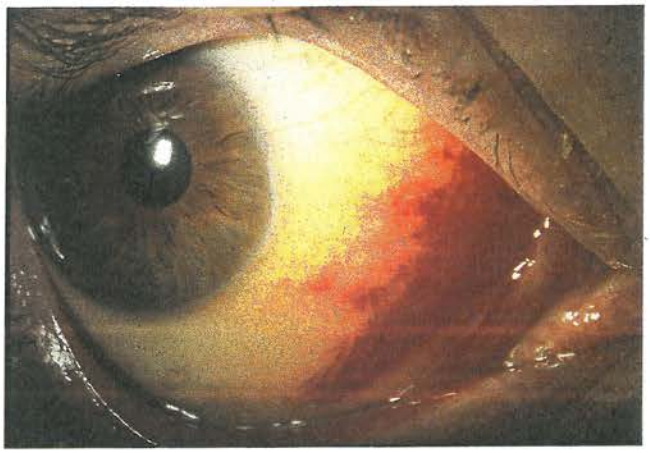


Figure 7.77 Kaposi sarcoma of the conjunctiva in AIDS

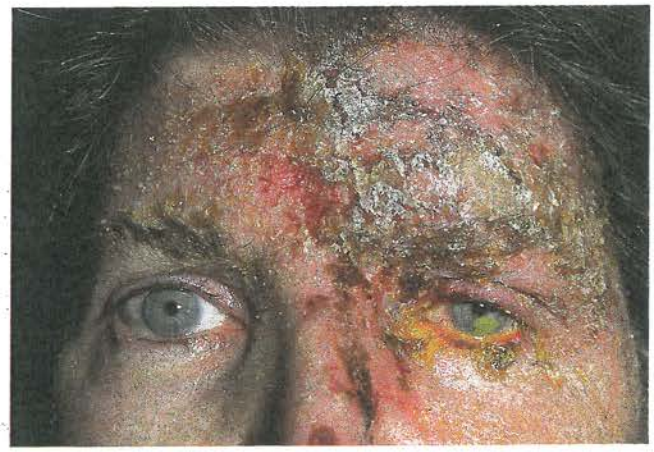


Figure 7.78 Very severe herpes zoster ophthalmicus in AIDS

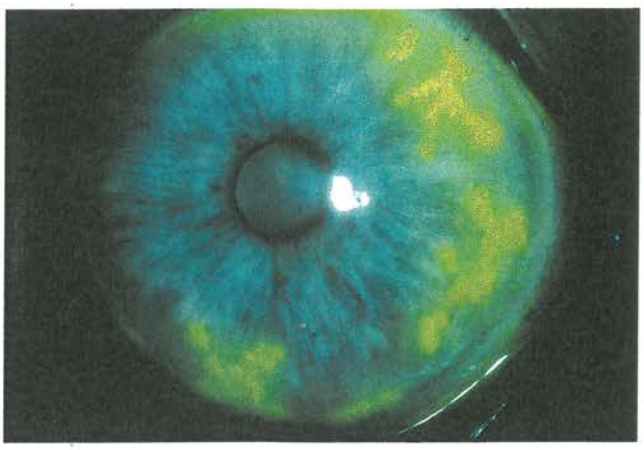


Figure 7.79 Peripheral dendritic ulcers in AIDS

RETINAL MICROANGIOPATHY

Retinal microangiopathy develops in 60% of patients with AIDS. It is characterized by cotton-wool spots (Figure 7.80) which may be associated with retinal haemorrhages and microaneurysms. The lesions may be mistaken for early CMV retinitis. However, in contrast to CMV retinitis, the cotton-wool spots are usually asymptomatic and almost invariably disappear spontaneously after several weeks. Possible causes of the microangiopathy include immune complex deposition and HIV infection of the retinal vascular endothelium.

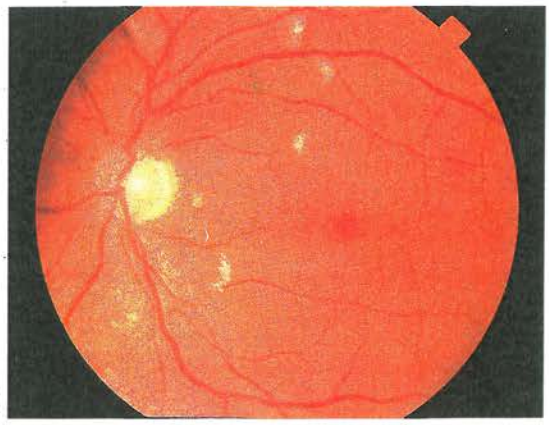


Figure 7.80 Multiple cotton-wool spots in HIV retinopathy

CYTOMEGALOVIRUS RETINITIS

CMV retinitis eventually affects 40% of patients with AIDS and its appearance usually signifies severe systemic involvement, although on rare occasions it is the initial manifestation of the disease.

1. **Signs of activity**
   (a) ***Indolent CMV retinitis*** frequently starts in the periphery and progresses slowly. It is characterized by a mild granular opacification which may be associated with a few punctate haemorrhages but there is no vasculitis (Figures 7.81, 7.82).
   (b) ***Fulminating retinitis*** is characterized by a dense, white, well-demarcated, geographical area of confluent opacification which frequently develops along the vascular arcades (Figure 7.83). Retinal haemorrhages may develop either within the area of retinitis or along its leading edge. Vitritis is mild. An uncommon associated finding is retinal venous sheathing similar to frosted-branch angiitis (Figure 7.84). The infective process spreads slowly but relentlessly as a 'brushfire-like' extension along the course of the retinal blood vessels (Figures 7.85, 7.86). Occasionally the optic nerve may also be involved (Figure 7.87).
2. **Signs of regression** are fewer haemorrhages, less opacification, and diffuse atrophic and pigmentary changes (Figure 7.88).
3. **Complications** include total retinal atrophy (Figure 7.89) and retinal detachment.
4. **Treatment**
   (a) ***Ganciclovir*** is initially given intravenously (induction) every 12 hours for 2–3 weeks and then every 24 hours. Patients with stable retinitis may be treated with oral ganciclovir. Ganciclovir is effective in 80% of patients but 50% subsequently relapse and require reinduction of ther-

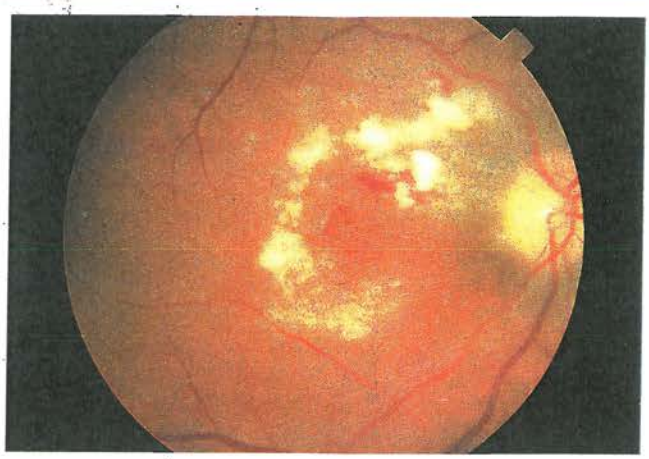


Figure 7.83 Early fulminant CMV retinitis

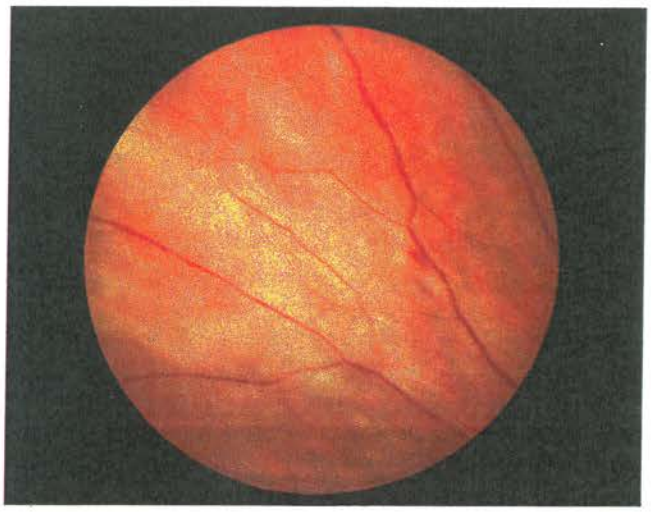


Figure 7.81 Mild, indolent, granular peripheral CMV retinitis

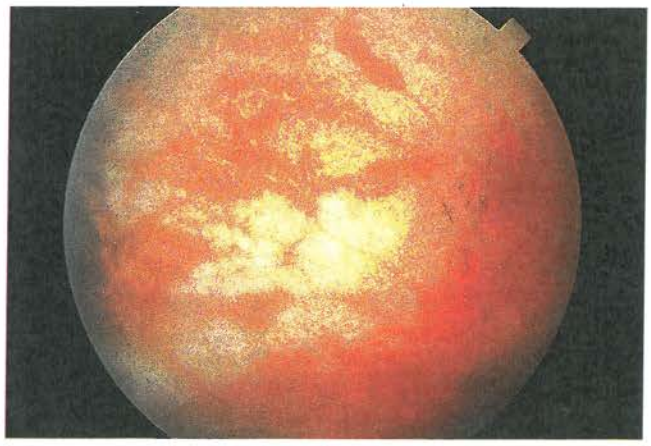


Figure 7.82 Extensive, indolent, granular CMV retinitis

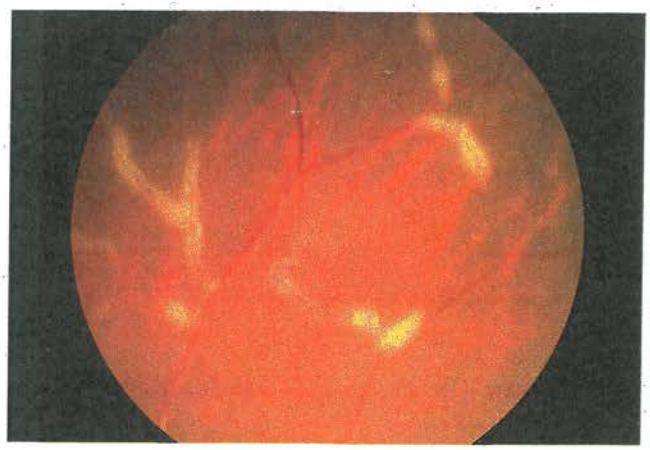


Figure 7.84 Frosted branch angiitis in CMV retinitis

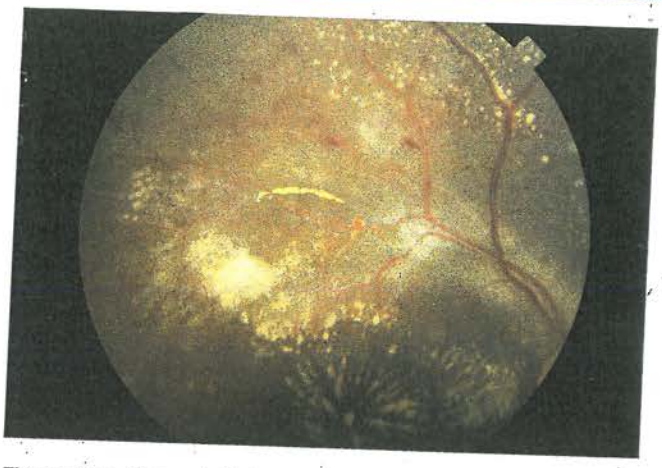


Figure 7.85 Advanced fulminant CMV retinitis

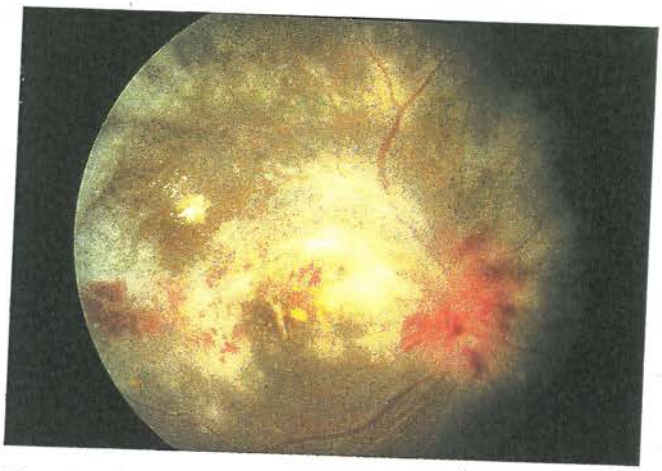


Figure 7.86 Very advanced fulminant CMV retinitis

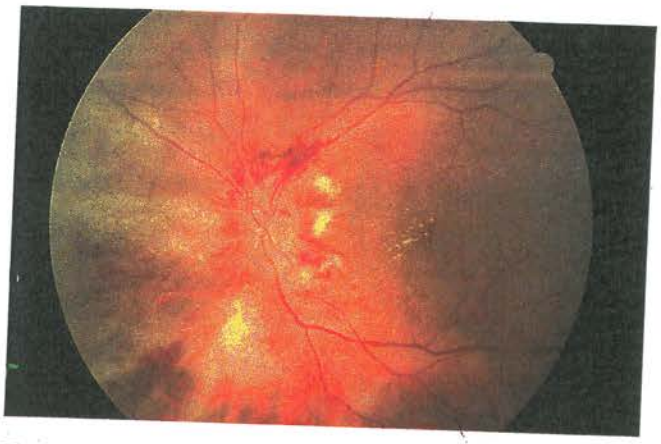


Figure 7.87 Fulminant CMV retinitis with involvement of the optic nerve head

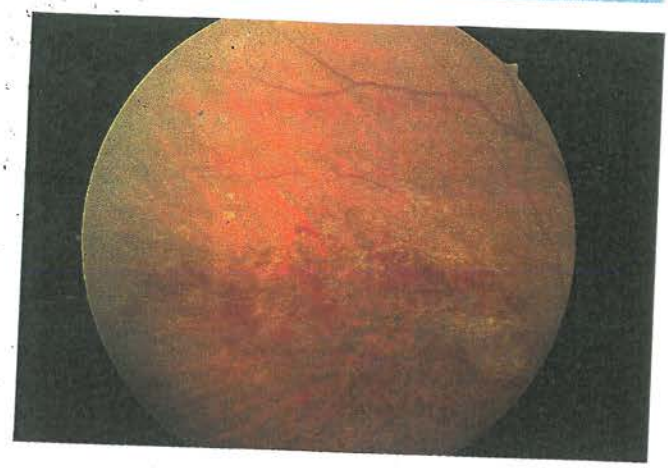


Figure 7.88 Inactive CMV retinitis

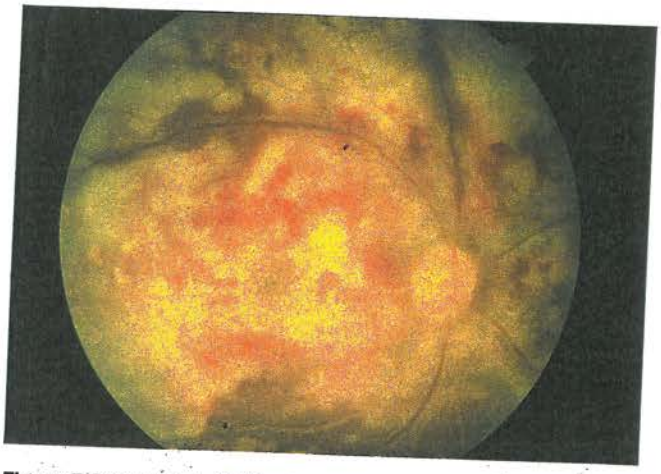


Figure 7.89 End-stage CMV retinitis

apy. The drug carries a high risk of bone marrow suppression.

(b) ***Intravenous foscarnet*** is initially given every 8 hours for 2–3 weeks and then every 24 hours. Its side effects include nephrotoxicity, electrolyte disturbances and seizures.

(c) ***Intravitreal ganciclovir***, in the form of either injections or slow-release devices, appears to be as effective as intravenous therapy. However, it fails to protect the fellow eye from retinitis. Intravitreal injections may also cause serious complications such as vitreous haemorrhage, retinal detachment and endophthalmitis.

(d) ***Intravenous cidofovir*** may be used where other agents are unsuitable. It must be administered in combination with probenecid. Side-effects include nephrotoxicity and neutropenia.

PNEUMOCYSTIS CARINII CHOROIDITIS

Pneumocystis carinii, an opportunistic protozoan parasite, is a major cause of morbidity and mortality in AIDS. The presence of choroidal involvement can be an important sign of extrapulmonary systemic dissemination. Most patients with choroiditis have received inhaled pentami-

dine as prophylaxis against *Pneumocystis carinii* pneumonia because systemic prophylaxis protects against choroiditis, while aerosolized pentamidine protects only the lungs, allowing the organisms to disseminate throughout the body. The presence of choroiditis implies a grave prognosis for life.

1. **Signs**
   (a) Variable number of flat, yellow, round, choroidal lesions which range in diameter from 0.3 to 3.0 mm (Figures 7.90, 7.91).
   (b) The lesions are frequently bilateral and there is no associated vitritis. Even when the fovea is involved there is little, if any, impairment of visual acuity.

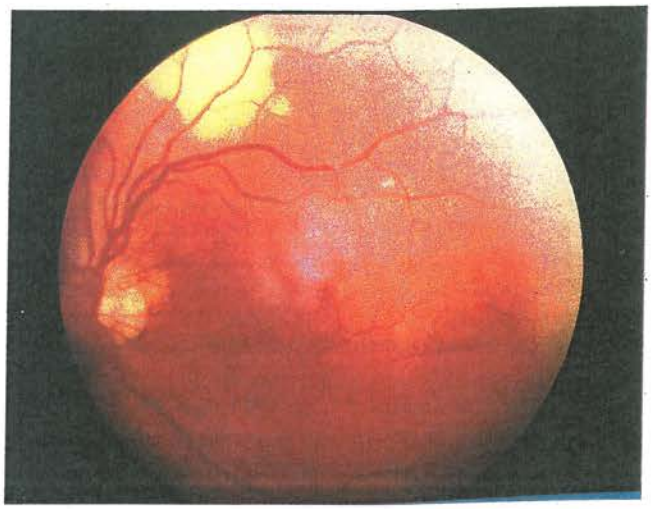


Figure 7.90 Mild choroidal pneumocystosis

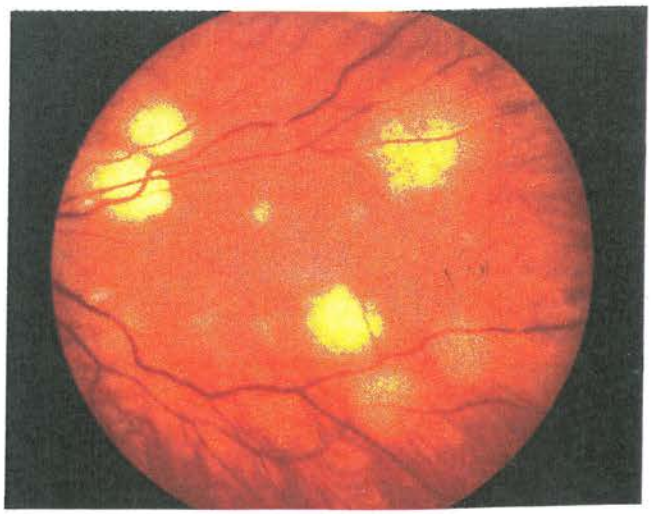


Figure 7.91 Extensive choroidal pneumocystosis

2. **Treatment** with intravenous trimethoprim, sulphamethoxazole or parenteral pentamidine causes resolution of the lesions within several weeks.

OTHER FUNDUS LESIONS

1. **Toxoplasma retinitis** in AIDS is different from the condition in immunocompetent patients and may need lifelong treatment. It tends to be more severe, bilateral, multifocal (Figure 7.92), not adjacent to old scars, and is often associated with CNS involvement.

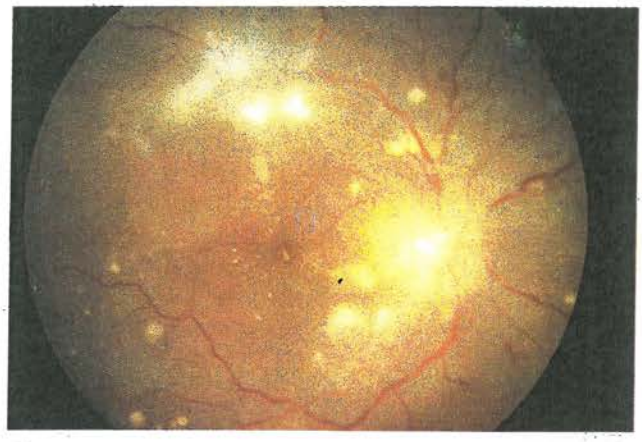


Figure 7.92 Atypical, multifocal toxoplasma retinitis in AIDS

2. **Progressive outer retinal necrosis** (PORN) is caused by varicella-zoster virus. It is a rapidly progressive necrotizing retinitis which responds poorly to antiviral therapy and most patients become blind in both eyes within a few weeks. PORN is distinguished from acute retinal necrosis by the absence of inflammation and early involvement of the posterior pole (Figure 7.93). It also differs from CMV retinitis

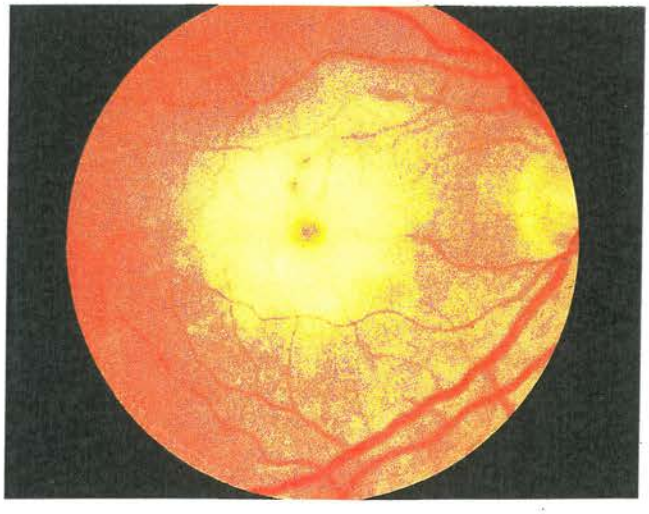


Figure 7.93 Macular involvement in progressive outer retinal necrosis

because it is multifocal, has diffuse deep retinal opacification and progresses more rapidly.

3. **Cryptococcus choroiditis** is usually associated with meningitis and is characterized by asymptomatic creamy choroidal lesions which are not associated with vitritis. Small white spheres at the vitreoretinal interface may also occur. Some patients with cryptococcosis may lose vision from coexisting cryptococcal involvement of the optic nerves which manifests as either disc swelling or retrobulbar neuritis. Other fungal infections that may involve the posterior segment in AIDS patients are candidiasis and, rarely, histoplasmosis.
4. **Large cell intraocular lymphoma** with retinal involvement may mimic CMV retinitis.

Acquired syphilis

SYSTEMIC FEATURES

Acquired syphilis is a sexually transmitted infection caused by the spirochaete *Treponema pallidum*. It is a systemic disease which, when untreated, has overt and covert stages:

1. **The primary stage** typically develops 9–90 days after exposure and is characterized by a painless ulcer (chancre) at the site of infection with associated regional lymphadenopathy.
2. **The secondary stage** usually appears by the eighth week of infection, although there may be considerable delay. Mucocutaneous involvement is usually the presenting feature. A macular, papular or mixed skin rash which may involve the trunk (Figure 7.94) or the palms and soles (Figure 7.95), is common. Systemic involvement may cause malaise, fever, generalized lymphadenopathy, meningitis, nephritis and hepatitis. The latent stage follows resolution of secondary syphilis and can be detected only by serological tests.
3. **The tertiary stage** occurs in about 30% of untreated patients within 5–30 years. The main lesions of tertiary syphilis are:
   (a) Aortitis.
   (b) Neurosyphilis which causes tabes dorsalis or general paralysis of the insane (GPI).
   (c) Benign late syphilis characterized by gummata in tissues other than the cardiovascular system and CNS.

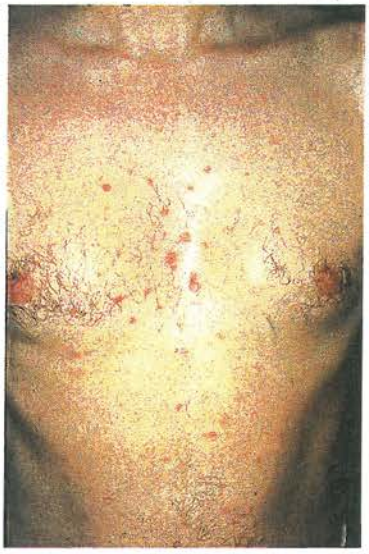


Figure 7.94 Rash in secondary syphilis

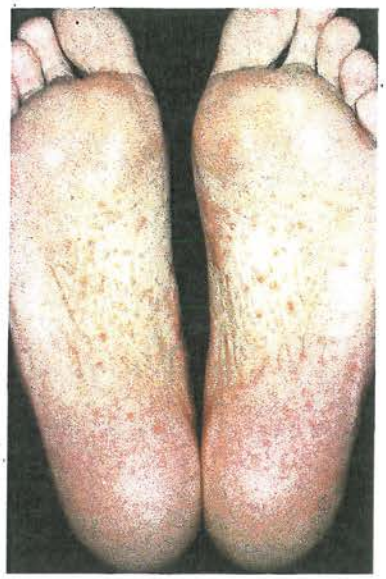


Figure 7.95 Rash in secondary syphilis

SYPHILIS AND AIDS

Patients at risk from AIDS are also at increased risk from other sexually transmitted diseases, such as syphilis, so that the two conditions may coexist. It appears that concomitant HIV infection may alter the natural course of syphilis, rendering the disease more aggressive with unusual manifestations. All patients with AIDS should therefore also be tested for syphilis and vice versa.

DIAGNOSTIC TESTS FOR SYPHILIS

1. **FTA-ABS** (fluorescent treponemal antibody absorption) test is a specific test to detect anti-treponemal antibodies. Once positive, it remains positive throughout the patient's life despite treatment. However, the test is not titratable and is read as: reactive, weakly reactive or non-reactive.
2. **VDRL** (Venereal Disease Research Laboratory) test is a non-specific reagin test which is useful for screen-

ing. If positive, one of the more specific tests should be performed. VDRL becomes positive shortly after the development of the primary chancre and negative after adequate treatment. If it fails to do so, the course of antibiotics may have been only partially effective or patient compliance poor. Further therapy should therefore be advised.

3. **MHA-TP** and **TPHA** (haemagglutination tests for *Treponema pallidum*) are useful specific tests for treponemal antibody but may be negative in early primary syphilis. They may also be positive in yaws.
4. **Dark-ground microscopic** examination is performed on a scraping from a chancre or mucocutaneous lesion for the presence of spirochaetes.

Both FTA-ABS and VDRL should be ordered when screening patients with uveitis for syphilis.

OCULAR FEATURES

Ocular syphilis is rare and there are no pathognomonic signs. Eye involvement typically occurs during the secondary and tertiary stages. The ability of syphilis to mimic many different ocular disorders can lead to misdiagnosis and delay of appropriate therapy. The disease must therefore be suspected in any case of intraocular inflammation that is resistant to conventional therapy.

1. **External features** include madarosis, primary chancre of the conjunctiva, scleritis and keratitis.
2. **Iridocyclitis** occurs in about 4% of patients with secondary syphilis. The intraocular inflammation is usually acute; it may be granulomatous or non-granulomatous and, unless adequately treated, becomes chronic. Both eyes are involved in about 50% of cases. In some patients, the iridocyclitis is first associated with the presence of dilated iris capillaries (roseolae) (Figure 7.96) which may develop into more localized papules and subsequently into larger, well-defined, yellowish nodules. Gummata, which are characteristically located at the root of the iris, are extremely rare. Various types of post-inflammatory iris atrophy may also occur.
3. **Multifocal chorioretinitis** occurs typically during the late secondary stage. Healed lesions appear as areas of chorioretinal atrophy associated with hyperpigmentation (Figure 7.97). Occasionally extensive pigmentary changes with perivascular bone spicules, similar to those seen in retinitis pigmentosa, may be associated with night blindness and a ring scotoma.
4. **Unifocal choroiditis** is less common and is frequently bilateral. It is characterized by an inflammatory focus near the disc (juxtapapillary choroiditis) or at the macula (central choroiditis).
5. **Neuroretinitis** (Figure 7.98) primarily involves the retina and optic nerve head and is independent of choroidal inflammation. The fundus shows disc

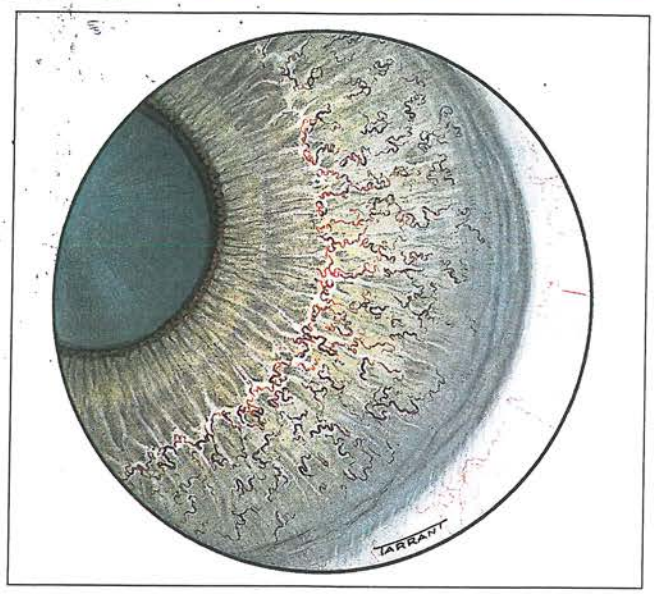


Figure 7.96 Early roseolae of the iris in secondary syphilis

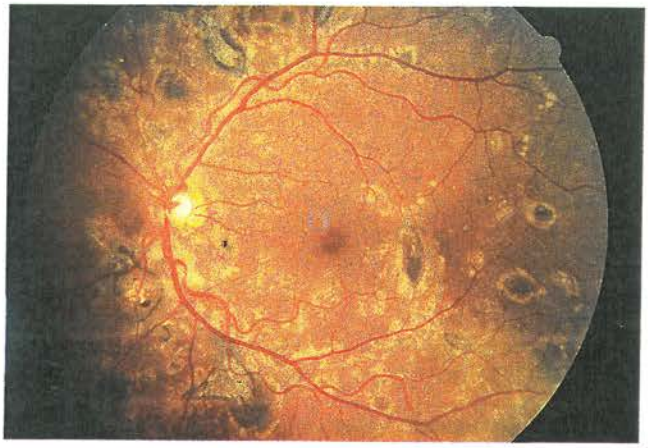


Figure 7.97 Old syphilitic multifocal choroiditis

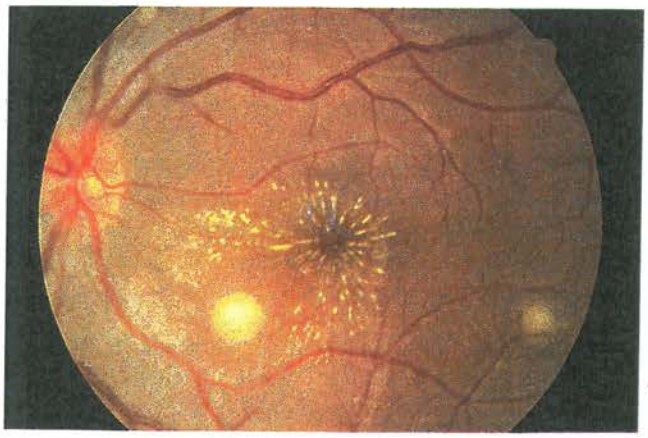


Figure 7.98 Active syphilitic neuroretinitis

oedema and a macular star. The retinal veins may be engorged, and peripapillary cotton-wool spots or flame-shaped haemorrhages may appear. Unless treated with antisyphilitic drugs, neuroretinitis is progressive. The retinal blood vessels eventually become replaced by white strands and optic atrophy ensues (Figure 7.99).

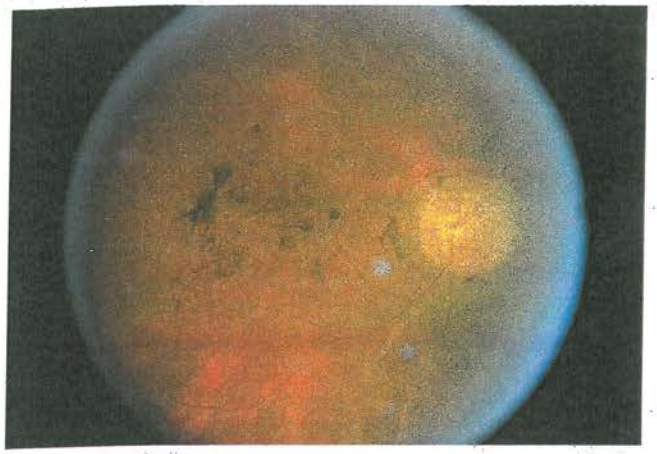


Figure 7.99 End-stage syphilitic neuroretinitis with hyperpigmentation, vascular sheathing and attenuation, and optic atrophy

NEURO-OPHTHALMIC FEATURES

1. **Argyll Robertson pupils** and other pupillary abnormalities.
2. **Optic nerve** lesions including retrobulbar neuritis, papilloedema and perioptic neuritis. The last is an inflammatory process of the meningeal sheaths of the optic nerve, usually seen in association with syphilitic meningitis.
3. **Ocular motor palsies** of the third and sixth cranial nerves.
4. **Visual field defects** caused by gummatous involvement of the brain.

MANAGEMENT OF OCULAR SYPHILIS

1. A lumbar puncture should be performed to rule out neurosyphilis.
2. Conventional doses of penicillin are inadequate in ocular syphilis and the therapeutic regimen is the same as for neurosyphilis. It consists of 12–24 mega units (MU) of aqueous penicillin intravenously daily for 10 days, followed by an intramuscular daily dose of 2.4 MU for 3 weeks. Penicillin-sensitive patients can be treated with oral tetracycline 500 mg four times daily for 30 days or oral erythromycin 500 mg four times daily for 30 days.

Tuberculosis

SYSTEMIC FEATURES

Tuberculosis (TB) is a chronic granulomatous infection caused by either bovine or human tubercle bacilli. The former is caused by the drinking of milk from infected cattle and the latter is spread by 'droplet infection'.

1. **Primary TB** occurs in subjects not previously exposed to the bacillus. It typically causes the 'primary complex' in the chest (Ghon focus + regional lymphadenopathy) which usually heals spontaneously and causes few if any systemic symptoms.
2. **Post-primary TB** is a result of reinfection or, rarely, recrudescence of a primary lesion, usually in a patient with impaired immunity. Clinical features include fibrocaseous pulmonary lesions and miliary TB from haematogenous spread to many parts of the body. In theory, seeding of the uvea by live bacilli may occur during the primary and miliary stages, giving rise to either caseating nodules or small miliary tubercles.

DIAGNOSTIC TESTS

1. **Sputum examination** for acid-fast bacilli.
2. **Chest radiograph** compatible with that for TB is of significance in a patient with uveitis. However, a negative chest radiograph does not necessarily exclude the possibility of TB.
3. **Tuberculin testing** may be useful in the diagnosis of extrathoracic TB. A negative test usually excludes the possibility of TB, whereas a positive test does not necessarily distinguish between previous exposure and active disease.
4. **Isoniazid test** is useful if TB uveitis is suspected. If isoniazid 300 mg daily for 3 weeks causes a dramatic improvement in the ocular inflammation within 1–2 weeks then the diagnosis of TB is highly probable.

OCULAR FEATURES

Uveitis is now rarely caused by TB. The possibility of TB is always presumptive and based on indirect evidence, such as intractable uveitis unresponsive to steroid therapy, negative findings for other causes of uveitis, positive systemic findings for TB and, occasionally, a positive response to the isoniazid test. There is no specific finding in TB uveitis and the clinical picture is pleomorphic.

1. **Chronic iridocyclitis**, which is usually granulomatous but may occasionally be non-granulomatous, is the most frequent feature.
2. **Choroiditis** may be unifocal or multifocal. Rarely, a large solitary choroidal granuloma may be mistaken for a choroidal tumour.

3. **Retinal vasculitis** is characterized by a moderate vitritis, severe ischaemic periphlebitis and peripheral retinal capillary closure, leading to neovascularization.

TREATMENT OF TUBERCULOSIS

Treatment is with isoniazid 300 mg daily and pyridoxine hydrochloride 10 mg daily (to prevent peripheral neuritis) combined with rifampicin (Rifanah) and pyrazinamide for 12 months.

Leprosy

SYSTEMIC FEATURES

Leprosy (Hansen disease) has the highest incidence of ocular complications of any systemic disease. The pathogenic agent responsible for leprosy is *Mycobacterium leprae* which has an affinity for skin, peripheral nerves and the anterior segment of the eye. The two types are lepromatous and tuberculoid leprosy. Uveal involvement in tuberculoid disease is less common than in the lepromatous form.

OCULAR FEATURES

1. **External lesions** include madarosis, conjunctivitis, episcleritis, keratitis and scleritis. Keratitis (Figure 7.100**a**) is the result of a combination of trichiasis, lagophthalmos (Figure 7.100**b**), corneal anaesthesia and secondary infection.
2. **Iritis** and its complications are the most common causes of blindness in leprosy.
   (a) ***Acute iritis*** is thought to be caused by immune complex deposition in the uvea. It may be associated with systemic symptoms such as fever and swelling of skin lesions. Occasionally, the intraocular inflammation is precipitated by the initiation or withdrawal of antilepromatous systemic therapy. Treatment is with topical steroids.
   (b) ***Chronic iritis*** is the result of direct invasion of the anterior uvea by bacilli. A pathognomonic sign of lepromatous leprosy is the presence at the pupillary margin of small, glistening 'iris pearls' resembling a necklace (Figure 7.101**a**). The 'pearls' slowly enlarge and coalesce before becoming pedunculated, dropping into the anterior chamber, from which they eventually disappear (Figure 7.101**b**). Eventually, the iris becomes atrophic, the pupil miosed and the associated formation of holes in the iris stroma may give rise to an appearance similar to essential iris atrophy (Figure 7.102). Chronic iritis is more resistant to conventional therapy than the acute type, because it may not be a true uveitis

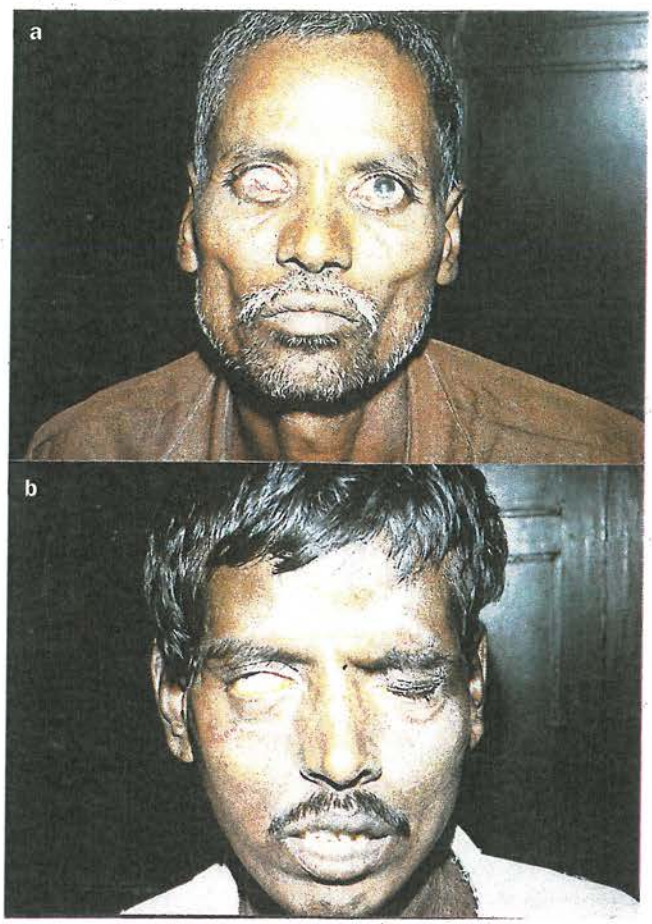


Figure 7.100 Leprosy. (**a**) severe corneal scarring; (**b**) lagophthalmos

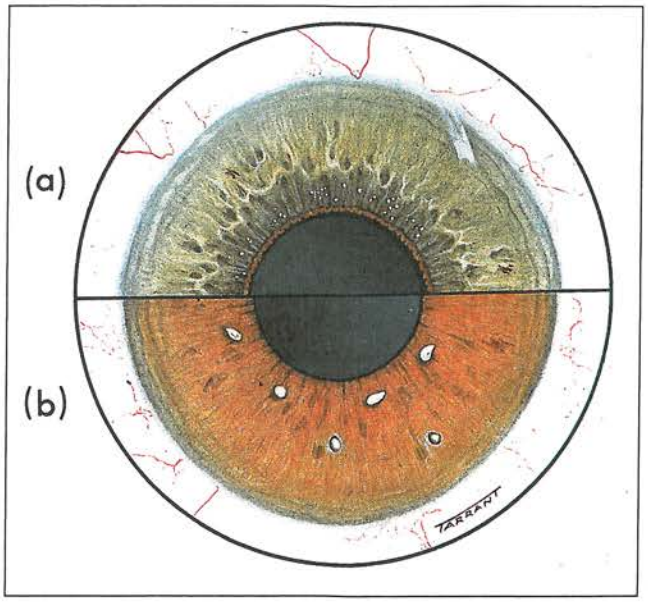


Figure 7.101 Chronic lepromatous iritis. (**a**) small iris 'pearl'; (**b**) large iris 'pearls' some of which have dropped into the anterior chamber

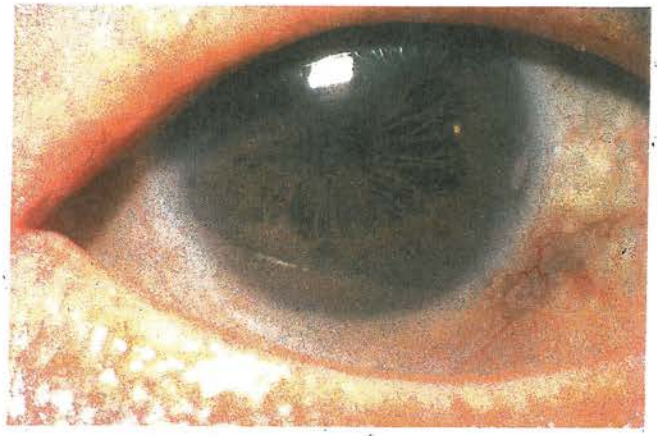


Figure 7.102 Severe miosis and iris atrophy in chronic lepromatous iritis

but a neuroparalytic inflammation caused by early involvement of the iris nerves.

Lyme disease

SYSTEMIC FEATURES

Lyme disease is an infection with the spirochaete *Borrelia burgdorferi* which is similar to the treponeme that causes syphilis. The disease is transmitted through the bite of its vector, the tick *Ixodes* sp. As in syphilis, both early and late manifestations develop in many organ systems.

1. **Stage 1** is characterized by a pathognomonic rash (erythema migrans) which may be accompanied by a 'flu-like illness. Treatment of the early stage is with tetracycline 250 mg four times daily or doxycycline 100 mg twice daily for 10–30 days. Erythromycin or penicillin can be used if tetracycline is inappropriate.
2. **Stage 2** develops within days to months and reflects dissemination of the spirochaete in many organs, especially the skin, heart, joints and CNS.
3. **Stage 3** can follow a disease-free period and may continue to produce problems for years. The main feature is a chronic or recurrent arthritis similar in presentation to rheumatoid arthritis.

OCULAR FEATURES

1. **Stage 1** is characterized by conjunctivitis and periorbital oedema.
2. **Stage 2** is characterized by intraocular inflammation in the form of granulomatous iridocyclitis, intermediate uveitis, retinal vasculitis and occasionally choroiditis.
3. **Stage 3** is characterized by episcleritis, stromal keratitis and orbital myositis.

TOXOPLASMOSIS

Introduction

Toxoplasma gondii is an obligate intracellular protozoan. The cat is the definitive host of the parasite and other animals, such as mice and livestock, as well as humans, are intermediate hosts.

1. **Forms of the parasite**
   (a) ***Sporocyst*** (oocyst) which is excreted in cat faeces.
   (b) ***Bradyzoite*** which is encysted in tissues.
   (c) ***Tachyzoite*** (trophozoite) which is the proliferating active form responsible for tissue destruction and inflammation.
2. **Ways of human infestation**
   (a) ***Ingestion of undercooked meat*** (lamb, pork, beef) containing bradyzoites of an intermediate host.
   (b) ***Ingestion of sporocysts*** following accidental contamination of hands when disposing of cat litter trays and then subsequent transfer on to food. Infants may also become infected by eating dirt (pica) containing sporocysts.
   (c) ***Transplacental spread*** of the parasites (tachyzoites) can occur to the foetus in a pregnant woman with acute acquired systemic toxoplasmosis.

Diagnostic tests

The diagnosis of retinitis caused by toxoplasmosis is based on a compatible lesion in the fundus and positive serology for toxoplasma antibodies. Any titre of antibody is significant because, in recurrent ocular toxoplasmosis, no correlation exists between the titre and the activity of ocular inflammation.

1. **Indirect immunofluorescent antibody tests** use killed organisms that are exposed to the patient's serum and antihuman globulin labelled with fluorescein, and examined under the fluorescent microscope. Although this test has largely replaced the Sabin–Feldman dye test, both false-negative and false-positive results may occur.
2. **Haemagglutination tests** involve coating of lysed organisms on to red blood cells which are then exposed to the patient's serum. Positive sera cause the red blood cells to agglutinate.
3. **Enzyme-linked immunosorbent assays** involve binding of the patient's antibodies to an excess of solid phase antigen. This complex is then incubated with an enzyme-linked second antibody. Assessment of enzyme activity provides the measurement of specific antibody concentration. The test can also be used to

detect antibodies in the aqueous humour which are more specific than those in the serum.

Systemic features

ACUTE ACQUIRED SYSTEMIC TOXOPLASMOSIS

Infestation in the immunocompetent individual is usually asymptomatic, although lymphadenopathy and fever may occur in some cases. A minority of patients develop meningoencephalitis characterized by convulsions and unconsciousness. The exanthematous form resembling a rickettsial infection is the rarest and most serious form of acute toxoplasmosis. Immunocompromised individuals, such as organ graft recipients and AIDS patients, are at risk of severe life-threatening disease. The most common manifestation in the AIDS patient is an intracerebral space-occupying lesion which resembles a cerebral abscess on CT.

CONGENITAL SYSTEMIC TOXOPLASMOSIS

Toxoplasmosis is transmitted to the foetus through the placenta when a pregnant woman contracts the acute form. If the mother is infected before pregnancy, the foetus will be unscathed. The severity of involvement of the foetus varies with the duration of gestation at the time of maternal infection. For example, infection during early pregnancy may result in stillbirth, whereas infection during late pregnancy may cause generalized convulsions, paralysis, hydrocephalus (Figure 7.103), and visceral involvement. Intracranial calcification may be seen on plain skull radiographs. However, just as in the acquired form, most cases of congenital systemic toxoplasmosis are subclinical. In these children, bilateral, healed chorioretinal scars (Figure 7.104) may be discovered later in life, either by chance or when the child is found to have defective vision.

Figure 7.103 Hydrocephalus and left anophthalmos in severe congenital toxoplasmosis

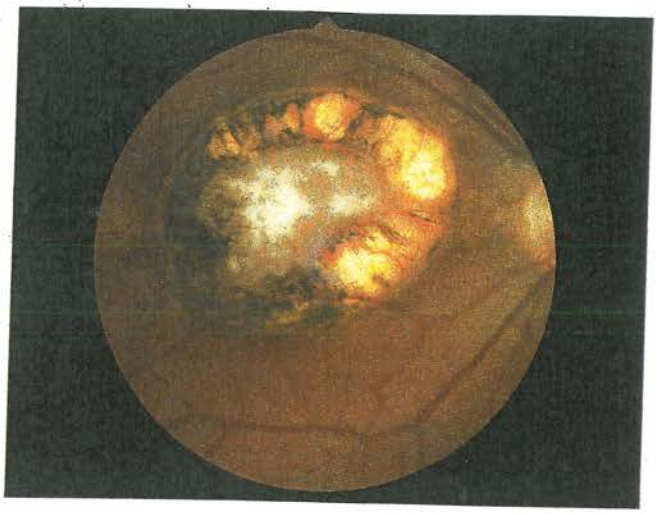


Figure 7.104 Large macular scar due to congenital toxoplasmosis

Toxoplasma retinitis

CLINICAL FEATURES

Recurrence of old, healed, congenital, ocular toxoplasmosis is by far the most common cause of infectious retinitis in otherwise healthy individuals. The recurrences usually take place between the ages of 10 and 35 years (average age 25 years) when the cysts rupture and release hundreds of tachyzoites into normal retinal cells. The clinical features are as follows:

1. **Iridocyclitis**, which may be granulomatous or non-granulomatous, is relatively common.
2. **Unifocal superficial necrotizing retinitis** which is adjacent to the edge of an old inactive pigmented scar ('satellite lesion') is by far the most common (Figures 7.105, 7.106). Although all parts of the fundus are at risk, the retinitis typically affects the post-

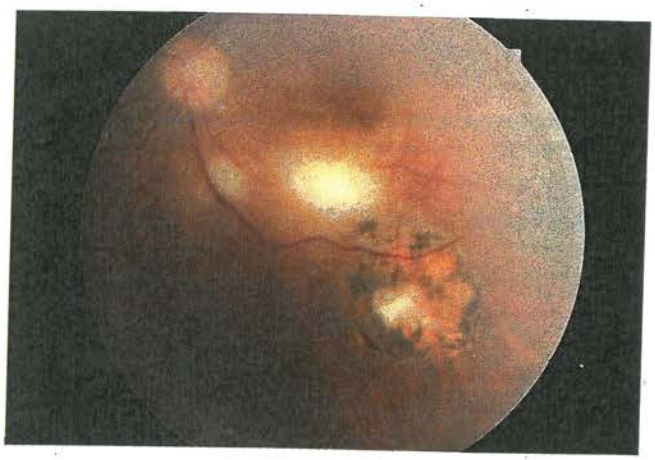


Figure 7.105 Active toxoplasma retinitis near an old scar

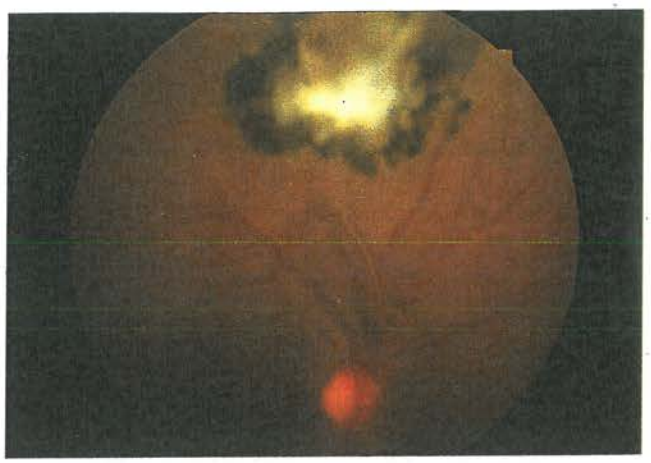


Figure 7.106 Active toxoplasma retinitis

equatorial fundus. The lesions may vary in size from one-tenth to five disc diameters and are associated with an overlying vitreous haze. Very severe vitreous involvement may greatly impair visualization of the fundus, although the inflammatory focus may still be discernible – the so-called 'headlight in the fog' appearance (Figure 7.107). In some cases the detached posterior hyaloid face becomes covered by inflammatory precipitates comparable to KP.

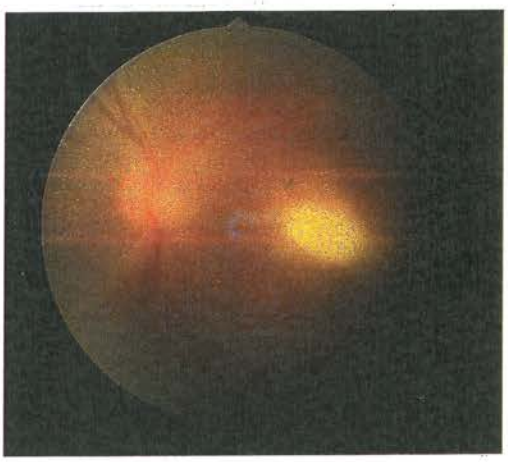


Figure 7.107 Active toxoplasma retinitis and severe vitritis giving rise to a 'headlight in the fog' appearance

3. **Papillitis** may be secondary to active retinitis located in the juxtapapillary area (Jensen choroiditis, Figure 7.108). Very occasionally, the optic nerve head itself is the primary site of involvement.

CLINICAL COURSE

The rate of healing is dependent on the virulence of the organism, the competence of the host's immune system,

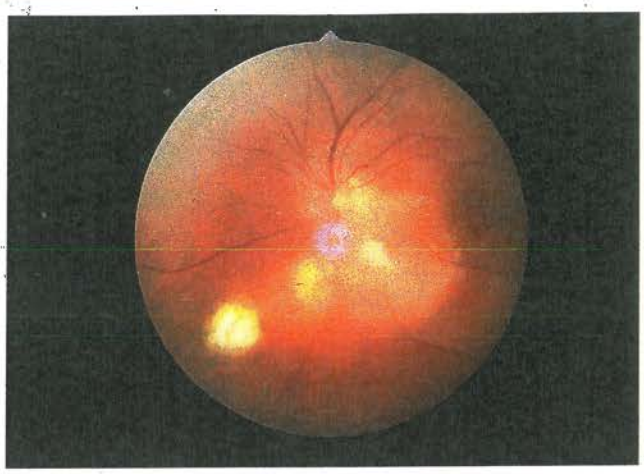


Figure 7.108 Severe toxoplasma retinitis adjacent to the optic nerve head

the size of the lesion and the use of antimicrobial drugs. In uncompromised hosts, the retinitis heals within 1–4 months. The vitreous haze gradually clears and the inflammatory focus is replaced by a sharply demarcated atrophic scar surrounded by a hyperpigmented border (Figure 7.109). The vitreous haze gradually clears although vitreous condensation may remain. Resolution of anterior uveitis is a reliable sign of posterior segment healing. After the first attack, the mean recurrence rate within 3 years is about 50% and the average number of recurrent attacks per patient is 2.7. Eyes with toxoplasmosis may lose vision from various direct or indirect causes:

1. **Direct involvement** of the fovea, papillomacular bundle, optic nerve head, or a major blood vessel.
2. **Indirect involvement** may result in cystoid macular oedema (Figure 7.110) and macular pucker.

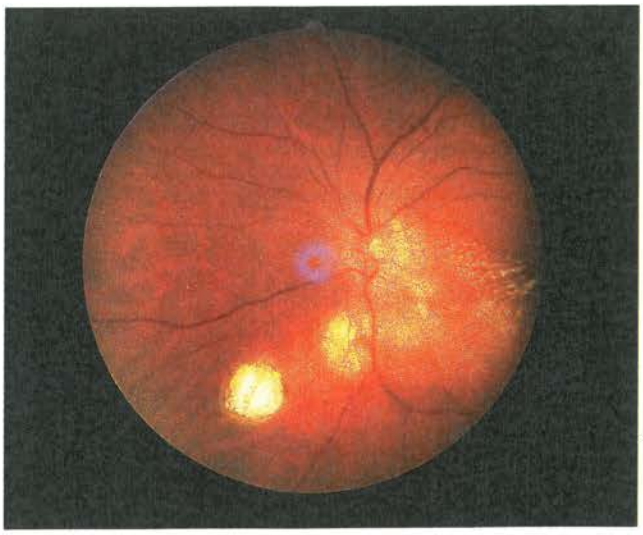


Figure 7.109 Appearance of the eye in Figure 7.108 after treatment

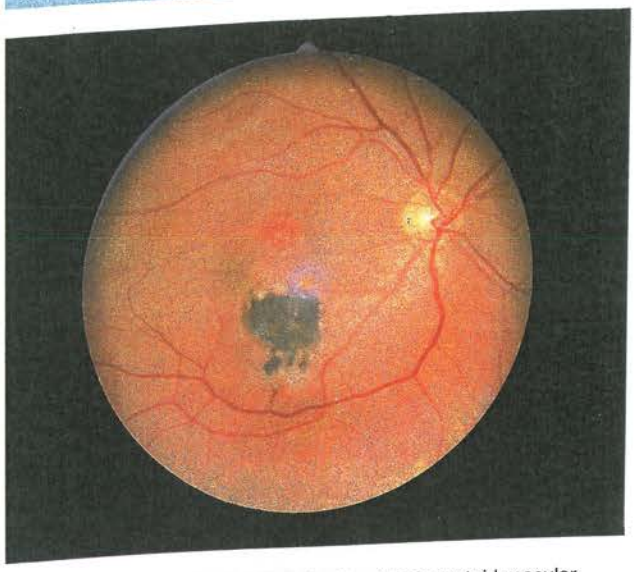


Figure 7.110 Macular hole secondary to chronic cystoid macular oedema adjacent to a toxoplasma scar

3. **Tractional retinal detachment** caused by extensive vitreous fibrosis is rare.

INDICATIONS FOR TREATMENT

In the immunocompetent patient not all active lesions require treatment because small peripheral foci are frequently self-limiting and innocuous. The following are the main indications for treatment:

1. A lesion threatening or involving the macula, papillomacular bundle, optic nerve head or a major blood vessel.
2. A very severe vitritis causing marked visual impairment, which may subsequently lead to vitreous fibrosis and tractional retinal detachment.
3. In AIDS patients all lesions should be treated irrespective of location or severity.

TREATMENT

Currently there is no universally agreed therapeutic regimen and the following drugs may be used:

1. **Systemic steroids** are recommended in eyes with vision-threatening lesions, particularly if associated with severe vitritis. Systemic steroids are, however, contraindicated in AIDS patients.
2. **Clindamycin** 300 mg four times daily is given orally for 3 weeks. However, if used alone in some patients, it may cause a pseudomembranous colitis secondary to clostridial overgrowth. Treatment of colitis is with oral vancomycin 500 mg 6-hourly for 10 days. The risk of colitis is reduced when clindamycin is used together with a sulphonamide that inhibits clostridial overgrowth.
3. **Sulphonamide** therapy is with either sulphadiazine or the mixed sulphonamide Sulphatriad (if available). The loading oral dose is 2 g followed by 1 g four times daily for 3–4 weeks. Side-effects of sulphonamides include renal stones, allergic reactions and Stevens–Johnson syndrome.
4. **Pyrimethamine** (Daraprim) is a strong anti-toxoplasma agent which may cause thrombocytopenia, leucopenia and folate deficiency. For this reason, weekly blood counts should be done and the drug used only in combination with oral folinic acid 4 mg three times a week (mixed with orange juice) because this counteracts the side-effects. The loading dose is 50 mg followed by 25–50 mg daily for 4 weeks. Pyrimethamine should not be used in patients with AIDS.
5. **Co-trimoxazole** (Septrin) is a combination of trimethoprim 160 mg and sulphamethoxazole 800 mg. When used in oral doses of 960 mg twice daily for 4–6 weeks, it may be effective alone or in combination with clindamycin. Side-effects are similar to those of the sulphonamides.
6. **Azithromycin** 500 mg daily on three successive days.
7. **Atovaquone** 750 mg three times daily has been used mainly in the treatment of pneumocystosis and toxoplasmosis in AIDS but it may also be useful in the treatment of toxoplasma retinitis in immunocompetent individuals. The drug is relatively free of serious side-effects but is expensive.

TOXOCARIASIS

Introduction

Toxocariasis is caused by infestation with a common intestinal ascarid (roundworm) of dogs called *Toxocara canis*. About 80% of puppies between the ages of 2 and 6 months are infested with this worm. Human infestation is by accidental ingestion of soil or food contaminated with ova shed in dogs' faeces. Very young children who eat dirt (pica) or are in close contact with puppies are at particular risk of acquiring the disease. In the human intestine, the ova develop into larvae which penetrate the intestinal wall and travel to various organs, such as the liver, lungs, skin, brain and eyes. When the larvae die, they disintegrate and cause an inflammatory reaction followed by granulation. Clinically, human infestation can take one of the following forms:

1. **Visceral larva migrans** (VLM) is caused by severe systemic infestation which usually occurs at about the age of 2 years. The clinical features, which vary in severity, include a low-grade fever, hepatosplenomegaly, pneumonitis, convulsions and rarely, death.

The blood shows a leucocytosis and marked eosinophilia.

2. **Ocular toxocariasis** differs markedly from VLM. Patients with ocular involvement are otherwise healthy and they have a normal white cell count with absence of eosinophilia. A history of pica is less common, and the average age at presentation is considerably older (7.5 years) compared with VLM (2 years). The three most common ocular lesions are: (a) ***a chronic endophthalmitis-like picture***, (b) ***posterior pole granuloma*** and (c) ***peripheral granuloma***. Other less common manifestations are a pars planitis-like syndrome, anterior uveitis, optic papillitis, a localized vitreous abscess and retinal tracks. Only the three most common lesions will be described; all affect only one eye.
3. **Diagnostic tests**
   (a) ***Enzyme-linked immunosorbent assay*** (ELISA) can be used to determine the level of serum antibodies to *Toxocara canis*. When ocular toxocariasis is suspected, exact ELISA titres should be requested, including testing of undiluted serum. Any positive titre is consistent with, but not necessarily diagnostic of, toxocariasis. It must therefore be interpreted in conjunction with the clinical findings. A positive titre does not therefore exclude the possibility of retinoblastoma.
   (b) **Ultrasonography** may be useful both in establishing the diagnosis in eyes with hazy media and in excluding other causes of leukocoria.

Chronic endophthalmitis

1. **Presentation** is between the ages of 2 and 9 years with leukocoria, strabismus or unilateral visual loss.
2. **Signs**
   (a) Anterior uveitis and vitritis (Figure 7.111).
   (b) In some cases, there may be a peripheral granuloma.
   (c) In other cases the peripheral retina and pars plana are covered by a dense greyish-white exudate, similar to the 'snowbanking' seen in pars planitis.
3. **Treatment**
   (a) Systemic or periocular steroids may be helpful in some cases.
   (b) Vitreoretinal surgery may be beneficial in some eyes with tractional retinal detachment (Figure 7.112).
4. **Causes of visual loss**
   Unfortunately, in most the visual prognosis is very poor and some eyes eventually require enucleation. The main causes of visual loss are:
   (a) Tractional retinal detachment secondary to contraction of vitreoretinal membranes.

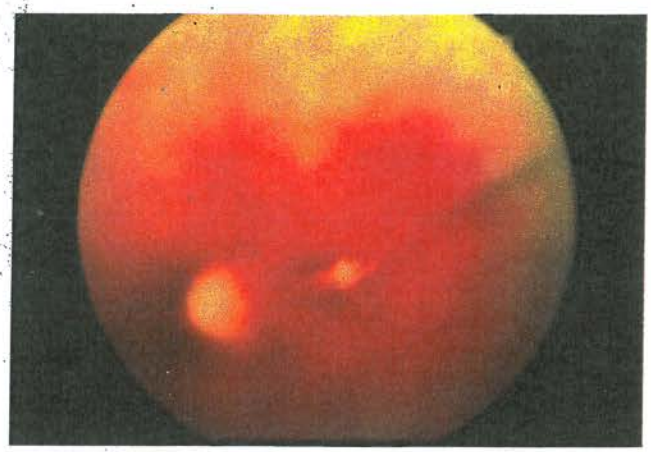


Figure 7.111 Vitritis in an eye with chronic toxocara endophthalmitis

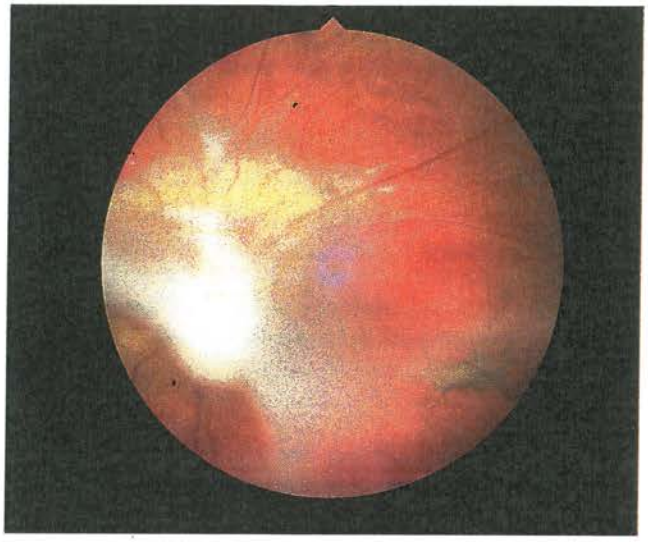


Figure 7.112 Tractional retinal detachment in chronic toxocara endophthalmitis

   (b) Ocular hypotony and phthisis bulbi caused by separation of the ciliary body from the sclera brought about by contraction of a cyclitic membrane.
   (c) Macular oedema and cataract.

Posterior pole granuloma

1. **Presentation** is typically with unilateral visual impairment between the ages of 6 and 14 years.
2. **Signs**
   (a) Anterior uveitis and vitritis are absent.
   (b) Round, yellow–white, solid granuloma whose size may vary between one (Figure 7.113) to two disc-diameters in size (Figure (7.114).

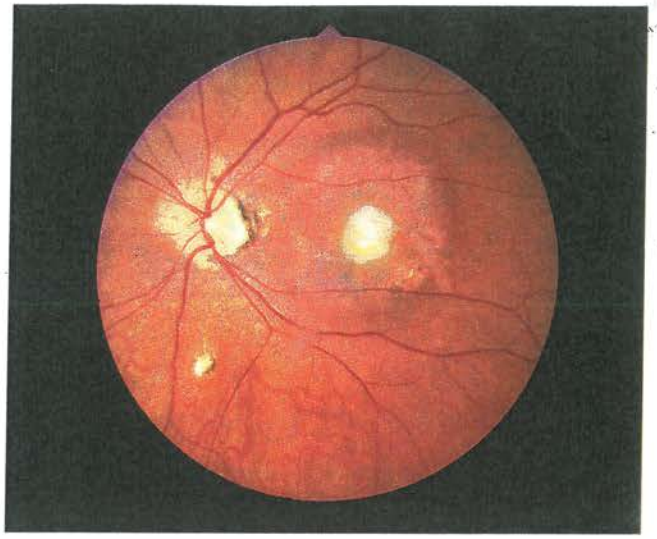


Figure 7.113 Small toxocara granuloma at the macula

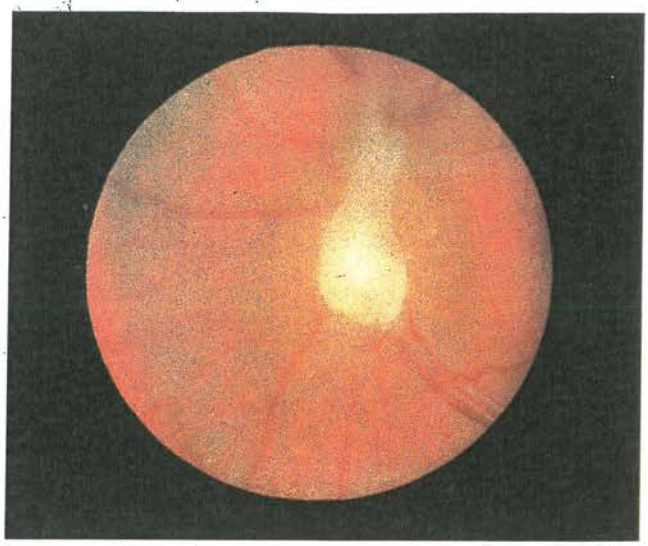


Figure 7.115 Toxocara granuloma involving the optic nerve head

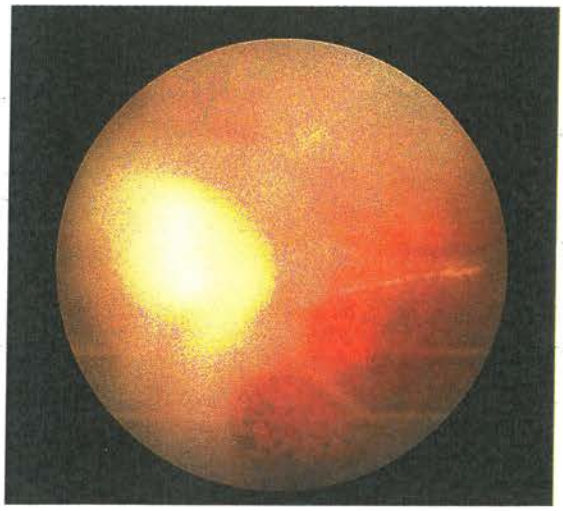


Figure 7.114 Large toxocara granuloma at the posterior pole

(c) Usually the granuloma is located either at the macula or between the macula and the optic disc.
(d) Occasionally the granuloma involves the optic nerve head (Figure 7.115).
(e) Associated findings include retinal stress lines, distortion of blood vessels, and occasionally the lesion is surrounded by yellow hard exudates.

3. **Causes of visual loss**
Once formed, the granuloma is usually stationary and the extent of visual loss is dependent on its location. Rare complications include serous retinal detachment and subretinal haemorrhage.

Peripheral granuloma

1. **Presentation** is usually during adolescence or adult life as a result of visual impairment from distortion of the macula or retinal detachment. In uncomplicated cases, the lesion may remain undetected throughout life.
2. **Signs**
   (a) Anterior uveitis and vitritis are absent.
   (b) A white hemispherical granuloma may be located at or anterior to the equator in any quadrant of the fundus (Figure 7.116).
   (c) Vitreous bands frequently extend from the lesion to the posterior fundus (Figure 7.117).
   (d) Contraction of the vitreous bands may give rise to 'dragging' of the disc and straightening of blood vessels (Figure 7.118).

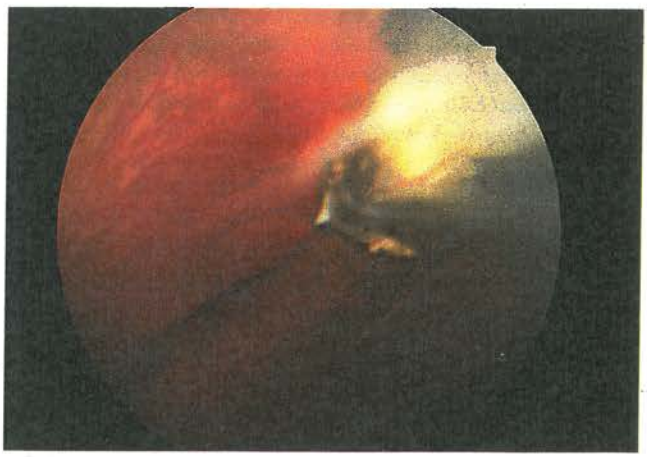


Figure 7.116 Peripheral toxocara granuloma

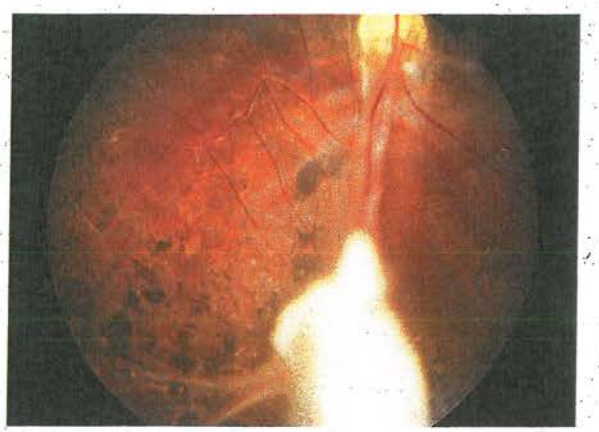


Figure 7.117 Large peripheral toxocara granuloma with vitreous bands

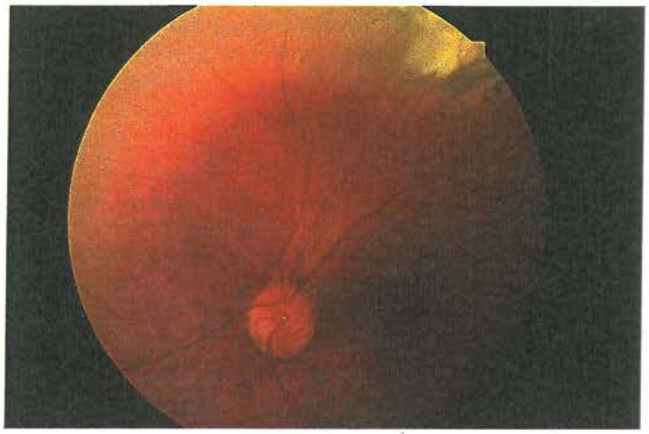


Figure 7.118 Vitreoretinal traction and 'dragging' extending from the disc towards a peripheral toxocara granuloma

3. **Causes of visual loss**
   In most cases the visual prognosis is excellent but a few severe cases may develop:
   (a) Heterotopia of the macula caused by contraction of the bands connecting the granuloma with the optic nerve head. The 'dragging' of the macula may give rise to a pseudoexotropia.
   (b) Retinal detachment (tractional or rhegmatogenous) from contraction of vitreoretinal bands. In some cases vitreoretinal surgery may be successful in reattaching the retina.

VIRAL UVEITIS

Herpes zoster iritis

CLINICAL FEATURES

Overall, about 40% of patients with herpes zoster ophthalmicus (HZO) develop iritis. Those with involvement of the external nasal nerve, which supplies the side of the nose (Hutchinson sign, Figure 7.119) are at particular risk.

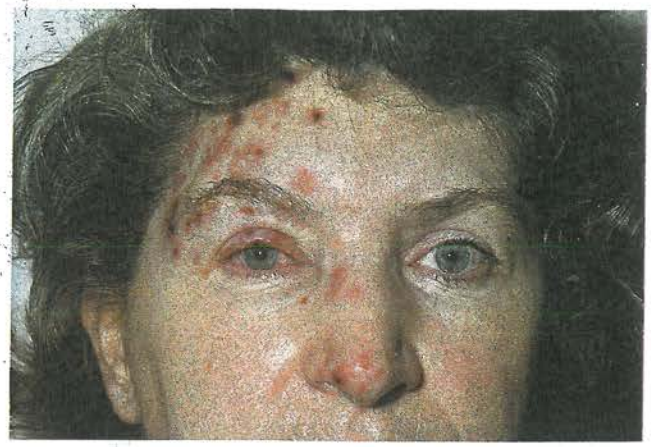


Figure 7.119 Involvement of the side of the nose (Hutchinson sign) in herpes zoster ophthalmicus

1. **Signs**
   (a) Non-granulomatous iritis with small keratic precipitates.
   (b) The anterior chamber reaction is usually fairly mild with a faint flare and a moderate number of cells, although rarely severe iris ischaemia causes hypopyon that may be tinged with blood.
2. **Complications**
   Unless treated vigorously, the anterior uveitis becomes chronic and may give rise to the following complications.
   (a) ***Iris atrophy*** occurs in about 20% of cases. It is characterized by sectoral loss of the iris pigment epithelium which can be seen on transillumination (Figure 7.120). Fluorescein angiography of the iris shows occluded blood vessels at the site of atrophy.
   (b) ***Secondary glaucoma*** occurs in about 10% of eyes with iritis. The pressure rise, which can

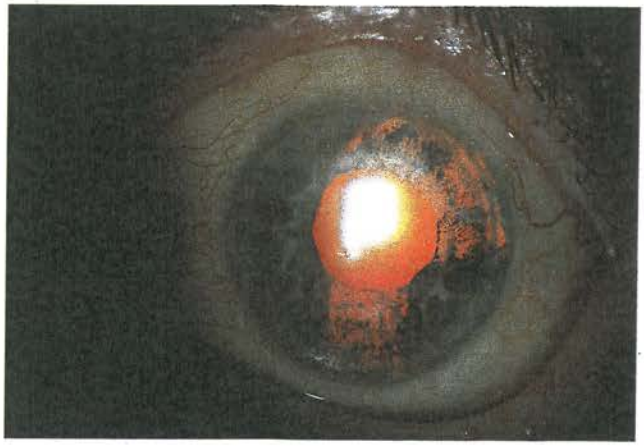


Figure 7.120 Iris atrophy secondary to herpes zoster iritis

sometimes be abrupt, is caused by a combination of inflammation of the trabecular meshwork (trabeculitis) and trabecular obstruction by inflammatory debris.

(c) ***Secondary cataract*** develops in a few patients with chronic anterior uveitis.

TREATMENT

Established iritis is treated with topical steroids. Treatment has to be continued for several months and then tapered very gradually.

DIFFERENTIAL DIAGNOSIS

Although, in the most cases, the diagnosis is straightforward, it is important to remember that severe uveitis may occur in patients with only a slight rash anywhere on the forehead. In these cases, the initial diagnosis of HZO might have been missed and the patient may present several months later with a chronic unilateral iridocyclitis. In order not to miss the diagnosis, always think of the possibility of HZO as a cause of anterior uveitis and perform the following tests:

1. Test corneal sensation because this is frequently diminished after zoster keratitis.
2. Examine the cornea for evidence of nummular lesions which may persist for many months.
3. Transilluminate the iris for evidence of atrophy.
4. Examine the patient's scalp at the hairline for evidence of post-herpetic scarring and pigmentation.

Acute retinal necrosis

Acute retinal necrosis (ARN) is a rare but devastating necrotizing retinitis. It typically affects otherwise healthy individuals of all ages. ARN is a biphasic disease which tends to be caused by herpes simplex in younger patients and herpes zoster in older individuals. The classic triad of ARN consists of the following:

- Arteritis and periphlebitis of the retinal and choroidal vasculature.
- Confluent necrotizing retinitis which preferentially affects the peripheral retina.
- Moderate-to-severe vitritis.

1. **Signs** in chronological order:
   (a) Peripheral sheathing of the retinal arterioles and the development of deep, multifocal, yellow–white, retinal infiltrates which may be associated with retinal haemorrhages (Figure 7.121).
   (b) The lesions gradually become confluent and represent a full-thickness necrotizing retinitis (Figure 7.122**a**).

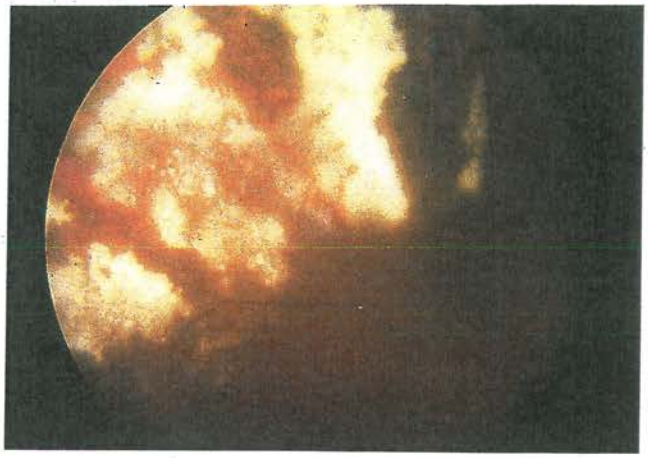


Figure 7.121 Severe retinal infiltration in acute retinal necrosis

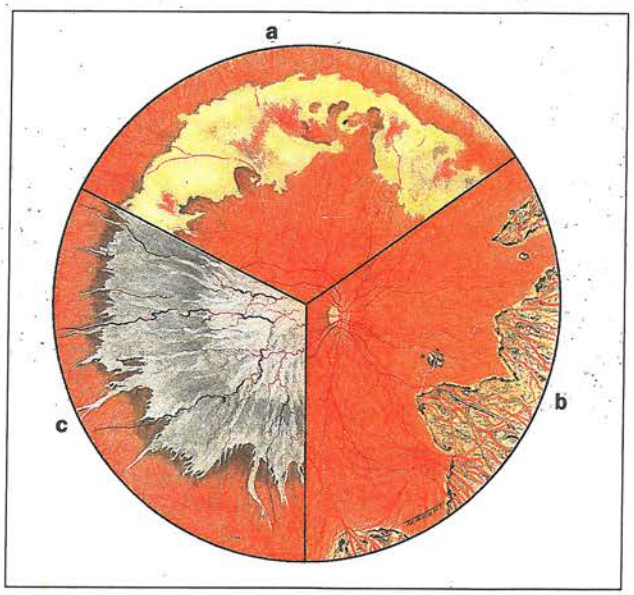


Figure 7.122 Progression of acute retinal necrosis (*see text*)

   (c) The posterior pole is usually spared until late so that visual acuity may remain fairly good despite severe necrosis of the surrounding retina.
2. **Clinical course**: the retintis resolves within 4–12 weeks, leaving behind a transparent and necrotic retina with atrophy of the retinal pigment epithelium (Figures 7.123, 7.122**b**). The second eye becomes involved in 30–50% of patients, usually within 2 months, although in some patients the interval may be much longer.
3. **Causes of visual loss**
   (a) ***Rhegmatogenous retinal detachment*** which develops as a result of the formation of retinal holes at the margin of uninvolved and involved zones (Figure 7.122**c**).
   (b) ***Tractional retinal detachment*** which is less common and caused by secondary condensation

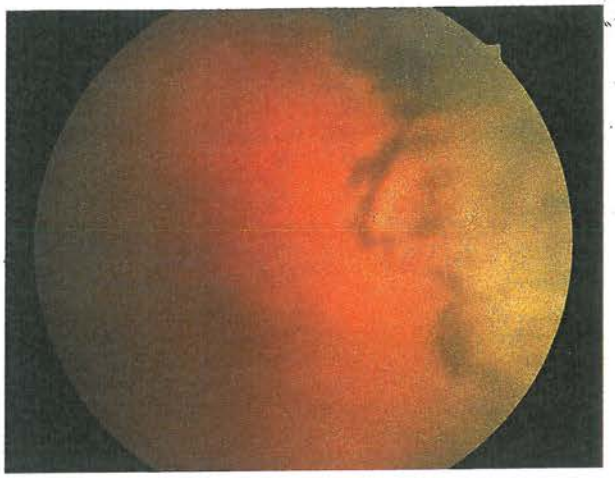


Figure 7.123 Resolved retinal necrosis

and fibrosis of the vitreous base. Both types of retinal detachment are extremely difficult to repair because of the frequent development of gross proliferative vitreoretinopathy.

(c) ***Ischaemic optic neuropathy*** caused by thrombotic arteriolar occlusion and infiltration of the optic nerve by inflammatory cells.

4. **Treatment**
   (a) ***Systemic acyclovir*** initially given intravenously for 10 days and then orally for 4–6 weeks may hasten resolution of the acute retinal lesions, but does not prevent either retinal detachment or involvement of the fellow eye. Long-term therapy may be required in some patients to prevent recurrences.
   (b) ***Systemic steroids*** are given a few days after the initiation of antiviral therapy.
   (c) ***Aspirin*** may be used in an effort to prevent vascular obstructive complications.
   (d) ***Laser photocoagulation,*** which creates a chorioretinal adhesion in areas of potential retinal break formation, may be effective in preventing retinal detachment if applied early.
   (e) ***Vitreoretinal surgery***, including silicone injection, may be successful in treating complicated retinal detachments.

Congenital rubella

SYSTEMIC FEATURES

Rubella (German measles) is usually a benign febrile exanthema. Congenital rubella results from transplacental transmission of virus to the foetus from an infected mother, usually during the first trimester of pregnancy. This may lead to serious chronic foetal infection and malformations. It appears that the risk to the fetus is closely related to the stage of gestation at the time of maternal infection. Fetal infection is about 50% during the first 8 weeks, 33% between weeks 9 and 12, and about 10% between weeks 13 and 24. Each of the various organs affected has its own period of susceptibility to the infection, after which no gross malformations are produced. Systemic complications of maternal rubella include: spontaneous abortion, stillbirth, congenital heart malformations, deafness, microcephaly, mental handicap, hypotonia, hepatosplenomegaly, thrombocytopenic purpura, pneumonitis, myocarditis and metaphyseal bone lesions.

OCULAR FEATURES

1. **Retinopathy** is the most common ocular complication, but the exact incidence is unknown because cataracts frequently impair visualization of the fundus. The characteristic finding is a 'salt and pepper' pigmentary disturbance, most often involving the posterior pole and most marked at the macula (Figure 7.124). The optic nerve head and retinal blood vessels are usually normal, although the foveal reflex may be absent. Retinopathy may occur in one or both eyes, and visual acuity is generally not affected, although a small percentage of eyes may lose vision as a result of secondary choroidal neovascularization.
2. **Cataract** is the second most common complication, affecting about 15% of infants. The pearly nuclear cataract may be bilateral or unilateral, and is frequently associated with microphthalmos.
3. **Microphthalmos** (Figure 7.125) occurs in 10–20% of infants and is associated with cataracts, optic nerve abnormalities and glaucoma.
4. **Glaucoma** develops in about 10% of eyes, usually during the neonatal period. It may or may not be associated with cataract. When occurring in a microphthalmic eye, the raised intraocular pressure may

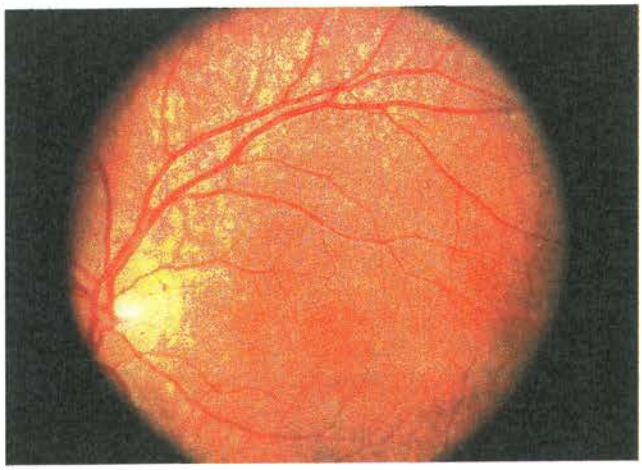


Figure 7.124 Old rubella retinopathy

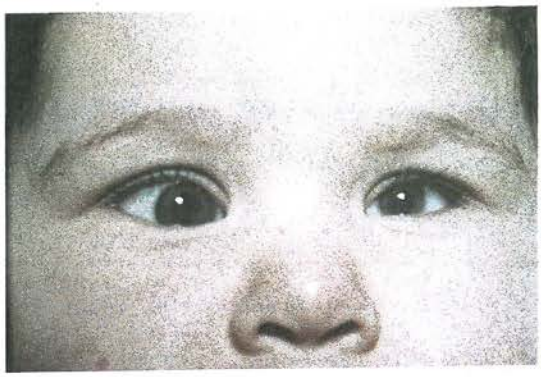


Figure 7.125 Left microphthalmos in rubella

enlarge the conea to normal size. When occurring in a normal-size eye the cornea may become larger than normal (buphthalmos). Corneal haze resulting from corneal oedema is also an important feature of glaucoma.

5. **Other complications**, which are less common, are corneal haze, iritis, iris atrophy and extreme refractive errors. Pendular nystagmus and strabismus may develop as a consequence of the various ocular abnormalities.

FUNGAL UVEITIS AND ENDOPHTHALMITIS

Presumed ocular histoplasmosis syndrome

SYSTEMIC FEATURES

Histoplasmosis is a fungal infection caused by *Histoplasma capsulatum*. The disease is acquired by inhalation and the organisms pass via the bloodstream to the spleen, liver and, on occasion, the choroid, setting up multiple foci of granulomatous inflammation. In the vast majority of patients, the fungaemia is innocuous and asymptomatic, because the organisms disappear after a few weeks. A small minority of patients with severe, disseminated, systemic histoplasmosis develop an endophthalmitis.

Although the presumed ocular histoplasmosis syndrome (POHS) has never been reported in patients with active, disseminated, systemic histoplasmosis, the disease has an increased prevalence in areas where histoplasmosis is endemic, such as the Mississippi–Missouri river valley. So far *Histoplasma capsulatum* has not been recovered from an eye with POHS. A syndrome identical to POHS has been reported in the UK where histoplasmosis is not endemic. In these patients, skin and serological tests are negative.

DIAGNOSTIC TESTS

1. **Histoplasma skin test** is positive in about 90% of patients with POHS.
2. **Complement fixation tests** are of limited value because they usually become negative several years after the original infection.
3. **Radiographs** may occasionally show old calcified granulomata in the lungs and spleen.
4. **Tissue typing** patients with POHS, particularly if associated with maculopathy, have an increased prevalence of HLA-B7.

OCULAR FEATURES

POHS is asymptomatic unless it causes a maculopathy. The earliest symptom of macular involvement is metamorphopsia. The following types of fundus lesion are seen in POHS.

1. **Atrophic 'histo' spots** consist of roundish, slightly irregular, yellowish-white lesions measuring between 0.2 and 0.7 of a disc diameter in size. Small pigment clumps may be present within or at the margins of the scars although some spots are not associated with pigmentation (Figure 7.126). The lesions are scattered in the mid-retinal periphery and the posterior pole (Figure 7.127).
2. **Peripapillary atrophy** is characterized, most frequently, by a diffuse, circumferential, choroidal atrophy extending up to 0.5 of a disc diameter beyond the disc margin (Figure 7.128). Less commonly, the peripapillary lesions are irregular and punched out, resembling the peripheral spots. In some eyes both diffuse and focal lesions are seen.

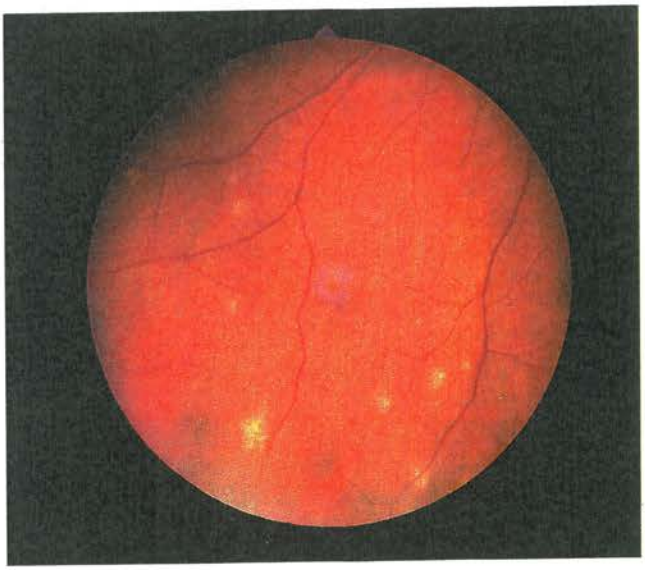


Figure 7.126 Peripheral 'histo spots' in presumed ocular histoplasmosis

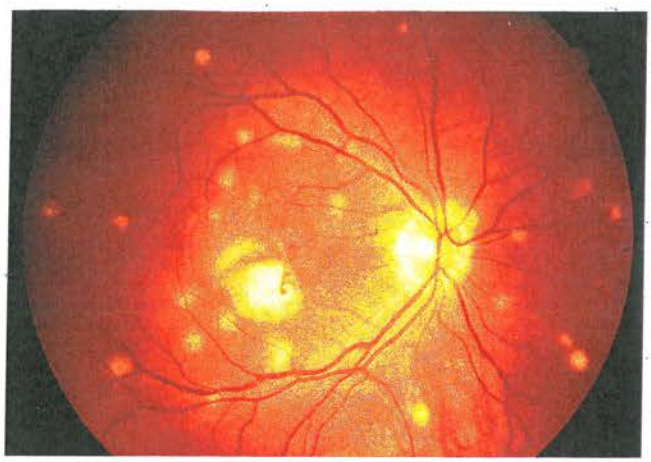


Figure 7.127 Extensive 'histo spots' and macular scarring in presumed ocular histoplasmosis

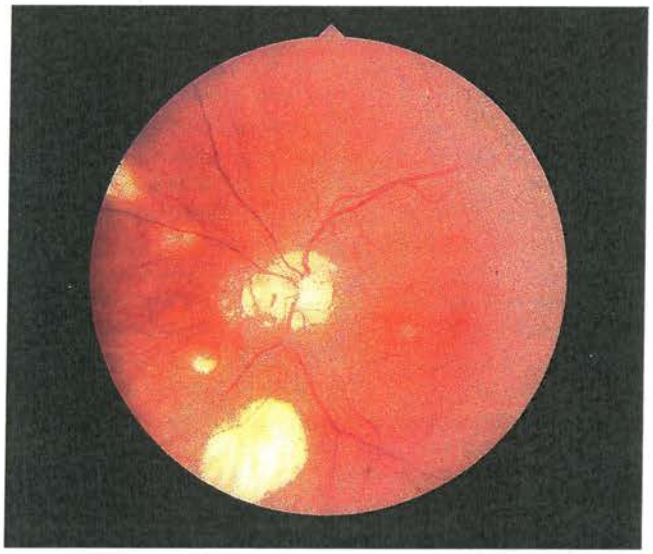


Figure 7.128 Peripapillary atrophy and retinal scars in presumed ocular histoplasmosis

3. **Linear streaks** of chorioretinal atrophy are seen in the fundus periphery (Figure 7.129).
4. **Choroidal neovascularization** (CNV) is a late manifestation of POHS which usually develops between the ages of 20 and 45 years. In most cases, CNV is associated with an old macular 'histo spot', although occasionally they develop within a peripapillary lesion. Very rarely, the CNV occurs in the absence of a pre-existing scar.
5. **The vitreous** remains clear and is never involved.

CLINICAL COURSE OF MACULOPATHY

The clinical course of maculopathy is variable and follows one of the following patterns:

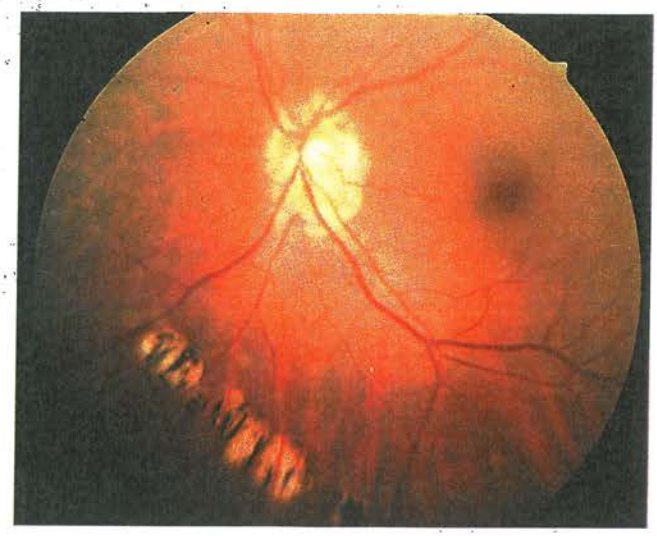


Figure 7.129 Linear streaks in presumed ocular histoplasmosis

1. The CNV may initially leak fluid and give rise to metamorphopsia, blurring of central vision and a scotoma. Careful slitlamp biomicroscopy with a fundus contact lens shows that the macula is elevated by serous fluid and an underlying focal yellow–white or grey lesion. In some eyes the subretinal fluid absorbs spontaneously and visual symptoms regress.
2. A dark green–black ring frequently develops on the surface of the yellow–white lesion and bleeding occurs into the sub-sensory retinal space causing a marked drop in visual acuity. In a few eyes, the subretinal haemorrhage resolves and visual acuity improves.
3. In some eyes, the initial CNV remains active for about 2 years giving rise to repeated haemorrhages. This finally causes a profound and permanent impairment of central vision resulting from the development of a fibrous disciform scar at the fovea (Figure 7.130).

Patients with maculopathy in one eye and an asymptomatic atrophic macular scar in the other are likely to develop a disciform lesion in the second eye. They should therefore test themselves every day with an Amsler grid to detect early metamorphopsia.

TREATMENT OF MACULOPATHY

The mainstay of treatment of CNV in eyes with POHS is argon laser photocoagulation (Figure 7.131). Without treatment, 60% of eyes have a final visual acuity of less than 6/60. The most favourable results of photocoagulation are achieved in eyes with CNV not closer than 0.25 of a disc diameter from the centre of the fovea and with intact capillary-free zones. Pre-treatment fundus fluorescein angiography is vital in evaluating the extent and location of neovascular membranes (Figure 7.132).

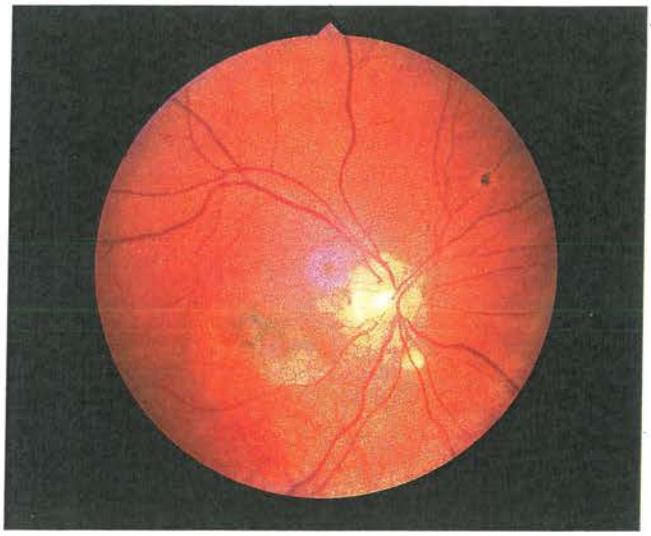
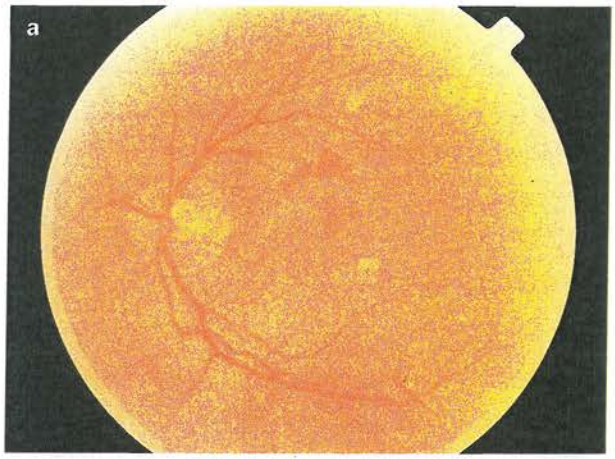


Figure 7.130 Macular scarring in presumed ocular histoplasmosis



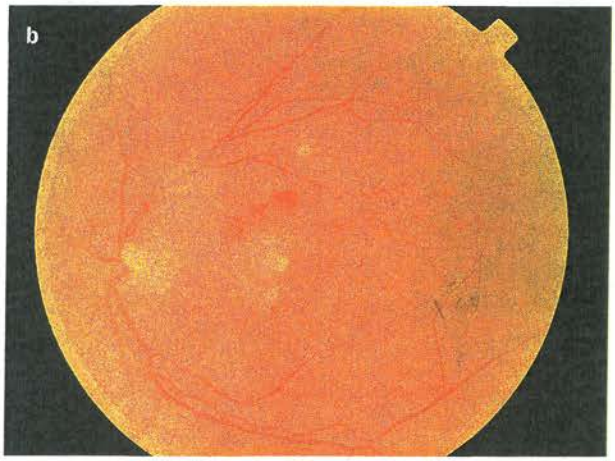
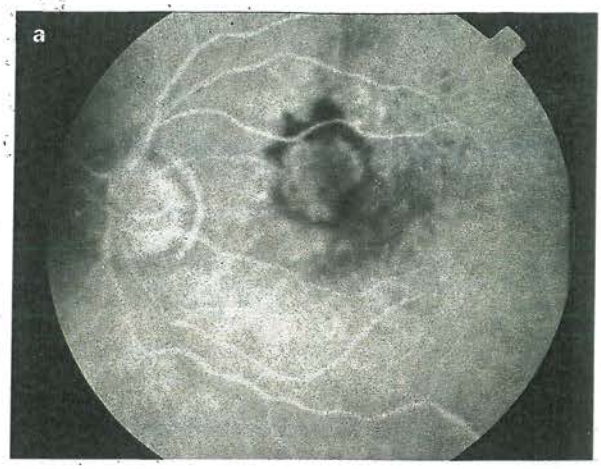


Figure 7.131 Maculopathy in presumed ocular histoplasmosis. (**a**) macular haemorrhage caused by choroidal neovascularization – appearance before laser treatment; (**b**) appearance after laser treatment



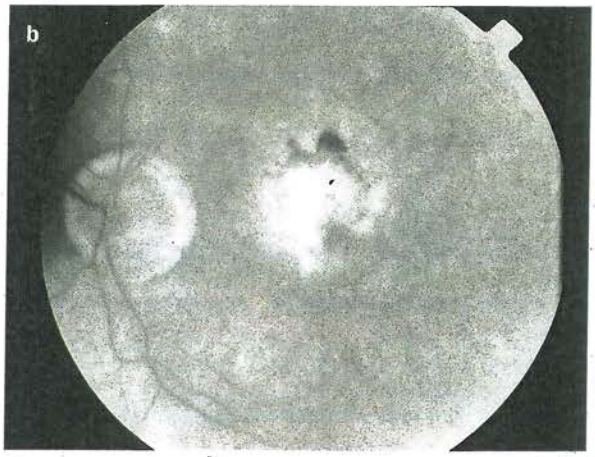


Figure 7.132 Fluorescein angiogram of choroidal neovascularization in presumed ocular histoplasmosis of the same eye as in the previous figure. (**a**) shows the classical lacy filling pattern of a choroidal neovascular membrane; (**b**) shows late leakage from the membrane

Candidiasis

SYSTEMIC FEATURES

Candida albicans, a yeast, is a frequent commensal of the human skin, mouth, gastrointestinal tract and vagina. Candidiasis is an opportunistic infection in which the organism acquires pathogenic properties. Candidaemia, which may result in ocular involvement, occurs in three main groups of patients.

1. **Drug addicts** may become infected through the use of non-sterile needles and syringes. Not infrequently, they have no obvious evidence of disseminated candidiasis, and negative blood and urine cultures for *Candida* sp. In this group, the diagnosis may be missed unless the skin is carefully examined for evidence of injection site scars.

2. **Patients with long-term indwelling catheters**, used for haemodialysis or intravenous nutrition following extensive bowel surgery, are at increased risk.
3. **Compromised hosts** include severely debilitated patients with decreased immunity either from an underlying systemic disease (AIDS, malignancies) or from long-term treatment with drugs, such as antibiotics, steroids and cytotoxic agents.

OCULAR FEATURES

In chronological order the signs are as follows:

1. The initial focus involves the choroid (Figure 7.133).
2. The organisms then invade the retina and give rise to a multifocal retinitis manifest as small, round, white, slightly elevated lesions (Figures 7.134**a**, 7.135).
3. Unless antifungal therapy is instituted, the small retinal lesions enlarge and extend into the vitreous gel, giving rise to floating white 'cotton ball' colonies (Figures 7.134**b**, 7.136).
4. Several colonies joined together by opalescent strands are referred to as a 'string of pearls' (Figure 7.134**c**).
5. Advanced lesions are characterized by endophthalmitis (Figure 7.137) and severe retinal necrosis.
6. Secondary vitreous organization may give rise to vitreoretinal traction (Figure 7.138) which if severe may result in tractional retinal detachment.

TREATMENT OF OCULAR LESIONS

1. **Medical treatment** is with a combination of oral 5-fluorocytosine (flucytosine) 150 mg/kg daily and ketoconazole 200–400 mg daily for 3 weeks. Alternative therapy in resistant cases is intravenous amphotericin B in 5% dextrose, given over a period of several days until a cumulative dose of 200 mg has been reached. The initial daily dose is 5 mg and after a few days this can be increased to 20 mg.

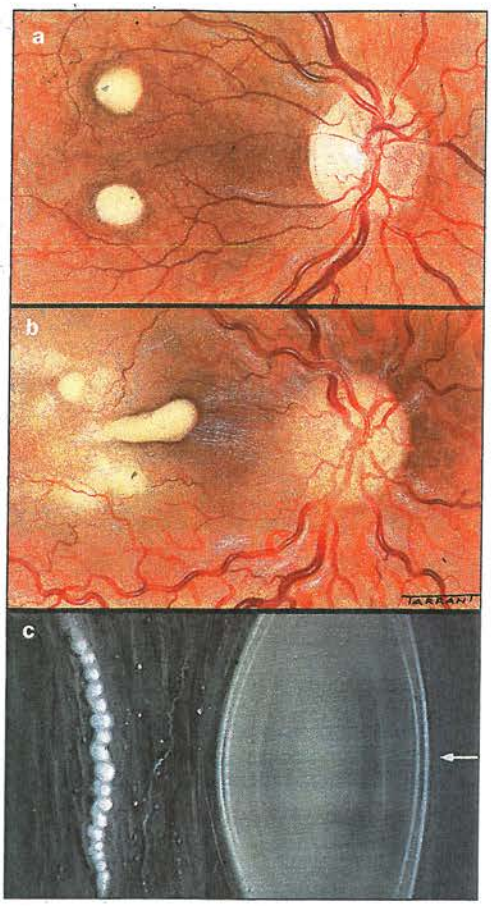


Figure 7.134 Progression of ocular candidiasis. (**a**) Multifocal retinitis; (**b**) extension into the vitreous; (**c**) 'string of pearls'

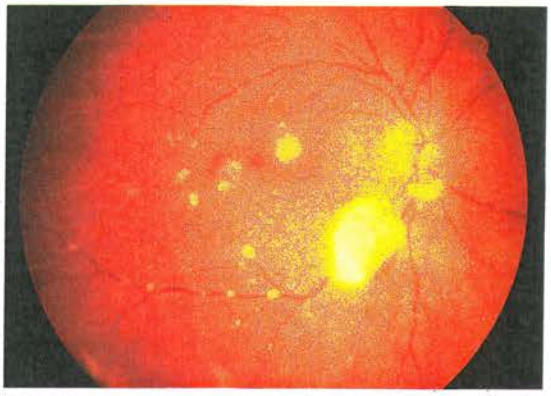


Figure 7.135 Multifocal candida retinitis and extension into the vitreous

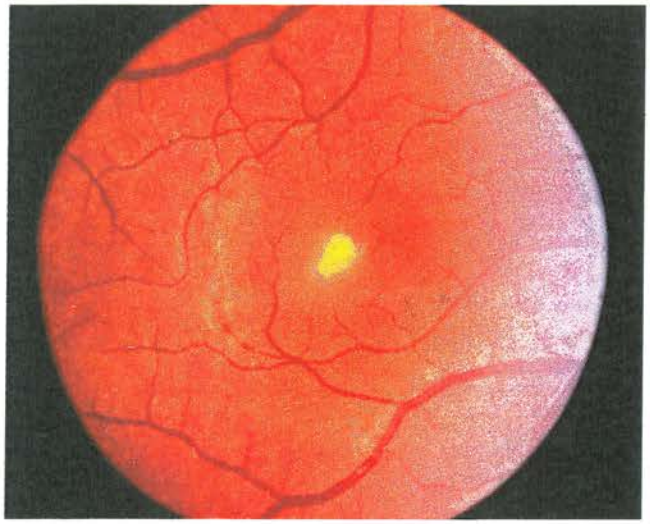


Figure 7.133 Early candida choroiditis

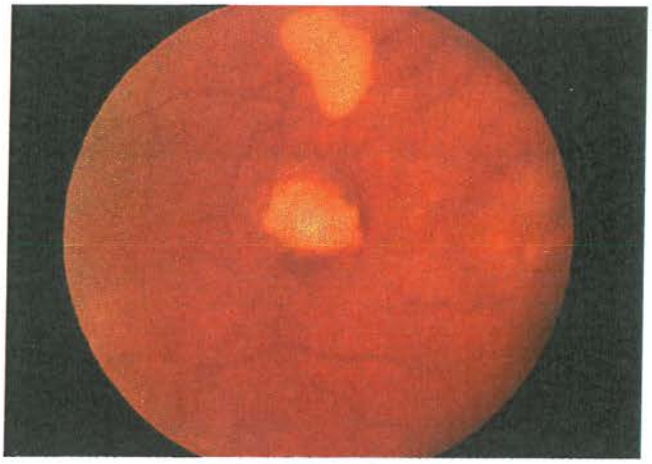


Figure 7.136 'Cotton ball' colonies of candida in the vitreous

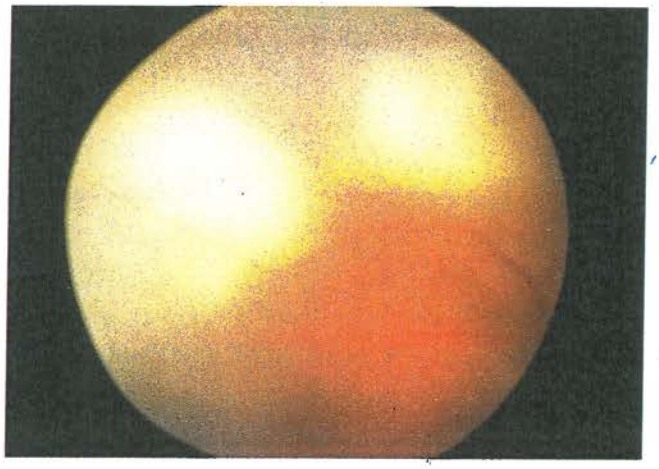


Figure 7.137 Candida endophthalmitis

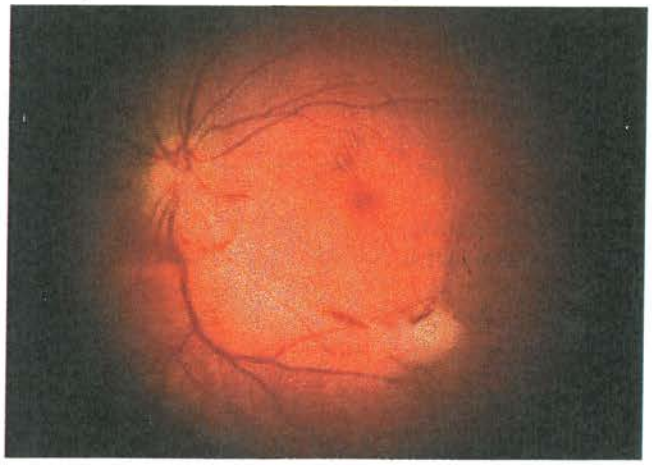


Figure 7.138 Residual vitreoretinal traction in inactive ocular candidiasis

2. **Pars plana vitrectomy** is indicated for moderate to severe vitreous involvement (endophthalmitis). At the time of vitrectomy, smears and cultures should be taken to confirm the diagnosis and test the sensitivity of the organisms to antifungal agents and an injection of 5 μg of amphotericin B should be given into the central vitreous cavity.

COMMON IDIOPATHIC SPECIFIC UVEITIS SYNDROMES

Fuchs uveitis syndrome

CLINICAL FEATURES

Fuchs uveitis syndrome (FUS) or Fuchs heterochromic cyclitis is a chronic, non-granulomatous, anterior uveitis which has an insidious onset. It typically affects one eye of a young adult, although it can also occur during childhood and may very occasionally be bilateral. Although FUS accounts for about 4% of all cases of uveitis, it is frequently misdiagnosed and overtreated. The heterochromia (difference in iris colour) may be absent in some patients or it may be difficult to detect, particularly in brown-eyed individuals, unless the patient is examined in daylight with undilated pupils.

1. **Presenting symptom** is frequently gradual blurring of vision secondary to cataract formation. A few patients complain of vitreous floaters and some notice a colour difference between the two eyes. Occasionally, the condition is detected by chance.
2. **Keratic precipitates** (KP) are characteristic and possibly pathognomonic. They are small, round or stellate, grey–white in colour and are scattered throughout the

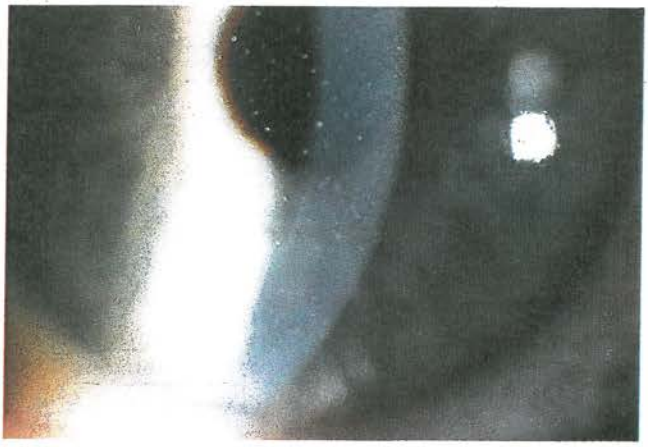


Figure 7.139 Keratic precipitates in Fuchs uveitis syndrome

corneal endothelium (Figure 7.139). They may come and go but they never become confluent or pigmented. Feathery fibrin filaments may be seen in between the KP.

3. **Aqueous humour** shows a faint flare and never more than +2 cells.
4. **Iris signs**
   (a) ***Absence of posterior synechiae*** is universal.
   (b) ***Iris stromal atrophy*** is typically diffuse. In early cases the only abnormal finding is a loss of iris crypts. More advanced stromal atrophy makes the affected iris appear dull with loss of detail giving rise to a washed-out appearance, particularly in the pupillary zone (Figure 7.140). The normal radial iris blood vessels appear prominent as a result of lack of stromal support.

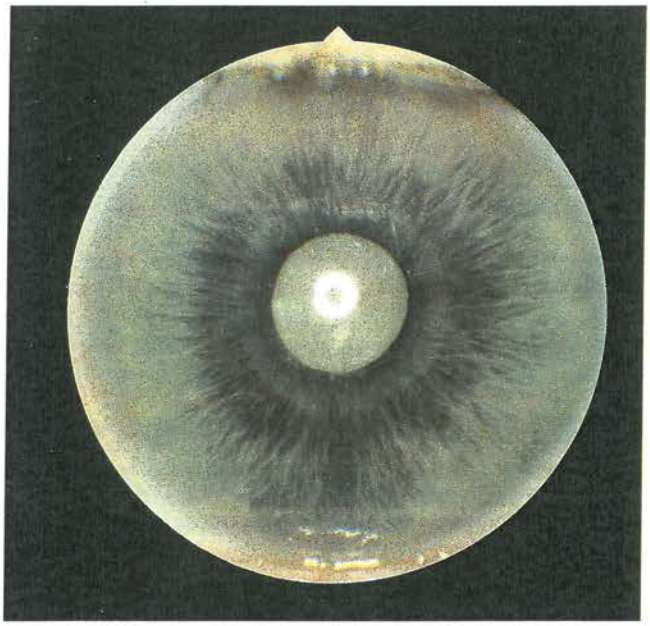


Figure 7.140 Iris atrophy and cataract in Fuchs uveitis syndrome

   (c) ***Atrophy of the posterior pigment layer*** is patchy and is best detected on iris transillumination (Figure 7.141).
   (d) ***Iris nodules*** are seen occasionally.
   (e) ***Rubeosis*** consisting of fine, irregular, fragile, neovascularization on the iris surface is fairly common.
   (f) ***Mydriasis*** resulting from atrophy of the iris sphincter may be present.
5. **Heterochromia iridis** (Figure 7.142).
   Most frequently the affected eye is hypochromic although in about 10% it is hyperchromic. In a small proportion of cases, the heterochromia is congenital. Factors determining the degree of heterochromia are the relative degrees of atrophy of the stroma and posterior pigment layer, as well as the patient's natural iris colour. In some patients with predominantly stromal atrophy, the posterior pigmented layer shows through and becomes the dominant pigmentation so that the eye becomes hyperchromic. In general, a brown eye becomes less brown and a blue eye assumes a more saturated blue colour.

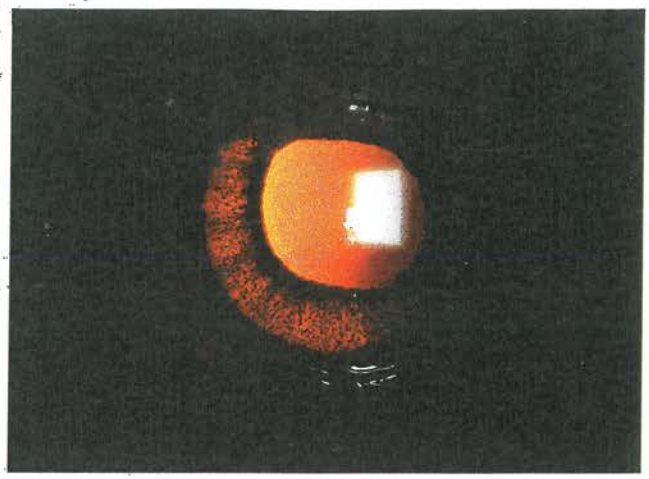


Figure 7.141 Extensive iris transillumination defects in Fuchs uveitis syndrome

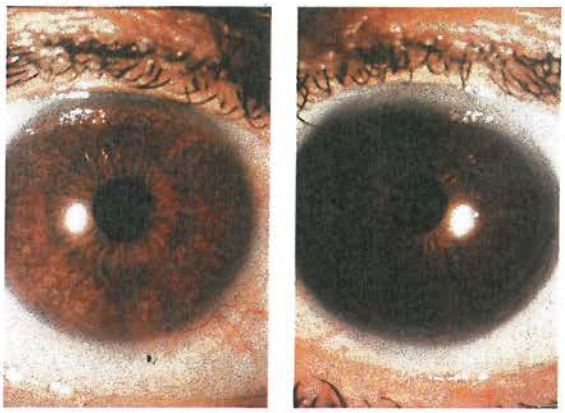


Figure 7.142 Heterochromia iridis in Fuchs uveitis syndrome

6. **Vitritis** and stringy opacities are common.
7. **Gonioscopy** may be normal or it may show one of the following:
   (a) Neovascularization characterized by the presence of fine radial twiglike vessels in the chamber angle is common (Figure 7.143). These vessels are probably responsible for the filiform haemorrhages which develop with anterior chamber paracentesis away from the puncture site (Amsler sign).
   (b) A membrane may obscure angle details.
   (c) Small, non-confluent, irregular, peripheral anterior synechiae are seen in some eyes.

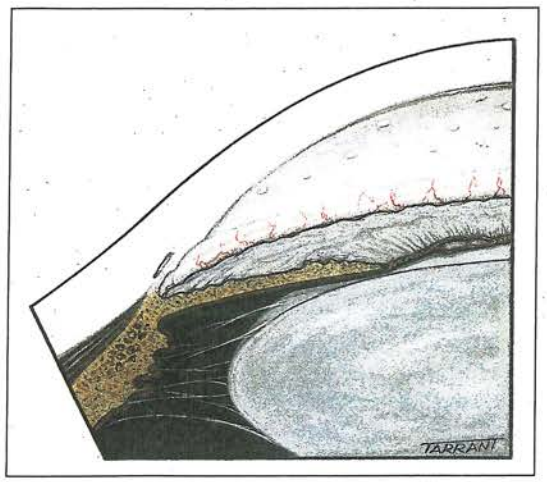


Figure 7.143 Angle new vessels in Fuchs uveitis syndrome

DIFFERENTIAL DIAGNOSIS OF HETEROCHROMIA IRIDIS

Apart from FUS, the following conditions may give rise to heterochromia:

1. **Hypochromia**
   (a) Congenital.
   (b) Horner syndrome, particularly if congenital.
2. **Hyperchromia**
   (a) Oculodermal melanocytosis (naevus of Ota).
   (b) Ocular siderosis.
   (c) Diffuse iris naevus or melanoma.
   (d) Sturge–Weber syndrome, rarely.
   (e) Unilateral use of topical latanoprost.

COMPLICATIONS

FUS runs a chronic course lasting many years. The two main complications are cataract and glaucoma both of which may be enhanced by the inadvertent use of topical steroids in some patients.

1. **Cataract** is extremely common and does not differ from that associated with other types of anterior uveitis. The results of cataract surgery with posterior chamber intraocular lens implantation are usually good, although in some cases the operation is complicated by hyphaema.
2. **Secondary glaucoma** is the most serious threat to vision and is frequent when the follow-up period is prolonged. Initially, the elevation of intraocular pressure is intermittent before becoming chronic. The glaucoma is usually of the open-angle type and is thought to be caused by trabecular sclerosis and not by synechial angle-closure. In some patients, glaucoma is precipitated by cataract extraction. It may become resistant to medical therapy and conventional trabeculectomy has a failure rate of about 50%. For this reason adjunctive antimetabolites may be required if surgery is contemplated.

TREATMENT

In the vast majority of cases, treatment with topical steroids produces no objective improvement. Mydriatics are unnecessary as posterior synechiae do not develop. However, the patient should be examined at approximately 6-monthly intervals to detect glaucoma.

Intermediate uveitis

CLINICAL FEATURES

Intermediate uveitis accounts for about 8% of all cases of uveitis. It is an idiopathic, insidious, chronic, intraocular inflammation which typically affects a child or a young adult. Although both eyes are affected in about 80% of cases, the severity of involvement is frequently asymmetrical. On long-term follow-up about 10% of patients subsequently develop features of sarcoidosis or multiple sclerosis.

1. **Presenting symptoms** are usually increasing floaters, although occasionally the patient presents with impairment of central vision secondary to macular oedema. In some cases the condition is diagnosed by chance.
2. **The anterior chamber** may be quiet or it may show a slight flare, a few cells and several small KP. Posterior synechiae are, however, absent.
3. **Vitritis**
   (a) Cells in the anterior vitreous (Figure 7.144).

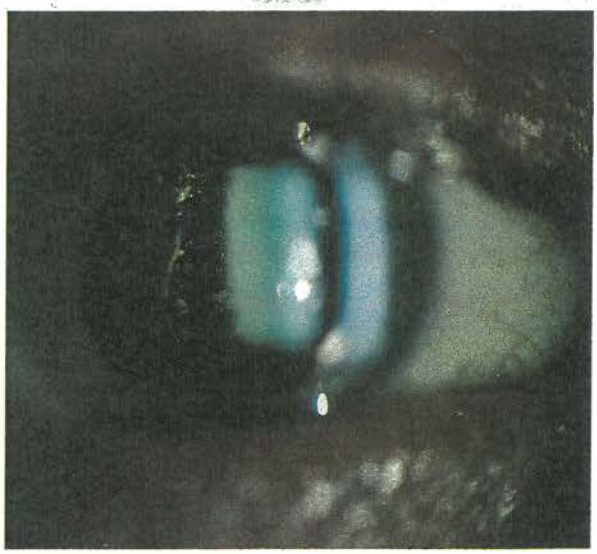


Figure 7.144 Cells in the anterior vitreous in intermediate uveitis

(b) Later gelatinous exudates ('snowballs' or 'cotton balls') appear (Figure 7.145).
(c) Sheet-like condensations may be present (Figure 7.146).
(d) In very advanced cases the entire vitreous may become opaque (Figure 7.147).

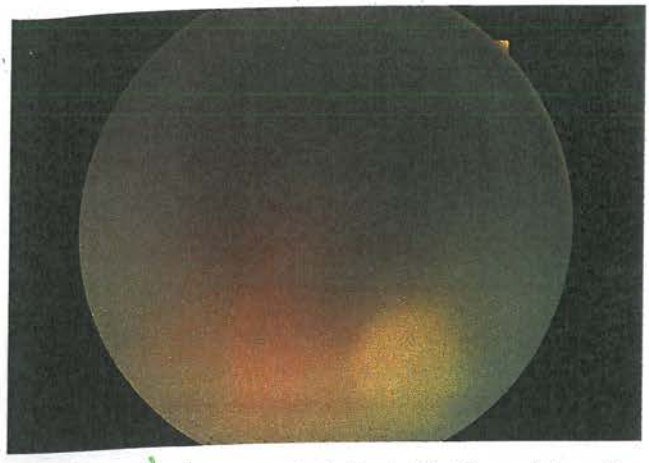


Figure 7.145 Severe vitritis and a 'cotton ball' in intermediate uveitis

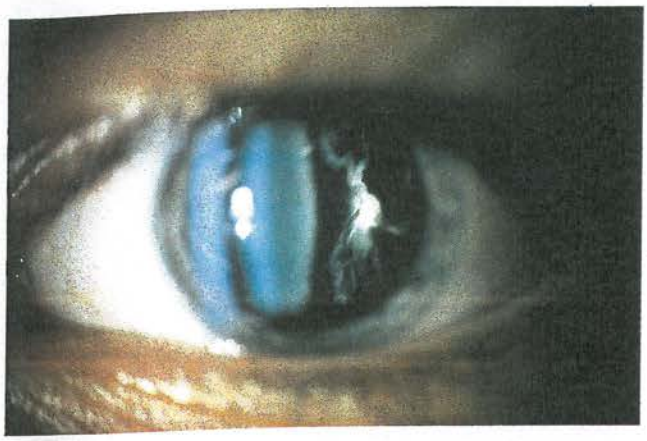


Figure 7.146 Anterior vitreous condensation in intermediate uveitis

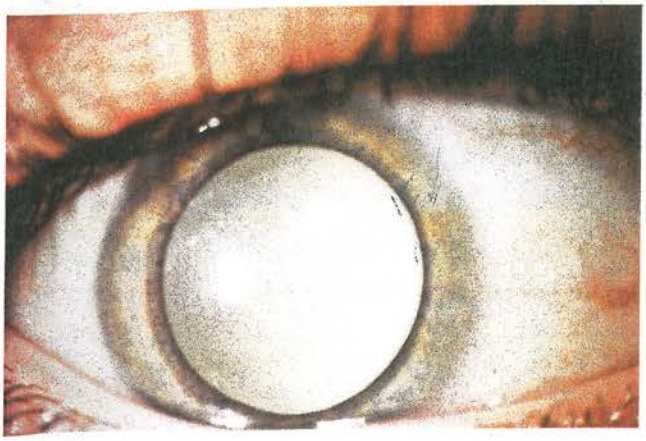


Figure 7.147 Severe vitreous opacification in intermediate uveitis

4. **Mild peripheral retinal periphlebitis** of the terminal venules is common.
5. **Snowbanking** is the hallmark of pars planitis which is merely a subset of intermediate uveitis. It consists of a grey–white plaque involving the inferior pars plana (Figure 7.148) which can be seen only with indirect ophthalmoscopy and scleral indentation. In advanced cases, the plaque may extend posteriorly to cover the peripheral retina.
6. **Clinical course** is variable. A few patients have a single, low-grade, self-limiting episode lasting several months. The majority, however, have a chronic smouldering course lasting several years which may be associated with subacute exacerbations and incomplete remissions. Despite this, the visual prognosis in most patients is relatively good.

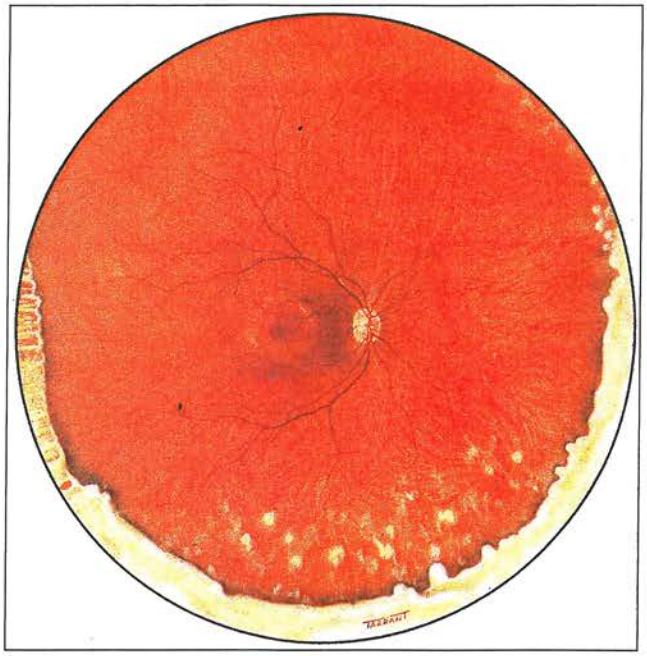


Figure 7.148 Inferior peripheral 'snowbanking' in pars planitis

COMPLICATIONS

1. **Cystoid macular oedema** is the most common cause of impaired visual acuity. If the oedema becomes chronic, cystoid changes develop which may subsequently lead to a permanent impairment of visual acuity from lamellar hole formation.
2. **Secondary cataract** tends to develop more frequently in eyes with severe and prolonged inflammation.
3. **Tractional retinal detachment** may occur in advanced cases as a result of contraction of fibrovascular tissue at the pars plana.
4. **Cyclitic membrane formation** as a result of massive proliferation of vascularized exudate on to and behind the posterior lens capsule.

TREATMENT

It is important not to over-treat this condition. The main indication for treatment is a visual acuity of less than 6/9 secondary to cystoid macular oedema.

1. **Posterior sub-Tenon steroid injections** (*see* Figure 7.166) of either triamcinolone acetonide (Kenalog) or methylprednisolone acetate (Depomedrone) are effective in most cases. The necessity for repeated injections is governed by the patient's visual acuity and not the severity of vitritis.
2. **Systemic therapy** with steroids, cytotoxic agents or cyclosporin can be used in the event of resistance to periocular injections.
3. **Cryotherapy** of the vitreous base may be useful in steroid-resistant cases and in those with active peripheral neovascularization. The rationale is to ablate the new vessels and the associated avascular peripheral retina, rather than to treat areas of exudation.

Juvenile chronic iridocyclitis

Although juvenile chronic arthritis is the most common systemic association of chronic iridocyclitis in children, many patients with juvenile chronic iridocyclitis are otherwise healthy. The majority of patients are also girls. As the onset of intraocular inflammation is frequently insidious and asymptomatic, most cases are not diagnosed until visual acuity is reduced from complicated cataract (*see* Figure 7.30) or the parents notice a white patch on the cornea caused by band keratopathy (*see* Figure 7.29). In a small number of cases the uveitis is detected by chance.

Acute anterior uveitis in young adults

Whilst ankylosing spondylitis is the most common systemic association of acute anterior uveitis, many patients have no underlying systemic disease, although about 45% carry HLA-B27. The risk to HLA-B27-negative patients (particularly females) of subsequently developing ankylosing spondylitis is very small, although some HLA-B27-positive patients (particularly males) will subsequently develop the disease.

IDIOPATHIC MULTIFOCAL WHITE-DOT SYNDROMES

Multiple evanescent white-dot syndrome

The multiple evanescent white-dot syndrome (MEWDS) is a rare, usually unilateral condition that typically affects healthy young women. There is no treatment but the prognosis is *excellent*.

1. **Presenting symptom** is an acute onset of unilateral visual impairment.
2. **Active lesions** consist of numerous, very small white dots at the level of the RPE which are most prominent at the posterior pole (Figure 7.149) and mid-periphery (Figure 7.150).
3. **The fovea** is granular and contains many tiny punctate orange dots which are much smaller and more uniform than the lesions elsewhere.
4. **Associated features** include mild vitritis and an enlarged blind spot.

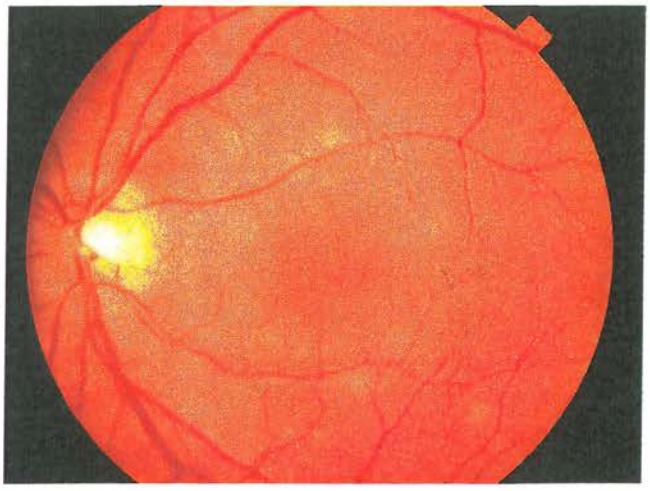


Figure 7.149 Central lesions in multiple evanescent white-dot syndrome

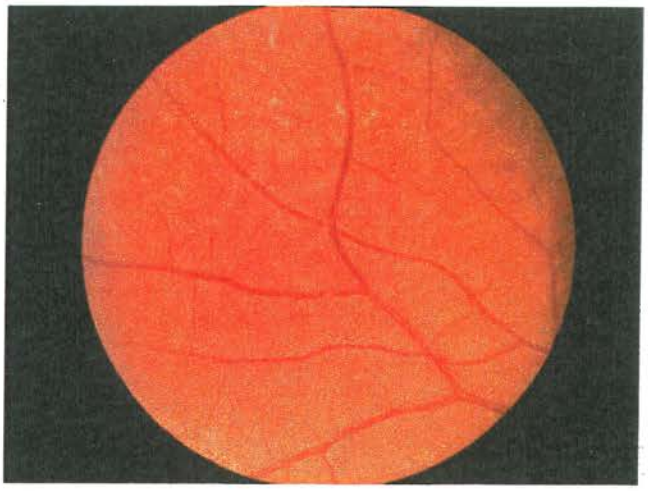


Figure 7.150 Peripheral lesions in multiple evanescent white-dot syndrome

5. **Clinical course**: the spots disappear spontaneously over several weeks and visual acuity returns to normal but the blind spot may remain enlarged. Rarely, there may be recurrences and involvement of both eyes.

Acute posterior multifocal placoid pigment epitheliopathy

Acute posterior multifocal placoid pigment epitheliopathy (APMPPE) is an uncommon condition which typically affects both eyes of young adults. Both sexes are affected equally and there is an association with HLA-B7 and DR2. There is no treatment but the visual prognosis is *good*.

1. **Presenting symptom** is a subacute unilateral impairment of visual acuity, followed a few days later by involvement of the fellow eye. About 50% of patients have a prodromal influenza-like illness which may be associated with erythema nodosum.
2. **Active lesions** consist of large, cream-coloured or grey–white, deep lesions involving the posterior pole and post-equatorial (Figure 7.151). Within a few days the fellow eye shows similar changes.
3. **Fluorescein angiography** shows early dense hypofluorescence followed by late staining (Figure 7.152).
4. **Associated features** include mild vitritis, and occasionally vascular sheathing and disc oedema.
5. **Clinical course**: in the vast majority of cases, the placoid lesions and vitritis resolve within a few weeks, and visual acuity returns to normal or near normal despite the presence of residual multifocal areas of depigmentation and clumping which involve the retinal pigment epithelium (Figure 7.153).

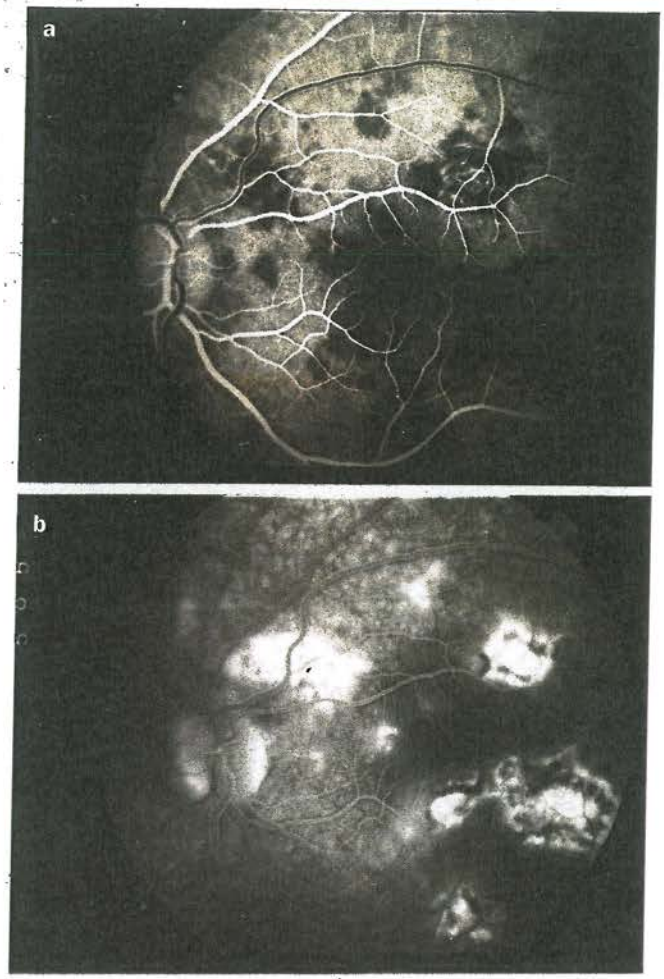


Figure 7.152 Fluorescein angiogram in acute posterior multifocal placoid pigment epitheliopathy. (**a**) dense hypofluorescence during the early stages; (**b**) late diffuse staining

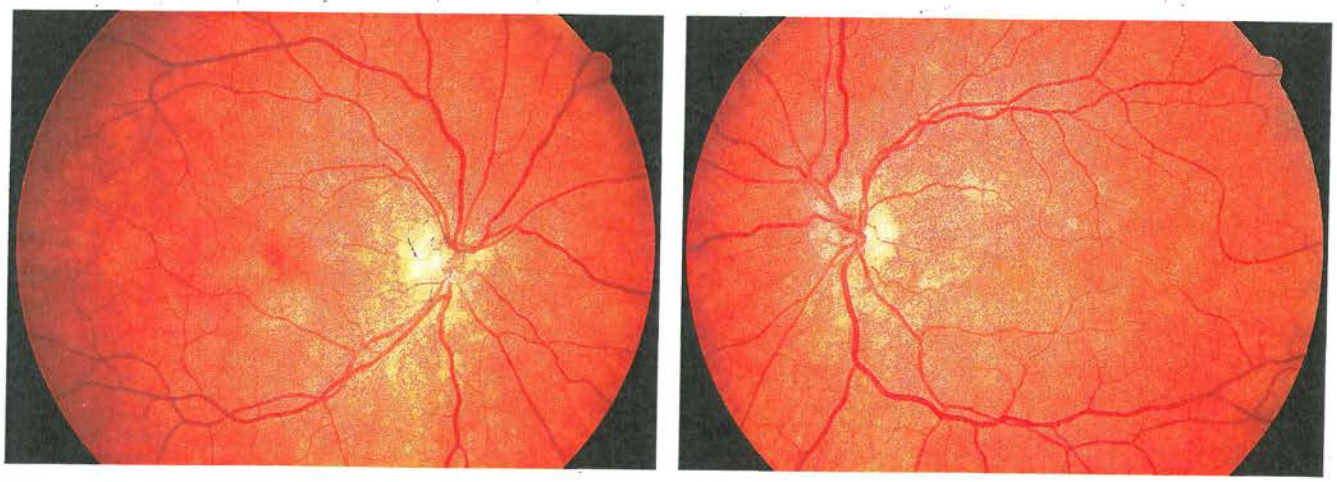


Figure 7.151 Acute lesions in posterior multifocal placoid pigment epitheliopathy

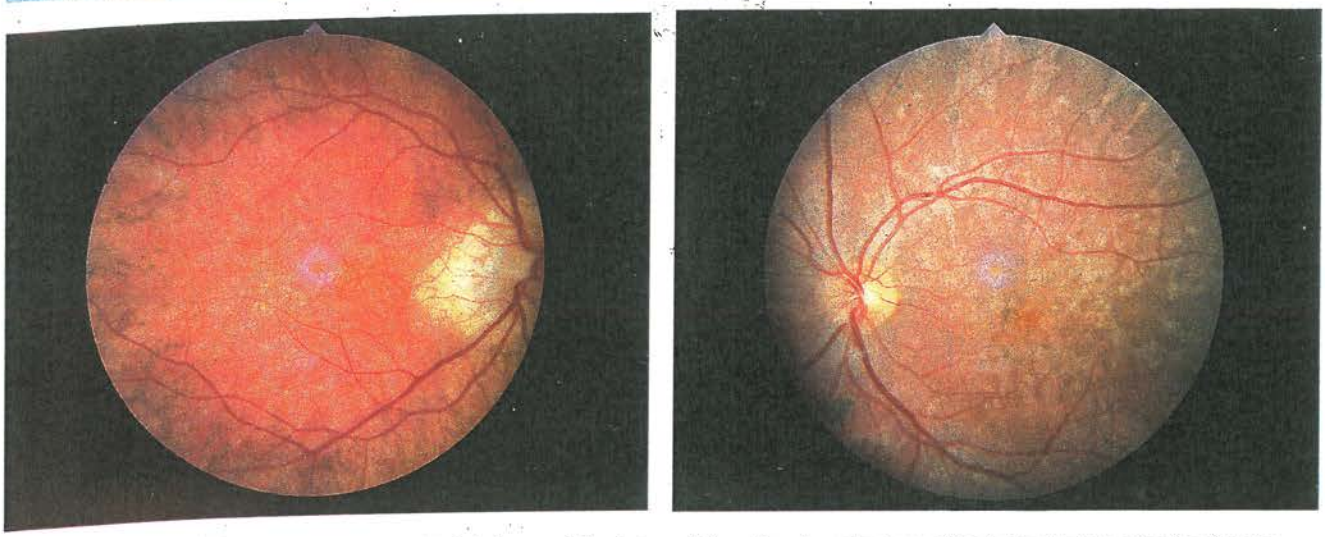


Figure 7.153 Residual retinal pigment epithelial changes following resolution of acute posterior multifocal placoid pigment epitheliopathy

Serpiginous choroidopathy

Serpiginous choroidopathy is an uncommon, idiopathic, chronic, progressive, bilateral disease which typically affects patients between the fourth and sixth decades of life. Both sexes are affected equally. It has a *poor* prognosis.

1. **Presenting symptom** is usually with initially unilateral visual impairment as a result of macular involvement. After a variable period the fellow eye also becomes affected.
2. **Active lesions** consist of deep, cream-coloured opacities with hazy borders (Figure 7.154) which later become brighter in colour (Figure 7.155). The lesions usually start around the optic disc and then spread

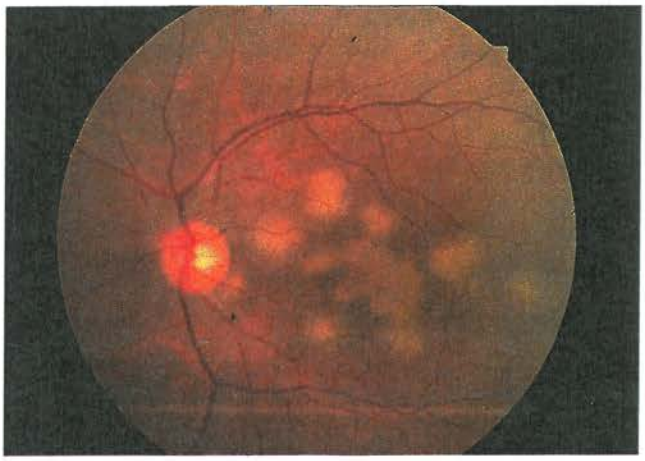


Figure 7.154 Early stage of serpiginous choroidopathy

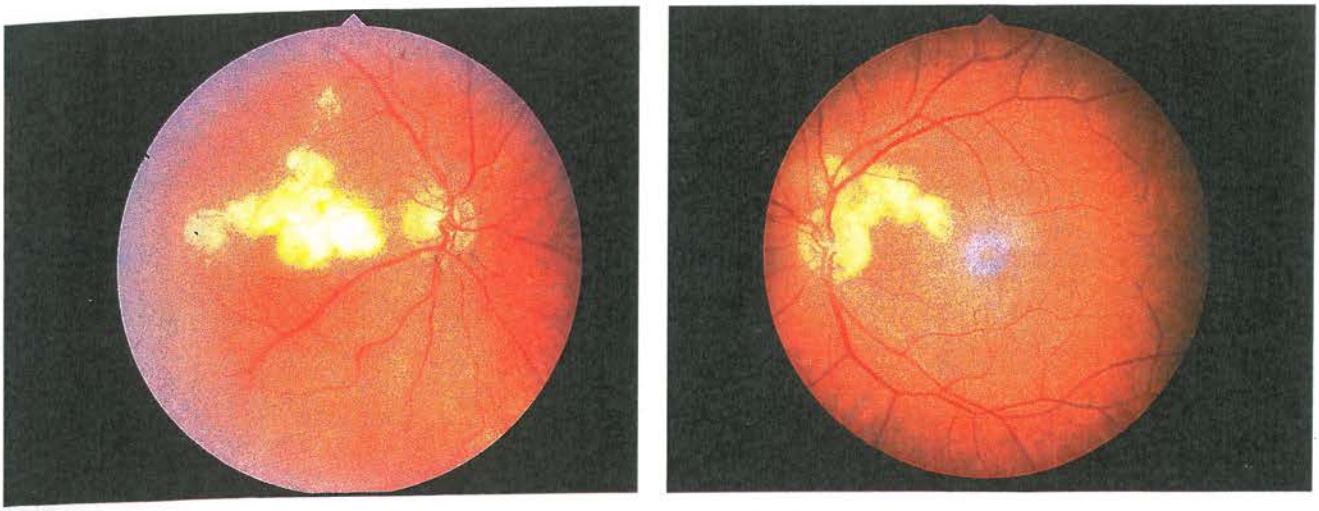


Figure 7.155 Active serpiginous choroidopathy

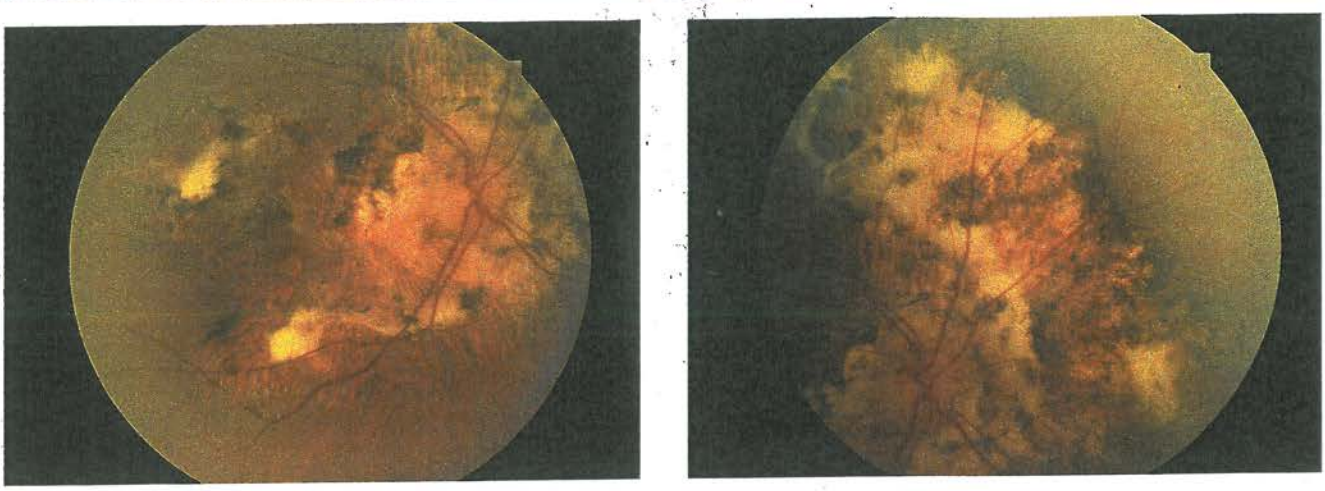


Figure 7.156 Extensive scarring in advanced serpiginous choroidopathy

outwards in all directions. Rarely, the initial lesions involve the macula.

3. **Associated features** include mild anterior uveitis and vitritis.
4. **Clinical course**: successive attacks result in extension of the destructive process from the peripapillary area in an irregular, convoluted, snakelike manner (Figure 7.156). Visual loss caused by involvement of the fovea is profound and permanent. Eyes in which the fovea is bypassed (Figure 7.157) are not always safe from future foveal involvement, because occasionally the lesions begin in an extrapapillary location and later spread centrally towards the optic disc. Inactive lesions consist of residual, scalloped, atrophic 'punched out' areas. Large choroidal blood vessels in the base of an area of atrophy are frequently the only visible remnants of the choroid.

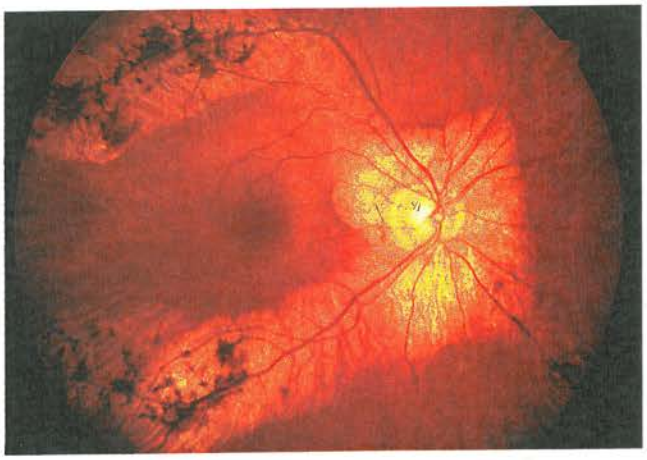


Figure 7.157 Macular sparing in serpiginous choroidopathy

5. **Complications**: choroidal neovascularization may occasionally develop.
6. **Treatment** of severe recurrent cases is with systemic steroids, azathioprine and cyclosporin. Laser photocoagulation may be required for secondary choroidal neovascularization.

Birdshot retinochoroidopathy

Birdshot retinochoroidopathy is an uncommon, bilateral, chronic condition which typically affects healthy middle-aged women who are positive for HLA-A29. It has a *guarded* prognosis.

1. **Presenting symptoms** are either vitreous floaters or, less commonly, impairment of central vision secondary to macular oedema.
2. **Acute lesions** consist of varying numbers of bilateral, flat, creamy-yellow, deep ovoid spots with indistinct margins which radiate from the optic disc towards the equator (Figure 7.158).
3. **Fluorescein angiography** shows late intraretinal and disc leakage (Figure 7.159).
4. **Associated features** include vitritis and cystoid macular oedema.
5. **Clinical course**: chronic lesions may become more confluent and spread to the macula. After weeks or months, the individual spots evolve into more atrophic, white, depigmented lesions which are more circumscribed but not associated with secondary hyperpigmentation (Figure 7.160).
6. **Complications** include maculopathy, retinal atrophy, optic atrophy, cataract and occasionally choroidal neovascularization.
7. **Treatment** with systemic steroids or steroid-sparing immunosuppressives is beneficial.

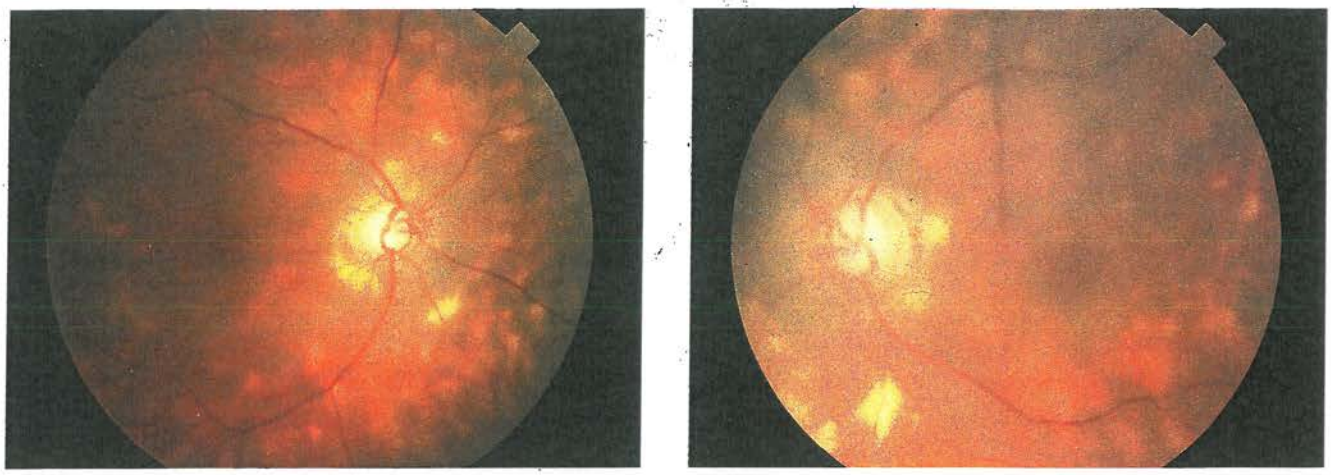


Figure 7.158 Active birdshot retinochoroidopathy

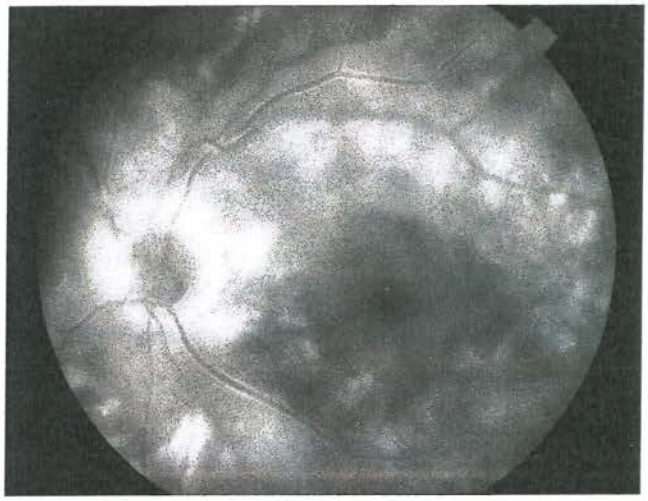


Figure 7.159 Late intraretinal and disc leakage of fluorescein in birdshot retinochoroidopathy

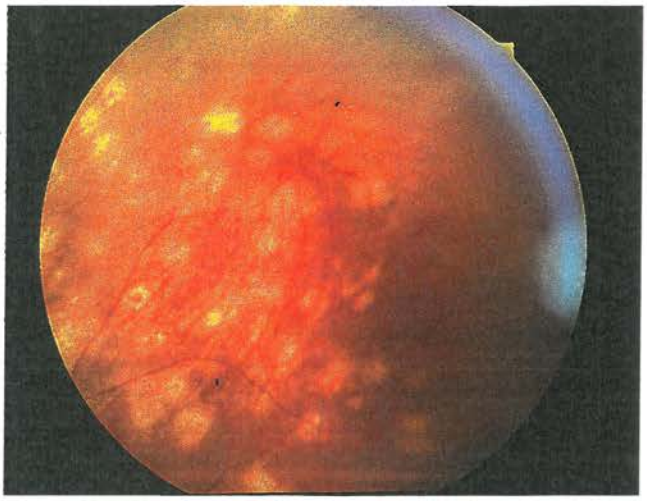


Figure 7.160 Atrophic scars following resolution of birdshot retinochoroidopathy

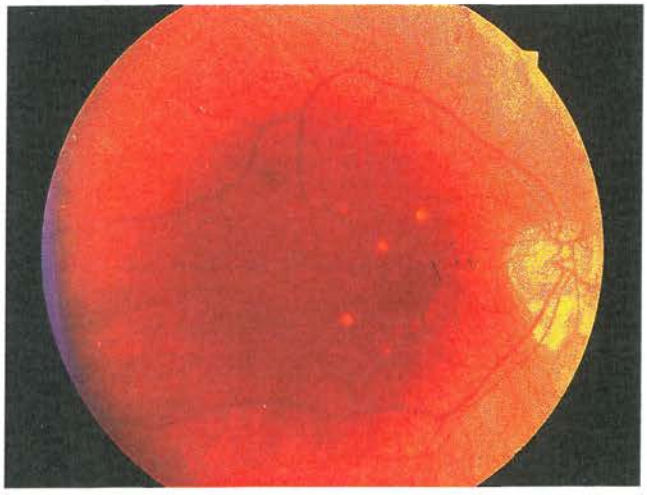


Figure 7.161 Active punctate inner choroidopathy

Punctate inner choroidopathy

Punctate inner choroidopathy (PIC) is an uncommon, usually eventually bilateral condition which typically affects young healthy myopic women. There is no treatment and the prognosis is *guarded*.

1. **Presenting symptoms** are an acute onset of scotomata and photopsia.
2. **Active lesions** consist of small, yellow, indistinct choroidal spots, all of the same age at the posterior pole (Figure 7.161). A serous retinal detachment may develop in some cases where the lesions are plentiful. There is no associated anterior uveitis or vitritis.
3. **Clinical course**: the acute lesions resolve within a few weeks to leave behind sharply demarcated atrophic scars which may resemble those associated with histoplasmosis (Figure 7.162). With time, the scars may

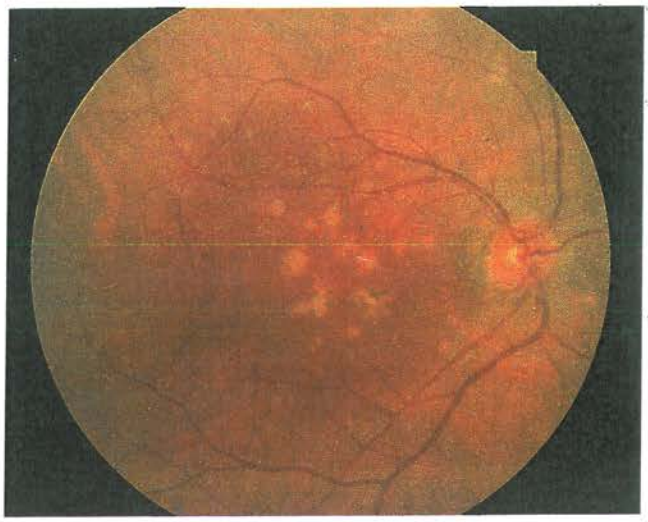


Figure 7.162 Inactive punctate inner choroidopathy

enlarge and become pigmented. After a variable period of time the fellow eye frequently becomes involved.

4. **Complications**: a few cases develop choroidal neovascularization in association with a scar which may require laser photocoagulation.

Multifocal choroiditis with panuveitis syndrome

Multifocal choroiditis with panuveitis is an uncommon, unilateral or bilateral condition, which may occur at any age but typically affects middle-aged women. It has a *fair* prognosis.

1. **Presenting symptom** is subacute blurring of vision.
2. **Active lesions** consist of multiple, small, discrete old and fresh choroidal lesions located at the mid-periphery and fewer at the posterior pole (Figure 7.163).
3. **Associated features** include vitritis in all cases, and anterior uveitis in 50%.
4. **Clinical course** is prolonged, with the development of new lesions and episodes of recurrent inflammation. Chronic lesions become more atrophic with sharp punched-out margins and variable amounts of pigmentation (Figure 7.164).
5. **Complications** include chronic cystoid macular oedema, subretinal fibrosis (Figure 7.165) and occa-

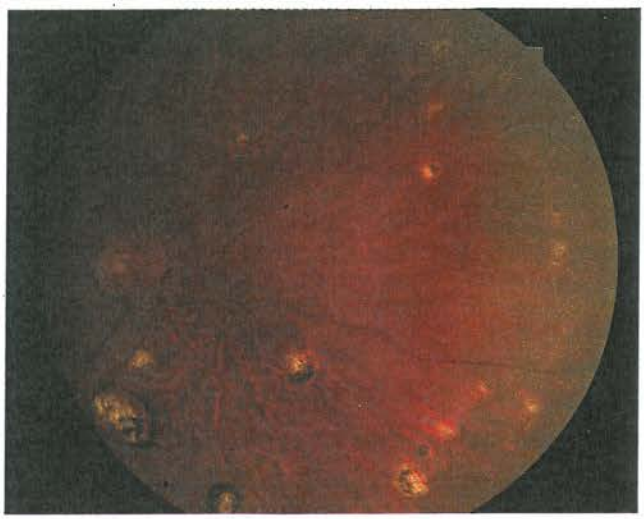


Figure 7.164 Atrophic spots following resolution of multifocal choroiditis

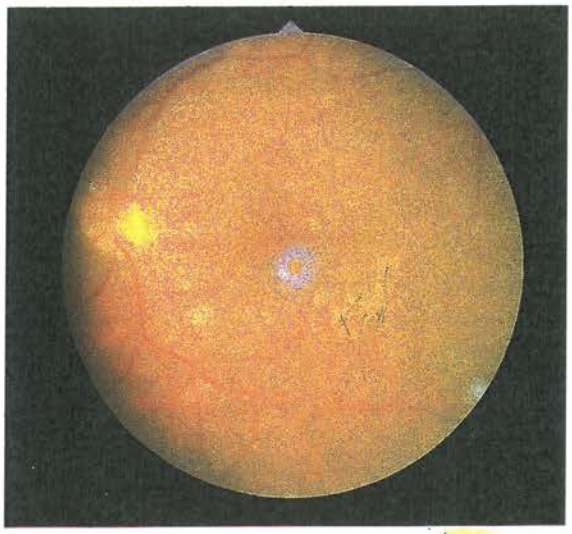


Figure 7.163 Active stage of multifocal choroiditis with panuveitis syndrome

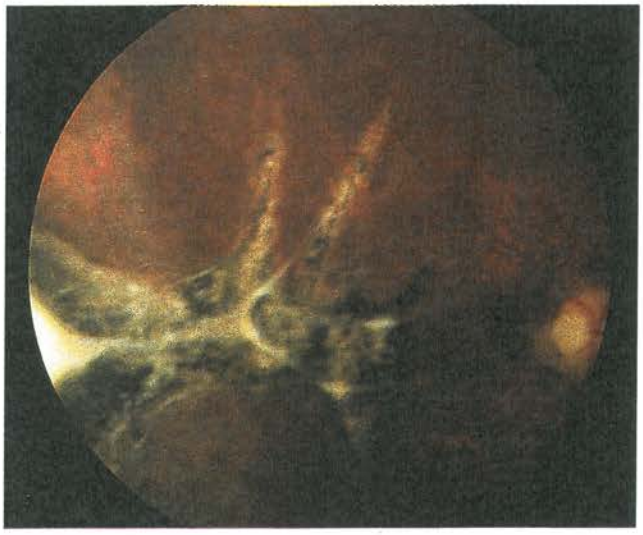


Figure 7.165 Subretinal fibrosis associated with multifocal choroiditis with panuveitis syndrome

sionally choroidal neovascularization associated with one of the scars.

6. **Treatment** with periocular and systemic steroids, during the active stage, can improve the prognosis. Laser photocoagulation for secondary choroidal neovascularization may be required.

TREATMENT OF UVEITIS

The aims of treating uveitis are:

1. **To prevent vision-threatening complications.**
2. **To relieve the patient's discomfort.**
3. **To treat the underlying disease, if possible.**

The four groups of drugs currently used in the treatment of uveitis are: (a) ***mydriatics***, (b) ***steroids***, (c) ***cyclosporin*** and (d) ***cytotoxic agents***. Patients with uveitis caused by infections should be treated with the appropriate antimicrobial or antiviral agent.

Mydriatics

The main indications for mydriatrics are:

1. **To give comfort** by relieving spasm of the ciliary muscle and sphincter of the pupil which occurs in severe acute anterior uveitis. This can be achieved with atropine which is the most powerful cycloplegic available. It is usually unnecessary to use atropine for more than 1–2 weeks. Once the inflammation is showing signs of subsiding it can be substituted by a short-acting mydriatic, such as tropicamide or cyclopentolate.
2. **To prevent formation of posterior synechiae** by using a short-acting mydriatic which keeps the pupil mobile. In mild cases of chronic anterior uveitis the mydriatic can be instilled once at bedtime to prevent difficulties with accommodation during the day. In eyes with chronic anterior uveitis, the pupil should not be kept constantly dilated because posterior synechiae can still form in the dilated position. In young children, constant atropinization of one eye may induce amblyopia.
3. **To break down synechiae**, if possible, by using either intensive topical mydriatics (atropine, phenylephrine) or subconjunctival injections of Mydricaine (adrenaline, atropine and procaine).

Steroids

Steroids are the mainstay of management of most cases of uveitis. They can be administered topically in the form of drops or ointment, by periocular injection or systemically.

TOPICAL ADMINISTRATION

Topical steroids are used only for anterior uveitis because they do not reach a therapeutic level in tissues behind the lens. Strong steroids such as dexamethasone, betamethasone and prednisolone must be used because weaker preparations such as fluorometholone and clobetasone are of very limited value. A solution penetrates the cornea better than a suspension or ointment. Ointment can, however, be instilled at bedtime. The frequency of instillation of drops depends on the severity of inflammation and can vary from one drop every 5 minutes to one drop every other day. In general, one should start with a high rate of instillation and then decrease as the inflammation lessens, rather than start with a low rate and work up. This principle applies to both topical and systemic administration of steroids.

1. **In acute anterior uveitis** treatment is relatively straightforward and the frequency of instillation can usually be reduced after a few days, and then discontinued after 5–6 weeks.
2. **In chronic anterior uveitis** treatment is very much more difficult because the inflammation may last for months and even years. Acute exacerbations of chronic uveitis with +4 aqueous cells are treated with hourly instillation for 2–3 days, and then the drops are tapered to four times a day. If the inflammation is controlled with no more than +1 aqueous cells, the rate of instillation can be gradually further reduced over the next few months and then stopped. Following cessation of drops, the patient should be re-examined within a few days to ensure that the uveitis has not recurred.
3. **Complications** which may occur from topical steroid administration include the following:
   (a) ***Glaucoma*** in susceptible individuals (*see* Chapter 6).
   (b) ***Posterior subcapsular cataract***, which can be induced by both systemic and, less frequently, topical steroid administration. The risk increases with the amount and duration of therapy (*see* Chapter 5).
   (c) ***Corneal complications***, which are uncommon, include: reduction of immunological protection against secondary infection with bacteria and fungi, enhancement of recrudescences and multiplication of herpes simplex virus, and corneal melting may be enhanced by inhibition of collagen synthesis.
   (d) ***Systemic side-effects***, which may be induced following prolonged administration, particularly in children.

PERIOCULAR INJECTIONS

1. **Advantages over drops**
   (a) They are able to reach a therapeutic concentration behind the lens.

(b) Drugs that are only water soluble and incapable of penetrating the cornea when given topically can enter the eye by penetrating the sclera when given by periocular injection.
(c) A long-lasting effect can be achieved if a depot preparation such as triamcinolone acetonide (Kenalog) or methylprednisolone acetate (Depomedrone) is used.

2. **Indications**
(a) Severe acute anterior uveitis, especially in patients with ankylosing spondylitis with a marked fibrinous exudate in the anterior chamber or hypopyon.
(b) As an adjunct to topical or systemic therapy in resistant cases of chronic anterior uveitis.
(c) Intermediate uveitis.
(d) Poor patient compliance to topical or systemic medication.
(e) At the time of surgery in eyes with uveitis.

3. **The technique of administration**
Periocular sub-Tenon injections can be given either anteriorly or posteriorly. Anterior sub-Tenon injections are usually given for severe anterior uveitis whereas the main indication for posterior sub-Tenon injections is intermediate uveitis. It is extremely important to have the conjunctiva very well anaesthetized before attempting a periocular injection. If this is done correctly, the injection can be given with minimal discomfort to the patient.

(a) ***The conjunctiva*** is anaesthetized as follows:
- Instil a topical anaesthetic such as amethocaine at 1 min intervals for 5 min.
- Place a small cotton pledget impregnated with amethocaine (or equivalent) into the conjunctival sac at the site of injection and leave it there for 5 min.

(b) ***Anterior sub-Tenon injection technique***
- Draw up 1 ml steroid into a 2-ml syringe and replace the drawing-up needle with a 25-gauge 3/8 inch (10 mm) needle.
- Ask the patient to look away from the site of injection.
- With toothed (St Martin) forceps, grasp the conjunctiva and Tenon capsule.
- With the bevel away from the globe, pass the needle through conjunctiva and Tenon capsule at the point where they are grasped.
- Slowly inject 0.5 ml of steroid.

(c) ***Posterior sub-Tenon injection*** **technique**
- Draw up 1.5 ml steroid into a 2-ml syringe and replace the drawing-up needle with a 25-gauge 5/8 inch (16 mm) needle.
- Ask the patient to look away from the site of injection, which is usually in the upper or lower temporal quadrant.
- Evert the eyelid and penetrate the bulbar conjunctiva with the tip of the needle bevel towards the globe, slightly on the global side of the fornix.
- Slowly insert the needle posteriorly, keeping it as close to the globe as possible. In order not to penetrate the globe accidentally with the top of the needle, make wide side-to-side motions as you are inserting the needle and watch the limbus; movement of the limbus means that you have engaged the sclera!
- When the needle has been advanced to the hub and cannot be inserted any further (Figure 7.166), withdraw the plunger slightly and, if no blood has entered the syringe, inject 1 ml. If the needle is too far away from the globe, adequate trans-scleral absorption of the steroid will not occur.

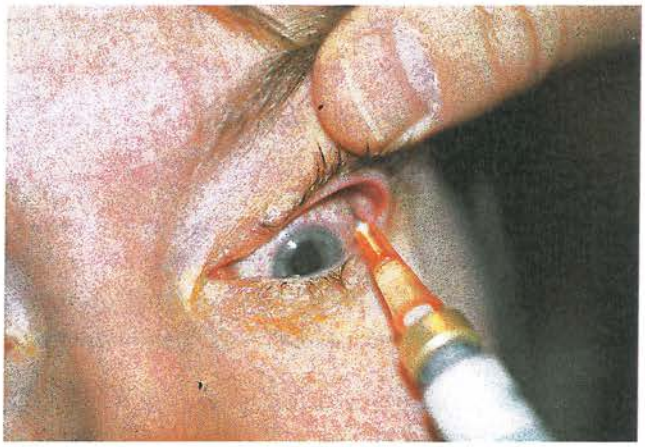


Figure 7.166 Technique of posterior sub-Tenon injection of steroid

SYSTEMIC THERAPY

1. **Preparations**
(a) Prednisolone 5 mg is the main oral preparation. Enteric coated (2.5 mg) tablets can be used in patients with a history of gastric ulceration.
(b) Injections of adrenocorticotrophic hormone (ACTH) can be used in the few patients who are intolerant to oral therapy.

2. **Indications**
(a) Intractable anterior uveitis which has failed to respond to both topical therapy and anterior sub-Tenon injections.
(b) Intermediate uveitis which has failed to respond to posterior sub-Tenon injections.
(c) Certain types of posterior or panuveitis, particularly with severe bilateral involvement.

3. **Rules of usage**
(a) Start with a large dose and then reduce.
(b) The initial dose of prednisolone is 1–1.5 mg/kg body weight.

(c) The total dose should be taken before eating breakfast.
(d) Once the inflammation is brought under control, reduce the dose gradually over several weeks.
(e) If steroids are given for less than 2 weeks there is no need for gradual reduction of the dose.

4. **Side-effects**, depending on the duration of administration, are as follows:
   (a) ***Short-term therapy*** can cause dyspepsia, mental changes, electrolyte imbalance, aseptic necrosis of the head of the femur and, very rarely, hyperosmolar hyperglycaemic non-ketotic coma.
   (b) ***Long-term therapy*** can cause a cushingoid state, limitation of growth in children (Figure 7.167), reactivation of infections such as TB, cataract, increase in severity of pre-existing disease such as diabetes, and myopathy.
5. **Contraindications**
   (a) Inactive disease with a chronic flare but no cells.
   (b) Very mild anterior uveitis.
   (c) Intermediate uveitis with normal vision.
   (d) Fuchs uveitis syndrome.
   (e) When antimicrobial therapy is more appropriate (e.g. candidiasis).

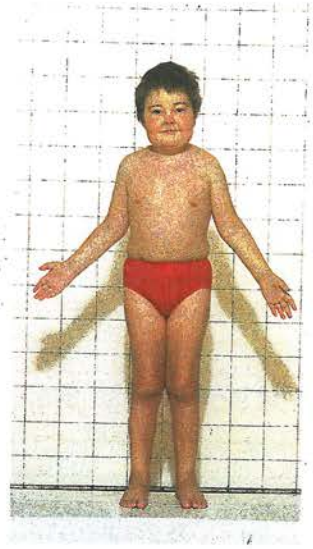


Figure 7.167 Stunted growth and Cushingoid habitus resulting from long-term systemic steroid administration

Cyclosporin

Cyclosporin is a powerful anti-T-cell immunosuppressive agent, which does not result in bone marrow suppression as do cytotoxic drugs. It is a very useful steroid-sparing agent. The main complications are hypertension and nephrotoxicity but if administered correctly these are more acceptable than side-effects associated with systemic steroid therapy. When used in low doses nephrotoxicity is usually not a problem.

Cytotoxic drugs

Since the advent of cyclosporin, cytotoxic drugs are being used less frequently. Currently azathioprine is the most commonly used cytotoxic drug, although mycophenolate mofetil looks very promising and may supersede it. The main indications are:

(a) Potentially blinding (usually bilateral), reversible, uveitis which has failed to respond to adequate steroid therapy or where cyclosporin therapy is inappropriate.
(b) Intolerable side-effects from systemic steroid therapy.