10 Intraocular Inflammation

David J Spalton
The uveal tract consists of the iris, ciliary body, and choroid lying in continuity; inflammation in this tract is known as uveitis. This can be classified according to the site of principle inflammation as anterior uveitis, intermediate uveitis (pars planitis), posterior uveitis or panuveitis. Because the uveal tract is continuous severe inflammation in one part may be accompanied by signs of overspill inflammation in another. For example, a severe anterior uveitis (iritis) may be accompanied by a cellular infiltrate in the anterior vitreous (some ophthalmologists would term this an iridocyclitis). Conversely, posterior uveitis may be accompanied by milder signs of an inflammatory response in the anterior chamber.

The onset of uveitis may be acute or chronic, which is defined as inflammation continuing for over 3 months. Acute inflammation produces pain, redness and photophobia and sometimes blurring of vision, depending on the degree of haze within the ocular media. Chronic inflammation occurs in a whiter eye. This distinction is not exclusive though, and the clinical appearance may change with time so that acute symptoms may be followed by chronic uveitis and vice versa. Granulomatous uveitis is differentiated from the nongranulomatous type by the appearance of the keratitic precipitates (KP). In granulomatous uveitis, these have a large pale and greasy appearance (mutton fat KP) and the eye is generally not particularly red. This was previously taken as an indication of a systemic granulomatous disease causing the uveitis (e.g. sarcoidosis, tuberculosis), but this clinical distinction does not have a firm basis as many of these patients have no underlying systemic disease. There is often considerable overlap in the appearance of KP and some diseases such as sarcoidosis may present with granulomatous or nongranulomatous KP.

Whilst uveitis is often thought of as a distinct entity, a secondary uveitis frequently plays an important role in many other ocular diseases, such as corneal infection, scleritis, ocular trauma or surgery, where it is responsible for many postoperative complications. Uveitis produces visual loss through cataract or loss of clarity of the ocular media; glaucoma, defective secretion of aqueous humour resulting in hypotony, retinal or choroidal destruction, macular oedema or neovascularization.

**Ocular Immunology and Uveitis**

The eye has a number of particularly unusual immunological features. The avascularity of the cornea, vitreous and lens and the physiological blood-aqueous and blood-retinal barriers normally isolate the eye from the general immune system. The eye has no lymphatic drainage, which implies that any ocular immune response must be mediated through the blood. The uveal tract can retain immunocompetent cells from a previous inflammatory reaction (or from elsewhere), and then mount a localized response when stimulated either as part of a generalized systemic response, or locally by a specific antigen. Damage to the blood-ocular barriers will result in the passage of antigens and cells into the eye or into the systemic circulation. The avascularity of the vitreous can then discourage the removal, conceivably stimulating and prolonging the inflammatory reaction. How these anatomical and physiological barriers influence human disease is still not understood.

Anterior and posterior uveitis appear to be entirely different diseases. Anterior uveitis is associated with a wide variety of systemic stimuli (e.g. ankylosing spondylitis, urethritis, bowel disease), where the initial immune event appears to be extraocular which then becomes targeted on the eye. Posterior uveitis is an example of an organ-specific disease mediated by T cells and expression of class 2 antigens to one or more specific antigens derived from the retina.

The discovery that a retinal protein (S antigen) could induce choroiditis has led to advances in the understanding of the mechanisms of posterior uveitis in experimental animals, although the application to human disease has so far been disappointing. Several retinal proteins, in addition to S antigen have been found to be uveitogenic, such as rhodopsin, opsin and interphotoreceptor binding protein.

**Signs of Uveitis**

Inflammation within the eye occurs with damage to the vascular endothelium of the intraocular vessels with consequent breakdown of the blood-ocular barrier and exudation of leucocytes and proteins into the eye. The signs of this process within the eye will depend upon the region most affected, the rapidity of onset, its severity and duration.

![Ciliary injection](image)

**Fig. 10.1** Ciliary injection is seen herein its classical form as a dusky red circumlimbal vasodilation in the area around the cornea, where the ciliary and scleroconjunctival circulations Anastomose. Its degree reflects the acuteness and severity of inflammation in the anterior uveal tract. With very severe inflammation, the whole of the conjunctiva can be involved and the appearances may be difficult to distinguish from the diffuse appearance of conjunctival inflammation.
Fig. 10.2 Cells in the anterior chamber are a sign of active inflammation within the eye. They are leucocytes which have crossed the vascular endothelium to float within the aqueous humour. In the slit-lamp beam, they have an appearance similar to particles of dust in a sunbeam. They are best seen by a narrow high density beam directed obliquely across the anterior chamber.

Fig. 10.3 A flare within the aqueous humour is the result of an abnormally high concentration of protein from the leaking intraocular blood vessels together with some local synthesis of immunoglobulin. It defines the slit-lamp beam within the anterior chamber rather like a car headlight cutting through a foggy night. A flare will usually be found in the presence of cells, although it often remains within the aqueous humour for some time after the cells have disappeared and is then an indication of persisting vascular damage rather than active inflammation.

Fig. 10.4 Severe vascular damage, usually seen with really acute inflammation, infection, or following surgery, will allow even the largest plasma proteins to exude into the aqueous humour. Such exudation is manifested by fibrin which clots in the anterior chamber to produce the ‘plastic’ uveitis so typical of HLA B27 associated acute anterior uveitis.

Fig. 10.5 Cells within the anterior chamber circulate through the aqueous humour to agglutinate and become deposited on the corneal endothelium. They are then known as keratic precipitates (KP) and are one of the classic signs of anterior uveitis. KP are typically deposited in the inferior quadrant of the cornea, probably because of gravity and convection currents within the aqueous humour. They vary in distribution and number, and also size, colour and shape.
With resolution of the uveitis with treatment or time, the KP will disappear. As they become chronic they tend to become more pigmented, as in this patient. These are typical mutton fat KP; note the whiteness of the eye.

Fig. 10.7 Pathologically KP consist of a mixture of polymorphs, macrophages and lymphocytes. Polymorphs predominate in newly formed KP while macrophages and lymphocytes are deposited later.

Fig. 10.8A massive leucocytic response with an acute anterior uveitis can occur with precipitation of the cells as a hypopyon. This is typical of B27 positive anterior uveitis, but is also seen with other causes of severe anterior uveitis such as Behcet's disease. A retinoblastoma, ocular lymphoma or ocular fungal infection can sometimes present in this way (as, of course, does intraocular infection).
Posterior synechiae are adhesions between the pupillary margin and anterior lens surface and always reflect a previous anterior uveitis. Pupillary dilatation retracts the iris from contact with the anterior lens capsule and prevents their formation. This is one of the aims of mydriasis in the treatment of uveitis which will sometimes break weak adhesions to leave telltale pigment on the lens. Ring adhesions will seclude the pupil and prevent aqueous humour flow forming iris bombe (see Chapter 8).

Prolonged and severe inflammation in the anterior chamber produces a cyclitic membrane which can also occlude the pupil.

Iris nodules are accumulations of leucocytes which lie on the iris surface. At the pupillary margin they are known as Koepppe nodules, and in the iris stroma as Busacca nodules.

Granulomas within the iris substance are seen occasionally. The iris of this patient with sarcoidosis appears swollen and thickened locally by granulomatous infiltrations between the seven and nine o'clock positions, with dilatation of the overlying blood vessels.
Fig. 10.13  Posterior uveitis produces a cellular vitreous infiltration, analogous to anterior chamber infiltration, but, because of the viscosity and structure of the vitreous gel, the cells tend to have a more restricted circulation and persist longer. Cells are sometimes seen more prominently in localized areas - over the ciliary body, the optic disc, or a focus of chorioretinitis, for example. Cells may lie in small clumps, larger groups known as 'snowballs' or as retrohyaloid precipitates on a detached posterior vitreous face. Persistent vitreous inflammation leads to collapse and vitreous detachment with haze and debris in the gel.

Fig. 10.14  Macular oedema can be seen with a posterior uveitis of any type or severity and is the most common cause of visual loss, although mild degrees can be compatible with normal vision. Depending on the duration and severity of the ocular inflammation, it either resolves with the uveitis leaving a normal macula, or progresses to permanent structural changes and persistent macular damage. Macular oedema is often difficult to visualize ophthalmoscopically, unless the macula is viewed with a stereoscopic technique, such as a fundus lens (see Chapter 1). Fluorescein angiography can be very useful in its assessment. In mild cases leakage will be seen from the parafoveal retinal capillaries, in more established cases there is pooling of fluorescein within the intra-retinal cystoid spaces, giving a petaloid appearance to the angiogram. Chronic oedema may lead these spaces to coalesce to form a partial thickness macular hole.
CAUSES OF UVEITIS

Anatomically uveitis is classified into anterior uveitis, intermediate uveitis (pars planitis), posterior uveitis or panuveitis but no classification is really satisfactory. For convenience of diagnosis, treatment and prognosis it is helpful to think of those with known systemic associations, those due to infections and those which with isolated idiopathic ocular disease which can be subdivided into various morphological categories. Another group of conditions masquerade as uveitis.

ANTERIOR UVEITIS

ACUTE ANTERIOR UVEITIS (AAU)

This is the most common type of uveitis with a prevalence of about 15:100 000 population per year. About 50% of patients are HLA B27 positive compared to about 8% of a normal population. Other factors are important in the pathogenesis of AAU as only 25% of patients with ankylosing spondylitis, almost all of whom are B27 positive, will suffer an attack of anterior uveitis; whereas 1% of a normal population with B27 will be affected by uveitis during their lifetime. The presence of B27 correlates with increased severity, uniconular involvement and joint disease, especially in men, but otherwise there are no distinguishing features. Between B27 positive and negative attacks. The common systemic associations of AAU, apart from B27, are ankylosing spondylitis, sarcoidosis and Reiter's syndrome. There are many other associations but these are uncommon and in the absence of any systemic signs or symptoms it is reasonable to restrict the investigation of a new patient to a blood count, sedimentation rate, chest and sacroiliac joint X-rays and possibly syphilis serology. Tissue typing and more extensive investigations should be reserved for the atypical case.

Ankylosing Spondylitis

This disease predominantly affects young adult males but females can be affected in a male: female ratio of 3:1. Of patients with ankylosing spondylitis, 98% have HLA B27. Attacks of anterior uveitis occur acutely, usually in one eye, and are not related to exacerbations of joint disease or its severity, or any other known predisposing factor. The attacks usually subside over 46 weeks, with treatment, and do not tend to cause residual ocular damage. Most patients can expect several attacks of acute anterior uveitis in either eye before the disease burns out in later life, but the degree to which any one patient is affected is extremely variable. There is increasing evidence that immune cross reactivity to bowel flora may have a etiological role.

Reiter's Disease

This syndrome is a triad of arthritis, urethritis or dysentery and acute anterior uveitis. Typically, a seronegative arthritis affects large peripheral joints such as the knees but the spine is also involved, especially the sacroiliac joints, and follows a few weeks after bacterial dysentery or a nonspecific urethritis.

Fig. 10.15 About 50% of B27 positive patients will have evidence of ankylosing spondylitis which is seen in its earliest form in the sacroiliac joints. There is sclerosis of the periarticular bone with narrowing and irregularity of the joint space progressing eventually to ankylosis. Similar changes are seen in the spine.

Fig. 10.16 This patient has the typical kyphoscoliotic posture of ankylosing spondylitis. He has had a total hip replacement for ankylosis of the joint. Note the swelling of the right knee and the deformity of the feet.
Conjunctivitis and uveitis occur in 30-50% of patients. Other systemic features are plantar fasciitis and keratoderma blennorrhagica on the penis, palms or soles of the feet. Aortic incompetence is rarely seen as a late complication. Males are usually affected; HLA B27 is virtually always present and there is evidence that the disease is related to chlamydial genital infection if it follows a nonspecific urethritis. Partial manifestations of the syndrome are common. Most patients recover over a few weeks but the arthritis can progress to chronic joint destruction.

Herpes Zoster Ophthalmicus

Keratitis and anterior uveitis are common features of herpes zoster ophthalmicus (see Chapter 4) and may occur independently of each other. It has been said that keratitis and uveitis are particularly frequent if the vesicles appear along the side of the nose - the cutaneous distribution of the nasociliary nerve, which also innervates the iris and pupil - but this is not invariably so.

The uveitis is frequently subacute in onset and is often associated with keratitis. It may persist for many months. Sector atrophy of the iris is commonly seen and is due to a vasculitis of the iris vessels. Retroillumination of the iris shows sectorial translucency to advantage. Corneal anaesthesia commonly persists, ocular nerve palsies and optic neuritis are occasionally seen and post-herpetic neuralgia can be disabling in a minority of patients. Oral acyclovir is helpful if given in the acute vesicular cutaneous stage of the disease; the rash heals more quickly with probably less post-herpetic neuralgia and a lower incidence of, and more mild, ocular involvement. The severity of the cutaneous disease does not necessarily correlate with the degree of severity of ocular involvement. Herpes zoster in young patients may rarely indicate an underlying systemic immunosuppressive illness such as HIV infection or malignancy.

Herpes Zoster Ophthalmicus

Keratitis and anterior uveitis are common features of herpes zoster ophthalmicus (see Chapter 4) and may occur independently of each other. It has been said that keratitis and uveitis are particularly frequent if the vesicles appear along the side of the nose - the cutaneous distribution of the nasociliary nerve, which also innervates the iris and pupil - but this is not invariably so.

The uveitis is frequently subacute in onset and is often associated with keratitis. It may persist for many months. Sector atrophy of the iris is commonly seen and is due to a vasculitis of the iris vessels. Retroillumination of the iris shows sectorial translucency to advantage. Corneal anaesthesia commonly persists, ocular nerve palsies and optic neuritis are occasionally seen and post-herpetic neuralgia can be disabling in a minority of patients. Oral acyclovir is helpful if given in the acute vesicular cutaneous stage of the disease; the rash heals more quickly with probably less post-herpetic neuralgia and a lower incidence of, and more mild, ocular involvement. The severity of the cutaneous disease does not necessarily correlate with the degree of severity of ocular involvement. Herpes zoster in young patients may rarely indicate an underlying systemic immunosuppressive illness such as HIV infection or malignancy.
systemic steroids, but in a few cyclosporin A or cytotoxic therapy may be needed. Cataract surgery is frequently required and is best performed by a lensectomy and vitrectomy technique. Secondary glaucoma is a serious complication and responds poorly to standard medical or surgical therapy.

Fig. 10.21 The typical features of chronic anterior uveitis in Still's disease. There is a moderately advanced band keratopathy with posterior synechiae and a dense cataract. There is no conjunctival injection. By courtesy of Mr J Kanski.

Fuch's Heterochromic Cyclitis

This is a distinctive entity with many features atypical to any other form of uveitis and is the cause of a substantial minority of cases of anterior uveitis. Small diffuse KP scattered over the whole of the corneal endothelium with a fluffy or feathery appearance at their border can be seen in contrast to the usual well circumscribed and inferiorly sited KP seen in other conditions. The eye is white and posterior synechiae do not form. The iris has a characteristic moth-eaten appearance and becomes depigmented, showing a bluish tinge in Caucasian patients. This depigmentation is not as obvious in heavily pigmented eyes but iris stromal atrophy can be seen. Heterochromic cyclitis is usually unilateral although bilateral cases do occur, which are more difficult to diagnose. Glaucoma may develop and is associated with a fine neovascularization of the angle (see Chapter 8). Cataracts are common and are hastened by steroid therapy, the indications for which are rather dubious. The aetiology is unknown. Pathological specimens show a plasma cell and mast cell infiltrate of the iris, with decreased pigmentation.

Fig. 10.22 The right eye of this patient is normal but the left shows depigmentation of the iris and fine KP on the corneal endothelium. Loss of detail of the anterior iris surface is seen and some lens opacity is present.

Fig. 10.20 This little girl aged 4 with pauciarticular disease has a swollen right knee on which she cannot weight bear. By courtesy of Dr B Ansell.
INTERMEDIATE UVEITIS (PARS PLANITIS)

Pars planitis is a definite but rather amorphous syndrome with variable clinical features. A cellular vitreous infiltrate is always present in the anterior vitreous gel, together with snowballs (accumulations of cells), which are usually seen inferiorly in the peripheral vitreous. A ‘snow bank’ or massive infiltrate is sometimes seen inferiorly over the pars plana and peripheral retina and, not infrequently, a mild periphlebitis, or small patches of peripheral retinal pigment epithelial atrophy are present. Macular oedema and mild optic disc swelling are common.

Pars planitis usually affects young adults and is frequently bilateral. Patients present with floaters from vitreous debris or blurred vision of gradual onset from macular oedema in white eyes. Most cases have no apparent aetiology, but similar findings may be rarely seen with sarcoidosis, Whipple’s disease and multiple sclerosis. Neovascularization of the optic disc or peripheral retina can occur in some eyes. In eyes with longstanding changes the ‘snow bank’ is composed of collapsed vitreous gel and proliferating retinal astrocytes and is sometimes associated with neovascularization. Most patients have a good visual prognosis, with the disease burning out over a number of years. The most common cause of visual loss is macular oedema and occasionally vitreous haemorrhage or retinal detachment (from an associated posterior vitreous detachment).

Fig. 10.23 This photograph shows the typical KP of this condition which cover the whole of the endothelial surface and have ‘spidery’ margins.

Fig. 10.24 This fundus painting shows cystoid macular oedema and an extensive ‘snow bank’ inferiorly, which is more marked than is commonly seen. In the inferior equatorial area there are focal patches of pigment atrophy and vitreous ‘snowballs’.
This 42-year-old man presented with uniocular symptoms but had bilateral signs. The optic disc is normal, but there is wrinkling of the internal limiting membrane and a trace of macular oedema producing blurring of vision in this eye.

There was a low grade cellular vitreous infiltration and, interiorly, 'snowballs' could be seen within the gel, in addition to a low grade periphlebitis of the equatorial retinal veins. The patient was systemically well and all investigations were normal.
POSTERIOR UVEITIS

This group of uveitic disorders are less common than anterior uveitis but have a more serious visual prognosis. In all but the mildest cases, systemic treatment is required to control the intraocular inflammation. A diagnostic grouping of some type can be put to about 70% of patients with posterior uveitis, the remaining patients have an entirely idiopathic and nonspecific intraocular inflammation. It is extremely important to recognize those cases with an infectious cause as specific therapy is usually available.

SYSTEMIC DISEASES

Sarcoidosis
Sarcoidosis causes about 5% of all cases of anterior uveitis and is also a common cause of posterior uveitis. It is a multisystem disorder and ocular involvement (which may be the presenting feature) is seen in about 25% of all patients with systemic disease. About 75% of patients presenting with ocular sarcoidosis will have positive chest X-ray findings; bilateral hilar lymphadenopathy in the acute form and pulmonary interstitial fibrosis in the chronic stage. Although chest X-ray changes provide good circumstantial evidence of sarcoidosis, the diagnosis should be confirmed, where possible, histologically by demonstrating noncaseating granulomas in biopsy tissue.

Bronchoscopy, with bronchial lavage and biopsy has now superseded the Kveim test which is cumbersome, affected by steroid therapy and difficult to interpret. The serum angiotensin enzyme is frequently raised in patients with systemic sarcoidosis, although it is not specific to this disease, and is a useful diagnostic pointer in patients presenting with uveitis. It can also act as a marker of disease activity and the response to treatment.

Anterior uveitis, panuveitis or posterior uveitis with retinal vasculitis are the most common features of ocular sarcoidosis. The anterior uveitis may be acute or chronic and either granulomatous or nongranulomatous. Patients with acute sarcoidosis and bilateral hilar lymphadenopathy with erythema nodosum tend to present with acute ocular inflammation, whereas those with more chronic systemic disease normally have less acute ocular signs. Patients should be examined for evidence of granulomas in other common sites such as the lacrimal glands, eyelids or conjunctiva. Biopsy in these areas is easy to perform and confirms a diagnosis.

Eales' disease is a rather vague term used for idiopathic retinal vasculitis, which often results in retinal neovascularization, with similar appearances to those of sarcoidosis.

Fig. 10.26  Positive findings of sarcoidosis are found on chest X-ray in about 75% of cases and especially in those with recent onset of the disease. These patients may have erythema nodosum. Bronchoscopy, bronchial lavage and biopsy confirms the diagnosis. Hilar lymphadenopathy usually resolves spontaneously, but systemic steroid therapy may be indicated in the presence of pulmonary interstitial fibrosis.

Fig. 10.27  Radioactive gallium is taken up by macrophages in granulomas and can be used to demonstrate the extent of systemic involvement with sarcoidosis. This patient shows uptake in the lacrimal glands, nasopharynx, and chest.
Fig. 10.28  Sarcoidal granulomas in this patient are seen along the lid margin and on the tarsal conjunctiva. 'Blind' biopsy of normal appearing conjunctiva with multiple sections will sometimes demonstrate non-caseating granulomas.

Fig. 10.29  Lacrimal gland infiltration is not uncommon. The gland must be biopsied with care if the transconjunctival approach is used, because of the risk of damaging the ductules and exacerbating the risks of a dry eye. Sarcoidosis is particularly common in American blacks.

Fig. 10.30  Biopsy of the lacrimal gland in the same patient shows multinucleated giant cells and marked granulomatous formation without caseation. These are the typical appearances of sarcoidosis.

Fig. 10.31  Retinal vasculitis and posterior uveitis can occur in the absence of anterior uveitis. Typically a creamy white exudation is seen around the equatorial retinal veins.
Fig. 10.32 More subtle changes may be observed on fluorescein angiography, which shows areas of segmental leakage around the retinal veins. This usually involves the smaller veins of the retina and major venous occlusions, such as central retinal vein occlusion, tend not to occur.

Fig. 10.33 Severe periphlebitis can lead to occlusion and peripheral vascular closure. This may be followed by neovascularization at the same site which, like new vessel formation from other causes, presents a serious threat to vision. The neovascularization is amenable to laser therapy, providing that intraocular inflammation has been adequately suppressed prior to photocoagulation.

Fig. 10.34 Optic disc swelling may result from local oedema, local infiltration by sarcoid granulomata, optic nerve compression by orbital granuloma or occasionally from raised intracranial pressure with neurosarcoid. Alternatively, optic atrophy can result from optic nerve infiltration.

Fig. 10.35 Focal atrophic retinal pigment epithelial (RPE) changes are often seen in the inferior fundus, particularly in middle-aged females with longstanding disease. They are probably due to granulomatous change in the RPE or choroid.
Fig. 10.36  Granulomas may be seen on the trabecular meshwork as a relatively specific feature of sarcoid. They can lead to secondary glaucoma from peripheral anterior synechiae.

Behget's Disease

Behget's disease was originally described in males of Eastern Mediterranean origin but is becoming increasingly recognized, often in less dramatic forms, in females and other racial groups. The diagnosis is always made on clinical signs and is based on the triad of uveitis with oral and genital ulceration. From the diagnostic point of view the clinical signs are divided into major criteria of mouth or genital ulceration, uveitis and skin lesions (erythema nodosum, thrombophlebitis, pustules) and minor criteria such as arthritis, gastrointestinal symptoms, vascular occlusions and neurological signs. The clinical spectrum can be further subdivided into the complete form, where all the major criteria are present, and incomplete varieties. Ocular involvement is particularly related to the presence of the HLA B51 antigen.

Many patients will respond to systemic steroids, but cytotoxic treatment can be indicated in patients with severe ocular disease, which carries a poorer visual prognosis than almost any other form of posterior uveitis. Cyclosporin A can be particularly useful in the management of these patients, although there is a risk of systemic toxicity from the drug and a florid relapse of uveitis may occur on withdrawal of the drug. The aetiology of Behcet's disease is unknown.

Fig. 10.37  Mouth ulcers are painful and episodic and cannot be distinguished clinically or pathologically from aphthous ulceration. Their presence often pre dates other symptoms.

Fig. 10.38  Genital ulcers are not seen as frequently as mouth ulcers. This patient has active ulceration but white scars can be seen at sites of previous ulceration. Genital symptoms occur more frequently in males.
Recurrent hypopyon is one of the widely recognized features of severe Behget’s disease. There is a brisk cellular reaction in the anterior chamber, but there is often a surprising disparity between the severity of the anterior chamber reaction and the lack of conjunctival injection. There is also often some disparity between the degree of anterior segment and retinal involvement in these patients.

The posterior uveitis of Behget’s disease is diffuse and may be asymmetrical or even unilateral. There is diffuse vascular leakage throughout the fundus; focal periphlebitis, as seen in sarcoidosis, is not a feature of Behget’s disease. This patient shows posterior uveitis with both optic disc oedema and retinal oedema.

White infiltrates of the inner retina, sometimes associated with intraretinal haemorrhage, occur during the active phases of Behget’s disease. These resolved over a period of two to three weeks with treatment to leave a relatively undisturbed retinal pigment epithelium and retinal vasculature.
Fig. 10.42  Oclusions of major retinal veins are feature of Behcet’s disease and are frequently followed by neovascularization. The association of posterior uveitis with a retinal vein occlusion should always prompt the consideration of the diagnosis.

Fig. 10.43  Major venous occlusions are seen elsewhere in Behcet’s disease. This patient had an inferior vena cava thrombosis with a caput medusae due to venous bypass through the cutaneous veins of the abdominal wall.

Fig. 10.44  In the terminal phase, the retina and its vasculature are destroyed with secondary optic atrophy, the retinal arterie s are then seen merely as white threads. Although there is some disturbance at the macula, pigmentary changes are comparatively sparse for the severity of the disease.

INFECTIOUS CAUSES OF POSTERIOR UVEITIS

These are an extremely important group of conditions to recognize as specific therapy is usually available.

Acquired Immune Deficiency Syndrome (AIDS)

Ocular complications of AIDS are common and can present to the ophthalmologist in a variety of ways. Both Kaposi’s sarcoma (see Chapter 3) and herpes zoster (see Chapter 4) can affect the anterior segment. Idiopathic cotton wool spots may be seen in a number of cases. These lesions are transient and disappear spontaneously within 68 weeks. The commonest form of retinal involvement is cytomegalovirus retinopathy, but a wide variety of other infections can occur less commonly, such as toxoplasmosis, cryptococcomycosis, herpes simplex or zoster retinitis and atypical mycobacteria. Secondary syphilis is well recognized and produces a more florid uveitis than in otherwise normal individuals.
HIV positive patients may develop cotton wool spots which do not differ in any way from those seen in other conditions. Histological examination has failed to show any evidence of viral infection in these lesions and it has been postulated that they are micro infarcts from high levels of circulating immune complexes. They may be a poor prognostic sign both for the development of further ocular problems and reduced life expectancy.

This 46-year-old homosexual presented with poor vision in his left eye. Examination showed a macular lesion with a peripheral lesion typical of cytomegaloviral (CMV) retinopathy with creamy intraretinal infiltrate associated with haemorrhage, often lying along the retinal vessels.

The patient was treated with ganciclovir when this drug was first available. The lesions improved but relapsed 3 weeks later after cessation of treatment with further retinal destruction and involvement of the fellow eye.

The patient responded to another course of ganciclovir and was maintained on maintenance therapy. At this stage the fundi are quiescent with areas of retinal atrophy, pallor of the optic discs and vascular attenuation.
Toxoplasmosis

Ocular toxoplasmosis is usually acquired by transplacental infection of the foetus in a nonimmunized mother. In some parts of the world, however, such as South America and West Africa, it is extremely common and it seems likely that in many cases ocular involvement is associated with acquired systemic disease. It is one of the few specific causes of uveitis that can be diagnosed by the fundal appearance. The animal reservoir is in the cat and the organism has a predilection for neurological tissue.

Toxoplasmosis does not cause anterior uveitis in the absence of lesions in the fundus. Pigmented, circumscribed scars are usually seen in the posterior poles of one or both eyes and visual acuity is lost if the macula or its axons are involved; field defects occur from lesions elsewhere. The parasite persists in an encysted state for many years following infection. The fundal lesions remain quiescent but have a tendency to reactivate in adults between 20-40 years of age, producing a fluffy, white chorioretinal lesion in the area of previous chorioretinal scarring with posterior uveitis. If the lesion is small, vitreous infiltration may be localized to this area. Retinal damage appears to be due to a combination of proliferation of toxoplasma organisms released from their encysted state directly invading the retinal cells causing retinal necrosis and an inflammatory response and possibly a secondary autoimmune reaction. The activity of the lesions subsides over several months with further retinal scarring. Many patients with mild reactivation of toxoplasma will settle without any treatment at all, but if the macula or optic disc is threatened, treatment with sulphonamides and pyrimethamine or clindamycin to destroy the organism, together with systemic steroids to suppress the inflammatory response is indicated. A positive dye test indicates previous infection with toxoplasma, but does not correlate with disease activity.

Fig. 10.49 Pathology from the same patient shows areas of complete retinal destruction with a sparse inflammatory cellular infiltrate and the typical 'owl eye' intracellular inclusions of CMV.

Fig. 10.50 This is a typical quiescent toxoplasma scar in the posterior pole. It is sharply circumscribed with retinal pigmentation and pigment epithelial atrophy. Note the associated nerve fibre defect.
Fig. 10.51  Seroconversion during pregnancy carries a high risk of foetal damage, particularly in the first trimester, but it is exceptional for visual acuity to be lost in both eyes. Maternal treatment during pregnancy appears to lower the prevalence of foetal damage. Severe intracranial infection in a foetus can produce intracranial calcification, hydrocephalus, mental retardation and epilepsy.

Fig. 10.52  The fellow eye of the same patient as in Fig. 10.50 shows reactivation in an area of previous scarring. A few weeks later, after treatment, the fresh creamy retinal exudate has become more discrete and the vitreous is clearing, leaving further retinal destruction and pigment atrophy. Note the associated posterior vitreous detachment.

Fig. 10.53  Acquired toxoplasmosis is rare. A fresh circumscribed lesion is seen in the fundus with no evidence of previous scarring or pigmentation. The patient had a systemic febrile illness with lymphadenopathy. IgM antibodies to toxoplasmosis were found in the blood.
Toxocara

This nematode has its reservoir in dogs, especially young puppies, and the ova persist for long periods in contaminated soil; it infests the eyes of children, especially if they have a tendency to eat dirt. Ocular toxocariasis is produced in two forms - a massive exudative white lesion containing the nematode in the posterior pole (sometimes presenting in a child as a poorly sighted eye with leucoria), and a peripheral form with smaller white lesions in the equatorial retina with bands of retinal traction. The disease is usually uniocular. Affected eyes are white and inflammatory signs are confined to the vitreous gel. Visceral larva migrans is the systemic form of acute toxocariasis. Compared to the ocular type of disease this form usually occurs in older children than the ocular disease and is associated with pulmonary infiltrates and transient eosinophilia. Ocular involvement is comparatively uncommon. A positive ELISA test on the blood confirms previous infection by toxocara and though this can be negative with ocular disease, it may be necessary to perform the test on aqueous humour to confirm the diagnosis. In young children it is extremely important to distinguish toxocariasis from its main differential diagnosis which is retinoblastoma. Drug treatment, apart from steroids to suppress the inflammatory response, is of no benefit but in some cases it is possible to remove the granuloma by vitreoretinal surgery and this may also be indicated to clear the vitreous gel if there is chronic endophthalmitis.

**Fig. 10.54** The pathology of toxoplasmosis is primarily retinal with secondary choroidal changes. The parasite remains encysted and intracellular in the retina for many years following infection as inactive bradyzoites. At some stage, for completely unknown reasons, the cyst ruptures to release the active trophozoites. These proliferate, producing a necrotic retinitis, and are then taken up intracellularly again.

Toxocara

**Fig. 10.55** This is the fundus appearance of a three-year-old child with a six month history of unilateral nonprogressive visual loss. There is a large white central granuloma present, with retinal traction. Visual acuity was counting fingers; the ELISA test was strongly positive and the family owned a young puppy.

**Fig. 10.56** Histology demonstrates a granuloma in the posterior pole of an infected eye. Serial sections and higher power demonstrate the encysted nematode.
Syphilis

Syphilitic infection during pregnancy infects the foetus and produces a retinopathy. Active lesions are rarely seen in the neonate, but are said to be focal yellowish, spotty retinal pigment epithelial changes, associated with vasculitis. This resolves to leave pigmentary scarring, with areas of focal pigmentation and atrophy in the peripheral retina, the so-called 'pepper and salt' fundus, which can sometimes be confused with retinitis pigmentosa. Following congenital syphilis, interstitial keratitis (see Chapter 6) may appear between the ages of 5 and 25 years of age. Patients may have other stigmata of infection, such as nasal and dental deformities, or nerve deafness. Progressive neurological deficit is, however, relatively uncommon.

Secondary syphilis, although rare, is becoming more common and should be considered in any atypical intraocular inflammation, whether anterior or posterior, both because of the ease of treatment and the serious sequelae of missing the diagnosis. The absorbed fluorescent treponemal antibody test (FTA ABS) is highly specific, and active infection can be distinguished from latent or treated infection by demonstrating IgM or IgG antibodies. The cerebrospinal fluid should be examined in all patients with ocular syphilis. Secondary syphilis is usually associated with a typical cutaneous maculopapular rash on the limbs, trunk, hands and feet. Acute iritis may be present with iris papules known as roseata. Chorioretinitis may be present and, if this is so, there is usually a mild posterior uveitis with focal yellowish subretinal infiltrates. The optic disc may be swollen and there may be a serous retinal detachment. Patients who are HIV positive tend to show a much more florid inflammatory response. Syphilitic retinopathy if untreated may resolve to leave a picture resembling retinitis pigmentosa, with arterial narrowing, optic disc pallor and retinal pigment epithelial atrophy and scattered intraretinal pigmentation. This can usually be distinguished from true retinitis pigmentosa, as visual fields and visual function are much better than would be expected with a retinal dystrophy.

Fig. 10.57  These photographs show the typical maculopapular distribution on the hands with secondary syphilis. Spirochetes can be found in the lesions by examining their exudate with dark field illumination.

Fig. 10.58  Patients with secondary syphilis usually have a mild posterior uveitis. Widespread yellowish subretinal infiltrates are a common feature and can suggest the diagnosis. This patient was also HIV and hepatitis B positive.

Fig. 10.59  This patient was known to have had congenital syphilis. The optic disc is pale, retinal vessels are attenuated and there is widespread chorioretinal atrophy. The equatorial retina of the fellow eye shows large clumps of intraretinal pigmentation. Patients often have good visual function in spite of their retinopathy. Visual loss is usually due to the keratitis and subsequent cataract formation.
Ocular Tuberculosis

This is a manifestation of tuberculosis rarely seen nowadays, but should still be considered in patients with atypical anterior uveitis, retinal vasculitis or choroidal infiltrates. These patients usually have a florid positive Mantoux test, although systemic evidence of active tuberculosis can be difficult to substantiate.

Circumstantial proof of the diagnosis is often demonstrated by rapid improvement in the ocular signs with a short course of anti-tuberculous chemotherapy. Systemic steroids may be required for control of the ocular inflammation but if there is a possibility of tuberculosis appropriate chemotherapy must be given to prevent systemic relapse.

Fig. 10.60 This patient had a chronic anterior uveitis with marked nodular involvement of the iris. There was a dramatic improvement in the iris appearance with a two week course of antituberculous chemotherapy.

Fig. 10.61 This patient had miliary tuberculosis and a choroidal tubercule can be seen as a creamy, diffuse subretinal swelling. After appropriate chemotherapy, nonspecific pigment epithelial scarring remains.
Florid retinal vasculitis can be associated with tuberculosis. These patients often have comparatively little posterior uveitis, but have marked retinal vasculitis, vascular closure and haemorrhage, which frequently progresses to neovascularization.

Acute Retinal Necrosis Syndrome

The acute retinal necrosis syndrome, which has been recognized since the 1970s, affects one or both eyes. Patients present with posterior uveitis with characteristic areas of confluent, whitish retinal necrosis in the peripheral fundus. A marked arteritis is present in some patients. Examination of pathological material suggests that the aetiology is usually due to a herpes virus infection, herpes zoster being most commonly found. Severe cases progress over weeks to untreatable retinal detachment, with giant tears occurring along the demarcation line between normal and affected retina but milder and less aggressive cases are being more frequently recognized. Patients are otherwise generally well. Treatment with acyclovir and systemic steroids may be helpful.

This fundus painting shows the areas of confluent peripheral retinal necrosis seen in a patient who later progressed to giant retinal tears and untreatable retinal detachment. By courtesy of Professor Alan Bird.

This patient presented with a total retinal detachment after a subclinical episode of acute retinal necrosis some weeks earlier. There is widespread peripheral pigment epithelial atrophy with small round holes at 7 o'clock. Subretinal fluid, obtained at surgery, showed high titres to herpes zoster.
Subacute Sclerosing Panencephalitis

This is a rare condition due to persistent measles infection in the brain. It affects children in the 6-14 year age groups and is fatal from progressive neurological degeneration over 1-2 years. Patients present with myoclonic jerks and mental impairment. The EEG and CSF are diagnostic.

THE RETINAL PIGMENT EPITHELIOPATHIES

Retinal pigment epitheliopathies are a group of conditions where the primary pathology seems to occur in the retinal pigment epithelium or choriocapillaris. They are characterized by deep, pale swelling of the pigment epithelium in the acute phase which masks fluorescence early in the angiogram, followed by staining in the later stages. The lesions heal leaving pigmentary changes. Inflammatory signs can be variable. The aetiology is presumed to be either a vasculitic or ischaemic lesion of the choriocapillaris with infarction of the overlying pigment epithelium or, alternatively, an immunological response directed at the pigment epithelium. It is not known whether the various varieties of fundus morphology and clinical presentation represent distinct conditions or different parts of the spectrum of the same basic disorder. Certainly,
Acute multifocal placoid pigment epitheliopathy, Vogt-Koyanagi-Harada's syndrome, and sympathetic ophthalmia have morphological fundus features in common. While the milder cases are usually restricted to the eye, systemic vasculitis can be seen with all types.

Acute Multifocal Placoid Pigment Epitheliopathy (AMPPE)

This syndrome usually occurs in young or middle-aged adults and tends to be bilateral. There is often a history of preceding flu-like illness or respiratory infection.

Patients present with blurred vision of fairly rapid onset over a few days. There is a vitreous infiltrate and a variable amount of acute anterior uveitis. Focal pale, swollen areas, with a fluffy border of about half a disc diameter, are seen deep to the neuroretina and are thought to represent areas of oedematous and swollen pigment epithelial cells. These produce characteristic appearances on fluorescein angiography. The lesions are hypofluorescent early in the angiogram, masking the background choroidal fluorescence. Later in the angiogram, the lesions leak and stain with fluorescein.

The lesions of AMPPE all appear and evolve in phase. Over two to three weeks, the acute phase of the condition resolves with subretinal pigmentary changes and, usually, a return to near normal acuity.

Fig. 10.67  Acute placoid lesions are seen as typical creamy white subretinal lesions, about a quarter to a half a disc diameter in size and scattered throughout the posterior pole with some early pigmentary changes. In the most acute stages serous retinal detachment can be present.

Fig. 10.68  Early and late fluorescein angiograms show typical masking of background fluorescence in the early stages with later leakage and staining of the lesion.
Fig. 10.69  Three months later, the acute lesions healed to leave irregular atrophy and scar of the retinal pigment epithelium. Vision returned to normal. Fluorescein angiography demonstrates the extensive pigmentary disturbance.

Vogt-Koyanagi-Harada’s Syndrome

Harada’s disease (posterior uveitis and cerebrospinal fluid pleocytosis) and the Vogt-Koyanagi syndrome (posterior uveitis, dysacousia and vitiligo) appear to be part of the same disease. The aetiology of the condition is unknown, but there is a strong racial influence in that it is much more common in the Far East and accounts for 6-7% of all cases of uveitis in Japan. Many patients with the disease have some oriental ancestry. An association with DR4 and certain Class II antigens has been observed in Japan and there are noticeable clinical and pathological similarities to sympathetic ophthalmitis, although the visual prognosis with the VKH syndrome is usually better. Young or middle-aged adults are affected. There is sometimes a short preceding illness of headache and mild malaise or meningism. Both eyes are affected. There is always some posterior uveitis, but the amount of anterior uveitis can vary from minimal to severe pan uveitis. Serous retinal or pigment epithelial detachments of varying size are seen over the posterior pole with mottling and scarring of the underlying pigment epithelium. In the active stages, fluorescein angiography shows multifocal leakage through the pigment epithelium.

In the acute stages, patients may have pleocytosis of the cerebrospinal fluid and dysacusia which tends to recover quite rapidly. Alopecia, vitiligo, and poliosis may follow weeks to months later.

Fig. 10.70  This 23 year-old Arab presented with a 2 week febrile illness with severe headache and hearing disturbances and then developed a severe bilateral posterior uveitis. Three months later he has greying of the hair and alopecia with some vitiligo around his mouth.

Fig. 10.71  A close-up photograph shows poliosis of his eyelashes and eyebrows.

Fig. 10.72  Examination of the fundi shows a moderate posterior uveitis with disc swelling and diffuse depigmentation.
Sympathetic ophthalmitis

It is doubtful whether sympathetic ophthalmitis occurs in the absence of a penetrating injury. In cases where this is not apparent, serial sections almost invariably reveal subclinical perforation of the globe; a few cases can be associated with perforating corneal ulcers or malignant melanoma with invasion of the sclera. Most cases, however, involve traumatic perforation of the anterior segment with damage to the iris or ciliary body. The disease has become much less common with recognition of the need for prompt microsurgical repair of ocular perforations and the meticulous removal of prolapsed uveal tissue from the wound. The incidence is thought to be in the order of 0.1% of ocular traumatic perforations. The disease occurs from childhood to old age and there is no sex or racial preponderance.

The latent interval between perforation and inflammation of the sympathizing eye is very variable. Frequently the exciting eye never completely settles down after the injury.
but sympathetic ophthalmitis can follow a completely quiet eye. About 65% of cases present within two weeks to three months of the original injury and the majority have occurred within two years, although a few cases have been reported to occur many years later.

The patient presents with an acute granulomatous uveitis of the sympathizing eye. Early enucleation prevents sympathetic ophthalmitis. Enucleation of the exciting eye within the first few weeks of development of symptoms appears to be beneficial to the sympathizing eye, although exciting eyes which have visual potential should not be removed. Visual acuity is lost from cataract, glaucoma, macular oedema and vitreous opacification, but providing the inflammatory reaction is controlled these eyes do well with further surgery. The previously poor visual prognosis has been improved by treatment with systemic steroids and cytotoxic drugs. The precise pathogenesis of the condition is unknown; however, there are two basic theories: the disease is either caused by some type of infection or an autoimmune process.

Sympathetic ophthalmia should be distinguished from phakoanaphylactic uveitis due to lens trauma, although this finding can only be made with certainty histologically. The distinction is made by the finding of choroidal involvement in sympathetic ophthalmitis and the absence of this phakoanaphylactic uveitis. Rupture in the lens capsule with associated pathological signs of phako-allergy is seen as an additional feature in 25-40% of cases of sympathetic ophthalmitis. There is recent evidence that some cases of phakoanaphylactic uveitis following cataract surgery are due to low grade infection with organisms such as propionibacter. These patients respond to treatment with appropriate antibiotics or removal of lens debris with the offending organisms.

Fig. 10.77 This case of sympathetic uveitis shows numerous pink-staining granulomas within the thickened choroid and in addition aggregates of lymphocytes. Modern techniques such as immunocytochemistry have shown that the majority of these cells are T lymphocytes. H&E, x 350. By courtesy of Dr Alison McCartney.

Fig. 10.76 This 63-year-old man developed sympathetic ophthalmitis 3 years after a perforating injury and multiple surgical procedures to his left eye, presenting with blurred vision, floaters and panuveitis. Fundus examination shows multiple focal areas of RPE depigmentation at the site of Dalen-Fuch's nodules. Fresh lesions have a fluffy creamy appearance; older lesions are whiter and more demarcated. Fluorescein angiography shows leakage from the optic disc, cystoid macular oedema, hyperfluorescence from the fresh lesions and window defects in the atrophic lesions.

Serpiginous or Geographic Choroiditis

This condition usually occurs in middle-aged patients, is bilateral, although frequently asymmetrical, and the changes in one eye may precede the other by many years. The eyes are white and there is relatively minimal vitreous infiltration. The characteristic early lesion is an area of pale retinal pigment epithelial atrophy in the posterior pole in the vicinity of the optic disc, which has a relapsing and remitting course over several years. Relapses are seen as an area of greyish subretinal swelling at the edge of a lesion which spread equatorially in a serpiginous fashion. In the active state, fluorescein angiography shows early masking followed by late leakage in the same area. The lesion resolves over several weeks with destruction of the overlying retina, to reappear elsewhere on the lesion's border at a later date. Visual acuity is lost if the macula is affected. No treatment seems to affect the course of the disease.
Birdshot Chorioretinopathy

Birdshot chorioretinopathy is a relatively recently recognized condition and an unusual cause of posterior uveitis, which usually affects both eyes. Patients present with visual loss from macular oedema with a very high association of HLA A29. There is usually a mild vitreous cellular infiltrate and cystoid macular oedema. Characteristic multiple areas of focal subretinal depigmentation with diffuse margins of about quarter to a half disc diameter are seen in the posterior pole. The lesions do not show any hyperpigmentation and do not have the same fluorescein angiographic appearance of hypo and hyperfluorescence as seen with the other types of retinal pigment epitheliopathies such as acute multifocal placoid pigment epitheliopathy, which probably indicates the birdshot lesions lie deeper in the choroid.

Fig. 10.79  This patient shows old serpiginous scarring in the posterior pole of the right eye with a fresh lesion on the temporal periphery. In the left eye there is a single patch of RPE atrophy.

Fig. 10.80  In contrast to other types of pigment epitheliopathy fluorescein angiography demonstrates minimal changes in the overlying retinal pigment epithelium.

Fig. 10.78  This patient shows old serpiginous scarring in the posterior pole of the right eye with a fresh lesion on the temporal periphery. In the left eye there is a single patch of RPE atrophy.
A number of noninflammatory diseases can simulate posterior uveitis and these should always be considered in cases where there is a progressive deterioration of the eye in spite of appropriate anti-inflammatory treatment. Malignant disease which can present in this way include retinoblastoma in children and ocular lymphoma in adults. Ocular fungal infection may also present as a posterior uveitis.

Ocular Lymphoma

Intraocular involvement with lymphoma is becoming increasingly recognized. Patients present with a uni- or bilateral posterior uveitis. The diagnosis should be considered in any patient with posterior uveitis, but particularly in the more elderly patient where there is failure to respond to a reasonable course of systemic steroids. Some patients will have focal fundus lesions, but in others there is no specific intraocular lesion. The diagnosis is confirmed by vitreous aspiration with cytology. Evidence of lymphoma elsewhere, particularly involvement in the CSF or intracranially, must be sought. Ocular involvement responds to radiotherapy. Patients have a high risk of developing intracranial lymphoma. The ocular lymphoma can be due to either B or T cell lymphomas, although the former is more common.

![Fig. 10.81](image1) This patient presented with posterior uveitis and subretinal infiltrates. He was treated with systemic steroids, but failed to improve, and the ocular signs deteriorated.

![Fig. 10.82](image2) Two months after these photographs were taken, the patient presented with intracranial focal lesions and lymphoma cells were recovered from the CSF.

![Fig. 10.83](image3) Ocular pathology of the same eye shows the retina and choroid are destroyed and densely infiltrated by lymphoma cells. Cell markers showed this to be a T cell lymphoma (slightly unusual as most ocular lymphomas are B cell tumours).

![Fig. 10.84](image4) This patient developed bilateral candidal endophthalmitis after prolonged intravenous feeding following multiple abdominal surgical procedures.

Candida Albicans Endophthalmitis

This is seen in immunocomprised patients, drug addicts and particularly in patients who have had longstanding intravenous catheters. Systemic evidence of infection is usually absent but it is important to do an echocardiogram and to take blood cultures to exclude a valvular endocarditis. The initial lesion originates as an embolic focus in a retinal vessel which bursts through into the vitreous and replicates there to form fluffy white masses in the posterior vitreous. These sometimes have the appearance of being linked together and are known as the 'string of pearls' sign. Patients present with a posterior uveitis. Diagnosis is made by culture of the organism obtained by vitrectomy and the disease responds to antifungal drugs and vitrectomy.
In the right eye there is a hazy vitreous with foci of candida. A whiter lesion can be seen attached to the retinal surface adjacent to the macula.

**Uveal Effusion Syndrome**

This is a rare disorder which usually occurs bilaterally. Patients present with choroidal detachment and sometimes associated non-rhegmatogenous retinal detachment in the absence of vitreous cellular infiltration. The syndrome occurs in two forms: nanophthalmic eyes which are very small with greatly thickened sclera or normal sized eyes which have abnormal deposition of glycosaminoglycans within the sclera. It is postulated that these eyes have a reduced transcleral outflow of fluid. In some patients the condition is self limiting or may respond to systemic steroids, otherwise partial sclerectomy cures the condition.

This patient has nanophthalmic eyes with axial lengths of less than 20mm.

He had bilateral choroidal effusions and subretinal fluid producing a characteristic 'leopard spot' change of the retinal pigment epithelium. The changes resolved, apart from the pigmentation, with deep partial thickness sclerectomy.
Index