THE RIDDLE OF UVEITIS*

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INFLAMMATION of the uveal tract, which comprises the iris, ciliary body and choroid, is the cause in 8.3% of cases of blindness in the fourth decade of life and in 2.5% of all cases of blindness in Britain (Sorsby 1956). In other words, about 2,500 of the 100,000 registered blind people in this country were blinded by uveitis and its complications, and this was particularly so in young people in the 30-40 decade. It is traditional to subdivide uveitis into anterior uveitis (or iridocyclitis) and posterior uveitis (or choroiditis), but it is only convenient to retain this concept if it can contribute a better understanding of the causes or mechanisms of the inflammatory process. It should nevertheless be remembered that it is an artificial distinction since the iris-ciliary-body-choroid is a continuous structure, derived from the mesoderm surrounding the optic cup, and this uveal tract is extremely vascular. It would indeed be surprising if inflammation of the anterior part did not affect the posterior part and vice-versa.

Mechanism of Blindness

Inflammatory exudate in the uveal tract leads to adhesions (synechiae) which ultimately stick the peripheral iris to the back of the cornea (anterior synechiae) or the iris adheres to the front of the lens (posterior synechiae) (Fig. 1). Over the years, the pupil aperture is obliterated and, with ciliary damage, leads to loss of accommodation; defective drainage leads to glaucoma; lens involvement leads to cataract formation; and finally macular involvement due to choroiditis directly leads to failure of vision. There is often an interplay of several of these factors (Fig. 2).

Classification of Endogenous Uveitis

Uveitis may be secondary to penetrating

wounds or other trauma, or follow chemicals which inflame any of the anterior layers of the eye. Uveitis may also follow surgical intervention or be secondary to some local intraocular cause. All these instances are usually obvious examples of exogenous or secondary uveitis. The ophthalmologist is not perplexed by the cause; and the management, whenever possible, is to remove the irritative source of the inflammation.

The riddle of uveitis lies in the causes and course of endogenous uveitis. Our present ignorance of the cause of the great majority of instances of endogenous uveitis precludes a satisfactory aetiological classification, and the anatomical classification into iridocyclitis and choroiditis is artificial and probably inaccurate. Our only means at present is a descriptive classification combining anatomical and aetiological (when known) features and defining direct complications when they add to the picture. Thus a patient with sarcoid uveitis might be classified as iridocyclitis, associated choroiditis, due to sarcoidosis, with glaucoma secondary to cyclitis. Likewise, choroiditis, peripheral, due to toxoplasmosis, with field defect due to macular lesion. This is the basis of coded classifications and will remain only until the multiple causes have been deciphered.

Iridocyclitis

The onset of an acute attack is abrupt with pain, photophobia, lacrimation and blurred vision. Vascular injection involves ciliary and conjunctival vessels, and the characteristic ciliary or circumcorneal congestion is deep to the conjunctiva. The pupil is small because of spasm, the iris is oedematous; there is an outpouring of inflammatory cells both into the aqueous and to become stuck to the back of the cornea (keratic precipitates). Fibrinous exudate leads to adhesions and the end result of repeated attacks may be secondary glaucoma or cataract formation.

*Based on the Presidential Address delivered to the Harveian Society of London, January, 15th, 1964.

FIG. 1.—The normal iris-corneal angle, and the consequences of anterior and posterior synechiæ.

Choroiditis

The onset is more insidious because pain is not a feature, but instead blurring of vision, a hazy vitreous containing inflammatory cells, and fluffy white choroidal lesions. If there is macular involvement then there is, of course, abrupt loss of vision. The choroidal lesion heals as a white atrophic scar with a black pigmented border.

Recognised causes

(Table 1)

Virus Infections

Iridocyclitis commonly accompanies keratitis due to herpes simplex or zoster viruses. The more severe the keratitis the greater the likelihood of an accompanying uveitis, which tends

FIG. 2.—Mechanisms of blindness due to uveitis.

to develop and persist in the later phase of infection. In addition to the non-specific iridocyclitis, herpes simplex infection produces dendritic keratitis with rows of vesicles. The virus may be isolated from the eye and neutralising antibodies can be demonstrated in the serum. In herpes zoster involving the ophthalmic nerve and Gasserian ganglion, there is in addition to the non-distinctive iridocyclitis, corneal anaesthesia; vesicles which may become secondarily infected spread beneath the corneal epithelium and along the eyelids; and there is inflammatory infiltration in the deep cornea. Haemorrhagic retinopathy, optic neuritis and extraocular motor palsies are occasional accompaniments. Spinal fluid pleocytosis is invariable.

Mumps has been incriminated as a rare cause of iritis.

Infections Possibly Viral

Two similar mucocutaneous syndromes—Behcet's disease and the Stevens-Johnson syndrome—are suspected of being viral but virus isolation studies are still inconsistent and inconclusive. *Behcet's disease* is characterised by recurring episodes of aphthous ulceration of the mouth and genitalia, polyarthritides and hydrarthroses, orchitis, phlebitis and fever. Periarteritis of the retina leads to retinal haemorrhages, subretinal fluid and retinal detachment, a cloudy vitreous and eventually inflammation, necrosis and atrophy of the iris frequently with a hypopion. *The Stevens-Johnson syndrome* is likewise characterised by recurring episodes of uveitis associated with superficial ulceration of mucocutaneous areas

such as the mouth and genitalia, fever and pneumonia, but a distinguishing feature is erythema multiforme exudativum. Complement-fixing antibodies to *Mycoplasma pneumoniae* should be sought in the serum (Ludlam, Bridges and Benn 1964).

The Vogt-Koyanaga-Harada or the uveo-encephalitic syndrome comprises bilateral uveitis, vitiligo, dysacusia, premature baldness and greying of the hair and CSF pleocytosis; it is in many respects similar to sympathetic ophthalmia.

Infectious mononucleosis may also be listed as an extremely rare cause of iritis.

Toxoplasmosis

The two forms of toxoplasmosis, congenital and acquired, are due to an intracellular protozoan, *Toxoplasma gondii*, about 4 to 7 μ long with a distinct nuclear chromatin but no flagellæ. As a result of transplacental spread, the infant may be born with choroidoretinitis, hydrocephalus, microcephaly, encephalomyelitis, hepatosplenomegaly and neonatal jaundice; to be followed eventually by cerebral calcification. Positive serological tests in mother and child place congenital toxoplasmosis beyond reasonable doubt as the cause of the posterior uveitis. But the problem of ocular toxoplasmosis does not lie here but rather in the differential diagnosis of posterior uveitis noticed in later life. It is now widely held that acute focal choroiditis in young adult life may represent late relapses of congenital toxoplasmosis. This is particularly likely when a fresh dense whitish satellite focus with blurred oedematous

TABLE 1.
RECOGNISED CAUSES OF UVEITIS. DISTINGUISHING CLINICAL AND SEROLOGICAL CHARACTERISTICS AND TREATMENT.

Uveitis	Clinical Accompaniments	Investigations	Treatment	Systemic Steroids
Herpes Simplex	Corneal Ulceration	Isolation Virus Neutralising Antibody	Iodo-Deoxyuridine	No
Herpes Zoster	Skin Vesicles	CSF Cells	Iodo-Deoxyuridine	Yes
Mumps	Parotitis	Isolation Virus Complement Fixation Test (CFT)		Yes
Behcet's Syndrome	Hypopion, Oral and Genital Ulceration, Hydrarthrosis			Yes
Stevens-Johnson Syndrome	Erythema Multiforme	CFT against Mycoplasma Pneumoniae		Yes
Vogt-Koyanagi-Harada Syndrome	Baldness, Greying of Hair, Vitiligo Dysacusia		Steroids	Yes
Infectious Mononucleosis	Lymphadenopathy, Jaundice	Blood Picture Paul-Bunnell		Yes
Toxoplasmosis	Peripheral Choroiditis, Lymphadenopathy	Dye Test CFT	Pyrimethamine Sulphonamides	Yes
Brucellosis	Fever. Sweats	Serum Agglutinins	Tetracycline	Yes
Leprosy	Anaesthetic Plaques, Thickened Nerves	Skin Smears	Sulphones	Yes
Focal Sepsis	Hunt Tonsils, Teeth, Sinuses, Bile, Kidneys		Widespread Surgery	No
Prostatitis	Urethritis Sacro-Iliitis Plantar Fasciitis Ankylosing Spondylitis		Ampicillin Tetracycline	No
Sarcoidosis	Skin and Lung Involvement		Local and Subconjunctival Steroids	Yes
Autoimmunity	Leaking Lens			Yes
Allergy				Yes

edges is noted adjacent to an old pigmented choroidal scar. There may be floating vitreous opacities and even occasional reactive iridocyclitis.

Whereas congenital toxoplasmosis causes

uveitis, the acquired form rarely does so. Acquired toxoplasmosis mimics glandular fever so the appropriate serological tests should be undertaken whenever the Paul-Bunnell test is negative. Surveys of well-documented cases of acquired toxoplasmosis only confirm the

rarity of uveitis as a manifestation of the acquired infection.

The difficulties of recognising clinical ocular toxoplasmosis are hampered still further by some uncertainty in interpretation of the serological tests, which comprise the cytoplasm-modifying antibody or dye test and the complement-fixation test. About one-third of normal adults' sera give a positive dye test titre up to 1:128, and about 1% of normal sera may be expected to register a titre of 1:256. Although these titres indicate past infection, they must be interpreted with caution when associated with a recent acute uveitis. Complement fixation test titres of 1:4 or more occur in about 5% of the adult population. The dye test is the one routinely used in Britain for screening purposes. A negative test helps to exclude toxoplasmosis and a fourfold rise or fall in titres suggests recent infection.

Bacterial Infections. *Brucellosis* and *leprosy* are insignificant causes of uveitis in Britain. In endemic zones, tuberculoid leprosy is commonly associated with troublesome iridocyclitis. It is interesting that leprosy should be almost entirely confined to the anterior uveal tract. Uveitis can no longer be ascribed to *human tuberculosis*, but anonymous or *unclassified mycobacteria* cannot be excluded as occasional causal agents, either of direct infection or, more likely, of hypersensitivity reactions involving the uveal tract. *Leptospirosis* may also be complicated by anterior or posterior uveitis, either due to direct haematogenous involvement or as a hypersensitivity phenomenon.

Focal sepsis is no longer fashionable unless the focus is in the prostate. Catterall (1961) investigated 211 men with uveitis and found prostatovesiculitis in 69% (in controls of the same age-group in the general medical and surgical wards of two hospitals the prevalence was 19%). Of male patients with acute anterior uveitis, no less than four-fifths had chronic prostatitis. Commonly associated with chronic prostatitis and uveitis were ankylosing spondylitis, arthritis, sacro-iliitis, conjunctivitis, urethritis and plantar fasciitis. Nevertheless, extensive investigations failed to reveal a causal organism. The fact that no such organism has been identified in the century and a half since Brodie (1818) first drew attention to the syndrome suggests that the cause may after all not be infective.

Sarcoidosis

Whereas eye involvement, predominantly

uveitis, occurs in one-quarter of patients with sarcoidosis, nonetheless sarcoidosis is responsible for only about 4% of cases of uveitis (James, Anderson, Langley and Ainslie 1964). Sarcoid uveitis is most commonly acute iridocyclitis. Evidence of involvement of other tissue systems is widespread, for iridocyclitis is accompanied by intrathoracic involvement in nearly three-quarters of instances, by skin lesions in one-half, and lymph node enlargement in one-third of cases. Sarcoid uveitis is part of a multisystem disease with diagnostic clinical features elsewhere. Moreover the negative Mantoux test and positive Kveim test also serve to distinguish this cause of uveitis.

Lens-induced Uveitis

It seems likely that certain individuals develop hypersensitivity to lens protein either due to local leaking or postoperatively if any lens material is left in the anterior chamber after cataract extraction.

Rheumatic Iridocyclitis

Iridocyclitis has been estimated to occur in 16% of patients with ankylosing spondylitis and 4.7% with rheumatoid arthritis (Woods 1961). We find rheumatic disease of either of these two types to be present in about 80% of patients with iridocyclitis, and some abnormality or another of the sacro-iliac joints in up to one-third of our series with iridocyclitis. These associations form part of a wide spectrum of disease pattern in men comprising prostatitis, plantar fasciitis, polyarthralgia and hydrarthrosis.

Treatment

The basis of treatment comprises local rest to the inflamed area by means of mydriatics; the anti-inflammatory benefit of local and also possibly systemic corticosteroids; and, of course, specific local and general treatment when such means exist.

Mydriatics

Frequently applied 1% atropine drops dilate the pupil, prevent the development of posterior adhesions to the lens, relax the ciliary muscle, and increase the communication between anterior and posterior chambers. If atropine eye drops are not sufficiently effective, subconjunctival mydricaine is indicated.

Corticosteroids

There are several effective commercial preparations for local treatment of iridocyclitis.

Eye drops should be administered at least four times daily and the more slowly absorbed ointment applied last thing at night. The response is usually immediate and dramatic, but if there is continuing undesirable inflammation after 10 to 14 days, then the more intensive anti-inflammatory effect of subconjunctival cortisone or a short intensive course of oral prednisolone should be considered. One scheme is to prescribe 5 tablets (prednisolone 5 mg; betamethasone or dexamethasone 0.5 mg) daily for 5 days, followed by 4 tablets daily for 4 days, 3 tablets daily for 3 days, 2 tablets daily for 2 days and 1 tablet on a final day. This course of 55 tablets in 15 days is complementary to rather than instead of local corticosteroid eye drops and ointments. This short intensive course of topical and oral steroids is usually sufficient to suppress acute iridocyclitis, but not for acute posterior uveitis which is inaccessible to topical applications. For acute choroidoretinitis, as for instance due to relapsing toxoplasmosis, prednisolone is continued in doses of 20 mg. daily as long as improvement occurs and for at least 3 months.

As in other fields of medicine, steroids can be expected to suppress acute inflammation but the response of chronic inflammatory processes is disappointing. Oral steroids will suppress acute exacerbations and may even prevent them, but the natural history of chronic uveitis remains virtually unchanged. It smoulders onwards with occasional exacerbations, and irreversible fibrosis gives rise to mechanical complications such as secondary glaucoma and cataract formation (Fig. 2).

Specific measures (Table 1).

5-Iodo-2'-deoxyuridine

Thymidine is needed for the intracellular synthesis of desoxyribonucleic acid. This pathway in viral synthesis may be interrupted by the halogenated pyrimidines, that most frequently used in clinical practice being 5-iodo-2'-deoxyuridine (IDU) (Kaufman, Nesburn and

Maloney 1962; Hall-Smith, Corrigan and Gilkes 1962). Inhibitory effects have been noted against herpes simplex, vaccinia and adenovirus, but viruses whose genetic information is in the form of RNA are unaffected by this group of compounds. The precise value of IDU eye drops remains in doubt for enthusiastic early claims have been critically countered; further controlled blind trials are in progress to define its use. Nevertheless attention has been focussed on a new field of antiviral chemotherapy, in which drugs may be designed to interrupt essential viral metabolic pathways.

Broad-spectrum Antibiotics

Ampicillin and tetracycline are effective broad-spectrum antibiotics for the control of contributory bacterial inflammation. Both may be used in turn a week apiece to eradicate troublesome prostatitis.

Pyrimethamine

The toxoplasma organism utilises the para-aminobenzoic acid-folic acid chain for its nutrition. Both the sulphonamides and pyrimethamine antagonise the chain, sulphonamides by competing with PABA and pyrimethamine by interfering with the conversion of folic to folinic acid. This is the rationale of the treatment of toxoplasmosis with pyrimethamine 50 mg. daily and sulphadiazine 1 gram daily for up to 3 months. Supplements of folinic acid or brewer's yeast may reduce the toxicity of pyrimethamine to the host without affecting its action on the parasite. The true worth of pyrimethamine in human toxoplasma uveitis remains in doubt. Moreover, if such treatment is to be given, serial blood counts are essential for the detection of macrocytic anaemia and leucopenia.

Sulphones

Leprosy uveitis is best treated by a combination of the anti-leprosy drugs, such as the sulphones, together with local and possibly systemic corticosteroids.

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