25.1 The eye in general medicine 6399 Tasanee Brai

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ESSENTIALS The integrity of ocular anatomy and physiology, the function of the visual system, and the perception of vision, our most prized sense, are intimately connected with our general health. Subtle visual signs and symptoms may therefore be the first manifestation of occult systemic disease. With a basic history and examination of the eyes and vision, the physician can narrow the differential diagnosis and ascertain whether there is any immediate threat to vision or even life. The major focus of this chapter is the eye in the context of a range of vascular, haematological, neoplastic, inflam- matory, endocrine, genetic, metabolic, toxic, and nutritional dis- orders. We also consider the leading causes of blindness globally, and common ocular presentations in primary care and general medical practice. Other isolated ocular conditions are excluded and neuro-ophthalmological conditions are referred to elsewhere in this book (Chapters 24.6.1 and 24.6.2). Assessment of the eye and visual system Important common symptoms include redness, pain, photosensi- tivity, discharge, loss of vision, double vision, visual field loss, floaters, flashing lights, and altered colour perception. Their dif- ferential diagnosis is summarized in Table 25.1.1. Important signs and their differential diagnosis are summarized in Table 25.1.2. Assessment of vision Long-distance and near visual acuity are tested using standard- ized charts or computerized systems. These present high contrast optotypes against a white background in a standardized arrange- ment. On a traditional Snellen chart the numerator is the test dis- tance and the denominator is the distance at which the optotype would be seen by an observer with normal vision (in the United Kingdom this is measured in metres, e.g. ‘6/36’). Using a logMAR chart, each optotype correctly identified has a score of -0.02 log units. This is more accurate and amenable to statistical comparison. LogMAR 1.00 is equivalent to Snellen 6/60, and 0.00 is equivalent to 6/6. If

acuity improves on testing with a pinhole (which negates some refractive error) then uncorrected refractive error is likely. If formal charts are not available at the bedside, near acuity can be approxi- mated using well-illuminated newspaper text at 40 cm. The World Health Organization (WHO) categories of vision impairment are summarized in Table 25.1.3. Ishihara pseudo-isochromatic test plates are held at 75 cm and used to identify congenital red-green colour vision defects, with minimal ability to assess acquired blue- yellow dyschromatopsia. Their speed and simplicity favours their use in clinical practice, over the more comprehensive Farnsworth- Munsell 100 Hues test. Contrast sensitivity, the threshold between visible and invisible, is measured using Pelli–Robson or Mars charts. Stereoscopic (depth) acuity requires binocular vision and is tested using Lang, Titmus Fly, or Frisby stereotests. A patient's central and peripheral field of vision can be either assessed to confrontation in comparison with the examiner (a red target is useful as red colour field loss may preceed white target field loss), or using formal auto- mated (e.g. Humphrey or Octopus) and manual (e.g. Goldmann) perimetry. An Amsler chart (Grid of lines) at 33 cm assesses dis- tortion or blind spots in the central 10 degrees of vision. Numerous psychometric instruments are also available to assess vision-related quality of life and vision-related daily functioning. Examination and investigation of the eyes A torch facilitates assessment of the orbit, eyelids, external eye, pu- pils, lens, and range of eye movements. Ocular surface integrity is assessed with 2% fluorescein drops under cobalt blue light. The optic disc is visualized at approximately x15 magnification with the direct ophthalmoscope. Examination of the macula and peripheral retina are enhanced with topical dilating drops, and varying the patient's direction of gaze. Tropicamide 0.5% has a good safety profile, achieves dilation after 15 minutes and lasts up to 4 hours. Cyclopentolate 1% achieves dilation after 30 minutes and lasts up to 24 hours. Phenylephrine 2.5% achieves dilation after 60 min- utes and lasts up to 7 hours, but may have cardiovascular side ef- fects in some individuals and children, and 2.5% rather than 10% drops should be used. Two agents are typically required in patients with dark brown irises. Ophthalmologists examine the posterior segment manually with lenses using a slit lamp or indirect oph- thalmoscope, and also have many ancillary diagnostic tests avail- able to them in specialist practice (see Table 25.1.4 and Fig. 25.1.1). Furthermore, the increasing application of ophthalmic imaging devices by community optometrists in the United Kingdom, 25.1 The eye in general medicine Tasanee Braithwaite, Richard W.J. Lee, and Peng T. Khaw

Section 25 Disorders of the eye 6400 including retinal photography and optical coherence tomography, is valuably aiding the detection and monitoring of a range of ocular conditions, particularly diabetes, where screening has had a sig- nificant impact on the incidence of blindness. Common ocular pathologies in adults Epidemiology of blindness and vision impairment There are an estimated 36.0 million blind people globally. The prevalence of blindness (visual acuity less than 3/60 in the better- seeing eye) ranges from 0.2% in high-income countries to 0.7% in North Africa and the Middle East. Blindness increases with age, affecting over 4% of adults over 50 years in some countries in Africa, Asia and the Middle East, and affects more women than men. A further 217 million people have moderate or severe vision impairment (visual acuity worse than 6/18 but 3/60 or better). This affects fewer than 5% of adults over 50 years in high-income re- gions, but up to 15% in South Asia (see Fig. 25.1.2). Approximately 65% of blindness has a preventable or treatable cause. The leading causes of blindness in older adults in high-income regions are age-related macular degeneration (16%), uncorrected refractive error (13%), cataract (20%), glaucoma (13%), and diabetic retinopathy (4%). The leading causes in low-income regions are cataract (37%), uncorrected refractive error (13%), trachoma (8%), macular degen- eration (6%), glaucoma

(4%), and diabetic retinopathy (2%). Leading causes of blindness and vision impairment Cataract Cataract is a loss of transparency of the crystalline lens that results in reduced vision and eventual blindness. The prevalence rises from less than 0.1% in young adults to between 60% and 90% in adults Table 25.1.1 Symptoms and key diseases to consider in the differential diagnosis Presenting symptom Differential diagnosis Red eye Potentially sight-threatening Orbital cellulitis, gonococcal conjunctivitis, cicatricial conjunctivitis, anterior scleritis, uveitis, exposure keratitis, microbial keratitis (bacterial, viral, or fungal), chemical injury, peripheral ulcerative keratitis, endophthalmitis, acute thyroid eye disease, acute angle closure (+/- glaucoma), carotid-cavernous fistula, corneal foreign body Common and seldom sight-threatening Bacterial, viral, and allergic conjunctivitis, episcleritis, blepharitis, subconjunctival haemorrhage, marginal keratitis, dry eye, corneal abrasion, recurrent corneal erosion Eye/orbit pain—dull ache Uveitis, ocular ischaemic syndrome, acute angle closure, carotid-cavernous fistula Eye pain—burning or stabbing Conjunctivitis, keratitis, blepharitis, corneal epithelial abrasion or erosion, moderate/severe dry eye Eye pain exacerbated by movement Optic neuritis, orbital myositis Transient visual obscurations (lasting seconds) Papilloedema, giant cell arteritis, impending central retinal vein occlusion, ocular ischaemic syndrome Sudden or subacute vision loss (transient— lasting minutes to one hour) Unilateral: Arteritic anterior ischaemic optic neuropathy (e.g. GCA), ‘Amaurosis fugax’ (passage of embolus) Bilateral: vertebrobasilar artery insufficiency, migraine Subacute vision loss (lasting from weeks to permanently) Keratitis involving the central cornea (e.g. microbial or exposure), Hydrops (in keratoconus), acute angle closure +/- glaucoma, vitreous haemorrhage, intermediate or posterior uveitis, endophthalmitis, central retinal artery occlusion, branch or cilioretinal artery occlusion involving tovea, central retinal vein occlusion, retinal detachment, choroidal neovascular membrane (e.g. wet AMD or high myopia), central serous chorioretinopathy, anterior ischaemic optic neuropathy—arteritic (e.g. GCA) or nonarteritic, posterior ischaemic optic neuropathy, optic neuritis (MS or atypical), cortical blindness Gradual vision loss (weeks to months) Corneal dystrophies, keratoconus, cataract, dry AMD +/- geographic atrophy, inherited macular dystrophy, diabetic maculopathy, tractional retinal detachment, cystoid macular oedema (e.g. associated with retinal vein occlusion, or uveitis), retinoblastoma, retinitis pigmentosa, glaucoma, optic neuropathy, chronic papilloedema Double vision Monocular – high astigmatism, edge effect from intraocular lens implant or spectacles, corneal opacity (e.g. oedema, scarring, dystrophies), corneal ectasia, lens subluxation, iris defect, functional Binocular Decompensating phoria Neuropathic—cranial nerve palsies (III, IV, and VI), brainstem lesions Neuromuscular junction—ocular myasthenia gravis Mechanical—thyroid eye disease, orbital cellulitis, myositis, orbital wall trauma, orbit infiltration or inflammation Floaters in the vision Posterior vitreous detachment, vitreous haemorrhage, intermediate uveitis, vitritis, asteroid hyalosis, amyloidosis, lymphoma, choroidal melanoma, retinal tear, retinal detachment Flashing, shimmering lights Vitreoretinal traction, retinal tear, retinal detachment, proliferative retinopathy (e.g. diabetes, sickle cell, retinopathy of prematurity), cancer-associated retinopathy, nonparaneoplastic autoimmune retinopathy, choroidal or retinal tumours Coloured lights or shapes Migraine, occipital lobe lesions Change in colour vision Optic nerve pathology, cone dystrophy, drug-induced (e.g. amiodarone, sildenafil citrate, digoxin, hydroxychloroquine) GCA, giant cell arteritis; AMD, age-related macular degeneration; MS, multiple sclerosis.

 Table 25.1.2 Systemic disease associations for key ocular signs, organized anatomically Sign Differential diagnosis Face Preauricular lymphadenopathy

Parinaud’s oculoglandular syndrome, lymphoma Key ocular differential: conjunctivitis (viral, chlamydial, gonococcal) Globe Proptosis Thyroid eye disease, orbital cellulitis, systemic vasculitis (e.g. GPA), tumours (e.g. optic nerve glioma, myeloid leukaemia, lymphoma, capillary haemangioma, lymphangioma, histiocytosis, dermoid cyst), carotid-cavernous fistula, orbital varices, orbital myositis, sarcoid, amyloid, sickle cell disease Enophthalmos Scleroderma, postirradiation, cicatrizing tumours, ageing, use of topical prostaglandin agonist e.g. latanoprost Eyelids Excessive eyelash growth Drugs (phenytoin, ciclosporin, topical prostaglandin analogues e.g. latanoprost), malnutrition, AIDS, porphyria, hypothyroidism, oculocutaneous albinism type 1, Hermansky-Pudlak syndrome, Cornelia de Lange syndrome, Oliver McFarlane syndrome Poliosis (patch of white hair) Vogt-Koyanagi-Harada syndrome, sympathetic ophthalmia, Waardenberg syndrome, chronic blepharitis Epicanthic folds Turner’s syndrome (XO), trisomy 18 (Edward’s syndrome), Down’s syndrome Ptosis Kearns–Sayre disease, myotonic dystrophy, Turner syndrome (XO), myasthenia gravis (variable), Ascher syndrome, Mucormycosis, preseptal and orbital cellulitis (erythematous), third nerve palsy, Horner syndrome, congenital (from birth), involutional (old age) Lid retraction Thyroid eye disease, uraemia, facial nerve palsy, misdirection of oculomotor nerve, drugs (e.g. sympathomimetics), Parinaud’s (dorsal midbrain) syndrome, congenital Conjunctiva (See anterior segment composite diagram for illustrations of some of these lesions) Follicles Most viral causes of conjunctivitis (e.g. adenovirus, HSV, VZV, rubella, EBV, influenza virus A, measles, mumps, Newcastle disease, molluscum contagiosum), Chlamydia trachomatis (types A to C and D to K), Lyme disease, chronic staphylococcal blepharoconjunctivitis, Parinaud’s oculoglandular syndrome, Reiter’s syndrome, lymphoma Papillae Most bacterial conjunctivitis, neonatal chlamydia, allergic conjunctivitis Telangiectasia Idiopathic, ataxia-telangiectasia, Osler-Weber-Rendu syndrome, Louis-Bar syndrome, Sturge–Weber syndrome, Fabry’s disease, fucosidosis Arterialised ‘Corkscrew’ vessels HIV microvasculopathy, dural arteriorvenous malformation, carotid-cavernous sinus fistula, squamous conjunctival neoplasia, idiopathic dilated episcleral veins Cicatricial bands-symblepharon, ankyloblepharon Erythema multiforme, Stevens–Johnson syndrome, TEN, Graft-vs.-Host disease, Ocular Mucous Membrane Pemphigoid (OMMP), Linear IgA disease, previous chemical or thermal or radiation injury, Lyme disease, chronic blepharitis, atopic keratoconjunctivitis, Trachoma Haemorrhage Conjunctivitis—viral (e.g. adenovirus, enterovirus 70, coxsackie virus A24, dengue, Ebola), or bacterial (e.g. Neisseria meningitidis, Streptococcus pneumonia, Leptospirosis), thrombocytopoenia, purpura, spontaneous (commonest cause) Episclera and sclera (See anterior segment composite diagram for illustrations of some of these lesions) Episcleritis TB, syphilis, Lyme, Leprosy, IBD, psoriatic arthritis, rheumatoid arthritis, SLE, relapsing polychondritis, dermatomyositis, polymyositis, PAN, eosinophilic granulomatosis with polyangiitis, Cogan’s, bisphosphonates Scleritis IBD, psoriatic arthritis, rheumatoid arthritis, SLE, relapsing polychondritis, PAN, eosinophilic granulomatosis with polyangiitis, Cogan’s, IgG4, primary hyperparathyroidism, bisphosphonates, TB, syphilis, leprosy, actinomyces israelii Necrotizing scleritis TB, IBD, rheumatoid arthritis, SLE, PAN, GPA Blue sclera Osteogenesis imperfecta, Marfans syndrome, Ehlers–Danlos, scleromalacia perforans (rheumatoid arthritis, IBD), Lowe syndrome Pigmented sclera Alkaptonuria, ethnic background Blue tinged sclera Osteogenesis imperfecta, connective tissue disorders (e.g. Marfan’s, Ehlers–Danlos, pseudoxanthoma elasticum), previous nectrotizing scleritis, incontinentia pigmenti, Turner’s syndrome, Russell–Silver syndrome Cornea (See anterior segment composite diagram for illustrations of some of these lesions) Kayser-Fleischer ring Wilson’s Phlycten (inflamed nodules) TB hypersensitivity, staphylococci, adenovirus, fungi, Neisseria, leishmaniasis Conjunctivilisation (limbal stem cell failure) Aniridia, previous chemical injury, OMMP, SJS/TEN, atopic keratoconjunctivitis, thermal injury, PUK, chronic contact lens wear,

preservative toxicity, ocular surface malignancy Interstitial keratitis TB (ocular infection), syphilis (congenital or acquired), leprosy, Lyme disease, Chagas' disease (American trypanosomiasis), sleeping sickness (African trypanosomiasis), sarcoid, Cogan's syndrome Keratic precipitates Causes of anterior uveitis Band keratopathy Idiopathic (50%), chronic anterior uveitis (e.g. juvenille idiopathic arthritis, sarcoid), chronic keratitis, silicone oil in the anterior chamber (following vitreoretinal surgery), primary hyperparathyroidism, chronic renal failure, hyperphosphataemia, hyperuricaemia (continued)

Section 25 Disorders of the eye 6402 Sign Differential diagnosis Exposure keratopathy Thyroid eye disease, facial palsy, suboptimal ocular surface protection in sub or unconscious patients (e.g. ITU, peroperative, poor lid closure during sleep) Ulcer (keratitis) Bacterial, fungal, viral (e.g. dendritic in HSV), staphlococcal hypersensitivity Vortex keratopathy Fabry's disease, hydroxychloroquine, chloroquine, tamoxifen, cardiac glycosides (e.g. amiodarone), chlorpromazine, atovaquone Crystalline keratopathy Infectious biofilm (e.g. Streptococcus viridans) or noninfectious deposition of lipid, cysteine, urate, immunoglobulin (lymphoma, multiple myeloma, Waldenstrom's macroglobulinaemia), or gold (treatment of rheumatoid arthritis) Corneal opacity Mucolipidoses, mucopolysaccharidoses, Lowe's syndrome, X-linked ichthyosis, tyrosinaemia, Tangier, trisomy 18 Thickened corneal nerves Acanthamoeba keratitis, Multiple endocrine neoplasia type IIb Keratoconus Atopy, retinopathy of prematurity, retinitis pigmentosa, Down's syndrome, Crouzon syndrome, Apert syndrome, Marfan syndrome, osteogenesis imperfecta, Ehlers–Danlos syndrome Lattice dystrophy Familial systemic amyloidosis (Meretoja syndrome), or isolated ocular lattice dystrophy Peripheral ulcerative keratitis Rheumatoid arthritis, PAN, GPA, SLE, relapsing polychondritis, eosinophilic granulomatosis with polyangiitis, idiopathic Iris (See anterior segment composite diagram for illustrations of some of these lesions) Lisch nodule Neurofibromatosis type 1 Koeppe nodules Granulomatous uveitis (e.g. sarcoid) Busacca nodules Granulomatous uveitis (e.g. sarcoid) Brushfield spots Down's syndrome Iris transillumination Albinism, HSV, and HZV, trauma, pseudoexfoliation syndrome, pigment dispersion syndrome Aniridia WAGR syndrome (Wilms tumour, aniridia, genital anomalies, mental retardation) Coloboma Klinefelters syndrome, Treacher Collins syndrome, Patau syndrome (trisomy 13), CHARGE syndrome (coloboma, heart defects, atresia of the nasal choanae, growth retardation, and genitourinary abnormalities) Heterochromia Hypochromic—congenital Horner syndrome, uveitis, Fuchs' heterochromic cyclitis, Waardenberg syndrome Hyperchromic—diffuse iris naevus or melanoma, drugs (e.g. latanoprost), siderosis (e.g. intraocular foreign body) Rubeosis Proliferative diabetic retinopathy, branch or central retinal vein occlusion (ischaemic), ocular ischaemic syndrome, sickle cell proliferative retinopathy, central retinal artery occlusion Leucoria (white pupil) Adults—cataract, inflammatory membrane Children—retinoblastoma, persistent fetal vasculature, retinopathy of prematurity, toxocara, retinal dysplasia (e.g. Patau syndrome, Edward syndrome, Norries disease), Coats' disease, incontinentia pigmenti Anterior chamber (See anterior segment composite diagram for illustrations of some of these lesions) Hypopyon Severe microbial keratitis, severe anterior uveitis (e.g. Behçet's), endophthalmitis, tumour necrosis Hyphaema Trauma (greater risk of hyphaema if sickle cell disease), causes of iris rubeosis Lens Lens dislocation Marfan syndrome, Ehlers–Danlos syndrome, homocystinuria, familial ectopia lentis, Weill–Marchesani, hyperlysinaemia, sulphite oxidase deficiency, Stickler syndrome, Crouzon syndrome, Sturge–Weber syndrome, aniridia Lenticonus Alport syndrome (anterior), Lowe syndrome (posterior) Microspherophakia Peters anomaly, Marfan syndrome, Weill–Marchesani syndrome, hyperlysinaemia, Alport syndrome, congenital rubella Cataract, infantile Galactosaemia, galactokinase deficiency, Down's syndrome, Lowe's syndrome

Cataract, adult Age-related, myotonic dystrophy, Wilson’s disease, neurofibromatosis type 2, Fabry’s disease, mannisidosis, Refsum’s disease, drugs e.g. topical steroids Vitreous Vitreous haemorrhage Proliferative diabetic retinopathy, haemorrhagic posterior vitreous detachment, retinal tear, sickle cell retinopathy (associated with ‘sea fans’ in HbSC), Eales Disease, proliferative radiation retinopathy, TB hypersensitivity, Whipples disease, Dengue, Behçet’s (neovascularization), Takayasu’s arteritis Retina (See posterior segment composite diagrams for illustrations of some of these lesions) Microaneurysms Diabetic retinopathy, hypertensive retinopathy, radiation retinopathy, Eales disease, HIV, Takayasu’s arteritis, ocular ischaemic syndrome Haemorrhages Diabetic retinopathy (dot and blot), hypertensive retinopathy (flame), radiation retinopathy, ocular ischaemic syndrome, sickle retinopathy (‘salmon patch’ and ‘black sunbursts’), Purtscher retinopathy, acute pancreatitis, fat embolization, amniotic fluid embolization, preeclampsia, HELLP syndrome (haemolysis, elevated liver enzymes, low platelets), Central retinal vein occlusion (4 quadrants), hemiretinal vein occlusion (superior or inferior hemiretina), branch retinal vein occlusion (quadrant), anaemia, hyperviscosity, leukaemia, TB, leptospirosis, HIV retinopathy, CMV retinitis, Dengue retinopathy, visceral Leishmaniasis (kala-azar), DUSN, sarcoid, Behçet’s, SLE, relapsing polychondritis, Takayas’s arteritis, tamoxifen, cisplatin, carmustine, interferon Table 25.1.2 Continued (continued)

25.1 The eye in general medicine 6403 aged 85 years and above. In addition to age, risk factors include sunlight, ocular trauma or surgery, intraocular inflammation, use of corticosteroids either systemically or as eye drops, smoking, and exposure to ionizing radiation. Systemic disease associations in- clude diabetes mellitus, myotonic dystrophy, hypoparathyroidism, and Wilson’s disease. Patients typically complain of gradual onset, painless blurring of the vision, glare, and seeing haloes around lights. Cataract surgery is a safe and effective, local anaesthetic, day case procedure, with excellent visual outcomes. Approximately 10% of patients require laser to the lens capsule within 2 years of cataract surgery to optimize vision. Rare complications include endophthalmitis (<1 in 1000), intraocular haemorrhage, and ret- inal detachment. Table 25.1.3 World Health Organization classification of visual function Vision loss category Definition by visual acuity LogMAR equivalent Distance mild vision impairment <6/12 but ≥6/18 0.22 to 0.48 Distance moderate vision impairment <6/18 but ≥6/60 0.50 to 1.00 Distance severe vision impairment <6/60 but ≥3/60 1.02 to 1.30 Distance blindness <3/60 ≥1.32 Near vision impairment <6/12 but ≥3/60 for near, and ≥6/12 for distance 0.22 to 1.30 (>0.20 distance) Sign Differential diagnosis Cotton wool spots (accumulations of axoplasmic material) Diabetic retinopathy, accelerated hypertension, ischaemic retinal vein occlusion, ocular ischaemic syndrome, emboli, hyperviscosity, severe anaemia (especially pernicious anaemia), vasculitis, HIV retinopathy, Purtscher retinopathy, acute pancreatitis, preeclampsia, HELLP syndrome (haemolysis, elevated liver enzymes, low platelets), leukaemia, SLE, relapsing polychondritis, cisplatin, carmustine, interferon Roth’s spots Septic emboli, leukaemia, HIV, severe anaemia, including pernicious anaemia, myeloma, hypertensive retinopathy Telangiectasia Idiopathic, Coats’ disease, retinopathy (diabetic, radiation, sickle, HIV), Eales disease, retinal vein occlusion, hypogammaglobulinaemia Macular ‘cherry red’ spot (usually due to swelling and pale appearance of surrounding retina) Sphingolipid metabolism disorders (GM1 gangliosidosis, Sandhoff’s, Niemann–Pick, Tay–Sachs disease), central retinal artery occlusion Pigmentary retinopathy (bone spicules) Retinitis pigmentosa, Usher’s disease, mitochondrial myopathy (some), Refsum’s disease, Kearns–Sayre disease, abetalipoproteinaemia, Hurler’s syndrome, Laurence–Moon syndrome, Bardet–Biedl syndrome Pale mass Toxocariasis (single or multiple), granuloma (e.g. sarcoid—small, peripheral, or TB) Pigmented lesion Typical

congenital hypertrophy of the retinal pigment epithelium (CHRPE), Gardner's syndrome (atypical CHRPE) Haemangioma Von Hippel–Lindau disease, Sturge–Weber syndrome, Wyburn–Mason syndrome Crystals Cystinosis, oxalosis, Alport sundrome Occlusive vasculopathy TB (hypersensitivity), Eales disease, sickle cell retinopathy, Coats disease, familial exudative vitreoretinopathy, Behçet, SLE Vasculitis Intermediate or posterior uveitis, Behcets, TB, Lyme, Whipple's disease, sarcoid, SLE, MS, toxoplasmosis, IRVAN syndrome (idiopathic retinal vasculitis, aneurysms and neuroretinitis), systemic vasculitidies (e.g. GPA, PAN, Takayasu's) Arteritis Acute retinal necrosis (e.g. HSV and VZV), and systemic vasculitidies (less common) Angioid streaks Idiopathic (50%), pseudoxanthoma elasticum, Ehlers–Danlos syndrome, sickle cell retinopathy, Paget's disease, acromegaly, haemoglobinopathies, Sturge–Weber, neurofibromatosis, tuberous sclerosis, abetalipoproteinaemia, haemolytic anaemia, hypercalcinosis, hyperphosphataemia, lead poisoning, high myopia Choroid (See posterior segment composite diagrams for illustrations of some of these lesions) Choroidal mass Choroidal neovascular membrane, granuloma (diffuse or multifocal, e.g. TB, syphilis, sarcoid), fungal infection, osteoma, haemangioma, metastasis, naevus, melanoma, posterior scleritis Multifocal choroiditis and chorioretinitis TB, syphilis, acute posterior multifocal placoid pigment epitheliopathy, Lyme disease Choroidal folds Idiopathic, hypermetropia, papilloedema, posterior scleritis, choroidal mass, hypotony, thyroid eye disease, retrobulbar mass Optic nerve head Swelling Raised intracranial pressure; local (usually unilateral) inflammation, ischaemia, infiltration, or infection Pallor Glaucoma (with increased cup to disc ratio) Previous optic neuritis (typical or atypical), previous ischaemic optic neuropathy (arteritic or nonarteritic), previous optic nerve trauma including tumour compression. Nutritional, toxic, drug-induced and hereditary optic neuropathy (e.g. Lebers). Congenital optic atrophy (e.g. Kjer's, Behr's, Wolfram's). CMV, cytomegalovirus; DUSN, diffuse unilateral subacute neuroretinitis; EBV, Epstein–Barr virus; GPA, granulomatosis with polyangiitis; HSV, herpes simplex virus; ITU, intensive therapy unit; PAN, polyarteritis nodosa; SLE, systemic lupus erythematosus; VZV, varicella zoster virus; SJS, Stevens–Johnson syndrome; OMMP, ocular mucous membrane pemphigoid; TEN, toxic epidermal necrolysis; TB, tuberculosis; IBD, inflammatory bowel disease; HIV, human immunodeficiency virus; PUK, peripheral ulcerative keratitis; DUSN, diffuse unilateral subacute neuroretinitis; MS, multiple sclerosis. Table 25.1.2 Continued

Section 25 Disorders of the eye 6404 Congenital cataracts affect 1 in 4000 live births. Causes include chromosomal abnormalities, many different genetic syndromes, metabolic storage disorders, and infections in utero. Urgent assess- ment, investigation, and surgery within the first few months of life is vital to maximize long-term visual function. Glaucoma Glaucoma is a sight-threatening optic neuropathy characterized by progressive retinal ganglion cell/axon degeneration associated with characteristic changes in the appearance of the optic nerve heads and visual fields. It is one of the most common neuropathies in the world. The global prevalence of glaucoma is 3.5%, with the highest prevalence of primary open angle glaucoma (POAG) in Africa (4.2%) and the highest prevalence of primary angle closure glau- coma (PACG) in Asia (1.1%). Risk factors for POAG include the level of intraocular pressure (glaucoma with intraocular pressure in the lower ranges), increasing age, myopia, diabetes, obstructive sleep apnoea, and family history in a first degree relative. Risk fac- tors for PACG include shorter axial globe length (e.g. hyperopia) and age. Normal tension glaucoma is associated with a history of migraine, Raynaud's, or previous major blood loss. Secondary glau- coma may develop in association with the use of topical steroids to the eye, chronic uveitis, neovascularization (iris rubeosis), ocular tumours, and causes of elevated episcleral venous pressure. These include Sturge–Weber syndrome, orbital varices, superior vena

cava obstruction, and cavernous sinus fistulae. Signs include narrowing, excavation and notching of the neuroretinal rim with an increase in the cup:disc ratio (see Fig. 25.1.3), asymmetry in the disc ap- pearance, bayonetting of the disc vessels, retinal nerve fibre layer haemorrhages, and peripapillary atrophy. Typical field defects in- clude a nasal step, paracentral scotoma, arcuate and altitudinal loss, and peripheral constriction. The patient with undiagnosed POAG is typically initially asymptomatic, despite high IOP, until advanced disease irreversibly impacts the central visual field. Patients with acute angle closure present with acute blurring, watering, and dis- comfort. Patients with glaucoma require lifelong follow-up. IOP is managed with topical agents (prostaglandin analogues, ß-blockers, sympathomimetics and carbonic anhydrase inhibitors), various laser procedures, and surgery (e.g. trabeculectomy or tube inser- tion). This usually prevents progressive nerve damage and field loss, but a small minority with aggressive disease go blind despite early diagnosis with maximal and timely intervention. Diabetic retinopathy Diabetic retinopathy (DR) is a chronic, progressive disease of the retinal microvasculature which may result in progressive vision loss from associated maculopathy and proliferative retinopathy. The pathogenesis relates to vascular leakage and increasing ret- inal ischaemia, with subsequent neovascularization. Diabetic ret- inopathy affects approximately 93 million people globally and is an important cause of vision loss in middle-aged and older people. Various DR classification systems assist diagnosis and screening (Table 25.1.5). A UK national DR screening programme using two field photography was introduced in 2003, and is linked to primary care records. All diabetic patients aged over 12 years are offered screening at least annually. The prevalence of any diabetic retinopathy among diabetic pa- tients is 34.6%, including 6.96% proliferative diabetic retinopathy, 6.81% macular oedema and 10.2% vision-threatening diabetic ret- inopathy. The prevalence increases with duration, haemoglobin A1c, and blood pressure level, and is higher in those with type 1 diabetes. The UK Prospective Diabetes Study and the Diabetes Control and Complications Trial established the importance of modifiable risk factors. The incidence and progression of diabetic Table 25.1.4 Key ophthalmic investigations Investigation Abbreviation Mechanism Electrodiagnostic tests: visual evoked potential, electro-oculography, electroretinography EDT: VEP EOG ERG Tests performed according to the International Society for Clinical Electrophysiology of Vision Standard, measuring the electrical activity arising from different tissues in response to specific stimuli Fundus autofluorescence FAF Confocal scanning laser ophthalmoscopy used to detect signals originating from intrinsically autofluorescent molecules of lipofuscin in the retinal pigment epithelium Fundus Fluorescein Angiography FFA A rapid sequence of fundus or ultra wide-field photographs are taken following intravenous injection of sodium fluorescein, using spectrally appropriate filters, in order to visualize the choroidal and retinal vasculature and perfusion. Some pathological changes appear hyperfluorescent, others hypofluorescent Heidelberg Retinal Tomography HRT Confocal scanning laser ophthalmoscopy used to generate a three-dimensional topographic image of the optic nerve head allowing measurement the absolute thickness of the retinal nerve fibre layer relative to a reference plane Indocyanine Green angiography ICG Like FFA, an intravenous contrast agent is injected, and followed by a series of images, to visualize the choroidal circulation. Pathological changes appear hyper- or hypofluorescent Optical coherence tomography OCT Noninvasive infrared light used to create cross-sectional and 3-dimensional images of the retina, choroid and optic nerve head, achieving resolution of 5 microns Optical coherence tomography angiography OCT angio A motion contrast microvascular imaging modality that enables visualization of the retinal microvasculature and capillary network without contrast media Ultrasound scan USS An 8–10 MHz transducer probe is applied to the closed eyelid with a coupling agent to visualize a cross-section of the globe. With a 50–100 MHz transducer the anterior segment can be visualized

25.1 The eye in general medicine 6405 retinopathy is reduced by intensive glycaemic and blood pres- sure control (Table 25.1.6). Diabetic retinopathy also develops when diabetes is secondary to haemochromatosis, acromegaly, or pancreatitis. Background and preproliferative diabetic retinopathy are fre- quently asymptomatic. However, diabetic maculopathy typically causes central vision blurring, while proliferative retinopathy may result in vitreous haemorrhage, noticed as a sudden onset of new Fig. 25.1.1 Investigations in a normal eye. (a) Fundus autofluorescence; (b) Fluorescein angiogram, showing hyperfluorescence (white) restricted within the retinal vasculature; (c) Fourier Domain optical coherence tomography (OCT) of the optic nerve head; (d) OCT angiography of the fovea showing normal peri-foveal microvascular architecture; (e) Fourier Domain OCT through the macula, revealing the cross-sectional retinal architecture to a resolution of 5 microns. Courtesy of Moorfields Eye Hospital.

Section 25 Disorders of the eye 6406 floaters with reduced vision, or a preretinal haemorrhage, noticed as a dark patch in the vision (Fig. 25.1.4). Dense vitreous haem- orrhage can take weeks to clear, sometimes necessitating a vitrec- tomy. Other symptoms include reversible visual blurring, caused by osmotic changes in the lens, or gradual vision loss associated with cataract. Complications of diabetic retinopathy include tractional retinal detachment (Fig. 25.1.5d), nonarteritic an- terior ischaemic optic neuropathy, retinal vascular occlusion, and rubeosis iridis (Fig. 25.1.5c) with secondary neovascular glaucoma. Eventually, proliferative diabetic retinopathy, treated (Fig. 25.1.5b) or untreated, will reach a quiescent involutional stage, in which the visual outcome depends upon the damage pre- viously sustained by critical ocular structures. Retinal fundus fluorescein angiography (FFA) highlights areas of leakage associated with exudates or new vessels, and areas of ca- pillary drop out associated with retinal ischaemia (Fig. 25.1.5a). Optical coherence tomography (OCT) facilitates quantitative monitoring of macular thickening and intraretinal fluid. The Early Treatment Diabetic Retinopathy Study and Diabetic Retinopathy Study established the efficacy and safety of pan retinal laser photo- coagulation for proliferative diabetic retinopathy (Fig. 25.1.5b). Laser to the peripheral retina reduces the risk of severe central vi- sion loss by over 50% at 12 months (Table 25.1.6). The potential efficacy and safety of anti-VEGF injections for proliferative dia- betic retinopathy remains uncertain. Diabetic macular oedema (DMO) was traditionally treated with focal and grid laser to areas of leakage. Intravitreal anti-VEGF agents significantly improve DMO vision outcomes compared to laser, with benefit extending to two years (Table 25.1.6). Intravitreal dexamethasone injections or im- plants and fluocinolone implants are also licensed for DMO, but have increased risk of cataract and elevation in intraocular pres- sure. Tractional retinal detachment can be treated surgically al- though success is variable. Fig. 25.1.2 World map illustrating the variation in the prevalence of moderate and severe vision impairment in adults 50 years or older. Reproduced courtesy of Professor Rupert Bourne, from the Vision Loss Expert Group’s Global Vision Database www.globalvisiondata.org. Fig. 25.1.3 Glaucomatous optic neuropathy with excavation and narrowing of the neuroretinal rim and increased cup:disc ratio. Courtesy of Moorfields Eye Hospital.

25.1 The eye in general medicine 6407 Age-related macular degeneration Age-related macular degeneration (AMD) is a painless, bilateral disease of the outer retina affecting central vision, and is responsible for 90% of blind registration in the United Kingdom. A complex interaction between genetic and environmental factors, pro- moted by complement de-regulation and oxidative stress, results in damage to the retinal pigment epithelium and choriocapillaris with accumulation of extracellular debris (drusen, see Fig. 25.1.3c). Advanced disease is manifest as geographic atrophy

(dry AMD) or choroidal neovascularization (wet AMD, see Fig. 25.1.6) in which fluid and blood leak into the subretinal space. The prevalence of wet AMD rises from 0.2% in people aged 50–54 years, to 8.3% in men and 11.1% in women aged over 80 years. Risk factors include age, smoking, family history, race (Caucasian), and hypertension. Dry AMD (90%) presents with gradually progressive blurring, distortion, and scotomata. Wet AMD (10%) presents acutely, with vision distortion and loss. Diagnosis and monitoring relies on ret- inal fluorescein angiography (FFA) and optical coherence tom- ography (OCT). The management and visual outcomes in wet AMD have dramatically improved in recent years on account of intravitreal injections of antivascular endothelial growth factor (VEGF) agents (see Table 25.1.6). There is currently no treatment for vision loss resulting from dry AMD, but antioxidant vitamin and mineral supplementation may delay progression to advanced AMD (see Table 25.1.6). Uncorrected refractive error Uncorrected refractive error is influenced by the affordability, avail- ability, and willingness of individuals to accept spectacles or other refractive correction. This includes contact lenses, laser refractive sur- gery, and intraocular surgery to augment or replace the natural lens. Changes in refractive error occur throughout life, as a result of a complex interplay between genetic, developmental, and envir- onmental factors that influence eye shape and growth. Infants are typically hyperopic (long-sighted) and shift towards emmetropia (no refractive error) within a few years. Hyperopia is associated with shorter axial globe length and peaks around 65 years of age. Myopia (short-sightedness) peaks in the mid-teenage years and stabilized in early adulthood. It is associated with longer axial globe length. A myopic shift may also develop in older adults, associated with cataract. Astigmatism (>0.75 dioptres of cylinder) occurs when the refractive power of the cornea or lens is not uniform in all meridia. Presbyopia, a near vision impairment associated with loss of lens accommodation, develops from 40 years, and affects virtually all older adults. Amblyopia, or ‘lazy eye’, (a misnomer as it is due to poor visual cortex connectivity and development) de- velops during the critical window for the visual system (birth to age 7 years), if refractive error, squint, or media opacity are not cor- rected, and especially if there is vision asymmetry. Management involves addressing the cause of reduced vision and occluding the better-seeing eye for a few hours daily. Established amblyopic vi- sion impairment cannot be corrected later in life. Common ocular complaints in nonspecialist practice Conjunctivitis Conjunctivitis is an inflammation of the mucous membrane covering the sclera and extending into the fornices, characterized by exudative discharge (Fig. 25.1.7a). It is the most frequent cause of a red eye, and associated signs are illustrated schematically in Fig. 25.1.8. Common causes include bacterial and viral infections, and acute or chronic allergic reactions. Useful features in the history, and typical symptoms and signs, are summarized in Table 25.1.1. Follicles (pale lumps of lymphoid tissue) indicate viral or chla- mydial infection, or drop hypersensitivity. Papillae, which contain a central core of blood vessels, indicate bacterial, allergic, or chronic contact lens-related irritation. Periocular features may indicate less common causes, including eczema, acne rosacea, and characteristic lesions of herpes simplex virus, herpes zoster virus, or molluscum contagiosum (see infectious inflammatory conditions, discussed Table 25.1.5 English Diabetic Retinopathy Screening Programme classification and referral pathways Screening criteria Based on grading two images (centred on the disc and macula) Pathway R0 No retinopathy Annual screening R1 Background retinopathy: MA(s), retinal haemorrhage(s) +/- any exudate Annual screening R2 Preproliferative retinopathy: multiple blot haemorrhages, IRMA, VB, venous reduplication Refer to hospital eye service R3a Proliferative retinopathy, active: • Newly presenting proliferative DR, or • Previous treatment not deemed stable by the treating ophthalmologist, or • New features (compared to a previous reference image set) indicating reactivation of PDR or potentially sight-threatening

change from fibrous proliferation Urgent referral to hospital eye service R3s Proliferative retinopathy, stable treated: evidence of peripheral laser treatment AND stable retina with respect to reference images taken at or shortly after discharge from the hospital eye service Discharge from hospital eye service with benchmark image set P0 No evidence of previous photocoagulation P1 Evidence of previous photocoagulation (focal/grid to macula or peripheral scatter) M0 No maculopathy Annual screening M1 Maculopathy: group of exudates within the macula, or single exudate within 1 disc diameter of the fovea, or single microaneurysm within 1 disc diameter of the fovea with visual acuity 6/12 or less Refer to hospital eye service MA, microaneurysm; VB, venous beading; IRMA, intraretinal microvascular abnormality; DR, diabetic retinopathy; PDR, proliferative DR; Macula, that part of the retina which lies within a circle centred on the fovea whose radius is the distance between the centre of the fovea and the temporal margin of the disc.

Section 25 Disorders of the eye 6408 Table 25.1.6 A summary of key Cochrane systematic reviews summarizing level 1 evidence from randomized controlled trials (RCTs) on the management of ophthalmic conditions (For latest updates please visit eyes.cochrane.org/links-our-reviews) Disease Intervention Studies (n participants) Summary outcome (95% CI) Interpretation of effect of intervention, in comparison to control or alternative intervention Certainty of evidence Citation Wet age- related macular degeneration Bevacizumab versus sham injection Pegaptanib versus sham injection Ranibizumab versus bevacizumab Aflibercept versus ranibizumab 2 (159) 1 (1186) 6 (2446) 9 2 (2412) RR For 15 L gain: 7.80 (2.44–24.98) 2.83 (1.23–6.52) RR 0.90 (0.73–1.11) RR Death 1.10 (0.78–1.57) RR SSAE 1.08 (0.90–1.31) RR 15 L gain: 0.97 (0.85 to 1.11) Anti-VEGF agents probably improve vision at 12 months (23–29% gain 15 letters compared to 3–6% controls) No significant difference in visual outcome Probably no significant difference in rate of death or SSAE. Of 1000 people treated with ranibizumab, 34 may die and 222 may develop SSAEs. Of 1000 people treated with bevacizumab, 27–54 may die and 200–291 may develop SSAEs Ranibizumab and aflibercept both result in around 32% people gaining 15 L vision at 12 months Solomon SD et al. 2014; Moja L et al. 2014; Sarwar S et al. 2016 Dry age- related macular degeneration Multivitamins versus placebo β-carotene versus placebo Vitamin C versus placebo Vitamin E versus placebo Multivitamins versus placebo Zinc versus placebo Lutein or zeaxanthin versus placebo Vitamin E versus placebo Omega 3 fatty acid supplements versus placebo 1 (14 233) 2 (22 083) 1 (14 236) 4 (55 614) 3 (2445) 3 (3790) 1 (6891 eyes) 1 (998) 2 (2343) Incident AMD RR 1.21 (1.02–1.44) RR 1.00 (0.88–1.14) RR 0.96 (0.79–1.18) RR 0.97 (0.90–1.06) Progression to late AMD: OR 0.72 (0.58–0.90) OR 0.83 (0.70–0.98) RR 0.94 (0.87 to 1.01) RR 1.36 (0.31–6.05) HR AMD progression over 5 years: 0.96 (0.84–1.10) Taking vitamin E, β-carotene, vitamin C or vitamin E supplements will not prevent or delay the onset of AMD Antioxidant multivitamin and mineral supplementation may delay the progression of AMD, lutein and zeaxanthin may have little or no effect, and vitamin supplementation may even have a harmful effect. No effect on progression to advanced AMD, or on vision outcomes Evans & Lawrenson JG 2017a; Evans JR & Lawrenson JG 2017b; Lawrence JG & Evans JR 2015 Diabetic retinopathy (DR) Proliferative DR Intensive versus standard blood pressure (BP) control Panretinal photocoagulation laser (PRP) Anti-VEGF and PRP versus PRP alone 15 4 (9276) 1 (61) RR incident DR at 5 years: 0.80 (0.71 to 0.92) RR DR progression at 5 years: 0.88 (0.73–1.05) RR severe vision loss 0.46 (0.24 to 0.86) RR progression 0.49 (0.37 to 0.64) RR loss of >15 L vision: 0.19 (0.05–0.81) More intensive BP control may reduce 5-year incidence of DR, but may not reduce rate of progression PRP laser probably reduces risk of severe vision loss, and the risk of progression at 12 months, by over 50% Anti-VEGF agents have uncertain benefit in the treatment of proliferative DR Do DV et al. 2015;

Evans JR et al. 2014; Martinez-Zapata M et al. 2014 Diabetic macular oedema Anti-VEGF agents (aflibercept, ranibizumab, or bevacizumab) versus macular laser photocoagulation 24 (6007) Network meta-analysis,
15 L gain in vision: Aflibercept RR 3.66 (2.79–4.79) Bevacizumab RR 2.47 (1.81–3.37) Ranibizumab RR 2.76 (2.12 to 3.59) Anti-VEGF therapy increases the likelihood of gaining 15 or more letters of vision at 12 m, from 10% (with laser) to between 25 and 37% (with anti-VEGF). No difference in systemic serious adverse events at 1 year Virgili G et al. 2017 Acute conjunctivitis Topical antibiotics versus placebo 6 (2116) RR (clinical, early) 1.36 (1.15–1.61) RR (microbial, early) 1.55 (1.37–1.76) Topical antibiotics probably improve rates of clinical and microbial remission at
2–5 days (‘early’), and also at days 6–10 Sheikh A et al. 2012 (continued)

25.1 The eye in general medicine 6409 Table 25.1.6 Continued (continued) Disease Intervention Studies (n participants) Summary outcome (95% CI) Interpretation of effect of intervention, in comparison to control or alternative intervention Certainty of evidence Citation Allergic conjunctivitis Topical antihistamines and mast cell stabilizers versus placebo Sublingual immunotherapy versus placebo 30 (4344) 36 (3399) Study heterogeneity SMD ocular symptom score –0.41 (–0.53 to –0.28) Interventions are safe and provide effective short term improvement in symptoms (itching, irritation, watering, and photophobia). The relative efficacy of different interventions in this group is unknown Sublingual immunotherapy probably induces significant reduction in mean total ocular symptom score Castillo M et al. 2015; Calderon MA et al. 2011 Chronic blepharitis Daily eyelid cleaning, and topical antibiotics or steroids 34 (2169) Study heterogeneity Probably no strong evidence for cure Lindsley K et al. 2012 Dry eye syndrome Artificial tears (AT) (over the counter) Autologous serum (AS) versus artificial tears 43 (3497) 5 (92) Study heterogeneity Study heterogeneity AT may be safe and effective in treating symptoms, but are not without side effects. Most agents may have similar efficacies AS may improve symptoms, but findings are inconsistent, and there is no effect on other objective clinical measures Pucker AD et al. 2016; Pan Q et al. 2017 Sickle cell proliferative retinopathy Laser versus no intervention 2 (238) Study heterogeneity Peripheral scatter laser probably prevents incident vitreous haemorrhage and probably reduces vision loss, with minimal adverse effects Myint K et al. 2015 Central retinal vein occlusion with macular oedema Intravitreal anti-VEGF versus sham injection Intravitreal steroids versus sham injection 6 (937) 2 (708) RR 15 L vision gain: 2.71 (2.10–3.49) RR 15 L vision loss: 0.20 (0.12–0.34) Study heterogeneity Anti-VEGF therapy increases the likelihood of gaining 15 letters of vision at 6 months, and reduces the risk of losing 15 letters by 80% Insufficient evidence to determine effect. Adverse effects may include elevated intraocular pressure and cataract Braithwaite T et al. 2014; Gewaily D et al. 2015 Acanthamoeba keratitis Topical chlorhexidine 0.02% versus polyhexamethylene biguanide 0.02%, 1 (55) RR resolution 1.10 (0.84–1.42) Both treatments resulted in similar infection resolution, vision outcomes and risk of needing surgery, and there were probably no serious side effects. Relative efficacy uncertain Alkharashi M et al. 2015 HSV epithelial keratitis (dendritic or geographic) Topical antiviral monotherapy versus placebo or other antiviral monotherapy
+/- debridement 137 (8333) Network meta-analysis with multiple outcomes Epithelial healing at 2 weeks versus placebo: Idoxuridine RR 1.74 (1.03– 2.91) Vidarabine RR 1.81 (1.09–3.01) Interferon RR 1.32 (1.06–1.64)

1. Topical antivirals were probably effective in promoting corneal epithelial healing at 2 weeks compared to placebo: idoxuridine (RR 1.74, 1.03–2.91), vidarabine (RR 1.81,

1.09–3.01) and interferon (RR 1.32, 1.06–1.64)
2. Compared to idoxuridine, multiple agents were more effective: vidarabine (RR 1.13, 1.02–1.25), trifluridine (RR 1.30, 1.18–1.43), acyclovir (RR 1.23, 1.14–1.34) and brivudine (RR 1.34, 1.18–1.51).
3. Compared to vidarabine, multiple agents were probably more effective: trifluridine (RR 1.17, 1.03–1.32) and acyclovir (RR 1.11, 1.03–1.19). The relative efficacy of gancyclovir, oral acyclovir, adjuvant interferon, and debridement is uncertain Wilhelmus KR 2015

Section 25 Disorders of the eye 6410 Disease Intervention Studies (n participants) Summary outcome (95% CI) Interpretation of effect of intervention, in comparison to control or alternative intervention Certainty of evidence Citation Fungal keratitis Topical natamycin 5% versus voriconazole 1% 3 (434) Study heterogeneity Natamycin may be more likely than voriconazole to achieve cure and improved vision outcome at three months FlorCruz N & Evans JR, 2015 Trachoma Topical antibiotics +/–
face-washing Mass antibiotic treatment with oral or topical antibiotics versus placebo Surgery for trichiasis 2 (2560) 14 (3587) 13 (8586) Study heterogeneity Study heterogeneity Study heterogeneity The effect of face-washing, alone or in combination with topical antibiotics, is uncertain Antibiotics reduce active trachoma, compared to placebo, with a relative risk reduction of approximately 20% at 12 m. The relative efficacy of topical and oral antibiotics is uncertain Inconclusive evidence for the relative efficacy of different surgical techniques, epilation and adjuvant antibiotics. Long-term impact of surgical intervention on vision unknown Ejere HOD et al. 2015; Evans JR & Solomon AW 2011; Burton M, et al. 2015 Toxoplasma retinochoroiditis Oral antibiotics versus placebo (or no treatment) Adjuvant corticosteroids 4 (268) 0 RR (recurrence) 0.26 (0.11–0.63) Treatment for 12 months probably reduces risk of recurrence during that period. Effect on visual acuity uncertain No RCT evidence Pradhan E et al. 2016 Jasper S et al. 2017 Onchocerciasis (river blindness) Ivermectin versus placebo Adjuvant doxycycline versus placebo 1 (200) 3 (466) RR (chorioretinitis) 0.02 (0–0.32) Not significant Treatment reduces microfilarial load in skin and eyes. Weak evidence of reduced risk of chorioretinitis in infected individuals. Adverse effects include postural hypotension. Effectiveness in preventing blindness unknown Inconclusive effect on vision outcome at 6 months Ejere HOD et al. 2012 Abegunde AT et al. 2016 Retinitis pigmentosa Vitamin A, Vitamin E, and docosahexaenoic acid versus placebo or each other 3 (866) Study heterogeneity No clear evidence of benefit in terms of mean change in visual field or ERG amplitudes at 1 year, or in mean change in visual acuity after 5 years Rayapudi S et al. 2013 AMD, Age-related macular degeneration; HR, hazard ratio; OR, odds ratio; RR, relative risk; SSAEs, serious systemic adverse effects; n, number of RCTs; SMD, standardized mean L, letter difference.GRADE Certainty of evidence: HIGH MODERATE LOW Table 25.1.6 Continued next). Eyelash examination rarely reveals Pthirus pubis (pubic louse). The preauricular and submandibular lymph nodes are typ- ically enlarged in viral, chlamydial and gonococcal conjunctivitis, and also in Parinaud oculoglandular syndrome, which is associated with Bartonella henselae (cat scratch) and Francisella tularensis (tu- laremia). Cicatricial bands of scarring develop in Stevens–Johnson syndrome, linear IgA disease, chemical injury with acid or al- kali, ocular mucous membrane pemphigoid, trachoma, and graft- versus-host disease (GvHD). Membranes and pseudomembranes develop in conjunctivitis associated with certain infections, and in Stevens–Johnson syndrome, GvHD and severe atopic (vernal) keratoconjunctivitis. Subconjunctival haemorrhage is seen with various viruses (e.g. epidemic outbreaks of enterovirus, coxsackie A24, Ebola, and dengue), and some bacteria. Conjunctival swabs for microscopy, culture, and PCR help to differentiate the

causative organism. Topical antibiotics (e.g. chloramphenicol or sodium fusidate) improve early clinical and microbiological remission rates (Table 25.1.6). There is no specific treatment for viral conjunctivitis, which is highly contagious and self-limiting, but can last several weeks or longer. Allergic con- junctivitis is treated with topical preservative-free lubricants, mast cell stabilizers, topical and oral antihistamines, short courses of topical steroid eye drops, or with sublingual immunotherapy (Table 25.1.6).

25.1 The eye in general medicine 6411 While conjunctivitis is largely benign, there are some important clinical exceptions. Severe, rapid onset, hyperpurulent discharge in a neonate or sexually-active adult indicates Neisseria gonor- rhoeae. This is an ocular emergency requiring immediate Gram stain, and admission for treatment with systemic and hourly top- ical antibiotics, to prevent endophthalmitis and perforation. The incidence of multidrug resistant N. gonorrhoeae is rising globally. Genital chlamydia is associated with a persistent, frequently uni- lateral, conjunctivitis in neonates or adults, which may be mis- taken for viral conjunctivitis. PCR differentiates these. Chlamydia positive patients should be referred to a sexual health clinic for screening and oral antibiotics. Haemorrhagic conjunctivitis in young children may indicate Neisseria meningitidis. Timely rec- ognition offers a valuable opportunity to treat with systemic antibiotics and topical penicillin or cefotaxime drops before men- ingeal involvement. Blepharitis Blepharitis is a common, chronic, noncontagious inflamma- tory condition of the eyelids affecting all ages. Symptoms include watering, itching, burning, or gritty discomfort, photosensitivity, and redness. Signs include injection of the eyelid margins and conjunctiva, crusting of eyelashes, eyelash loss, and occlusion or Fig. 25.1.4 Proliferative diabetic retinopathy and maculopathy: A: microaneurysms; B: dot/blot intraretinal haemorrhages; C: venous dilatation; D: venous loop; E: intraretinal microvascular abnormality; F: new vessels at the disc; G: new vessels elsewhere; H: preretinal haemorrhage; I: circinate hard exudates. Courtesy of Moorfields Eye Hospital.
Fig. 25.1.5 Other features of diabetic eye disease and its treatment: (a) fluorescein angiogram showing enlargement of the foveal avascular zone and a large area of ischaemic capillary shut down in the temporal macula; (b) panretinal photocoagulation scars in peripheral retina; (c) iris rubeosis; (d) advanced diabetic eye disease with tractional retinal detachment and severe maculopathy. Courtesy of Moorfields Eye Hospital.

Section 25 Disorders of the eye 6412 infection of the sebaceous glands and eyelash follicles leading to styes and chalazia (Figs. 25.1.7b and 25.1.8). Blepharitis is also as- sociated with rosacea, seborrhoeic dermatitis, and staphylococcal dermatitis, and can be due to viral and parasitic infections, but in the absence of these treatment is typically conservative with daily eyelid cleaning, warm compresses and lid scrubs (Table 25.1.6). Severe blepharitis can cause toxicity to the ocular surface, however sight-threatening complications are rare. Dry eye/Ocular surface disease Dry eye is a multifactorial disease resulting in tear film in- stability, visual disturbance, and discomfort, associated with inflammation and potential damage to the corneal epithelium. Punctate epithelial erosions are best visualized under cobalt blue light following topical administration of fluorescein sodium (Fig. 25.1.7c). Dry eye results from disturbance to the integrated function of the lacrimal glands, ocular surface, eyelids, and as- sociated sensory and motor nerves, and predisposes to ocular surface infection. The major causes include those resulting from tear deficiency and those resulting from increased tear evapor- ation. Causes of tear deficiency include: primary and secondary Sjogren syndrome; primary lacrimal failure (e.g. age-related, congenital alacrima, familial dysautonomia); secondary lac- rimal failure (e.g. sarcoidosis,

lymphoma, AIDS, GvHD; lacrimal duct obstruction (e.g. due to trachoma, oral mucous membrane pemphigoid, erythema multiforme, chemical and thermal burns); hyposecretion from reflex sensory block (e.g. diabetes, neurotrophic keratitis, contact lens wear); hyposecretion from reflex motor block (e.g. central damage for the facial nerve involving the nervus intermedius, multiple neuromatosis); and side effects of systemic drugs (e.g. antihistamines, β-blockers, antispasmodics, diuretics). The causes of increased evaporative loss include: intrinsic causes, including meibomian oil defi- ciency, low blink rate (e.g. a physiological phenomenon during certain tasks requiring concentration, or a feature of extrapyr- amidal disease), disorders of the lid aperture (e.g. proptosis, high myopia), or a drug action (e.g. isotretinoin); and extrinsic causes, including vitamin A deficiency, contact lens wear, ocular surface diseases such as allergy, and the use of topical drugs (e.g. the pre- servative benzalkonium chloride). Dry eye affects 4.3% of men and 7.8% of women aged 50 years and above in the United States. First-line treatment for tear deficiency is unpreserved lubricants such as hyaluronate, carmellose, polyvinyl alcohol, hypromellose, acetylcysteine, or paraffin. Additional lu- bricants contain osmoprotectants or lipids and patients may also be advised to avoid periocular cosmetics, and modify their diet (increase omega-3 fatty acids). Second-line treatments include soft contact lenses, punctual plugs, topical corticosteroid drops, oral pilocarpine, topical cyclosporine A, and in more severe cases, bio- logical tear substitutes, such as autologous serum. Fig. 25.1.6 Age-related macular degeneration: (a) wet age-related macular degeneration with subretinal haemorrhage at nasal border of neovascular membrane; (b) corresponding optical coherence tomography (OCT) image showing subretinal fluid in wet AMD; (c) dry age-related macular degeneration showing subretinal drusen (pale yellow lesions); (d) corresponding OCT showing drusen in dry AMD. Courtesy of Moorfields Eye Hospital.

25.1 The eye in general medicine 6413 Subconjunctival haemorrhage Benign, sudden onset subconjunctival haemorrhage (Fig. 25.1.7d) usually has no underlying cause. In a minority it is consequent to trauma (e.g. contact lens use) ocular surface disorders, or acute haem- orrhagic conjunctivitis. If subconjunctival haemorrhage develops fol- lowing blunt trauma, globe rupture, or retrobulbar haemorrhage must be excluded. Uncommon systemic risk factors include hypertension, aspirin use, and thrombocytopenia. Subconjunctival haemorrhage is rarely recurrent or persistent, but if so investigation is merited. Manifestations of systemic disease in the eye Vascular The retina has a dual blood supply and approximately 20% of the population have an additional cilioretinal artery. In contrast, the optic nerve head is supplied by collaterals and end arteries, and the latter place it at particular risk of ischaemic injury. Signs associ- ated with retinal vascular disease are summarized schematically in Fig. 25.1.9. Thromboembolic vascular occlusion Central and branch retinal artery occlusion Reduction in flow in the ophthalmic artery, central retinal artery or ciliary arteries results in retinal hypoxia, infarction, and vision loss. Embolic sources include atherosclerotic plaques in the carotid artery, paroxysmal atrial fibrillation, patent ductus arteriosus, cal- cified heart valves, bone fractures releasing fat, peri-natal amniotic fluid, clots dislodging during neurosurgery, septic foci, and foreign bodies (e.g. intravenous talc in drug users). The incidence of central retinal artery occlusion and branch retinal artery occlusion is es- timated to be 0.85 per 100 000 per year in the United States, with a 10-year cumulative incidence of retinal emboli of 1.5%. Risk factors in older patients include hypertension, diabetes mellitus, and giant cell arteritis. Less frequent risk factors include raised intraocular pressure, thrombophilia, sickle cell anaemia, antiphospholipid syndrome, Takayasu’s arteritis, and Susac’s syndrome. Vascular occlusive events result in sudden onset, painless, unilateral vision loss. Amaurosis fugax describes uniocular, fleeting, darkening of the vision, typically associated with passage of an embolus

through a major vessel. Central retinal artery occlusion typically presents with significant vision loss (both central and peripheral), to ‘counting fingers’ or ‘perception of light’, whereas a branch ret- inal artery occlusion results in an altitudinal field defect (superior or inferior quadrantanopia or hemianopia). Examination reveals pale, oedematous retina in the territory of the blocked vessel (Figs. 25.1.9e and 25.1.10a), and emboli may be visualized in some pa- tients, typically at bifurcations. In central retinal artery occlusion, a ‘cherry red spot’ may be seen at the fovea on account of the un- affected underlying choroidal vasculature. Subsequently, the retina becomes atrophic, the affected vessels narrow and sclerose, and disc pallor develops, with an associated relative afferent pupil defect. Fig. 25.1.7 Common presentations: (a) conjunctivitis; (b) blepharitis; (c) dry eye, with punctate epithelial erosions visualized with sodium fluorescein under cobalt blue light; (d) subconjunctival haemorrhage. Courtesy of Moorfields Eye Hospital.

 There is no evidence-based treatment for retinal infarction. If the patient presents early (within 24 hours), management approaches include ocular massage and reduction of intraocular pressure. Urgent referral for cerebrovascular accident (CVA) risk strati- fication is important, to reduce the risk of blindness in the other eye and cerebrovascular events. The visual prognosis for infarcted retina is poor, but neovascularization of the iris or retina is un- common. Vision typically improves in only 22% with nonarteritic central retinal artery occlusion, but in 67% of those 20% who have a spared cilioretinal artery (Fig. 25.1.10a), and in 82% with transient occlusion. In contrast, vision of 6/12 or better is achieved in 89% of branch retinal artery occlusion cases and 100% with transient branch retinal artery occlusion. Ocular hypoperfusion Ocular ischaemic syndrome Ocular ischaemic syndrome is characteristically a unilateral, blinding condition affecting older men who have critical carotid artery stenosis. The estimated incidence is 7.5 cases per million per- sons per year. Common risk factors include hypertension, diabetes, peripheral vascular disease, giant cell arteritis, and aortic arch syn- drome. In younger patients it may be associated with Takayasu’s arteritis, hyperhomocysteinaemia, radiotherapy to the neck, thy- roid orbitopathy, Moyamoya disease, neurofibromatosis, and scleroderma. It is frequently asymptomatic, but may present with episodes of light-induced transient vision loss and a dull, constant ocular pain, which worsens when upright. Examination may reveal fairly subtle signs including retinal haemorrhages, low IOP, and in- flammation in the anterior chamber. In more severe cases, features include conjunctival injection, sluggish pupil reactions, dilated iris vessels, cataract, narrowed retinal arteries, dilated but not tortuous retinal veins, microaneurysms, cotton wool spots (white patches at sites of nerve fibre layer ischaemia), and neovascularization. Unlike diabetic retinopathy, there is usually marked asymmetry between the eyes. FFA reveals delayed choroidal filling and prolonged ar- teriovenous transit time (Fig. 25.1.10b). Carotid endarterectomy may improve vision if there has not been irreversible ischaemic ret- inal injury. Microvascular damage (nonvasculitic) Transient visual obscurations are experienced as momentary darkening of the vision. They are typically associated with tran- sient microvascular interruptions to the retina, or optic nerve head. Nonarteritic ischaemic optic neuropathy develops when re- duced circulation in the short posterior ciliary arteries causes a retrolaminar optic nerve head compartment syndrome in ana- tomically susceptible ‘crowded’ discs. The clinical presentation is covered elsewhere (Chapter 24.6.1). Cilioretinal artery occlusion Cilioretinal artery occlusions (CLRAO) account for approximately 5% of all arterial occlusions. Patients present with sudden onset vision loss associated with a central, centrocaecal, or altitudinal Fig. 25.1.8 Schematic diagram illustrating signs associated with a red eye: A: herpetic vesicles; B: blepharitis with blocked meibomian glands and flakes at bases of eyelashes; C: follicles on the tarsal conjunctiva; D: papillae on the tarsal

conjunctiva; E: microbial keratitis (corneal ulcer); F: mutton fat keratic precipitates on the corneal endothelium; G: hypopyon; H: iris posterior synechiae; I: Koeppe's iris nodules at pupil margin; J: Busacca's iris nodules on the surface of the iris; K: dendritic ulcer staining green with fluorescein (e.g. herpes simplex virus); L: Synechial bands between bulbar and tarsal conjunctiva (symblepharon); M: perilimbal conjunctival injection; N: bulbar conjunctival injection; O: Tarsal conjunctival injection with purulent discharge. Fig. 25.1.9 Schematic diagram illustrating posterior segment vascular signs: A: scars in peripheral retina from recent sectoral laser photocoagulation; B: diabetic retinopathy (Grade R3M1-see Table 25.1.5), with a circinate exudate within the macula, microaneurysms, dot blot intraretinal haemorrhages, a venous loop, cotton wool spots and new vessels elsewhere; C: hypertensive retinopathy with flame- shaped nerve fibre layer haemorrhages and part of a macular star; D: macroaneurysm; E: branch retinal artery occlusion secondary to embolus, with distal retinal pallor; F: branch retinal vein occlusion with cotton wool spots (ischaemic subtype).

25.1 The eye in general medicine 6415 Fig. 25.1.10 Vascular disease affecting the retina: (a) central retinal artery occlusion with cilioretinal artery sparing; (b) fluorescein angiogram showing delayed choroidal filling time (dark choroid) and prolonged arteriovenous transit time in ocular ischaemic syndrome; (c) anastamotic loop with peripheral capillary shutdown (stage 2 sickle cell retinopathy); (d) regressing sea fan in peripheral retina (stage 4 sickle cell retinopathy); (e) central retinal vein occlusion (ischaemic); (f) OCT of cystoid macular oedema in central retinal vein occlusion (CRVO); (g) branch retinal vein occlusion (BRVO); (h) fluorescein angiogram of BRVO showing dilation of the superotemporal venous arcade and its branches (white), and capillary shut down (dark) in the corresponding territory. Courtesy of Moorfields Eye Hospital.

Section 25 Disorders of the eye 6416 visual field defect. They often occur in isolation, with good visual prognosis. However, 40% are associated with central retinal vein occlusion (CRVO) with a moderate visual prognosis, and 15% are associated with arteritic anterior ischaemic optic neuropathy (AION), with a very poor visual prognosis. Examination reveals pallor and oedema in the territory of the affected vessel. There is no specific treatment, providing AION has been excluded. Hypertensive retinopathy Hypertensive retinopathy affects up to 17% of the population and is frequently asymptomatic. However, malignant hypertension may cause headaches, eye pain, and reduced acuity in association with optic disc swelling. Increasing duration and severity of hyperten- sion, age, male gender, and ethnicity influence risk. The clinical features depend on whether the blood pressure is acutely or chron- ically elevated, and may not necessarily follow a classic sequence. For example, arteriolar narrowing may precede the onset of hyper- tension. Chronic features include focal and generalized arteriolar narrowing ('silver' or 'copper wiring'), resulting from intimal thickening with media wall hyperplasia and hyaline degeneration, and arteriovenous nipping. Disruption of the blood-retina barrier with exudation of lipids and blood results in dot, blot, and flame- shaped haemorrhages, microaneurysms, and hard exudates, which may form a 'star'-like distribution around the fovea, and cotton wool spots, which represent interruption to axoplasmic flow in the retinal nerve fibre layer (Fig. 25.1.11). Hypertensive retinopathy is an indicator of end organ microvascular damage, indicating the need to optimize management. Quantitative computer software analyses of digital retinal images are exploring associations be- tween retinal vascular features and the risk of cardiovascular dis- ease. Genome wide association studies have identified novel loci for retinal venular calibre, and may advance understanding of the mechanisms underlying changes in the microcirculation that lead to

cardiovascular disease. Sickle cell retinopathy Sickle cell disease (Chapter 22.6.7) is the most common inherited blood disorder, particularly prevalent in populations of African- American and Hispanic descent. Characteristic ocular features include a vaso-occlusive peripheral retinopathy, but vision loss is un- common. This typically presents between the ages of 10 and 40 years, most commonly in individuals with haemoglobin C with sickling (HbSC) and sickle β-thalassemia genotypes. Proliferative retinop- athy is reported in approximately 43% of HbSC patients by their mid- 20s, compared to 14% of sickle cell haemoglobin (HbSS) patients. Early signs of retinopathy include salmon patch haemorrhages, glistening iridescent spots and black sunbursts (flat areas of hyper- pigmentation). In Goldberg Stage I nonproliferative retinopathy, peripheral precapillary arteriole occlusion leads to ‘silver wiring’ and areas of retinal pallor. In Stage II, nonleaking arteriovenous (AV) anastomoses develop at the border of perfused and non- perfused peripheral retina (Fig. 25.1.10c). In stage III, at a typical latency of 18 months, leaky ‘sea-fan frond’ neovascular complexes develop from the AV anastomoses (Fig. 25.1.10d). These fre- quently autoinfarct and resolve asymptomatically, or leak fluid, which promotes vitreous degeneration and retinal traction. Stage III disease is effectively treated with scatter laser photocoagula- tion to the peripheral retina, aiming to reduce the ischaemic drive (See Table 25.1.6). The benefit of using intravitreal injections of anti-VEGF agents is under investigation. In stage IV, charac- terized by vitreous haemorrhage, and stage V, characterized by tractional retinal detachment, surgical intervention may be ne- cessary. Central vision may also be affected by occlusion of the posterior ciliary arteries causing choroidal infarction and sub- sequent atrophy of the outer retina, which is best visualized on OCT. Ultrawide-field FFA helpfully assesses peripheral perfusion and neovascularization (Fig. 25.1.10d). Other clinical features seen in HbSS include angioid streaks (Fig. 25.1.23b), which de- velop in 1–2% with advancing age, and increased retinal vascular tortuosity. Endogenous pneumococcal endophthalmitis is a rare complication. Orbital involvement is also rare and may include recurrent lacrimal gland swelling, infarction of the orbital bones in children, orbital haematomas causing an orbital compression syndrome, and retrobulbar ischaemic optic neuropathy. Patients may present with fever, lid swelling, facial pain, proptosis, restric- tion of eye movements and associated diplopia, or with sudden vision loss requiring urgent orbit decompression. Minor blunt trauma may also precipitate a hyphaema, with secondary acute elevation in the intraocular pressure and sight-threatening ret- inal arterial occlusion. Radiation retinopathy Radiation retinopathy is a progressive, obliterative angiopathy that develops from months up to 8 years following ionizing radiation to the orbit, globe, head, or neck. It has an estimated incidence of 3–20%, depending on the location of the tumour, treatment char- acteristics (i.e. radiation type, dose and schedule), and use of adju- vant chemotherapy. Patient risk factors include diabetes mellitus, arterial hypertension, and coronary artery disease. It is initially asymptomatic, but vision loss slowly progresses. Clinical fea- tures are variable, and similar to diabetic retinopathy, including microaneurysms, retinal haemorrhages, cotton wool spots,
Fig. 25.1.11 Features of hypertensive retinopathy: A: generalized arteriolar narrowing; B: arteriovenous nipping; C: flame-shaped nerve fibre layer haemorrhages; D: dot/blot intraretinal haemorrhages; E: microaneurysms; F: macular star of hard exudates; G: cotton wool spots. Courtesy of Moorfields Eye Hospital.

 macular oedema with hard exudates, vein and artery occlusions with subsequent ghost vessels, and microvascular nonperfusion with associated neovascularization. OCT reveals inner retinal thinning. The differential diagnosis includes severe anaemia, leu- kaemia, and human immunodeficiency virus (HIV) retinopathy. The evidence base for

treatment is limited, with a potential role for laser and intravitreal injection of anti-VEGF agents. Visual prog- nosis depends on the degree of capillary nonperfusion. Purtscher retinopathy Purtscher retinopathy is a rare, sight-threatening condition associ- ated with trauma (e.g. head trauma, chest compressions), with an annual UK incidence of 0.24 cases per million population per year. Purtscher-like retinopathy is described in association with sys- temic diseases including acute pancreatitis, renal failure, fat em- bolism syndrome, and some connective tissue disorders. Patients typically present with reduced visual acuity or visual field, which is bilateral in 50%. Examination reveals retinal haemorrhages, cotton wool spots, disc swelling and 'Purtscher flecken' - multiple discreet areas of inner retinal whitening in the posterior pole. The clinical diagnosis is supported by FFA. There is no evidence-based treat- ment but systemic steroids are often given, and microvascular risk factors managed. The signs resolve within 6 months and in 50% of cases, vision improves. Chronic features include optic disc pallor and atrophy of the retinal pigment epithelium. Susac's syndrome (Retinocochleocerebral vasculopathy) Susac's syndrome is a rare microangiopathy, first described in 1979, which is characterized by a triad of branch retinal artery occlusion, low frequency hearing loss, and encephalopathy. Plaque-like chronic accumulations of serous material lie between the basement mem- brane and nonluminal side of the retinal arterioles (Gass plaques) in retinal arterioles are highly suggestive of the diagnosis. FFA is used to monitor disease activity and guides systemic management. MRI of the brain is also undertaken to identify associated abnormalities of the corpus callosum or active cerebral ischaemia. Audiology and tools to assess mood changes and paranoia are also valuable for moni- toring disease activity. The mainstay of therapy to prevent vision loss, hearing loss, and neurological damage is immunomodulation with high dose corticosteroids and intravenous immunoglobulins. Other immunosuppressive agents such as mycophenolate mofetil and monoclonal antibody therapies may also be required. Venous occlusion Central (CRVO), hemi (HRVO) and branch (BRVO) retinal vein occlusions develop in response to thrombus formation and oc- clusion in the retinal venous vasculature, and may be ischaemic or nonischaemic. The prevalence of branch retinal vein occlusion is 4.4 per 1000, and of CRVO is 0.8 per 1000. Risk factors include age, ethnicity (higher in Hispanics and Asians, lower in blacks and whites), hypertension, diabetes, and hyperlipidaemia. Rare associ- ations include glaucoma, hyperhomocysteinaemia, hyperviscosity, and systemic inflammatory disorders. Many patients are asymptomatic initially, and notice reduced vision if macular edema develops. Presentation is usually uni- lateral, but bilateral in 5% of branch retinal vein occlusion and 10% of CRVO. Clinical features include increased dilatation and tortuosity of retinal veins, extensive superficial and deep retinal haemorrhages, cotton wool spots, macular oedema, and disc oedema (Figs. 25.1.10e and g). A relative afferent pupil de- fect indicates extensive capillary nonperfusion. Over time the retinal appearance normalizes, but collateral vessels may form at the disc or in affected areas of the retina, along with perivenous sheathing, arteriolar narrowing, and capillary telangiectasia. Sight-threatening complications include persistent macular oedema, and iris and retinal neovascularization. Baseline in- vestigation includes serum glucose, FBC, and ESR. Further investigations are guided by the history. FFA differentiates is- chaemic and nonischaemic subtypes (Fig. 25.1.10h), and OCT enables monitoring of macular oedema, and treatment response (Fig. 25.1.10f) (see next). At presentation, 80% of central retinal vein occlusions are nonischaemic and 20% are ischaemic; however, up to 30% of the nonischaemic subtype convert to become ischaemic over 3 years. Nonischaemic central retinal vein occlusion may resolve completely without treatment of macular oedema, but the visual acuity gener- ally decreases over time, and visual outcomes are especially poor in the ischaemic subgroup. Up to 60% of untreated branch retinal vein occlusion cases also retain good acuity of

6/12 or better at 1 year, but a quarter have poor final acuity of 6/60. Initial observation is appropriate for nonischaemic branch retinal vein occlusion and central retinal vein occlusion if the presenting visual acuity is good. In all cases, underlying systemic risk factors should also be sought and addressed. Intravitreal anti-VEGF agents or steroid implants are now the mainstay of therapy for macular oedema secondary to venous occlusion (see Table 25.1.6), although modified adjunctive macular grid laser may still be applied in certain circumstances. Peripheral retinal ablation with laser photocoagulation is also used to avoid or treat the neovascular complications of ischaemic disease. Haematological Anaemia Anaemia results in conjunctival pallor. Retinopathy commonly oc- curs in severe anaemia (Hb <8 g/dl) or thrombocytopenia (plate- lets <50 × 109/litre), but is often asymptomatic. Examination reveals flame-shaped, deep, or Roth spot-like retinal haemorrhages, and fundal pallor. Less frequently, anaemia may be associated with ar- teriolar and venous tortuosity, cotton wool spots, a macular star, and papilloedema. Hyperviscosity High plasma viscosity causes venous stasis and hypoperfusion. It is associated with bone marrow hyperproliferative states. These include the leukaemias, myeloproloferative disorders, polycy- thaemia, and essential thrombocytosis, and with increased circu- lating immunoglobulin in multiple myeloma and Waldenstrom's maculoglobulinaemia. Patients present with potentially reversible blurred vision. Examination may reveal dilation and segmenta- tion of the retinal veins, retinal haemorrhages, or vein occlusions. Investigations include FBC, serum viscosity, peripheral blood smear, and serum and urine electrophoresis. Coagulopathies Bleeding diatheses are genetic or acquired coagulation defects. Hypocoagulation results in a tendency to bleed. Genetic causes

 include haemophilia and von Willebrand disease. Acquired co- agulation defects include vitamin K deficiency, liver failure, leu- kaemias, scurvy, pharmacological anticoagulation, platelet storage pool deficiency (e.g. Hermansky–Pudlack syndrome), idiopathic thrombocytopenic purpura, thrombotic thromboyctopenic pur- pura, and the haemolytic anaemia elevated liver enzymes and low platelet count syndrome (HELLP). Ophthalmic presentation is uncommon. Signs include subcutaneous petechiae and pur- pura, hyphaema, and haemorrhages which may be located in the subconjunctival space, choroid, retina (Fig. 25.1.10a) or vitreous. These may develop spontaneously or in response to minor trauma. Hypercoagulability is seen in protein C and S deficiencies, factor V Leiden, activated protein C resistance, disseminated intravas- cular coagulation, and antiphospholipid syndrome. It may cause sight-threatening occlusion of the choriocapillaris by fibrin clots, resulting in ischaemic outer retinal injury, disruption of the outer blood-retina barrier, and serous retinal detachment, or retinal vein occlusion. FFA identifies areas of poor perfusion. Neoplastic Lymphoproliferative diseases Leukaemia There is a variety of manifestations of leukaemia in the orbit and eye, and these can result from direct infiltration, haem- atological abnormalities, opportunistic infection, or treatment (e.g. graft-versus-host disease following bone marrow transplant). Retinopathy is characterized by retinal haemorrhages with or without Roth spots (focal collections of white cells) (Fig. 25.1.12a), cotton wool spots, and slow venous flow or venous obstruction (CRVO and BRVO), but may be asymptomatic. Opportunistic infections commonly include toxoplasmosis and herpes viruses. Direct infiltration of the orbit and adnexa may cause proptosis or mass effects but infiltration of the anterior segment is rare. Lymphoma Ocular lymphoma can be separated into adnexal, orbital (Fig. 25.1.12b), and intraocular (Fig. 25.1.12c) lymphomas. Primary intraocular lymphoma (PIOL) has two distinct subtypes: primary vitreoretinal lymphoma (PVRL) involving the vitreous, retina, and optic nerve, and uveal lymphoma, involving the iris, ciliary body, or choroid. PVRL is the commonest intraocular lymphoid malig- nancy and can masquerade as uveitis. Measurement of intraocular cytokine

concentrations, with a high interleukin (IL)-10 relative to IL-6 level is increasingly used to help differentiate PVRL from uve- itis, but vitreous biopsy remains the mainstay of diagnosis. Primary vitreoretinal lymphoma is usually a diffuse large B-cell non- Hodgkin lymphoma, or rarely a T-cell lymphoma. Patients require a full neurological work-up because primary CNS lymphoma may be present at diagnosis (20%) or develop subsequently (60–80%). In contrast, uveal lymphomas are typically extranodal marginal zone B-cell lymphomas and may be associated with systemic lymphoma, Fig. 25.1.12 Neoplastic signs (a) leukaemia, causing peripapillary intraretinal haemorrhages with Roth spots; (b) ‘salmon patch’ in conjunctival lymphoma; (c) vitreoretinal lymphoma; (d) choroidal metastasis located within the macula. Courtesy of Moorfields Eye Hospital.

 but typically not CNS lymphoma. Treatment of PIOL includes sys- temic chemotherapy and/or local radiation or intravitreal chemo- therapy. Orbital and adnexal lymphoma presents insidiously with lacrimal gland enlargement, eyelid swelling, proptosis, motility problems or conjunctival masses, and may also be associated with systemic lymphoma. Systemic metastasis to the eye Choroidal metastases (Fig. 25.1.12d) occur in all cancer types, and are the most common malignant lesion in the eye. The most fre- quent associations are with lung and breast carcinomas. Treatment depends on the nature of the primary malignancy. Lung and breast metastases are typically radiosensitive, but systemic chemotherapy is also used, and local treatments such as photodynamic therapy and intravitreal anti-VEGF agents have also been reported to be effective. Although the overall response of ocular lesions to treat- ment is often good, the average survival following diagnosis of uveal metastases remains just seven months. Inflammatory eye disease Ocular inflammation may result from infectious or noninfectious causes. The latter are frequently autoimmune and are thought to in- volve dysregulated antigen-specific adaptive immunity. A smaller number of rare autoinflammatory conditions, such as Blau’s syn- drome, affect the eye, which also implicates dysfunction of the innate immune system. Many of these conditions have overlapping symptoms and signs, but the treatment options and prognosis vary depending on the underlying diagnosis. Common clinical presentations Keratoconjunctivitis sicca (‘dry eye syndrome’) is common in many inflammatory diseases. Symptoms range from mild ocular surface discomfort with grittiness and burning sensations, to chronic, severe pain and blurred vision. Corneal examination with topical fluorescein under cobalt blue light reveals punctate epithe- lial staining (Fig. 25.1.7c) and mucus filaments, and Schirmer’s Test reveals aqueous tear deficiency. An uncommon complication of some inflammatory diseases is peripheral ulcerative keratitis (Fig. 25.1.13a). This results from immune complex deposition at the corneal limbus, obliterative vasculitis and corneal melting, and has a risk of globe perforation. Cicatrizing conjunctivitis is a feature of several rare dis- eases (discussed next) and can result in symblepharon forma- tion (Fig. 25.1.13b). Episcleritis is a relatively painless pinkness of the eyes, which disappears with topical phenylephrine 2.5%. Scleritis is characterized by severe, constant, boring pain, radi- ating periorbitally, and typically keeping patients awake at night. The associated vessel injection does not disappear with topical phenylephrine. At first presentation, patients should be inves- tigated for associated systemic disease, which occurs in 50%. Fig. 25.1.13 Corneal signs associated with inflammation: (a) peripheral ulcerative keratitis; (b) symblepharon; (c) limbal stem cell failure with secondary corneal neovascularization and central corneal opacification; (d) band keratopathy in an opaque cornea. Courtesy of Moorfields Eye Hospital.

 Useful investigations include ANA, ANCA, urinalysis, chest X-ray, rheumatoid factor, anti-CCP, interferon-γ release assays for TB, and syphilis serology.

Necrotizing scleritis is associated with a range of systemic vasculitides, and requires urgent investigation and treatment. Uveitis is inflammation of the uveal tract (iris, ciliary body, and choroid). It has an incidence of 52 per 100 000 people. Anterior, intermediate, posterior, and panuveitis are anatomically classi- fied according to the ‘Standardization of Uveitis Nomenclature’ criteria. Anterior uveitis (iritis) usually presents with acute, red, painful, photosensitive eyes, with or without hypopyon (Figs. 25.1.15a and b) and reduced vision. Inflammatory cells and haze are seen in the anterior chamber (Fig. 25.1.15a). It is typ- ically treated with intensive topical steroids tapering over six weeks. Intermediate uveitis presents with floaters in the vision, or reduction in central vision associated with cystoid macular oedema. Signs include vitreous cells, vitreous haze, snowballs, snowbanking and peripheral retinal vascular sheathing (Figs. 25.1.16E and F). Posterior uveitis has many different presenta- tions. Retinitis (Fig. 25.1.16I) and choroiditis (Figs. 25.1.16D and G) may be paucifocal (usually infection), multifocal, placoid or serpiginous, and usually require systemic treatment including immunotherapy. Retinal vasculitis (Figs. 25.1.16A and 16B) may be asymptomatic, or cause painless vision loss. Examination re- veals vascular sheathing, associated with perivascular staining, vascular leakage, and capillary nonperfusion on FFA, and this is best visualized in the periphery using a ultrawide-field system. Most uveitis affecting the posterior segment is eye-limited, or un- differentiated (‘idiopathic’), but there are numerous systemic and infective associations. Initial work-up typically includes a full blood count, chest X-ray (in particular to look for hilar lymph- adenopathy, which if found is followed up with a high-resolution CT scan of the thorax), serum angiotensin converting enzyme as a biomarker for sarcoidosis, an interferon-γ release assay for TB, syphilis serology (FTA antibodies) and Lyme serology (in en- demic areas or in travellers). PCR on aqueous or vitreous samples may also be valuable to exclude infection (especially viral). Liver and renal function tests are added if systemic therapy is likely to be needed and additional investigations, such as for systemic vas- culitides, are guided by the context of the presentation. Patients requiring therapeutic immunosuppression to treat noninfectious uveitis (e.g. in association with sarcoidosis or multiple sclerosis) are also at risk of opportunistic ocular infections, including viral retinitis and toxoplasmosis. Noninfectious inflammatory conditions HLA-B27-associated diseases The HLA-B27-associated seronegative spondyloarthropathies, including ankylosing spondylitis (AS), inflammatory bowel dis- ease (IBD), psoriasis, and reactive arthritis affect between 0.5 and 1.9% of the population. Ocular manifestations develop in approximately 33% of patients with AS, 50% with reactive arth- ritis, 3.5–12% with IBD, 10% with psoriasis, and 31% with psori- atic arthritis, and may precede systemic diagnosis. The uveitis is typically anterior, and affects both eyes recurrently, but each epi- sode is usually unilateral. Uveitis in ankylosing spondylitis may be severe, with hypopyon (Fig. 25.1.15a), but posterior segment involvement is uncommon. In IBD, episcleritis (Fig. 25.1.14a) and scleritis are common, and may indicate systemic disease activity. Rarer ocular associations of IBD include retinal artery occlusion (Fig. 25.1.10e and g), ION, optic neuritis, neuroretinitis, retinal vasculitis, Brown syndrome, and orbital myositis. In psoriatic arthritis, patients frequently present with conjunctivitis, and may also develop keratoconjunctivitis sicca, episcleritis, scleritis, and keratitis. Compared to the other spondyloarthropathies, patients with psoriatic uveitis are more likely to have an insidious onset and posterior uveitis. Reactive arthritis is triggered by cross-reactivity to an infection elsewhere in body, typically a genitourinary (e.g. chlamydia) or gastrointestinal (e.g. salmonella, campylobacter, shigella) infection. Clinical features develop weeks after infection, and include arthritis of large joints, conjunctivitis or uveitis, and urethritis (men) or cervicitis (women). After the underlying infec- tion is treated, the arthritis and inflammatory ocular features are usually self-limiting, and seldom recurrent or chronic and pro- gressive. Very rarely, it is associated with panuveitis,

multifocal choroiditis, and optic disc oedema. Rheumatoid arthritis Rheumatoid arthritis is commonly associated with keratoconjunc tivitis sicca, Sjogren syndrome, episcleritis, scleritis, which may be diffuse or nodular, and necrotizing or nonnecrotizing, and marginal keratitis or peripheral ulcerative keratitis. Painless Fig. 25.1.14 Episcleral and scleral signs associated with inflammation: (a) episcleritis; (b) scleromalacia, revealing the underlying pigmented uvea. Courtesy of Moorfields Eye Hospital.

25.1 The eye in general medicine 6421 scleromalacia perforans in a noninflamed, white eye, leads to scleral thinning, and typically affects older women with active sys- temic seropositive disease and vasculitis (Fig. 25.1.14b). Posterior scleritis and retinal vasculitis are less common. Ocular surface disease is managed like other causes of dry eyes. Nonnecrotizing scleritis is an indication for initiation or increased immunosup- pression, and often requires a combination of systemic corticoster- oids and other immunosuppressive drugs, such as mycophenolate mofetil or anti-TNFα agents. Juvenile idiopathic arthritis Juvenile idiopathic arthritis is characterized by persistent joint inflammation presenting before the age of 16 years, and is clas- sified according to the ‘International League of Associations of Rheumatologists’ criteria. One-third develop chronic, usually low-grade, anterior uveitis. Uveitis is more frequent in girls with ANA-positive oligoarticular disease, but more severe in boys. It is frequently asymptomatic, or atypical in presentation, with a white eye on examination. Adherence to screening guidelines is therefore Fig. 25.1.15 Anterior chamber signs associated with inflammation (a) small (1 mm) hypopyon and anterior chamber haze; (b) large (5 mm) hypopyon associated with fungal keratitis; (c) mutton fat keratic precipitates; (d) Koeppe’s iris nodules; (e) iris posterior synechiae revealed against an underlying opacified lens; (f) endogeneous endophthalmitis in a patient with pseudomonas septicaemia. Courtesy of Moorfields Eye Hospital.

Section 25 Disorders of the eye 6422 essential. Vitritis and peripheral retinal vasculitis are uncommon but can occur. Detection and aggressive treatment of uveitis are vital to reduce the incidence of chronic, sight-threatening compli- cations, which include band keratopathy, cataract, glaucoma, and cystoid macular oedema. The systemic management of juvenile idiopathic arthritis has changed considerably in recent years and is discussed elsewhere. Uveitis is treated initially with tapering top- ical corticosteroids. If not controlled on twice daily steroid drops, systemic methotrexate is added, and if this also fails, anti-TNFα agents are used. Multiple sclerosis Multiple sclerosis (MS) is a neuroinflammatory condition diag- nosed according to the 2010 revised McDonald’s criteria, with a UK prevalence of between 100 and 140 cases per 100 000 population. Ophthalmic manifestations include optic neuritis, eye movement disorders, and intermediate uveitis. Between 7 and 11% of patients with isolated intermediate uveitis are subsequently diagnosed with MS, but neuroimaging is not undertaken in these patients with isolated intraocular inflammation unless required to exclude MS prior to anti-TNFα treatment for refractory disease. Sarcoidosis Sarcoidosis is a multisystem granulomatous inflammatory disorder of unknown aetiology, which presents in the eye in 25% of patients, often before other organs are involved. Risk factors include African- American race and female sex, with peak onset before 40 years. The most common presentation is granulomatous acute anterior uveitis, accompanied by ‘mutton fat’ keratic precipitates, and Koeppe and Busacca iris nodules (Fig. 25.1.15d). Other presentations include lac- rimal gland enlargement, orbital involvement, keratoconjunctivitis sicca, and yellowish conjunctival or scleral nodules. Less frequent are band keratopathy, secondary to hypercalcaemia and chronic uveitis, and interstitial keratitis. Posterior segment features occur in up to a third of

patients. These include vitritis, in which cells tend to aggregate into clumps, and mid-peripheral periphlebitis with perivascular sheathing. Severe periphlebitis of branch veins is only rarely occlusive, with associated focal haemorrhages. Multiple small, pale granulomata in the peripheral retina are character- istic, but large choroidal nodules and optic nerve granuloma may also be seen. Peripheral retinal neovascularization is uncommon. Investigations include chest radiograph, chest CT, and serum angiotensin converting enzyme, but definitive diagnosis requires supportive histopathology, and the conjunctiva is one potential bi- opsy site. Treatment is typically initiated with corticosteroids, with early addition of second-line immunosuppressive agents such as methotrexate or mycophenolate mofetil. Behçet's disease Behçet's disease is a rare systemic inflammatory disease associ- ated with occlusive vasculitis of unknown cause, involving small arteries and veins (Figs. 25.1.17a and b). Eye problems develop in 60–80% of patients, and are more severe in men with the HLA- B5 haplotype, and especially the BW51 subtype. Behçet's is most prevalent in Japan and countries along the 'Silk Route'. Ocular features include bilateral, usually sequential, recurrent, acute an- terior, or panuveitis, which is severe and may be accompanied by hypopyon (Fig. 25.1.15a). Retinal vasculitis results in inflamma- tory branch retinal vein occlusions associated with focal haemor- rhages and cotton wool spots. White, fluffy patches suggestive of focal retinal infiltration by polymorphonuclear lymphocytes are also typical, and can be difficult to clinically differentiate from in- fectious retinitis. Cystoid macular oedema may cause blurring of central vision. If not therapeutically controlled, progressive obliter- ation of the entire retinal vasculature, detected with FFA, results in neovascularization and vitreous haemorrhage, with eventual optic nerve and retinal atrophy and vessel sheathing. High dose cor- ticosteroids are used to treat acute attacks, followed by long-term immunosuppression and early escalation to the use of biologics. Anti-TNFα drugs are often used if concomitant TB has been ex- cluded, but in TB endemic areas interferon-α-2a is preferred. In the prebiologic era visual prognosis was poor, with blindness in half of patients within 5 years of the first episode of uveitis. Systemic lupus erythematosis Systemic lupus erythematosis (SLE) is a multisystem autoimmune disease that affects 28 per 100 000 population, especially non- caucasian young women. It is associated with ocular manifest- ations in a third of patients. Keratoconjunctivitis sicca is common. Less frequent presentations include episcleritis, scleritis (necro- tizing or nonnectrotizing, anterior or posterior), and peripheral ulcerative keratitis. Orbital inflammation is rare, and presents acutely with lid oedema, proptosis, conjunctival injection and chemosis, motility restriction, elevated IOP, and pain associated with myositis. Uveitis is not a feature of SLE. A bilateral, but often asymmetric, microangiopathic retinopathy may develop, resulting Fig. 25.1.16 Schematic diagram illustrating posterior segment inflammatory signs: A: occlusive vasculitis with segmental perivenous sheathing; B: phlebitis; C: acute neuroretinitis with swelling of the optic nerve head and fine exudates at the macula (e.g. bartonella); D: multifocal choroiditis (e.g. sarcoid); E: snowbanking in vitritis; F: snowballs in vitritis, and peripheral periphlebitis; G: choroidal granuloma; H: chorioretinal scar (e.g. toxoplasma); I: focal retinitis.

 from complement and immunoglobulin deposition in arteriolar vessel walls. This may be subtle, or lead to retinal haemorrhages, cotton wool spots, arterial narrowing, and venous dilatation with tortuosity. Hypertensive retinopathy may develop if there is renal involvement. Lupus choroidopathy leads to single or multifocal serous detachments of the retina and retinal pigment epithelium, detected with FFA. These mimic central serous chorioretinopathy (CSR) but, unlike CSR, settle quickly with steroid therapy. The optic nerve is infrequently involved, but may develop anterior or posterior ischaemic optic neuropathy. Rarely, a

severe vaso- occlusive ischaemic retinopathy extending out to the far retinal periphery, with neovascularization, may cause vision loss. This is detected with FFA, and is more common in patients with anti- dsDNA. It is associated with CNS lupus, and a poor survival prog- nosis. Antiphospholipid syndrome is also associated with retinal vein and, to a lesser extent, artery occlusions. Patients with sys- temic lupus erythematosis require systemic immunosuppression, titrated to their disease severity. Familial juvenile systemic granulomatosis (Blau syndrome) Blau syndrome is a rare autosomal dominant autoinflammatory disease associated with a mutation in the NOD2/CARD15 gene. Clinical features include a triad of chronic anterior or panuveitis with multifocal choroiditis, polyarthritis, and a granulomatous papulo-erythematous rash involving the trunk and extremities. The wider central nervous system and other organs may also be involved. It is increasingly appreciated that Blau's mutations may have been an unrecognized underlying cause of disease in some patients previously diagnosed with juvenile sarcoidosis. Treatment is with systemic immunosuppression. Sjogren's syndrome Sjogren's syndrome is an autoimmune disease that may be pri- mary, or secondary to a connective tissue disease (e.g. rheuma- toid arthritis, systemic lupus erythematosis, systemic sclerosis, primary biliary cirrhosis, thyroid disease). It is an unusual cause of dry eye, resulting from slowly progressive inflammation of the exocrine glands, and can be accompanied by dry mouth. The USA incidence is 4 per 100 000 population per year. Women are affected nine times more frequently, typically from the fourth and fifth dec- ades. Ocular surface features include keratoconjunctivitis sicca, which may be mild or progress to more severe corneal vascular- ization and scarring. Investigations reveal positive ANA, rheuma- toid factor, anti-Rho, and anti-La antibodies. The main treatment is preservative-free topical lubricants, but topical ciclosporin can also be used in more severe disease. Scleroderma (systemic sclerosis) Scleroderma is a multisystem disorder of unknown aetiology re- sulting in fibrosis which may be localized to the skin, or include internal organs. The prevalence is 44 per 100 000 (Canada), and eyelid involvement occurs in two-thirds. It more commonly affects women and people of African descent. Common fea- tures include skin tightness resulting in blepharophimosis, and occasional lagophthalmos, telangiectasia of the eyelids, and keratoconjunctivitis sicca. Hypertensive retinopathy, and retinal vein and artery occlusions may also develop. Most patients are ANA positive; anticentromere, Scl-70, or anti-RNA polymerase III may also be positive. Blood pressure control is important, and preservative-free topical lubricants are used to manage the ocular surface symptoms. Relapsing polychondritis Relapsing polychondritis is a rare multisystem autoimmune dis- order involving hyaline cartilage in the eyes, ears, nose, respira- tory system, and joints. It has an incidence of 3.5 cases per million per year, with a peak onset at 40–60 years. Half of patients have ophthalmic manifestations. Clinical features frequently include episcleritis and scleritis, which may be anterior or posterior. Less frequent are anterior uveitis, keratoconjunctivitis sicca, peripheral ulcerative keratitis, retinopathy (with cotton wool spots and haem- orrhages), vein occlusions, and ischaemic optic neuropathy. It is treated with systemic immunosuppression. Dermatomyositis and polymyositis Dermatomyositis and polymyositis are rare systemic vascular disorders associated with chronic striated muscle inflammation. The incidence is between 2 and 10 per million per year, and it oc- curs more frequently in women. It may develop in association with drugs (e.g. tamoxifen, penicillamine), viral illnesses, auto- immune and mixed connective tissue disorders, and some cancers. Ocular features include conjunctivitis, episcleritis, and anterior uveitis. Retinal ischaemia with cotton wool spots is uncommon, and closure of retinal capillaries may rarely result in ischaemic vi- sion loss. Myositis involving the extraocular muscles is also rare. Dermatomyositis is associated with a characteristic heliotrope rash involving the periorbital area. Treatment usually also involves sys- temic immunosuppression. Large vessel vasculitidies Giant

cell arteritis (GCA) presenting with sudden, painless, severe vision loss from anterior ischaemic optic neuropathy, typically to perception of light, is an ophthalmic emergency as it can rapidly progress to sequential, bilateral, irreversible blindness. Urgent treatment with high dose corticosteroids is required pending fur- ther investigation with a temporal artery biopsy. Takayasu's arteritis is a granulomatous vasculitis predomin- antly affecting the aorta and its main branches. It has an incidence of 1 to 3 per million per year (in Japan and United States), and is most common in young women. One-third develop ophthalmic involvement including hypertensive retinopathy and Takayasu's retinopathy. This may evolve from dilation of small vessels and microaneurysm formation, to arteriovenous anastomoses, then neovascularization with vision-threatening sequelae, including vitreous haemorrhage and neovascular glaucoma. Less frequent ocular presentations include ocular ischaemic syndrome, arteritic ischaemic optic neuropathy, and PION. Treatment is with cortico- steroids, and subsequent steroid sparing agents for severe or refrac- tory disease. Medium vessel vasculitidies Polyarteritis nodosa is an ANCA-negative necrotizing vasculitis. The incidence is less than one per million per year in the United Kingdom, and ophthalmic manifestations occur in 10 to 20%. It is associated with hepatitis B, HIV, and parvovirus B19. Clinical features include keratoconjunctivitis sicca, peripheral ulcerative

 keratitis, episcleritis, scleritis (which may be necrotizing), serous retinal detachments, ION, and cranial neuropathies. The most fre- quent ocular manifestations are retinal and choroidal vasculitis, and hypertensive retinopathy secondary to glomerulonephritis. Treatment involves corticosteroids and pulsed IV cyclophospha- mide followed by antiviral agents and plasma exchange. Kawasaki disease has its highest incidence among children under 5 years in Japan, at 216 cases per 100 000 per year, with a peak in children 9–11 months old. Features include bilateral conjunctivitis without discharge, and anterior uveitis, in the context of fever, rash, lymphadenopathy, and involvement of other mucosae and nails. Optic neuritis and occlusion of the ophthalmic artery are rare. Kawasaki disease is treated with high dose aspirin and intravenous immunoglobulin, but the eyes do not require specific treatment. ANCA-associated small vessel vasculitidies The ANCA-positive small vessel vasculitidies include granulo matosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis, and microscopic polyangiitis. The latter is only rarely associated with ocular disease. Treatment to induce remission typ- ically requires oral corticosteroids and pulsed IV cyclophospha- mide, or rituximab, with chronic treatment of less severe disease achieved with an antiproliferative immunosuppressant such as mycophenolate mofetil. Granulomatosis with polyangiitis is a multisystem, granuloma- tous vasculitis of unknown aetiology, associated with tissue ne- crosis, predominantly affecting the upper respiratory tract, kidneys, and lungs. It is rare, with a prevalence of 3–16 per 100 000 (United States and Northern Europe), and is slightly more common in men. Approximately half develop ocular manifestations, most frequently involving the orbit, and sight loss develops in approximately 8%. Symptoms include ocular redness, and pain associated with nec- rotizing scleritis, cicatricial conjunctivitis, or peripheral ulcerative keratitis. Retro-orbital granuloma causes proptosis, optic nerve compression or infiltration with disc swelling and choroidal folds, and ocular motility disturbance. Nasolacrimal duct damage causes epiphora. Other presentations include uveitis, occlusive retinal vas- culitis, and ischaemic optic neuropathy. Investigation frequently reveals positive proteinase 3. Treatment involves chronic systemic immunosuppression, initially with prednisolone and pulsed IV cyclophosphamide or rituximab. Churg-Strauss syndrome is a myeloperoxidase ANCA-positive primary eosinophilic vasculitis with granuloma formation, which affects multiple organs, primarily the lungs, joints, and peripheral nerves. The prevalence is 10–15

per million and ocular involvement is uncommon. Presentations include conjunctival nodules, periph- eral ulcerative keratitis, episcleritis, scleritis, retinal vasculitis, and rarely uveitis, retinal artery occlusion, ischaemic optic neuropathy, cranial neuropathies, and orbital inflammation. Cogan's syndrome Cogan's syndrome is a rare vasculitis affecting the eyes and ears, associated with inner ear antibodies, ANCA, and antiendothelial antibodies. In the typical form, patients develop vestibuloauditory symptoms, including sensorineural hearing loss, tinnitus and vertigo, and recurrent interstitial keratitis, which may result in corneal vascularization and blindness. In the atypical form, which is associated with rheumatoid arthritis and aortitis, other ocular structures may be inflamed, leading to episcleritis, scleritis, and choroiditis. It is traditionally treated with prompt corticosteroids to reduce the risk of deafness, and death from aortitis. There may also be a role for biological agents such as infliximab. Vogt-Koyanagi-Harada disease Vogt-Koyanagi-Harada disease is a multisystem, nonnecrotizing granulomatous inflammatory disease. It is thought to be of auto- immune aetiology characterized by T-lymphocyte responses against melanocyte targets. It is strongly associated with certain human leukocyte antigens (HLA), including DR4. The true popu- lation prevalence is unknown, but it appears to be slightly more common in pigmented races, accounting for approximately 7% of all uveitis clinic referrals in Japan, and between 1 and 4% of refer- rals in the United States. Patients typically present in young adult- hood with symptoms including headache, meningism, tinnitus, hearing loss, blurring of the vision, photosensitivity, watering, and orbital pain. Clinical diagnosis requires an absence of a pre- ceding history of penetrating ocular injury or surgery because sympathetic ophthalmia can have a similar presentation. The ocular features are characterized by a bilateral granulomatous panuveitis, exudative retinal detachments associated with multi- focal inflammation and thickening of the choroid, with nodular inflammatory deposits located between Bruch's membrane and the retinal pigment epithelium, and disc hyperaemia or oedema. Useful investigations in the acute setting include lumbar punc- ture, which reveals CSF pleocytosis, ultrasound, OCT, FFA, and ICG. The acute management includes high dose systemic cor- ticosteroids tapering over 3–6 months, and additional immuno- suppressive agents may be required to prevent relapses. After the initial uveitic presentation, further inflammatory sequelae may develop over subsequent months, including vitiligo, poliosis, alopecia, and hearing impairment. These may be followed by a chronic recurrent phase, in which other eye signs develop, such as perilimbal vitiligo ('Sugiura's sign'), choroidal depigmentation from loss of choroidal melanocytes, which results in a pale disc and a bright orange-red 'sunset glow' fundal appearance, and small well-circumscribed yellow areas of chorioretinal atrophy, particularly in the inferior mid-peripheral retina. Early, aggres- sive corticosteroid treatment of acute disease can achieve good long-term visual outcomes, but sight-threatening complications may develop in chronic, recurrent disease, and include subretinal fibrosis, choroidal neovascular membranes, cataract, glaucoma, and extensive chorioretinal atrophy. Sympathetic ophthalmia This rare, bilateral, nonnecrotizing, granulomatous uveitis de- velops after penetrating eye injury or vitreoretinal surgery, at a latency of days to decades, but most frequently within 3 months. It results from immune recognition of normally sequestered intraocular proteins in the injured eye, leading to an adaptive auto- immune inflammation in the contralateral eye. As the injured eye is often already poorly functioning, this sympathetic ophthalmia in the better eye poses a serious risk to vision. The UK incidence is 0.03 per 100 000 people per year. Symptoms include photophobia, mild pain, watering, and blurring. Ocular features can involve both the anterior and posterior segment of the eye. Dalen-Fuchs

25.1 The eye in general medicine 6425 nodules are characteristic yellow-white deposits in the mid-retinal periphery which represent granulomatous inflammatory lesions adjacent to retinal pigment epithelium. Optic nerve swelling and exudative retinal detachment may also occur. Rapid treatment with adequate, high dose systemic immunosuppression is indi- cated to preserve sight. Paraneoplastic and autoimmune retinopathy Autoimmune retinopathy (AIR) encompasses a spectrum of rare autoimmune diseases, including cancer-associated retinopathy (CAR), melanoma-associated retinopathy (MAR) and presumed nonparaneoplastic autoimmune retinopathy (npAIR). These dis- eases primarily affect outer retinal function, and extensive inves- tigation is required to make this diagnosis of exclusion. Patients typically present from the fifth decade (range 24 to 85 years) with rapidly progressive, sequential, bilateral, painless vision loss, and variable additional symptoms: reduced colour vision, photosensi- tivity, shimmering lights, central scotoma and glare, indicating predominant cone dysfunction; or night blindness, ring scotoma and peripheral field loss, indicating predominant rod or bipolar cell dysfunction. Examination reveals a retina and optic disc which is normal in appearance. Cancer-associated retinopathy usually pre- sents weeks to years after diagnosis, most frequently, of small cell lung cancer, breast or ovarian carcinoma, or haematological ma- lignancy. Melanoma-associated retinopathy presents, on average, 3.6 years (range 1 month to 19 years) after melanoma diagnosis, or in the context of metastatic disease. An electroretinogram, OCT, and fundus autofluorescence assist diagnosis. Access to serological investigation for antiretinal antibodies is limited, and of uncertain value. Treatment approaches include systemic immunosuppres- sion, intravenous immunoglobulin, or plasmapheresis, but lack an evidence base. Diagnostic delay and poor visual outcomes, some- times within months of onset of symptoms, are common. Other, very rare, paraneoplastic retinopathies presenting with rapidly progressive bilateral vision loss include: diffuse uveal melanocytic proliferation, in which orange mottling of the fundus and serous retinal detachment are seen in association with car- cinoma; and paraneoplastic vitelliform maculopathy, most com- monly associated with melanoma. IgG4-related disease IgG4-related disease is a single or multiorgan, fibroinflammatory process of unknown pathophysiology. It is characterized histologically by a lymphoplasmacytic cell infiltrate rich in IgG4 plasma cells, obliterative phlebitis, and fibrosis. Clinical presenta- tions may include sclerosing dacroadenitis, orbital nerve enlarge- ment associated with orbital myositis and lacrimal gland disease, sclerosing orbital inflammation, scleritis, uveitis, or optic neur- opathy. Treatment includes corticosteroids, B-cell depletion with rituximab and TNF-blockers such as infliximab. There is an asso- ciated increased risk of lymphoma. Cicatrizing diseases Numerous rare disorders are associated with sight-threatening cicatricial conjunctivitis. Features include progressive conjunctival scarring, limbal stem cell deficiency, and ocular surface failure, re- sulting in vision loss from corneal opacification. The annual UK incidence of ocular mucous membrane pemphigoid (OMMP) is 0.8 per million, of Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) 0.2 per million, and of other causes of cicatrizing conjunctivitis, 0.2 per million. Other causes in- clude atopic keratoconjunctivitis, Sjogren’s syndrome, ocular ros- acea, drug-induced conjunctival cicatrization, graft-versus-host disease, epidermolysis bullosa acquisita, linear IgA disease, and paraneoplastic mucocutanous disorders. Ocular mucous membrane pemphigoid Mucous membrane pemphigoid is a systemic autoimmune dis- ease. Loss of immune tolerance to basement membrane antigens precipitates inflammation which results in recurrent blistering of the skin and mucous membranes, with consequent progres- sive scarring. Ocular involvement occurs in 70%, and blindness in a third without early diagnosis and appropriate immunosup- pression. Acute and rapidly progressive disease is uncommon; patients typically present with persistent low-grade conjunctiv- itis, gradually developing dry eye, symblepharon, cicatricial en- tropion, trichiasis, and

ptosis. Conjunctival and oral mucosal biopsies for direct immunofluorescence show linear deposition of IgG, IgA, and complement on the epithelial basement mem- brane. Positive indirect immunofluorescence demonstrates circu- lating antibodies. Treatments include dapsone or sulphasalazine for mild inflammation, antimetabolites (mycophenolate mofetil, methotrexate or azathioprine) for moderate inflammation, and methyl prednisolone, rituximab, or cyclophosphamide for severe inflammation. Stevens–Johnson syndrome and toxic epidermal necrolysis Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are immune-mediated dermatobullous diseases. Patients present with fever, followed by cutaneous and mucous membrane signs, resulting from separation of the epidermis from the dermis, and necrosis. TEN is more severe that SJS, and is often drug re- lated. Associations include sulpha containing drugs, NSAIDs, various vaccinations, and some Chinese herbal medications. HIV increases the risk of SJS a hundredfold. Long-term complications develop in 50–90% of patients. Functional alteration of the con- junctiva and lacrimal system result in scarring and cicatrization. The diagnosis is confirmed by biopsy which reveals full thickness epidermal necrolysis. Initial acute management includes stop-ping the trigger, supportive care with adequate nutrition and fluid replacement coupled with both local and systemic cortico- steroid therapy. Ocular pseudomembranes are left in place as they typically separate, and lower lid crusting is reduced with saline washes. Immunosuppression with ciclosporin may slow disease progression but the evidence for this is anecdotal. Linear IgA disease Linear IgA disease is a very rare, chronic, acquired, subepithelial blistering disease which causes cicatricial conjunctivitis and chronic ocular surface discomfort. It affects people of all ages, but most commonly those over 60 years. The incidence is less than 0.5 per million per year. It may be precipitated by infection or drugs (e.g. vancomycin, penicillins). Direct immunofluorescence reveals IgA antibody deposition along the conjunctival basement mem- brane. Treatment includes dapsone or sulphonamides. The ma- jority enter spontaneous remission.

 Infectious inflammatory conditions Clinical presentations Infection of the orbit, adnexa, and eye by bacteria, fungi, rick- ettsia, viruses, protozoa, and helminths results in a variety of clinical presentations. Sight-threatening presentations, includ ing endophthalmitis (Fig. 25.1.15f), orbital cellulitis, keratitis (Fig. 25.1.20), and posterior uveitis (Fig. 25.1.21), require urgent recognition and management. Cavernous sinus thrombosis, which is most commonly associated with a staphylococcal skin abscess and sepsis is discussed elsewhere. Endophthalmitis Endophthalmitis (Fig. 25.1.15f) is typically caused by bacteria or fungi, and may be exogeneous or endogeneous. Exogeneous endophthalmitis results from the introduction of microorgan- isms into the eye, following surgery or trauma. Postoperative endophthalmitis is rare, with an incidence of 0.03–0.2%, and is most frequently associated with staphylococci and streptococci. Endophthalmitis following ocular trauma is uncommon in the ab- sence of a retained intraocular foreign body. The common organ- isms include staphlococci, streptococci, Gram negative bacteria (e.g. pseudomonas and enterobacteriaceae) and aspergillus spe- cies. Symptoms include redness, pain, and eyelid swelling, floaters, photosensitivity, and rapid onset of reduced vision. Signs include cells in the anterior chamber, a hypopyon (Fig. 25.1.15a), dense fi- brinous exudate in the anterior chamber, and a reduced view of the fundus. Endogeneous endophthalmitis is less common, accounting for 2 to 16% of all endophthalmitis. Fungal infection with candida and aspergillus species is a major subgroup, especially in intra- venous drug users. Endogeneous endophthalmitis results from haematogeneous spread of microorganisms to the eye, and is bi-lateral in a third of cases. Risk factors can be identified in only 50%, and include immune compromise, diabetes mellitus, malig- nancy, abscesses, indwelling lines, and endocarditis. In

candida endophthalmitis, characteristic small, dense, white ‘snowballs’ are seen in the vitreous with white foci of infection in the choroid and retina (Fig. 25.1.21a). Endophthalmitis is sight-threatening, and requires prompt clin- ical diagnosis and urgent treatment with intravitreal and systemic antimicrobial agents. Aqueous and vitreous samples are taken for microscopy, culture, and sensitivity. A range of molecular diag- nostic approaches are also available. Suspected cases require sys- temic work-up, with blood, urine and sometimes CSF sampling, and imaging to identify infective foci and guide systemic therapy. Visual outcomes are variable, and often very poor if the presenta- tion or management is delayed. Fig. 25.1.17 Inflammatory posterior segment signs in the retina and choroid (infectious and noninfectious): (a) fluorescein angiogram of peripheral occlusive vasculitis (dark areas are nonperfused); (b) severe occlusive vasculitis with retinal vascular whitening and intraretinal haemorrhage; (c) multiple choroidal granulomas; (d) burnt out, atrophic chorioretinal scars in a patient who has previously had multifocal chorioretinitis. Courtesy of Moorfields Eye Hospital.

25.1 The eye in general medicine 6427 Orbital and preseptal cellulitis Orbital cellulitis is a sight-threatening infection of the tissues pos- terior to the orbital septum, which most commonly results from ethmoid sinus infection. Other causes include direct inocula- tion following trauma or surgery, extension of infection from periorbital structures, and haematogeneous spread. Preseptal cel- lulitis is infection of the tissues of the eyelid and orbit anterior to the septum. Orbital cellulitis is rare, with an incidence of 0.1 per 100 000 adults, but it is more than 10 times more common in chil- dren. Risk factors in children include upper respiratory tract in- fections and sinus disease, and the most common organisms are streptococci, haemophilus, and staphlococcus species. Risk factors in adults include immunosuppression and trauma, and the organ- isms are more variable, including aspergillus and other moulds. Patients with preseptal cellulitis present with eyelid erythema, but a white globe and no signs of orbital or optic nerve involvement (Fig. 25.1.19). In children, preseptal cellulitis can evolve into or- bital cellulitis rapidly, necessitating frequent review. Patients with orbital cellulitis are typically systemically unwell, and present with conjunctival chemosis and oedema, restriction of eye movements, pain, diplopia, and proptosis. Optic nerve compromise is indicated by blurred vision, changed colour perception, reduced field, an af- ferent pupil defect, and disc swelling. While preseptal cellulitis can be treated with oral antibiotics, orbital cellulitis requires admission for intravenous therapy, orbital imaging, and surgical drainage of any orbital or subperiosteal abscess. Rarely, orbital cellulitis can spread intracranially. Keratitis Keratitis is an ulcerating corneal infection that, without prompt treatment, can lead to scarring, thinning, perforation, and vision loss. Bacterial keratitis, usually pseudomonal, is 15 times more common in soft contact lens wearers (Fig. 25.1.20b). Patients present with an acute onset, painful red eye. Examination under cobalt blue light with topical fluorescein typically re- veals a circular corneal epithelial defect with underlying stromal opacification (infiltrate), often near to the centre of the cornea. Intensive treatment with hourly topical antibiotics for 48 hours is necessary, with review of treatment response. Various topical antibiotics are efficacious, including fluoroquinolones and forti- fied aminoglycoside-cephalosporin combinations, but the role of adjuvant corticosteroids is uncertain (Table 25.1.6). With prompt treatment the visual prognosis is usually good. Acanthamoeba infection causes a more indolent, potentially blinding keratitis in contact lens wearers or following corneal abra- sion. The annual UK incidence is 1.3 per million adults, and 21.1 per million in contact lens wearers. Risk factors include living in Fig. 25.1.18 Optic nerve signs: (a) atypical optic neuritis (e.g. sarcoid); (b) optic atrophy in the same patient, six months later. Courtesy of Moorfields Eye Hospital. Fig. 25.1.19 Preseptal cellulitis: (a) photograph showing eyelid

erythema and swelling; (b) corresponding axial orbital computerized tomography scan revealing preseptal abscess (arrow). Courtesy of Moorfields Eye Hospital.

Section 25 Disorders of the eye 6428 a hard domestic water region. Characteristically, patients present with severe pain, photosensitivity and watering, out of proportion to the signs, which include epithelial irregularity and subepithelial infiltrates. Later signs include ring infiltrates (Fig. 25.1.20a), sat- ellite lesions, scleritis, uveitis, thickening of peripheral corneal nerves, corneal thinning, and perforation. The diagnosis is con- firmed with corneal scrape and culture for acanthamoeba, and confocal microscopy. The evidence for the comparative efficacy of topical chlorhexidine 0.02% and polyhexamethylene biguanide 0.02% is inconclusive, and a long course of combination therapy is usually given. The visual prognosis may be poor following delayed diagnosis. Primary herpes simplex virus infection causes a vesicular rash on the eyelids, which typically heals over 3–7 days, with or without associated conjunctivitis. Secondary reactivation is associated with recurrent episodes of dendritic epithelial keratitis (Figs. 25.1.20c and d), which responds to topical antivirals (Table 25.1.6), but can be worsened with inadvertent topical steroids. Recurrent epi- sodes of deeper stromal keratitis are associated with increased risk of scarring and vision loss, and require topical steroid with oral antiviral cover. Disciform lesions represent endothelial in- flammation with anterior uveitis, and also require topical steroid and oral antivirals. Herpetic uveitis may be associated with raised intraocular pressure and iris transillumination defects. Varicella zoster virus can also cause keratitis and anterior uveitis. Fungal keratitis (Fig. 25.1.15b) is common in lower income coun- tries with warm, tropical climates, and in agricultural areas. It is less common in the United Kingdom, with an annual incidence of 0.32 cases per million population. The most frequent organism is Candida albicans (56%), and two-thirds of patients have prior ocular surface disease treated with topical steroid. Filamentary fungal infection (e.g. Fusarium solani and Aspergillus flavus) is more common following ocular trauma. Other risk factors in high- income settings include contact lens wear, diabetes, and inoculation while gardening. Visual outcomes are very poor (<6/60) in nearly half of patients. Diagnosis is confirmed by culture and confocal mi- croscopy. Treatment typically involves prolonged topical antifungal agents, such as natamycin (Table 25.1.6), debridement, and occa- sionally a partial keratectomy or keratoplasty for perforation. Fungal infections Histoplasma capsulatum is a notable cause of vision loss in young American adults in endemic areas such as the Mississippi basin. Haematogeneous spread from the lung results in a multifocal, scarring chorioretinitis leaving small, characteristic punched-out ‘histo spots’. Initial infection is usually asymptomatic, but the scars predispose to choroidal neovascularization which can threaten vi- sion even decades later. Mucormycosis is a potentially life-threatening, un- common, opportunistic fungal infection that typically affects
Fig. 25.1.20 Keratitis: (a) ring ulcer associated with acanthamoeba; (b) epithelial defect within corneal ulcer staining with fluorescein sodium, visualized under cobalt blue light; (c) dendritic ulcer associated with herpes simplex virus (HSV), staining with fluorescein sodium under cobalt blue light; (d) dendritic ulcers associated with HSV, staining with rose bengal. Courtesy of Moorfields Eye Hospital.

25.1 The eye in general medicine 6429 immunocompromized patients, including those with poorly con- trolled diabetes. It may involve the periocular tissues of the orbit, nasopharynx and the central nervous system, and spreads rapidly producing characteristic necrotic tissue blackening. Other signs include periorbital oedema and erythema, proptosis, ptosis, and complete ophthalmoplegia. Posterior extension can also invade the cavernous sinus. Treatment involves urgent systemic

antifungals and surgical debridement. Cryptococcus neoformans is a small, budding encapsulated yeast, found in soil and pigeon droppings, which is typically acquired through inhalation, or by direct skin contact or ingestion. Ocular manifestations result from haematogeneous spread, or leptomen- ingeal spread from associated meningitis (immunocompetent people are also at risk). Clinical presentations include anterior uve- itis, posterior uveitis with a focal mass, multifocal choroiditis or retinitis, and neuro-ophthalmic involvement. Bacterial infections Chlamydia Chlamydia trachomatis is the leading infectious cause of blind- ness worldwide, endemic in over 50 countries in Asia, Africa, Australia, and the Middle East, in poor and remote areas. Chlamydia is an obligate intracellular organism. Serovars A, B, and C are responsible for trachoma, while serovars D to K are associated with genital infection and occasional follicular con- junctivitis. Approximately 40.6 million people suffer with active trachoma, and 8.2 million have trichiasis. In endemic commu- nities, children are the main reservoir, and transmission is pro- moted by poor sanitation and the eye-seeking fly Musca sorbens. Trachoma causes follicular conjunctivitis, and chronic, repeated infection results in conjunctival scarring, trichiasis (inward mis- direction of the eyelashes) and entropion. Resolved follicles at the corneal limbus leave a pathognomonic sign, ‘Herbert’s pits’. Aqueous tear deficiency, corneal scarring, and a vascular pannus may develop, causing opacification and vision loss. The WHO trachoma grading scheme determines the proportion of the popu- lation with follicular trachoma, inflammatory trachoma, trach- omatous scarring, trachomatous trichiasis, and corneal opacity. Inflammatory trachoma is infectious and needs prompt treat- ment, while the burden of trachomatous trichiasis indicates the need for surgical services, and the burden of corneal opacity in- dicates the magnitude of trachoma blindness in the community. The ‘SAFE’ strategy aims to reduce the burden of disease through Surgery for trichiasis, Antibiotics to treat the community (a single oral dose of azithromycin 20 mg/kg, up to 1 g, if the prevalence of follicular trachoma exceeds 10% in children under 10 years of age), Face- washing to reduce transmission, and Environmental change to sustain transmission reduction, but the evidence these meas- ures are effective remains weak (Table 25.1.6). Tuberculosis Global tuberculosis (TB) prevalence is declining, with an estimated 11 million infected people in 2013, of whom the majority have la- tent infection. Ocular manifestations of tuberculosis are pro- tean, but there are no gold standard diagnostic tests, and clinical diagnosis is usually presumptive, as few patients have active pul- monary infection. The most common presentation is a peripheral occlusive retinal vasculitis, in which there is sheathing of periph- eral vessels, and risk of neovascularization. Secondary infection, via extrapulmonary haematogeneous dissemination of the bacilli, can present in many ways: with lupus vulgaris, episcleritis, scler- itis (which may be necrotizing), interstitial keratitis, subretinal abscess, retinal periphlebitis, optic disc granuloma, focal, multi- focal or diffuse choroidal granuloma (tubercles) (Fig. 25.1.17c), multifocal choroiditis and chorioretinitis (Fig. 25.1.17d), or a serpiginous-like choroidopathy. Signs of previous ocular tubercu- losis include pigmented perivascular chorioretinal scars and scler- osed venules. Active disease can affect any part of the eye, but if the anterior segment is involved, there are typically ‘mutton fat’ keratic precipitates and broad based posterior synechiae (Fig. 25.1.15c and e). Host genetic factors may influence disease severity. Direct infection of the periocular skin and ocular tissues can also occur, enabling biopsy and definitive diagnosis. Ocular TB diagnosis is supported by a positive interferon-γ release assay against tu- bercular antigens, a tuberculin skin test, and a good response to antituberculous therapy without recurrence. In peripheral occlu- sive vasculitis (Fig. 25.1.17a), wide-field FFA highlights areas of nonperfusion which may be ablated with laser treatment. Vitrectomy and endolaser may be required for recurrent vitreous haemorrhage. Syphilis The ocular manifestations of syphilis, which develop in 1% of pa- tients with secondary and early

tertiary disease, are so varied that it is known as the ‘Great Mimicker’. The annual UK incidence is 9.7 per 100 000 population, but is rising through resurgence of in- fection, especially among certain high risk populations (e.g. men who have sex with men). The spirochete, Treponema pallidum, spreads from the infection site, via haematogeneous and lymph- atic routes, to remote organs, causing granulomatous inflam- mation and tissue damage. Patients can present with anterior, intermediate, posterior, or panuveitis. Historically, syphilis fre- quently involved the optic nerve but neurosyphilis is now un- common. There are several patterns of posterior uveitis that are particularly suggestive of syphilis. The most common is a necro- tizing, sectoral retinitis with satellite lesions affecting large con- fluent areas with nonocclusive retinal vasculitis and overlying vitritis. Others include punctate inner retinitis, and an acute pos- terior placoid chorioretinopathy. Other presentations of ocular syphilis may include interstitial keratitis, episcleritis, scleritis, dilated iris capillaries (roseola), or a central retinal vein occlu- sion. The Argyll Robertson pupil, which is small, irregular, and responsive to accommodation but not to light, is a late sign. HIV positive patients have atypical presentations, with more frequent posterior uveitis, and coinfection should be excluded. Congenital syphilis is associated with interstitial keratitis and ‘salt and pepper’ retinopathy. Investigation, systemic treatment, notifica- tion, and contact tracing for syphilis are important and are dis- cussed elsewhere. Ocular syphilis is treated according to the 2015 UK National Guidelines on the management of syphilis, with ad- juvant topical or systemic corticosteroids for anterior or posterior inflammation, respectively. Full visual recovery is possible with prompt recognition and treatment, but late presentation, or inad- vertent steroid monotherapy can be rapidly blinding.

Section 25 Disorders of the eye 6430 Lyme disease Lyme disease results from transmission of Borrelia burgdorferi through a bite from an infected Ixodes tick, found in areas of North America, Europe and Asia (Chapter 8.6.33). Ocular Lyme disease is uncommon in the United Kingdom, with an annual incidence of 0.3 per million. It can manifest at any stage, but often presents a few years after initial infection. Early infection results in a mild, non- specific, self-limiting conjunctivitis; stage 2 disease often includes neuro-ophthalmic complications; and later there is unilateral or bilateral panuveitis, with chorioretinitis or retinal vasculitis. Other features include stromal keratitis, episcleritis, and symblepharon. Patients require systemic investigation and treatment. Residual ocular inflammation is treated with adjuvant topical, local, or sys- temic corticosteroids, depending on the site, with a good visual prognosis in over 90% of patients. Leptospirosis Infection with the spirochete Leptospira interrogans occurs most commonly in tropical regions, in people directly exposed to diseased animals, especially rodents, or to infected wet soil or water. Acute infection is frequently asymptomatic, but may cause nonspecific fever and malaise. Haematogeneous spread to the eye during the acute phase causes conjunctival injection, subconjunctival haemorrhage, retinal haemorrhages, disc hyper- aemia, or retinal vasculitis. Months to years after initial infection, a typically nongranulomatous anterior or panuveitis can develop, with associated hypopyon (Fig. 25.1.15a), nonocclusive vasculitis, and optic disc oedema. Investigation and systemic treatment are discussed elsewhere (Chapter 8.6.35). Uveitis is treated with top- ical, local, or systemic corticosteroids depending on the site and severity. Visual outcomes are good in most treated patients. Other bacterial infections Leprosy persists in a few small areas in low-income countries. Infection with Mycobacterium leprae or Mycobacterium lepro- matosis frequently involves the ocular adnexa and anterior seg- ment. Beading of corneal nerves (lepromas) is an early sign, and bilateral interstitial keratitis is highly suggestive. Facial palsy and reduced corneal sensation, with lagophthalmos and associated ex- posure keratopathy, ulceration, and scarring, can

cause blindness. Episcleritis, scleritis, and chronic anterior uveitis with iris pearls (coalesced nonviable lepromatous bacilli) are common. Posterior involvement with retinal pearls is rare and may result in retinal scarring, uveal effusion, and retinal detachment. Brucellosis is a rare zoonosis, endemic in parts of the Mediterranean, Middle East, Central and South America, which typically affects farm and slaughterhouse workers. A minority of patients develop posterior uveitis Actinomyces israelii, a commensal in the oral cavity, can cause a treatable ulcerating keratitis and associated anterior uveitis, chronic inflammation of the nasolacrimal canaliculi or very rarely endophthalmitis. Nocardia infection is also associated with chronic keratitis, scleritis, and endophthalmitis associated with focal chorioretinitis. Bartonella henselae ('Cat scratch disease') is associated with fever and Parinaud's oculoglandular syndrome (lymphadenop- athy and follicular conjunctivitis). Patients rarely present with unilateral, painless acute vision loss associated with intermediate uveitis, neuroretinitis, and focal or multifocal retinitis, choroiditis, or chorioretinitis. Bartonella quintana ('Trench fever'), trans- mitted by human body lice, is also associated with fever, uveitis (anterior, intermediate or posterior) and neuroretinits. It is im- portant to exclude syphilis and toxoplasmosis, which can have similar presentation. The rickettsiae are a diverse group of Gram negative, nonspore forming, highly pleomorphic, obligate intracellular bacteria, which are transmitted by mites, ticks, and lice. Infrequent ocular manifestations include Parinaud's oculoglandular syndrome, cor- neal ulceration, uveitis, retinal vasculitis, endophthalmitis, and anterior ischaemic optic neuropathy. Whipples disease, a very rare multisystem infection caused by Tropheryma whippelii, which predominantly affects middle-aged Caucasian men, involves the eye in approximately 5% of cases. Clinical features include uveitis, vitreous haemorrhage, retinitis, and optic neuritis. Pneumocystis jiroveci occasionally spreads haematogeneously from the lungs in immunocompromized patients (typically with CD4 counts of <100 cells/mm3) to cause a relatively asymptomatic multifocal chorioretinitis, in which multiple, pale yellow-white, rounded lesions are visible in the posterior pole. Viral infections Herpes simplex virus and varicella zoster virus In addition to keratitis, herpes simplex (HSV), and varicella zoster (VZV) infection have numerous other ocular manifestations. Patients with ophthalmic shingles should be referred for slit-lamp examination if there is red eye or visual impairment because these patients are at risk of uveitis, secondary glaucoma, and delayed cra- nial nerve palsies, including optic neuropathy or Adie tonic pupil. Acute retinal necrosis presents with a rapidly progressive, sight- threatening, aggressive retinitis. The annual UK incidence is 0.63 cases per million population. The most common cause is VZV followed by herpes simplex virus, with herpes simplex virus typ- ically presenting in younger patients with more exudative retinal detachment. Herpetic CNS disease, resulting in encephalitis and meningitis, is a predisposing risk factor. Clinical features include peripheral deep retinal whitening resulting from full thickness necrosis, minimal haemorrhage, and marked vitritis. The clin- ical diagnosis is based on criteria established by the American Uveitis Society (1994). The differential diagnosis includes Behçet's and toxoplasmosis, but the latter tends to affect the posterior pole. Viral PCR from anterior chamber or vitreous samples is helpful. Complications include retinal detachment and eventual retinal at- rophy, with a poor visual prognosis in advanced cases. Acute ret- inal necrosis is treated with intravitreal foscarnet and systemic antivirals such as valaciclovir. Adjunctive corticosteroid therapy is also sometimes judiciously used to control vision-threatening in- flammatory sequelae (e.g. optic nerve swelling). Progressive outer retinal necrosis (PORN) is a rare and devastating necrotizing retinitis caused by VZV, affecting immunocompromized patients whose CD4 lymphocyte count is typically under 50 cells/mm3. Patients present with rapid, painless vision loss. Clinical features include rapidly coalescing, multifocal, deep outer retinal lesions with early involvement of the macula, late

25.1 The eye in general medicine 6431 diffuse thickening, and no vitritis (Fig. 25.1.21d). It is treated with systemic antivirals, and vision can be irreversibly lost bilaterally within days without prompt treatment. Human immunodeficiency virus As the CD4 lymphocyte count falls, HIV commonly causes an asymptomatic microvasculopathy. This is manifest in the con- junctiva as corkscrew vessels and in the retina as bilateral but asymmetric cotton wool spots arranged around the optic disc in as- sociation with vascular tortuosity and intraretinal haemorrhages, Roth spots, microaneurysms, and telangiectasia (Fig. 25.1.21c). Retinal venous occlusion and branch arterial occlusions may also occur, resulting in vision loss. If the CD4 lymphocyte count is de- pleted then opportunistic ocular infections are common, including VZV, herpes simplex virus, cytomegalovirus (CMV), tuberculosis, aspergillus, Molluscum contagiosum Pneumocystis jirovecii, and microsporidiosis and cytomegalovirus. Treatment of opportun- istic infection involves both antimicrobials and the initiation of highly active antiretroviral therapy (HAART) in order to achieve immune reconstitution. This, in turn, might later precipitate an immune recovery uveitis. Cytomegalovirus Cytomegalovirus (CMV) retinitis presents in patients who are immunocompromized, and is rare if the CD4 count exceeds 100 cells/mm3. It has, therefore, declined in incidence and severity since HAART was introduced for the management of HIV. Patients may initially report only floaters, but can subsequently develop permanent blindness. The ocular features are fairly char- acteristic, and typically include extensive retinal haemorrhages in an arcuate distribution, vitritis, and patchy areas of retinal pallor associated with necrotic retinitis around branch vessels. These patches gradually enlarge and spread contiguously over a period of weeks, giving the fundus the appearance of ‘pizza’ (Fig. 25.1.21b). Other features include perivascular sheathing, and exudative ret- inal detachment. Differentiation from toxoplasma retinitis can be difficult and a vitreous biopsy for CMV PCR is helpful. Treatment options include intravitreal foscarnet and oral valganciclovir, and if this is toler- ated, most patients respond well and have a good visual outcome if diagnosed and treated promptly. Immune recovery is the best treat- ment, and reactivation may occur if the CD4 count drops again. After resolution, black pigment clumping is seen in the retina, with greyish gliosis, which can be mistaken for active disease. Without HAART, the development of CMV retinitis in a patient with AIDS is associated with a life expectancy of approximately 9 months. Mosquito-borne viral infections Dengue, transmitted by Aedes aegypti, is endemic in the tropics and is the most common mosquito-borne virus in the world. Ocular manifestations are uncommon and typically present a week after the onset of systemic symptoms, in association with Fig. 25.1.21 Inflammatory posterior segment signs in the retina and choroid, often associated with immune suppression: (a) candida endophthalmitis with dense vitritis; (b) cytomegalovirus retinitis; (c) human immunodeficiency virus retinopathy with cotton wool spots; (d) progressive outer retinal necrosis (PORN). Courtesy of Moorfields Eye Hospital.

Section 25 Disorders of the eye 6432 thrombocytopenia. Patients most commonly present with blurred or distorted vision and central scotomata in association with a maculopathy, although subconjunctival, retinal and vitreous haem- orrhages, uveitis, and optic neuritis can also occur. Visual field and OCT are particularly helpful for diagnosis and monitoring. 1 in 20 cases develop sight-threatening complications, including per- sistent central scotomas, but visual prognosis is generally good. Chikungunya is an arbovirus principally transmitted by Aedes aegypti. It presents with high fever, malaise, arthralgia, petechial rash, and low back pain. Ocular manifestations commonly in- clude conjunctivitis and a hypertensive anterior uveitis. Retinitis, choroiditis, and optic neuritis are uncommon. Most patients with vision loss recover following topical or systemic

steroid treatment. Zika is another virus transmitted by Aedes aegypti, first reported in humans in 1954, but seldom causing infection until a major human epidemic began in 2007. It typically causes mild infection in adults, including fever, arthralgia, maculopapular rash, and con- junctivitis. The greatest risk is during pregnancy as infection can result in a range of severe central nervous system abnormalities including microcephaly. Ocular features of this recently described congenital Zika syndrome include focal retinal pigment mottling, chorioretinal atrophy, and optic nerve abnormalities. The virus may persist in aqueous humour for more than 3 months. Other viral zoonoses The RNA virus Ebola, thought to be transmitted by fruit bats, appeared in sporadic small epidemics prior to the West African pandemic in 2014–2015. It presents with bilateral, asymptomatic, nonhaemorrhagic conjunctivitis, and influenza-like symptoms. The case fatality rate in Ebola is estimated to be up to 76%, and the onset of haemorrhagic conjunctivitis is predictive of death within days. Convalescent Ebola virus disease is associated with ocular complications including an aggressive, hypotonous panuveitis in approximately 14–18% patients, in which there can be persistence of the virus in the aqueous humour many months after viraemia clearance. This may respond well to topical steroids. Human cowpox is transmitted by infected domestic cats or ro- dents. Painful, haemorrhagic pustules or black eschars on the hands and face may be accompanied by lid swelling, preauricular lymphadenopathy, follicular conjunctivitis and chemosis, and rarely by keratitis. Orf virus is occasionally transmitted to humans by infected sheep and goats. It causes eyelid infection with ulceration, fol- licular conjunctivitis, and lymphaedenopathy. Coxsackie virus causes hand, foot, and mouth disease. Ocular manifestations include haemorrhagic conjunctivitis, and rarely a unilateral, self-limiting, posterior uveitis with acute macular chorioretinitis, which is best seen on OCT and occasionally re- quires systemic corticosteroid therapy to rescue vision. Other viral diseases Measles is a significant cause of childhood blindness globally, and is making a recurrence in more developed countries on account of suboptimal vaccination coverage. It typically presents with con- junctivitis, fever, and coryzal symptoms before the appearance of a characteristic rash. Less commonly, keratitis and corneal ul- ceration develop, especially in the context of malnourishment and vitamin A deficiency. These may lead to permanent scarring and vision loss. Rarely, measles causes a blinding, rapidly pro- gressive, necrotizing retinitis affecting the macula, or optic neur- itis. These typically develop in the context of subacute sclerosing panencephalitis, which is associated with significant mortality. There is no specific treatment for measles, but the WHO recom- mend vitamin A supplementation. Mumps is associated with epidemic parotitis, and while it infre- quently affects the eye, it can cause bilateral painful dacroadenitis with conjunctival chemosis. Sclertiis, keratitis, anterior uveitis, choroiditis, and optic neuritis are rare. Molluscum contagiosum results in typical umbilicated, dome- shaped lesions that may affect the periocular area, and if close to the lid margin, may cause a chronic follicular conjunctivitis. Treatment involves surgical excision. Protozoal infections Ocular toxoplasmosis Infection with the obligate intracellular protozoan parasite Toxoplasma gondii is the most common cause of infectious pos- terior uveitis and retinitis in adults worldwide. Transmission can occur by eating undercooked meat or through contamination of food or water with faeces from an infected cat. Toxoplasmosis is more prevalent in parts of South America, Eastern and Central Europe, the Middle East, Southeast Asia, and Africa, than in nor- thern European countries and North America. The cumulative incidence of symptomatic congenital or postnatal toxoplasmosis presenting in childhood (<16 years) in the United Kingdom is 1.6 cases per 100 000 live births. If primary infection is acquired up to 6 months before, or during, pregnancy it can result in miscarriage, premature birth, and congenital multisystem infection. Congenital toxoplasmosis may remain asymptomatic, or become symptom- atic as a result of reactivation. Ocular disease typically

presents with blurred vision and floaters. Examination reveals anterior uveitis with medium-sized keratic precipitates (Fig. 25.1.15c), posterior synechiae (Fig. 25.1.15e) and foci of white, fluffy, nec- rotizing chorioretinitis, with overlying dense vitritis, and occa- sional associated vasculitis. Intraocular pressure is also sometimes raised. Except in primary acquired infection, active retinal lesions are adjacent to well-demarcated, hyperpigmented chorioretinal scars with atrophic centres (Fig. 25.1.16H). Ocular toxoplas- mosis in immunocompromized patients presents with minimal vitritis and more diffuse and sight-threatening retinitis. Imaging to exclude cerebral toxoplasmosis is important in neonates and immunocompromized individuals. The diagnosis is presumptive and based on the presence of characteristic retinal lesions and positive serology indicating pre- vious infection. Aqueous and vitreous samples may also be posi- tive for toxoplasma PCR. Active ocular toxoplasmosis is usually self-limiting, with lesions healing over several months. The more aggressive South American strains are associated with frequent re- currence of eye symptoms. There is inconclusive evidence for the benefit of different antibiotic regimens on visual outcome (Table 25.1.6), but treatment is typically now started, unless the patient has minimal symptoms and the lesion is limited to the retinal per- iphery, and always in immunocompromized individuals. Typical regimens include azithromycin or trimethoprim-sulfamethoxazole

 monotherapy, or triple therapy with pyrimethamine, sulfadiazine, and folinic acid. Intravitreal injections of clindamycin are also increasingly used. Adjuvant systemic corticosteroids reduce in- flammation and lessen vision loss, but they are not given alone or administered intravitreally, because this can precipitate rapid, ir- reversible vision loss from diffuse retinitis. Treatment is effective against the tachyzoites but does not eliminate encysted bradyzoites, and does not prevent recurrent reactivation, which mostly occurs within the first year. Prophylactic trimethoprim-sulfamethoxazole for 12 months after an acute episode of chorioretinitis reduces the frequency of ocular recurrence for the duration of therapy. Other protozoal infections Malarial retinopathy is associated with Plasmodium falciparum cerebral malaria. Retinal microvascular obstruction results in ret- inal pallor, vessel dilatation, and increased vascular tortuosity. FFA reveals capillary nonperfusion and leakage resulting from blood- retina barrier breakdown. Visual acuity usually improves upon recovery, but the severity of retinal sequestration corresponds to cerebral parasite sequestration, which is a prognostic indicator for fatality. Leishmaniasis is an obligate intracellular protozoan which is transmitted through sandfly bites. The cutaneous form (L. tropica) rarely causes eyelid nodules and ulceration, and can be diagnosed by direct smears. In contrast, the mucocutaneous form (L. brazil- iensis) may cause intense necrotic inflammation of the conjunctiva that can lead to loss of the eye. The visceral form (L. donovani, kala- azar) is infrequently associated with retinopathy (retinal haemor- rhages, increased vascular tortuosity, perivascular whitening and cotton wool spots), uveitis, chorioretinitis, central retinal vein oc- clusion, and keratitis. Chagas' disease (American trypanosomiasis), which is en- demic in south and central America, is caused by a bite from a reduviid 'kissing' bug infected with Trypanosoma cruzi, and may also be transmitted via blood transfusion, organ donation, and the placenta. Sleeping sickness (African trypanosomiasis) which occurs in regular outbreaks in sub-Saharan Africa, is caused by Trypanosoma brucei transmitted by bites from infected tsetse flies. Both may cause interstitial keratitis, painless periorbital oedema (Romana's sign) and lymphadenopathy lasting several months. Helminth infections Toxocariasis Ocular toxocariasis is usually caused by Toxocara canis, which is transmitted directly through contact with dog faeces, or indir- ectly, through poor hand hygiene and ingestion of contaminated soil, sand (e.g. in playgrounds), or raw meat. Children are more frequently infected, and the average age at

presentation is 8 years. Ocular disease is usually unilateral and seldom coincident with systemic disease. The typical presentation is of painless vision loss, sometimes associated with a new childhood squint, leukocoria (white pupil reflex), a mild panuveitis and a retinal or subretinal granuloma (typically a white spherical mass). The granuloma may cause retinal detachment requiring surgery. Presumptive diag- nosis is based on typical clinical features and a positive serum T. canis ELISA test. Active infection is treated with anthelmintic drugs such as albendazole, and adjuvant corticosteroids. Onchocerciasis Onchocerciasis, or 'river blindness', is caused by an inflamma- tory reaction in response to the filaria nematode (roundworm) Onchocerca volvulus, transmitted by a black fly that breeds in fast- flowing rivers. There are two subtypes (Savanna and Rainforest). It is endemic in many countries in sub-Saharan Africa, but also in limited areas in South America and in Yemen. Over 25 mil- lion people are infected globally, with blindness affecting an es- timated 300 000 people and vision impairment a further 800 000. Patients present with red, sore eyes associated with anterior uve- itis. Microfilariae are visible in the anterior chamber, and may also infect the cornea, resulting in punctate epithelial keratitis or sclerosing keratitis with neovascularization, which may cause blindness. Patients also present with night blindness and field constriction. Fundus examination reveals hyperpigmentation, scarring and atrophy (chorioretinitis), shiny white intraretinal de- posits, optic neuritis, and eventual optic atrophy. Treatment with the microfilaricide ivermectin reduces the microfilarial load in the skin and eye, and may reduce the risk of chorioretintis (Table 25.1.6). The efficacy of concurrent doxycycline, which aims to kill Wolbachia bacteria in the guts of adult worms thereby killing them, remains uncertain. Over the past few decades mass commu- nity treatment programmes giving ivermectin twice annually have reduced the prevalence of river blindness, and are aiming to eradi- cate the disease. Other helminth infections Intraocular cysticercosis results from ingestion of Taenia solium eggs in contaminated water or food (e.g. undercooked pork). Eggs develop into larvae in the gut then spread via blood and lymph- atics to highly vascularized organs including the eye. They form pro-inflammatory cysts in the vitreous, subretinal space, or orbit. Patients present with bilateral, gradual, painless reduction in vi- sion. The motile cysticercus has to be removed surgically, avoiding rupture. Systemic therapy can precipitate a dramatic and blinding inflammatory reaction and retinal detachment. Diffuse unilateral subacute neuroretinitis (DUSN) is caused by various roundworm species invading the subretinal space. It commonly affects children and young adults in endemic regions, including south-eastern United States and South America. Early infection is typically asymptomatic and unilateral. Gradual, sig- nificant vision loss may develop in association with clusters of grey-white lesions in the outer retina, retinal haemorrhages, serous retinal detachment, choroidal neovascularization, progressive ret- inal pigment epithelium degeneration, and optic atrophy. If the nematode is visible, it can be laser photocoagulated. Otherwise, anthelmintic drugs are given orally. Loa loa is endemic in 11 countries in central and western Africa. The filarial worms ('African eye worm') invade and migrate through the subcutaneous and subconjunctival tissues following a bite from an infected Chrysops fly, causing pain and itching. Larvae of the nematode Thelazia callipaeda, 'Oriental eye worm', are transmitted by flies to the eyelid and lacrimal glands, and less frequently enter the subconjunctival space. Gnathostoma spinigerum is responsible for the rare multisystem disease gnathostomiasis (larva migrans profundus), is endemic in many countries in Southeast Asia, and is acquired by eating undercooked meat and fish. It rarely causes intraocular

 infection, but larvae may be visible in the vitreous. Trichinela spira- lis infection arises from eating raw or undercooked meat (especially pork) containing

encysted larvae. Nonspecific symptoms of fever and gastrointestinal disturbance are typically followed by periocular tissue oedema, painful limitation of eye movements and eosinophilia, when the organism infiltrates striated muscle cells. Sparganosis, caused by larvae of Spirometra tapeworms, is a rare cause of focal nodular conjunctivitis, proptosis, and occasionally blindness, and is reported most frequently in Eastern Asia. Orbital or ocular myiasis is a rare infection caused by the larva of Hypoderma bovis (hornet fly) or Wohlfahrtia magnifica (flesh fly) and typically occurs in individuals with skin wounds living in areas of poor environmental sanitation in the tropics. Migration of the larvae within the eye and orbit can cause presentations varying from simple irritation to significant tissue de- struction and blindness. Schistosomiasis is an occasional cause of urticarial conjunctivitis associated with egg deposition, but the in- terior of the eye is rarely involved. Endocrine disorders This section considers the ocular manifestations associated with disorders of the thyroid, parathyroid, and adrenal glands. The ocular manifestations of diabetes mellitus are already outlined. For the hypothalamic-pituitary syndromes involving the optic nerve and visual pathways, including septo-optic dysplasia (de Morsier syndrome), Kallman's syndrome and empty sella syndrome, and other rare disorders including McCune–Albright syndrome and Triple-A syndrome (Allgrove's syndrome). Thyroid eye disease Thyroid eye disease (or Graves' ophthalmopathy) is an auto- immune disease characterized by acute, self-limiting inflamma- tion of the orbital extraocular muscles and fat. It is more frequent in women, but often more severe in older men, and in smokers. At presentation, thyroid eye disease patients are typically hyperthy- roid (85%), but may be hypothyroid (10%) or euthyroid (5%). Signs can be unilateral, or bilateral, and asymmetric. Orbital inflamma- tion and secondary venous congestion leads to eyelid oedema and redness, proptosis, conjunctival injection, and chemosis, and re- stricted ocular motility (often with vertical diplopia which is most prominent on waking) (Fig. 25.1.22). It is also facially disfiguring, significantly affecting quality of life. Thyroid eye disease should be differentiated from other causes of orbitopathy, in particular to ex- clude an orbital mass, with an MRI scan. In its most severe form, acute thyroid eye disease is sight- threatening as raised intraorbital pressure compresses the optic nerve resulting in blurred vision, reduced colour perception, visual field loss, and an afferent pupil defect. It is treated with intravenous steroids and, if required, prompt surgical decom- pression of the orbit. However, most patients have mild disease which is managed by controlling their thyroid function, smoking cessation, oral selenium, and topical lubricants. A quarter of af- fected individuals have moderately severe disease which also re- quires systemic immunosuppression. This is often administered as interval infusions of intravenous methylprednisolone which may be augmented with an oral second-line immunosuppressive agent such as cyclosporine, azathioprine, or mycophenolate mofetil. Adjuvant, fractionated, low-dose, external beam orbital radio- therapy is also widely used, especially when there is significant ocular motility restriction and diplopia. The evidence base for biologic therapies, such as anti-CD20 monoclonal antibodies, is limited but evolving. In the postinflammatory fibrotic phase of thyroid eye disease, restriction of eye movements can result in persistent strabismus and diplopia. This is initially managed with spectacle prisms or botulinum toxin injections to extraocular muscles. Orbital decom- pression may then be necessary to reduce proptosis, followed by strabismus surgery to recess tight, fibrotic muscles (e.g. inferior rectus) once oculomotility has fully stabilized. Finally, eyelid repo- sitioning surgery addresses lid retraction and improves cosmesis. Other thyroid diseases involving the eye Ascher syndrome is a rare disease characterized by benign thyroid gland enlargement, double lip, and bilateral blepharochalasis. The latter develops from puberty, and progresses from intermittent painless eyelid swelling to ptosis and prolapse of the orbital fat and lacrimal gland. In multiple endocrine neoplasia syndrome type 2B, which is as-

sociated with medullary thyroid carcinoma, a characteristic ocular feature is thickened corneal nerves. Neuromas of the eyelids, cornea, and sclera also occur. Parathyroid disease Primary hyperparathyroidism is associated with hypercalcaemia, which may result in band keratopathy, conjunctival calcification, conjunctivitis, and scleritis. The patient may be asymptomatic, or present with gritty ocular discomfort and redness. Hypoparathyroidism can develop following total thyroid ectomy, in the context of severe magnesium deficiency or in as- sociation with autoimmune disease. Rarely, it is associated with papilloedema from intracranial hypertension. Autoimmune polyendocrine syndrome type I is a rare autosomal recessive disease characterized by adrenocortical insufficiency, hypoparathyroidism, and chronic mucocutaneous candidiasis in which associated keratoconjunctivitis and dry eye may result in vi- sion loss from corneal scarring.
Fig. 25.1.22 Photograph showing active thyroid eye disease, with conjunctival chemosis (oedema) and injection, globe proptosis, lid retraction, and inferior scleral show. From Donaghy M (ed) (2009). Brain's Diseases of the Nervous System, 12th edn, by permission of Oxford University Press.

25.1 The eye in general medicine 6435 Cushing’s syndrome Cushing’s syndrome is usually exogeneous (secondary to chronic corticosteroid use), but may rarely be endogeneous. Ocular mani- festations include elevated intraocular pressure, increased retro- orbital fat deposition resulting in exophthalmos, and cataract. Genetic disorders Connective tissue disorders The ocular features of Marfan syndrome include blue sclera, myopia, keratoconus and superotemporal lens dislocation (Fig. 25.1.23a). The lens may also dislocate in Weill–Marchesani syndrome, typ- ically forward into the anterior chamber, on account of the small, round lens shape (microspherophakia). Stickler syndrome is asso- ciated with myopia, liquefaction of the vitreous, and retinal detach- ment. Osteogenesis imperfecta and Ehlers–Danlos are associated with blue sclera and keratoconus. Ehlers–Danlos is also associ- ated with angioid streaks (Fig. 25.1.23b), as is pseudoxanthoma elasticum. Phakomatoses Most phakomatoses are associated with mutations in tumour sup- pressor genes, variably expressed with autosomal dominant in- heritance. Sturge–Weber and Wyburn–Mason syndrome arise sporadically. These diseases manifest with neurological, cuta- neous, and ocular signs and a tendency to develop hamartomatous tumours. Neurofibromatosis type 1 (NF1, von Recklinghausen) is the most common phakomatosis, with a prevalence of 1 in 4000 people. Two out of seven core features are required to make a diagnosis of NF1 and of these, three features are ocular signs. These are Lisch nodules (≥2) on the iris muscle (yellow-brown raised nodules), optic nerve glioma, and pulsatile proptosis resulting from an encephalocoele associated with sphenoid bone dysplasia. Other features include prominent corneal nerves, iris mammilations (diffuse tiny nodules covering the iris surface) (rare), lid neuro- fibroma, choroidal naevi, which have a risk of malignant trans- formation, retinal astrocytoma, and glaucoma. Children with NF1 need an annual eye exam. Around 60% with glioma develop total vision loss. Neurofibromatosis type 2 (NF2, Multiple Inherited Schwannomas, Meningiomas, and Ependymomas, MISME syn- drome) has a prevalence of 1 in 40 000. Ocular features are neither necessary nor sufficient for diagnosis. They include cataracts (be- fore 30 years of age), and a combined hamartoma of the retinal pig- ment epithelium and retina. Tuberous sclerosis results from mutation in the TSC1 (hamartin) or TSC2 (tuberin) genes, and has a prevalence of 1 in 6000. Ocular features include retinal astrocytoma and periocular angiofibromas. Von Hippel–Lindau syndrome is rare and results from mutations in the VHL gene involved in vascular proliferation. Patients require an annual ophthalmic examination from the age of 5–10 years, then six-monthly to the age of 30 years, with follow-up thereafter, to screen for retinal capillary haemoangiomata (Fig.

25.1.24a). These are usually bilateral, multiple, slowly enlarging lesions lo- cated in the mid-peripheral retina. Early detection and laser treat- ment avoids progression to larger lesions that bleed and cause retinal detachment. Sturge–Weber is rare, presenting at birth with facial naevus flammeus (‘port wine stain’). Features include episcleral haem- angioma, ciliary body, and iris haemangioma, diffuse choroidal haemangioma (Fig. 25.1.24b), which may cause exudative retinal detachment, and glaucoma in 50%. MRI imaging in infancy ex- cludes central haemangioma. Wyburn–Mason syndrome is very rare. Ocular features include orbital, periorbital or retinal arteriovenous malformations (‘ra- cemose haemangioma’), in which multiple dilated vessels commu- nicate directly without an intervening capillary bed. Chromosomal syndromes Down’s syndrome is the most common autosomal trisomy, af- fecting 1 in 650 live births. Visually significant features may in- clude myopia, astigmatism, strabismus, keratoconus, cataracts, a hypoplastic optic disc, and nystagmus. Other features that assist in phenotype recognition include mongoloid palpebral fissures, epicanthic folds, hypertelorism, ectropion, and Brushfield spots on the iris. Blepharoconjunctivitis may cause symptoms of ocular surface irritation. Turner syndrome affects 1 in 2000 live female births. Visually significant ocular features include cataract, red-green colour Fig. 25.1.23 Genetic connective tissue disorders: (a) superotemporal lens dislocation in Marfan syndrome, shown with retroillumination; (b) angioid streaks. Courtesy of Moorfields Eye Hospital.

 deficiency, and strabismus and convergence insufficiency. Other features include hypertelorism, ptosis, antimongoloid palpebral fissures, and epicanthus. Klinefelters syndrome affects 1 in 500 to 1000 live births, and is associated with strabismus, microphthalmia, and colobomas of the iris, optic nerve, and choroid. Ocular abnormalities are common in Edwards and Patau syn- drome, but infants born with these trisomy syndromes seldom sur- vive more than one year. Pigmentary retinopathy associated with systemic disease Retinitis pigmentosa (RP) is characterized by bilateral, progressive dysfunction of the photoreceptors, eventually resulting in wide- spread retinal atrophy. Retinitis pigmentosa is most frequently an isolated ocular disease, affecting approximately 1 in 5000 people. However, family pedigree may reveal an autosomal dominant, autosomal recessive, or X-linked inheritance pattern. These have different phenotypes and visual prognoses. More than 60 associ- ated gene mutations have been identified; 18% of RP patients have Usher syndrome (autosomal recessive sensorineural deafness). Many other inherited retinal dystrophies may be confused with retinitis pigmentosa. These include cone-rod and cone dystrophy, Lebers congenital amaurosis, Bardet–Biedl syndrome (polydactyly-obesity-kidney-eye syndrome), Refsum syndrome (phytanic acid a-hydrolase deficiency), Neuronal ceroid lipofuscinosis (Batten’s disease), Senior–Loken, and Kearns–Sayre syndrome. The differ- ential also includes rubella retinopathy, congenital or acquired ocular syphilis, autoimmune and cancer-associated retinopathy, and drug toxicity (e.g. chloroquine). Patients typically present with night blindness and slowly pro- gressive, symmetrical peripheral field loss, but central vision can be affected. Examination reveals symmetrical mottling of the retinal pigment epithelium, ‘bone-spicule’ pigmentation, attenu- ation of retinal vessels and optic nerve head pallor (Fig. 25.1.25a). OCT demonstrates outer retinal thinning. FAF monitors pro- gression, frequently showing peripheral hypofluorescence and a hyperfluorescent ring around the fovea, at the border between func- tional and dysfunctional retina. Some patients retain useful naviga- tional peripheral vision, which can be monitored with Goldmann or Octopus visual fields. Retinitis pigmentosa cannot be cured and there is no evidence for vitamin A or docosahexaenoic acid supple- mentation (see Table 25.1.6). Retinitis pigmentosa patients often develop cystoid macular oedema, and carbonic anhydrase

inhibi- tors may have a role in treatment. Fig. 25.1.25 Other genetic conditions: (a) retinitis pigmentosa/pigmentary retinopathy; (b) aniridia and corneal limbal stem cell deficiency in WAGR syndrome (Wilms tumour, aniridia, genitourinary anomalies, and mental retardation syndrome). Fig. 25.1.24 Phakomatoses involving the eye: (a) peripheral retinal capillary haemangioma in Von Hippel–Lindau; (b) diffuse choroidal haemangioma in Sturge–Weber syndrome.

25.1 The eye in general medicine 6437 Other genetic conditions Absence of the iris (aniridia) resulting from a sporadic microdeletion in the PAX6 gene is associated with foveal hypoplasia, reduced vi- sion, and nystagmus, corneal opacification secondary to limbal stem cell deficiency and glaucoma (Fig. 25.1.25b). Deletions involving the adjacent gene result in WAGR syndrome (Wilms' tu- mour, aniridia, genitourinary abnormalities, reduced intelligence, and craniofacial dysmorphism). Children with WAGR require fre- quent renal ultrasound surveillance. Gardner's syndrome (familial adenomatous polyposis) is associ- ated with bilateral, multiple, widely separated, dark brown, irregu- larly pigmented retinal lesions (atypical congenital hypertrophy of the retinal pigment epithelium). Identification of these lesions, which do not require treatment, necessitates referral to gastro- enterology for further investigation. Metabolic syndromes Carbohydrate disorders Cataract formation in infancy is the most frequent manifestation of galactosaemia, galactokinase deficiency, and mannosidosis. Lens opacification may be reversible in galactosaemia with early diagnosis and appropriate dietary restriction. Lipid disorders Most disorders of sphingolipid metabolism show autosomal re- cessive inheritance and result in a 'cherry red spot' at the macula (Fig. 25.1.26a) and optic atrophy (Fig. 25.1.18b). These develop in GM1 gangliosidosis (b-galactosidase deficiency), Tay–Sachs (Hexosaminidase A deficiency), Sandhoff's (Hexosaminidase A and B deficiency), and Niemann–Pick (Sphingomyelinase deficiency). Optic atrophy is also seen in Krabbe's disease (Galactocerebrosidase deficiency) and metachromic leukodystrophy (Arylsulphatase-A deficiency). Fabry's disease (a-galactosidase deficiency) is X-linked, and features include vortex keratopathy, cataract, and tortuous retinal vessels. Abetalipoproteinaemia (triglyceride transfer pro- tein deficiency), and Refsum syndrome, result in cataracts and pigmentary retinopathy. Batten's disease gradually leads to the development of macular discolouration, retinitis pigmentosa-like changes, and optic atrophy. Electrodiagnostic testing is valuable in suspected cases. Amino acid disorders The ocular phenotype in disorders of amino acid metabolism is het- erogeneous. Features of homocystinuria (cystathione synthetase deficiency) include myopia, glaucoma, and inferonasal lens dis- location (Fig. 25.1.26b), which may occur in 90% of patients by the age of 30 years. Crystalline keratopathy occurs in cystinosis (lysosomal transport protein deficiency). Features of Lowe syn- drome include a small lens, cataracts, blue sclera, anterior segment dysgenesis, and glaucoma. Features of Zellweger syndrome in- clude optic nerve hypoplasia, pigmentary retinopathy, and glau- coma. Scleral darkening develops in alkaptonuria (homogentisic acid dioxygenase deficiency) (Fig. 25.1.26c). Herpetiform corneal ulceration is seen in tyrosinaemia type II (tyrosine transaminase deficiency). Albinism results from a variety of abnormalities in melanin synthesis. Around 90% of patients have autosomal recessive oculocutanous albinism, and 10% have X-linked ocular albinism, associated with an OA-1 gene mutation. In both, infants display delayed visual maturation, commonly manifesting with inatten- tion until 3 to 8 months of age, and nystagmus, which reduces with convergence. Children may have reduced stereopsis, and develop ametropia or strabismus, with a risk of amblyopia if not managed. Examination reveals iris hypopigmentation and transillumination defects (Fig. 25.1.26e), fundus hypopigmentation, and macular hypoplasia (Fig. 25.1.26f). Electrodiagnostic testing is helpful, with visual evoked potentials displaying crossed asymmetry.

Patients with autosomal recessive gyrate atrophy (ornithine 5-aminotransferase deficiency), associated with an OAT-gene mutation, are stratified based on responsiveness to dietary B6 supplementation. Responders develop a milder phenotype. Symptoms develop in late childhood and include night blindness, peripheral field loss, and reduced visual acuity. Features include high myopia, astigmatism, cataract, and well-defined patches of peripheral chor- oidal atrophy, which enlarge and coalesce, and may be associated with cystoid macular oedema. Plasma and urine ornithine levels, electroretinography, and OCT help confirm the diagnosis. Mineral disorders The ocular features of Wilson's disease (copper binding protein deficiency) include a 'sunflower' cataract and corneal Kayser- Fleischer ring (Fig. 25.1.26d). Optic atrophy is seen in Menkes syndrome (copper transport protein deficiency). Glycosaminoglycan disorders The most frequent ocular feature in the mucopolysaccharidoses is corneal clouding. This is seen in Hurler-Scheie (type I, deficiency of α-iduronidase), Morquio (type IV, Galactose-6-sulphatase de- ficiency), Maroteaux-Lamy (type VI, N-acetyl-galactosamine- 4-sulphatase deficiency), and Sly (type VII, β-glucuronidase deficiency). Pigmentary retinopathy and optic atrophy are fea- tures of Hurler–Scheie, Hunter (type II, iduronate sulphatase defi- ciency), and Sanfillipo (type III, Heparan-N-suplhatase deficiency) syndromes. Toxic and nutritional disorders Drug effects and toxicity A diverse range of significant ocular adverse effects are associated with various toxic substances and systemic drugs. If detected early, most resolve. Additional detail on drugs associated with optic at- rophy is given elsewhere Bone protection agents Ocular inflammation (e.g. conjunctivitis, episcleritis, scleritis, uve- itis) may develop following administration of bisphosphonates, particularly pamidronate (intravenous doses of 30–90 mg, onset typically 48 hours) and alendronate (oral doses of 5–40 mg daily or 35–70 mg weekly, onset typically 2–14 days, extending up to one year). Antiepileptics and antipsychotics Topiramate may precipitate acute, bilateral iridocorneal angle closure resulting in high intraocular pressure and risk of glau- comatous optic nerve damage. This occurs more frequently in

 women, and presents with pain and headache, blurred vision, and nausea. Signs include corneal oedema, conjunctival hyperaemia, a fixed pupil, bilateral acute myopia, periorbital oedema, bleph- arospasm, myokymia, suprachoroidal effusions, nystagmus, and diplopia. Toxicity develops within two weeks (range 1–49 days), at doses over 50 mg. Discontinuation usually results in full recovery. Vigabatrin causes bilateral, symmetrical, irreversible, peripheral and nasal visual field constriction in up to 40% of patients. Men are affected twice as frequently as women. Patients typically pre- sent after more than 12 months of treatment, with tunnel vision and navigation difficulties, which may be severe enough to limit driving and daily activities. Vigabatrin should not be given with other retinotoxic agents. Baseline suprathreshold visual field assessment to at least 45 degrees of eccentricity is recommended in all patients with a developmental age over nine years. Perimetry should be re- peated six-monthly for five years, then extended annually if normal. Thiordiazine can cause maculopathy at total daily doses ex- ceeding 800 mg. Patients typically present with blurred vision, brown-red vision discolouration, and night blindness. Vision usually improves upon discontinuation but maculopathy may be Fig. 25.1.26 Genetic metabolic and mineral disorders: (a) cherry red spot at the macula in Tay–Sachs; (b) inferonasal lens dislocation in homocysteinuria, with visible broken zonules; (c) scleral pigmentation in alkaptonuria; (d) Keisher–Fleisher ring in Wilson's disease; (e) diffuse iris transillumination defects in oculocutaneous albinism; (f) foveal hypoplasia and peripheral 'blonde' fundus in albinism.

25.1 The eye in general medicine 6439 progressive. Chlorpromazine can cause maculopathy at doses of 1200–2400 mg/day. Oculogyric crisis with miosis and blurred vi- sion has also been reported. Antimicrobial agents Ethambutol can cause multiple dose and time dependent adverse effects, including bitemporal visual field defects, central scotomas, and reduced acuity, or colour vision. Optic neuropathy typically begins 2–8 months after starting therapy, and may be bilateral and progress for several months after discontinuation, resulting in optic atrophy. The risk of optic neuropathy increases, from 1% at under 15 mg/kg/day, to 50% at 60–100 mg/kg/day. Vision loss can be se- vere and irreversible. Baseline visual acuity is recommended, with advice to discontinue the drug immediately if any visual symptoms develop. Isoniazid can also rarely cause optic neuritis. Aminoquinolines Aminoquinolines have selective affinity for melanin and concen- trate in the retinal pigment epithelium, where they inhibit critical metabolic pathway enzymes. Hydroxychloroquine is associated with reversible corneal changes (an enhanced Hudson-Stahli line and vortex keratopathy), and retinal toxicity. Retinal changes in- clude retinal vascular attenuation, peripheral retina fine granular pigment changes, and parafoveal granularity of the retinal pig- ment epithelium, which may progress to ‘bull’s eye’ maculopathy (Fig. 25.1.27). Patients present with ocular surface discomfort, dis- torted colour vision, difficulty reading, and central or paracentral scotomas. Recent guidelines in the USA recommend baseline vi- sion assessment (within 1 year) by an ophthalmologist, including OCT and visual field. This is not recommended in the UK unless there are vision symptoms prior to commencing the drug, but all patients should be warned of the risk of retinopathy. Annual screening is recommended after 5 years of treatment, or sooner if there are major risk factors. These include a dose more than 5.0 mg/kg absolute body weight, reduced glomerular filtration rate, liver disease, tamoxifen use, and pre-existing macular disease. Toxicity may be irreversible and continue after drug discontinu- ation. Whilst significant vision loss from hydroxychloroquine ret- inopathy has previously been considered rare, outer retinal damage on OCT is reported in 7.5% of those taking it for more than 5 years, rising to 20% after 20 years of treatment. Similar presentation, base- line assessment, and monitoring guidelines apply to chloroquine therapy, with six-monthly assessment for higher risk patients (dose exceeding 2.3 mg/kg absolute body weight or other risk factors). Quinine is occasionally used as a cutting agent in the preparation of heroin for recreational use, and this has also been associated with retinal and optic nerve toxicity and blindness. There are updated guidelines on the Royal College of Ophthlamologists webpage (https://www.rcophth.ac.uk/wp-content/uploads/2018/03/Hydroxychloroquine-and-Chloroquine-Retinopathy-Screening- Guideline-and-Recommendations.pdf). Cancer therapies Tamoxifen is associated with dose-dependent ocular toxicity. The incidence is 1–2% for dosages under 20 mg/day. Patients present with reduced visual acuity and colour vision after more than one year of therapy (total dose >100 g). Features include whorl-like corneal opacities and macular changes, including deposition of yellow/white refractile opacities in the inner retina, cystoid oe- dema, pigmentary changes, and haemorrhages. Vision often im- proves on discontinuation of treatment. Cisplatin and carmustine have been associated with a pigmen- tary maculopathy, macular exudates, disc swelling, cotton wool spots and intraretinal haemorrhages, and vasculitic arterial occlu- sion which can lead to marked reduction of visual acuity and be irreversible. Interferon-associated retinopathy, characterized by cotton wool spots and retinal haemorrhages, usually resolves on cessation of treatment. However, it may be complicated by sight-threatening branch artery and vein occlusion and macular oedema. Corticosteroids Both topical and oral corticosteroid use is associated with the de- velopment of posterior subcapsular cataracts, elevated intraocular pressure, glaucoma, and central serous chorioretinopathy. Cardiac glycosides Cardiac glycosides, including amiodarone, accumulate in

intracytoplasmic lysosomes and are not readily eliminated. Patients may complain of blurred vision and blue-green coloured rings around lights. Vortex keratopathy develops in a majority after one month, but is not visually significant. Anterior subcapsular lens opacities may also develop. The effects are reversible on discontinuation. Erectile dysfunction agents Sildenafil, vardenafil, and tadalafil infrequently cause dose- dependent, reversible, changes in colour and brightness perception, flashing lights, and blurred vision. These begin 15–30 minutes after ingestion and peak around one hour. The incidence with sildenafil rises from 3% (dose 50 mg) to 50% (dose 200 mg). A rare, but unproven, association with nonarteritic anterior ischaemic optic neuropathy has also been reported. Fig. 25.1.27 Bulls eye maculopathy resulting from drug toxicity. Courtesy of Moorfields Eye Hospital.

Section 25 Disorders of the eye 6440 Vitamin derivatives Isotretinoin (13-cis retinoic acid) is a treatment for severe acne. It is secreted in tears, causing meibomian gland dysfunction and ocular surface discomfort with transient blurring. Headaches and tran- sient visual obscurations require prompt assessment to exclude papilloedema, because intracranial hypertension also occurs in 9% of treated patients. The risk is potentiated with concomitant use of vitamin A or tetracyclines. Conversely, in the presence of low vitamin A levels isotretinoin may induce night blindness due to its inhibitory effect on retinal photo-transduction (see next). Nicotinic acid (vitamin B3, niacin) is used to treat hyperchol- esterolaemia, pellagra, and general malnutrition. It may cause cystoid macular oedema at doses exceeding 3 g/day, which usually resolves on cessation. Recreational drugs and toxic substances Cocaine, a vasoactive sympathomimetic stimulant, and hallu- cinogens, including ecstasy and lysergic acid diethylamide (LSD), cause temporary pupil dilation and blurred vision. Cocaine is also associated with acute angle closure glaucoma, ischaemic bone de- struction, retinal vasospasm, optic neuropathy, and exacerbation of myasthenia gravis. Narcotics, including heroin, methadone and morphine, induce temporary pupil constriction. Methanol inges- tion, leading to formic acid production, may result in blurred vi- sion and field loss within 24 hours, associated with retinal oedema, or permanent blindness with early optic disc hyperaemia, and later atrophy. Another compound in antifreeze, ethylene glycol, can precipitate rapid onset blurred vision and blindness. Inhalation of ‘poppers’ (volatile nitric oxide donors) may cause unilateral or bilateral persistent vision loss resulting from retinal photo- receptor damage. Cyanide toxicity results from smoke inhalation in residential or industrial fires, other environmental exposure, and occasionally from heavy chronic tobacco smoking (‘tobacco amblyopia’). Improper preparation of cassava (manioc, tapioca, Brazilian arrowroot), a major source of dietary carbohydrate in the tropics, can leave sufficient residual cyanide to cause chronic or acute toxicity. The severity of presentation depends upon the type, dose, and route of entry of cyanide. Optic neuropathy results in field loss, vision loss, and eventual optic atrophy. Vitamin deficiency Vitamin A deficiency is associated with xerophthalmia, a constel- lation of symptoms and signs, which are mostly reversible with timely vitamin A replacement. An early symptom is night blindness, which results from reduced availability of rhodopsin. Conjunctival xerosis with Bitot spots results from keratinizing metaplasia and bacterial colonization. Abnormal tear secretion and loss of mucous-producing goblet cells leads to corneal xerosis and thinning (keratomalacia). Corneal scarring results in vision loss. Fundus fea- tures include small, discrete, yellow-white dots that are deep to the peripheral retinal vessels and fade with treatment. Treatment with oral retinyl palmitate (200 000 IU) is effective, and importantly re- duces childhood deaths from other infectious diseases. Vitamin E deficiency may be isolated, or develop in the context of short bowel syndrome, cystic fibrosis, or abetalipoproteinaemia. Ocular features include upgaze limitation and nystagmus, visual

field constriction, night blindness, and even blindness. Treatment is with intramuscular vitamin E. Magnesium deficiency results in involuntary eye movements. Nutritional optic neuropathies are un- common, and associated with Vitamin B12 (cobalamin) and folate deficiency. They either present with gradual vision loss and optic atrophy (Fig. 25.1.18b) or more acute vision loss and disc swelling. Current research and innovation Knowledge gaps The James Lind Alliance established priorities for ophthalmic re- search in the United Kingdom in 2013. The latest Global Burden of Disease Study estimates (2017) highlight the need for further epi- demiological research on blindness and eye disease. Cochrane Eyes and Vision continue to summate the evidence base for diagnostic test accuracy and the efficacy and safety of medical and surgical interventions. Further genetic research has also been greatly facili- tated by the 100 000 Genomes Project, which aims to better under- stand rare ocular diseases and cancers, and also the UK Biobank. Understanding the role of epigenetics and the impact of post- translational modification of the genome on disease pathogenesis will also facilitate methods to assess risk of developing disease and stimulate development of new therapeutic interventions. Diagnostics Ocular imaging technology continues to evolve, offering novel non invasive modalities and enhanced image resolution. Research into the use of artificial intelligence for image analysis promises to en- able cost-effective, early detection, and disease monitoring. Whole genome sequencing further increases the potential for truly person- alized ophthalmic care, with improved risk stratification (e.g. AMD susceptibility genes), genetic diagnosis, prenatal screening, and counselling. Some of the unique diagnostic technology such as ocular coherence tomography is providing cellular level information and in- sights beyond ophthalmology, for example, on the CNS (nerve fibre layer) which correlates with early cognitive loss and also treatment outcomes in multiple sclerosis and other neurological diseases. Therapeutic innovations Robot and laser-assisted surgery are evolving to enhance outcomes in cataract, corneal, and vitreoretinal surgery. The recent explosion in local administration of intraocular therapeutics tailored to indi- vidual inflammatory or neovascular pathologies is set to continue to transform ocular care, in particular through the development of advanced slow release formulations and devices. Furthermore, for patients with blinding retinal diseases, ‘bionic eye’ retinal implants are already able to restore some vision to those with loss of macular function. Microdevices may lower pressure to levels associated with minimal disease progression in glaucoma. Clinical trials are also underway for gene therapy using viral vectors and stem cell therapy to treat diseases including Lebers congenital amaurosis, choroideremia, and Stargardt’s disease. In the future, gene editing using CRISPR- Cas9, which is already established in the setting of animal models of eye disease, might additionally offer the possibility of prenatal gene correction of ocular disease.

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