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"The Really"

Current Ophthalmology

The Electronic Book that is continuously being up-dated

Third Edition

"August 2000"

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CONTENTS

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- In the table of contents, click on any arrow-head pointing to the right (in the recent version of Acrobat-reader there is a + sign instead of an arrow-head). This will open some second and third headings. If you keep doing that, all the headings and sub-headings of the book will be displayed. Point at the text you wish to read and click the left mouse, this will move the screen directly to the part of the book.

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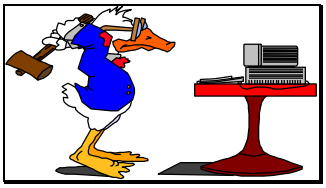

Introduction

"The future is for electronic books!"

My goal of writing this book, is to provide the reader with a book that will be continuously expanded and updated to meet the rapid developments in Ophthalmology. In my opinion, the only way to keep up with all the development is by keeping up with the literature. For busy ophthalmologists, this can prove difficult.

Nowadays, when medical knowledge is changing with such an alarming speed, it will be very difficult to provide a continuously expanding and updated book in the usual printed format. It would be much easier and more practical to produce such a book in an electronic format. This can be updated and expanded much faster and easier.

I intend to update my book every three months by producing a new disc to replace the old one. I hope, by doing this, I will be able to provide the reader with a ***Really Current*** and up to date book. The book is not intended for the beginner ophthalmologists, it does not contain ophthalmic basic knowledge. My book is meant to complement other basic ophthalmology books.

I believe the book can make a useful addition to any ophthalmologist library "or hard disc". It will complement other basic text books, and it will also save on the time spent in the library looking through the ophthalmic journals. I intend to update the book regularly, add photos and diagrams and also possibly produce the book on a CD rather than a floppy disc.

I have included a ***New Chapter***, in this edition, about the common ophthalmic presentations. This chapter has been requested by many non-ophthalmologists who deal with eye problems e.g. General Practitioners and Optometrists. This chapter contains basic Ophthalmology about the most common ophthalmic symptoms.

Magdy A Nofal
August 2000

About The Author

Magdy Nofal is an ophthalmic surgeon in Torbay general hospital, Torquay, Devon, UK. He was born in Egypt and qualified in medicine in Cairo university in 19975 (MB ChB). He has been working in the UK since 1980.

The author passed his FRCS Diploma examination in 1983, from the Royal College of Surgeons in Edinburgh, and was also awarded the fellowship of the College of Ophthalmologists of the UK in 1990. He spent some time working in Saudi Arabia. The author's main interest in Ophthalmology is anterior segment, oculoplastic and lacrimal surgery.

Magdy Nofal is also the co-author of the book ***"An update in topics in Ophthalmology"*** with Mr. Fathi El-Sayyad, from Cairo, Egypt. This book has a similar idea as this electronic book. It is, however, renewed every year. The book is distributed to ophthalmologists and ophthalmic students, in Egypt, for free. A copy of this book can be obtained by writing to the author.

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Common Ophthalmic Presentations *NEW*

4 General Practitioners and Optometrists

This chapter is aimed at GPs, Optometrists and non-Ophthalmologists dealing with eye problems. It deals with the common ophthalmic disorders, basic manifestations, differential diagnosis, primary care and the indications for referral to an ophthalmologist.

This chapter of the book is mainly tables, so it would be better if you hide the table of contents and bookmarks column, on the left of the screen, to increase the screen area for the text material. You can open the table of contents again when you want to go to a different destination in the book. The word "more", in this chapter, indicates a link, to another part of the book, for more relevant information. Clicking on it will take you to that part of the book.

Acute red eye.

Common causes

1. Conjunctivitis
2. Iritis
3. Acute closed angle glaucoma
4. Episcleritis, scleritis.
5. Corneal ulceration, foreign body or abrasion.

Differential diagnosis

Disease	Main manifestations	What to do?	Comments
Conjunctivitis	sticky or watery discharge, no or mild visual loss, bright clear cornea, normal pupil.	treat with topical antibiotics. **Refer** if persistent.	*see additional points below*
Iritis	photophobia, may be slight decrease of vision, the cornea may or may not be cloudy, ma be irregular pupil.	**Refer** within a day for diagnosis and treatment	often idiopathic. May be associated with ankylosing spondylitis, sarcoidosis. May be associated with posterior uveitis (severe visual loss). more
Acute glaucoma	sudden and severe very painful loss of vision, bluish-red discoloration, very cloudy cornea, dilated and fixed pupil, sickness and vomiting,	phone and **Refer** the patient **immediately** for medical treatment followed by laser treatment peripheral iridotomy.	warn the patient that hospitalisation and laser treatment will be needed.
Episcleritis	bright red eye, no discharge, localised or diffuse, with or without nodules, no severe visual loss, bright cornea, normal pupil.	**Refer** (to exclude scleritis), may need topical steroids.	**scleritis** is rarer. Dull boring pain, bluish-red discoloration, may be visual loss, often associated with systemic diseases. **Refer** to diagnose the cause, often need systemic immuno-suppression.
Corneal abrasion	history of trauma, pain, foreign body sensation, and photophobia, watery discharge, deep anterior chamber, + fluorescein staining.	exclude foreign body (if you have a microscope), topical antibiotics with cycloplegic, with or without a pad.	**Refer**, to exclude infection, if the symptoms are out of proportion to the degree of staining. more

- If conjunctivitis does not resolve in a few days, with topical antibiotics treatment, consider:

⇒ Viral coniunctivitis
⇒ Allergic conjunctivitis
⇒ Chlamydial conjunctivitis
⇒ Chronic blepharoconjunctivitis
⇒ Dry eyes syndrome

Differential diagnosis of conjunctivitis

Disease	Main manifestations	What to do?	Comments
Viral conjunctivitis	history of recent URTI, often bilateral, watery discharge, conjunctival follicles, tender and palpable lymphadenopathy.	very infectious, often self limited, cold compresses and antibiotics to prevent secondary bacterial infection.	If conjunctival follicle persists for more than 6 weeks think of chlamydial infection (secondary to genital infection) which need systemic tetracycline treatment. **Refer**
Allergic conjunctivitis	seasonal, itching, thick ropy discharge, papillary reaction.	antihistamine, cromolyn sodium, or lodoxamide.	**Refer** if resistant to exclude vernal disease, may need steroids and other second line treatment. more
Chronic blepharo-conjunctivitis	discharge, lid margin thickening, hyperaemia and crusting.	topical antibiotics, lid hygiene.	beware this might lead to marginal corneal ulceration.
Chlamydial conjunctivitis	chronic follicular conjunctivitis in a young sexually active patient, may be urethritis or cervicitis, palpable lymph nodes.	confirm the diagnosis by an immunofluorescent studies of a conjunctival swab,	treat with systemic and topical tetracycline or azithromycin, also investigate and treatment the patient sexual partner.
Dry eyes syndrome	burning, FB sensation, may be epiphora, worse at the end of the day, Rose bengal staining, decreased Schirmer's test and tear break up time.	artificial tear drops and lubricants.	**Refer** if precipitant for punctal occlusion by plugs.

- If severe purulent fulminating conjunctivitis occur very rapidly, think of ***hyper-acute conjunctivitis*****:**

⇒ Intense chemosis in a few hours with purulent discharge.
⇒ Caused by gonococcus infection
⇒ High risk of corneal perforation
⇒ **Refer immediately** for definite diagnosis and systemic penicillin (or ceftriaxone) treatment.

Conjunctivitis in babies
(Ophthalmia neonatorum)

- Purulent conjunctivitis in a new born (ophthalmia neonatorum) should be **referred** to the hospital for investigations, possible admission and treatment.
- Exclude congenital nasolacrimal duct obstruction and glaucoma.
- All patients should gave a full microbiological studies.

Causes and differential diagnosis of Ophthalmia neonatorum

Causes	Features	What to do?
Chemical	rare nowadays, appears within few hours after instilling silver nitrate drops, lasts only 24-36 hours.	Nothing if sure
Neisseria gonorrhoeae	within the first few days, rapidly progressive, mother may have an infection. Gram negative intracellular bacilli	hospitalisation under ophthalmologists and paediatrician, blood and CSF culture, parenteral administration of ceftriaxone or cefotaxime. Topical antibiotics. All babies should also be treated for chlamydial infection. Treat the mother and her sexual partner.
Chlamydial	often presents in the second week of life. Basophilic intra-cytoplasmic inclusion bodies and polymorphonuclear leucocytes.	Systemic and topical erythromycin, treat the mother and her sexual partner.
Bacterial	gram positive or negative cocci	treat according to gram stain and cytology.
Herpes simplex	may have the typical dendrites and skin rash.	Topical and systemic acyclovir.

A short summery of uveitis

Uveitis can be anatomically classified into:

1. Anterior uveitis: the inflammation occurs mainly in the iris and the anterior chamber
2. Intermediate uveitis: the inflammation occurs mainly in the vitreous cavity
3. Posterior uveitis: the inflammation occurs mainly in the choroid and the retina. It may be due to infectious or non-infectious causes.
4. Pan-uveitis: all the previous layers show signs of inflammation.

The common causes of anterior uveitis include:

- Idiopathic, (the most common type).
- Trauma, and postoperative, (easy to diagnose from the history).
- Iritis associated with arthritis, e.g.:

Disease	Main manifestations
Ankylosing spondylitis	low back pain, abnormal sacroiliac X ray, HLA B27
Psoriasis arthritis	iritis with psoriasis is often associated with arthritis, rheumatologist opinion.
Reiter's disease	chlamydial infection, young adult, conjunctivitis or iritis, polyarthritis, urethritis, increased ESR, HLA B27
Juvenile rheumatoid arthritis	often chronic, young girls, whit eye with no pain, bilateral, positive antinuclear antibodies, mainly in pauciarticular arthritis, negative rheumatoid factor, high ESR, associated cataract and glaucoma, paediatrician opinion.

- other conditions:

Disease	Main manifestations
Sarcoidosis	typically black patients, bilateral, may be granulomatous with posterior uveitis, abnormal chest X ray, positive gallium scan, high ACE, positive biopsy. more
Syphilis	rash, vascular papules on the iris, positive VDRL, FTA-ABS or RPR serological test
Tuberculosis	typical chest X ray, posterior uveitis may be present.
Lyme disease	history of a tick bite, headache, meningitis and facial weakness, general illness, muscle and joint pain, bull's eye or erythematous skin lesions, arthritis, high anti-Borrelia burgdorferi serum titre by the ELISA test.
Inflammatory bowel diseases	chronic intermittent diarrhoea and constipation.
Behcet disease	young adults, acute hypopyon in a white eye, aphthous mouth and genital ulcers, erythema nodosum, positive skin puncture test, retinal vasculitis, HLA-B27 or HLA-B5 positive. more.
Medications	Rifabutin, sulphonamides, cidofovir.

- Investigations of patients with anterior uveitis are often tailored according to the clinical presentation.
- Anterior uveitis may be a manifestation of associated posterior uveitis and dilated fundus examination is necessary.
- Other non-inflammatory conditions should be considered as they may masquerade as uveitis. These conditions are called “Masquerade Syndrome”.

Masquerade Syndrome

Disease	Main manifestations
Posterior segment tumours	e.g. leukaemia and retinoblastoma in children, malignant melanoma in adults and old patients, and reticulum cell carcinoma in elderly patients.
Retinal detachment	diagnosed by fundus examination
Juvenile xanthogranuloma	children, spontaneous hyphaema, iris nodules, orange skin lesion
Anterior or posterior scleritis	ultrasound scan is often helpful.

Common causes of infectious uveitis

Disease	Main manifestations
Toxoplasmosis	yellow white retinal lesions near to an old pigmented chorioretinal scar mainly in the peripheral retina, severe vitritis, a negative undiluted antibody titre exclude the diagnosis in an immunocompetent patient. more
Histoplasmosis	mainly in endemic areas, white choroidal lesions in the posterior pole, peripapillary atrophy, macular dry degeneration, may be choroidal neovascular membrane, minimal to no vitritis
Syphilis	may mimic anything rely on the serological tests
Tuberculosis	variable manifestations, diagnosis is based on lab. tests, a two weeks trial with Isoniazid should resolve the uveitis
Cat scratch disease	unilateral, stellate macular exudates, optic nerve swelling, vitritis, enlarged lymph nodes, positive Bartonella serology more
Rubella	infants of mothers infected in pregnancy, salt and pepper retinal pigmentation, microphthalmos, cataract, increased antibody titre
Toxocara infection	in children, unilateral, macular granuloma, peripheral granuloma, or endophthalmitis, a negative undiluted serology ELISA test exclude the disease.
Postoperative or post-trauma	more

Common causes of non-infectious uveitis

Disease	Main manifestations
Sarcoidosis	granulomatous iritis, vitritis, vitreous opacities, sheathing of the retinal veins, iris or choroidal nodules, optic disc swelling, erythema nodosum, hilar lymphadenopathy on CXR, raised angiotensin converting enzyme, positive conjunctival nodule biopsy, others, more
Multiple white dot syndrome	often in young women, acute unilateral vision loss, history of viral illness, multiple white fundus lesions few vitreous cells, enlarged blind

	spot, good prognosis for vision.
Recurrent multifocal choroiditis	often young myopic women, unilateral visual loss, bilateral multiple small round inflammatory lesion at the choroid, may be associated with choroidal neovascular membrane, some activity in the anterior chamber and the vitreous, respond to systemic steroids, may be recurrent.
AMPPE	young adults after viral illness, acute visual loss, multiple grey subretinal lesions in the posterior pole, serous retinal detachment, mild inflammatory signs, may be CNS signs. Self limited.
Behcet disease	young adults, bilateral, white eye with iritis and hypopyon, retinal haemorrhage and vascular sheathing, recurrent mouth and genital ulcers, erythema nodosum, arthritis. more
Vogt-Koyanagi-Harada syndrome	dark patients from Asian or American origin, anterior uveitis with mild vitritis, serous retinal detachment, optic disc swelling, meningeal signs, vitiligo and alopecia, hearing loss and tinnitus. more
Birdshot choroiditis	middle age women, bilateral multiple creamy yellow lesions in the mid-retinal periphery, vitritis, positive HLA-A29, cystoid macular oedema and choroidal neovascular membrane may occur.

intermediate uveitis “pars planitis”

main features	Other features	treatment	others
floaters and blurred vision in a 15-45 years old, photophobia, occasionally red eye, bilateral disease. fundus examination reveal vitreous snow-banking and snowball vitreous opacities.	iritis, vascular sheathing, lens opacities, secondary glaucoma, vitreous haemorrhage, retinal detachment.	only if the visual acuity is affected by CMO or by severe vitritis. Treatment is often by topical, periocular or systemic steroids. Retinal cryotherapy or vitrectomy may also be needed in resistant cases.	more

Corneal fluorescein staining (corneal ulcer)

Common causes:

1. Bacterial ulcers, the most serious
2. Herpes simplex virus ulcer
3. Fungal ulcer
4. Acanthamoeba ulcer
5. Marginal ulcer
6. Corneal abrasion

Differential diagnosis of keratitis and corneal ulcers

Disease	Main manifestations	What to do?	Comments
Bacterial	red eye, pain, discharge, decreased vision, white infiltrate in case of keratitis or central staining in case of ulceration.	**Refer urgently**	needs admission, any central infiltrate or ulcer should be considered bacterial until proved otherwise by lab. tests. more
Heroes zoster ophthalmicus	skin rash on one side of the forehead and scalp and pain, headache may precede the rash, may be associated with corneal dendrites, keratitis or iritis with or without raised IOP.	Start a course of systemic acyclovir and **Refer** to exclude ocular involvement.	if the tip of the nose is involved with the rash it is likely that the eye will also be affected.
Herpes simplex	eye lid vesicles, cold sores, dendritic-shaped ulceration,	**Refer**	topical steroid can only be prescribed by an ophthalmologist at onset and also in the future.
Fungal	feathery infiltrate, satellite lesions,	**Refer urgently**	needs admission, must be considered after trauma with vegetable material (tree branches)
Acanthamoeba	extreme pain and photophobia for several days (out of proportion to the degree of corneal infiltrate), contact lens wearer, stromal ring shaped infiltrate, radial keratitis.	**Refer urgently**	needs admission, should be considered in any contact lens wearer and in non-responding bacterial or viral ulcers. Keep the contact lens for culture. more
Marginal	often marginal, mild or no visual loss, may	**Refer**	out-patient

keratitis	be very painful, associated with blepharitis.		treatment, treatment is by steroids, make sure it is not marginal herpes simplex ulcer before using steroids.

It is safe to say that all patients with central corneal ulceration should be referred immediately to an ophthalmologist for diagnosis and treatment.

Sudden onset of painful loss of vision.

Common causes

With a red eye	Without a red eye
• acute glaucoma • keratitis and corneal ulcers	• temporal arthritis • optic neuritis

Differential diagnosis

Disease	Main manifestations	What to do?	Comments
Retrobulbar or optic neuritis	sudden loss of vision in a 18-45 years old patient, RAPD, normal or swollen optic nerve head, orbital pain with ocular movements, altered perception of moving objects, worsening of vision with increased body heat.	**Refer**, needs IV steroids in demyelinating diseases and an MRI for ? CNS involvement. more	optic neuritis may be caused by many causes, young adult patients need a neurologists opinion to diagnose of exclude MS, in children it is often due to viral infection and complete spontaneous improvement is often expected.
Arteritic anterior ischaemic optic neuropathy	sudden loss of vision in a 50 or older patient with RAPD, severe headache and temporal tenderness, no temporal artery pulsation, severely ill patient, no pain with ocular movements, pale optic nerve head with flame shaped haemorrhage, high ESR and CRP. More	**Refer** immediately for IV and oral steroids (80-100 mg of prednisolone daily) and confirmation with a blood test and/or temporal artery biopsy. Medical referral is also advisable. More	a very quick action is needed as permanent and total loss of vision is a major risk even with the full steroids treatment.

- Anterior ischaemic optic neuropathy may be non-arteritic, vision loss is often painless and non-progressive, patients are often younger, altitudinal visual field defect is typical, normal ESR and CRP, steroids do not often help very much, **Refer** to exclude the arteritic type.

Sudden onset of painless loss of vision

Common causes:

1. Retinal artery occlusion
2. Retinal vein occlusion
3. Retinal detachment and vitreous haemorrhage.
4. Macular changes
5. Central visual field loss
6. Central serous retinopathy

Differential diagnosis

Disease	Main manifestations	What to do?	Comments
Retinal artery occlusion (central or branch)	sudden severe (if central retinal artery occlusion) loss of vision, RAPD, whitening of the retina with a cherry-red spot, segmentation of the retinal vessels, with or without retinal emboli.	**Refer** to consider treatment (effective if administered in the first 24 hours), needs carotid artery ultrasound to exclude source of embolization, exclude giant cell arteritis by an ESR.	Giant cell arteritis often present by anterior ischaemic optic neuropathy but central retinal artery occlusion may also be the presenting feature of the disease
Retinal vein occlusion (central or branch)	diffuse retinal haemorrhage, cotton wool spots, disc and macular oedema, collateral and new blood vessels.	Exclude hypertension, diabetes, and other cardiovascular disease, consider stopping oral contraceptives, **Refer** to exclude glaucoma and papilloedema and to consider fluorescein angiography and possible laser treatment.	Retinal vein occlusion may be ischaemic or non-ischaemic. The ischaemic type has a worst prognosis and need a closer follow-up.
Retinal detachment and vitreous haemorrhage	history of floaters and flashing light, curtain moving across the vision, loss of the central or the peripheral vision, retinal elevation, with loss of the red reflex, with or without vitreous haemorrhage.	**Refer urgently** if the central vision is still good (macula is still on) or if the patient is young or if the detachment is of recent onset (better prognosis after surgery). **Refer** soon if the central vision is lost or if the detachment is of long duration. Referral is also useful if there is a doubt about retinoschisis.	any case with sudden onset of vitreous haemorrhage (in a non-diabetic patient) should be considered as caused by a detachment or retinal tear until proved otherwise. *see other types of detachment below.*
Macular changes	often elderly patients, rapid onset of distortion or loss of vision (not as sudden as vascular occlusion), subretinal macular haemorrhage, exudates or fluid. History	check blood pressure, **Refer** urgently as fluorescein angiography is often needed and laser photocoagulation may be possible,	10% of all patients may benefit from laser treatment. Other methods of treatment are developing. more

	of similar problem in the fellow eye.		
Central visual field loss	history of a recent stroke, often bilateral hemianopia or quadrantonopia, normal ocular examination and no RAPD.	check blood pressure and CAT scan for any space occupying lesion and for any treatable cause of the stroke, **Refer** for proper visual field testing, bitemporal hemianopia needs further investigations for the pituitary gland. May need a medical referral.	Suspect this when patients complain of s a sudden onset of visual loss in both eyes with good visual acuity.
Central serous retinopathy	blurred and distorted vision (rather than loss of vision), young patients with type A personality, localised detachment of the serous retina mainly at the macular area,	do not give steroids (it makes it worse), **Refer** for confirmation by fluorescein angiography, often self limited in about 6-8 weeks, laser photocoagulation may be needed in long-standing case.	severe cases may rarely occur leading to a widespread exudative detachment.

Types and causes of retinal detachment

Rhegmatogenous	Exudative	Traction
history of floaters and/or flashing lights, elevation of the retina with a retinal tear, pigmented cells in the vitreous, needs urgent referral for surgical treatment	minimal to severe visual loss with visual field defects, elevation of the retina with no tears, shifting of the subretinal fluid according to head posture, caused by retina or choroidal primary or secondary ***tumours***, and also by inflammatory conditions (Vogt-Koyanagi-Harada syndrome and posterior scleritis) and others. Treated by treating the cause.	visual loss, immobile retina, may result from penetrating ocular trauma, diabetes or vascular retinal disorders. Needs surgical treatment.

Differential diagnosis of the common intraocular tumours more

Tumour	Features
Choroidal melanoma	may be asymptomatic, floaters or decreased vision of visual field loss, may be pigmented or non-pigmented, elevated mass, vitreous haemorrhage, typical ultrasound features.
Choroidal haemangioma	in young adults, may be asymptomatic, may present with change of refraction, red orange lesion, mild elevation, typical fluorescein angiography features.
Choroidal metastases	may be asymptomatic, creamy white colour mass, flat or slightly elevated, history of cancer mainly in the breast or the lung.
Retinoblastoma	children, white nodular mass, may extends in the vitreous or under the retina, iris neovascularisation, pseudo-hypopyon, vitreous seeding.

Gradual loss of vision

Common causes:

1. Cataract (by far the most common cause)
2. Macular degeneration
3. Glaucoma
4. Corneal dystrophies
5. Optic neuropathies

Differential diagnosis

Disease	Main manifestations	What to do?
Cataract	slow progressive visual loss, glare, loss of contrast sensitivity, change of refraction towards myopia in some cases, opacification of the crystalline lens.	**Refer** to an optician to check if correction of refractive error will be enough, opticians usually suggest referral to an ophthalmic surgeon to consider surgery if glasses are not enough.
Macular degeneration	Difficulty with near and reading vision mainly, it only affects the central vision, distortion of vision, macular drusen, retinal pigment epithelium atrophy, subretinal elevation, exudate or haemorrhage. the most common type of macular degeneration s the age related type in elderly patients.	if there are retinal elevation, exudate or haemorrhage **Refer** urgently as laser photocoagulation may be effective in preventing progression. If the degeneration is mainly dry and atrophic **Refer** to consider low visual aid and poorly sighted registration.
Glaucoma	often discovered during routine eye tests and may not be associated with any symptoms, patients may notice gradual deterioration of vision and loss of the peripheral vision, may be associated with headache if the IOP is very high, high IOP, cupped optic nerve head, loss of peripheral visual field.	If in doubt **Refer** to an optician to measure the IOP and the visual field, referral to an ophthalmologist is often suggested by the optician.
Corneal dystrophies	Gradual deterioration of the vision associated with corneal changes with no signs of inflammation or vascularisation of the cornea, may be inherited. Some types of corneal dystrophies may cause recurrent painful corneal erosions.	**Refer** for diagnosis and consideration of corneal graft surgery (or hard contact lens in cases of keratoconus).
Optic neuropathies	painless progressive visual loss, RAPD, loss of colour vision (by the Ishihara test), associated with central scotoma and may be associated with peripheral visual field loss.	**Refer** for diagnosis and treatment

The main types of stromal corneal dystrophies are:

1. Lattice dystrophy
2. Granular dystrophy
3. Macular dystrophy
4. Keratoconus

Differential diagnosis

Disease	Main manifestations
Lattice dystrophy	refractile branching corneal lines, dots and scarring of the central cornea, may be recurrent corneal erosions.
Granular dystrophy	white deposits in the central cornea separated by clear areas of healthy cornea, the corneal periphery is often clear, appears in the first decade of life but become symptomatic later in adulthood.
Macular dystrophy	grey white corneal deposits covering the whole cornea with no clear areas in-between the deposits.
Keratoconus	often affects young adults, slowly progressive irregular corneal astigmatism often discovered by the optician, may be associated with sudden onset of pain and red eye if corneal hydrops develop. May be associated with systemic diseases e.g. Down's syndrome and atopy.

Common causes of optic neuropathies:

1. Non-arteritic ischaemic neuropathy (the arteritic type is often painful with headache)
2. Tobacco and/or alcohol abuse (malnutrition)
3. Iatrogenic (chloramphenicol, ethambutol, isoniazide, chloroquine, others)
4. Compressive neuropathy (optic nerve glioma, meningioma)
5. Leber's neuropathy
6. Dominant optic atrophy

Transient loss of vision

The main causes:

1. Papilloedema
2. Amaurosis fugax (unilateral)
3. Vertebrobasilar insufficiency (Bilateral)
4. Anterior ischaemic optic neuropathy and giant cell arteritis
5. Migraine

Differential diagnosis

Disease	Main manifestations	What to do?
Papilloedema	visual loss or obscuration lasts only seconds, optic disc head swelling, may be associated with headache and symptoms of raised intracranial pressure.	check BP and **Refer** urgently for a head MRI
Amaurosis fugax	monocular loss of vision for few minutes, appears as a curtain moving across vision, retinal emboli or retinal cotton wool spots indicating retinal ischaemia, dilated retinal vessels with mid peripheral retinal haemorrhage, retinal or disc neovascularisation indicating ocular ischaemia. may be associated with systemic neurological manifestations.	start aspirin therapy, and **Refer** for investigations including carotid artery ultrasound.
Vertebrobasilar insufficiency	Bilateral loss of vision that lasts for minutes or more, may be associated with flashing lights and ataxia, vertigo, and hemiparesis.	start aspirin therapy, and **Refer** for investigations including carotid artery ultrasound.
Anterior ischaemic optic neuropathy (giant cell arteritis)	sudden loss of vision in a 50 or older patient with RAPD, severe headache and temporal tenderness, no temporal artery pulsation, severely ill patient, no pain with ocular movements, pale optic nerve head with flame shaped haemorrhage, high ESR and CRP.	**Refer** immediately for IV and oral steroids (80-100 mg of prednisolone daily) and confirmation with a blood test and/or temporal artery biopsy. Medical referral is also advisable. more
Migraine	young patients, recurrent episodes, often lasts between 10 and 45 minutes, the diagnosis is often made after excluding all the other causes.	**Refer** to exclude all the other causes.

Floaters and flashing lights

Common causes of floaters

1. Posterior vitreous detachment
2. Posterior uveitis
3. Vitreous haemorrhage
4. Vitreous degenerative conditions (like asteroid hyalosis)
5. Migraine

Differential diagnosis of floaters and flashing lights

Disease	Main manifestations	What to do?
Posterior vitreous detachment	seeing floaters, cob webs, circles or tadpole that move with eye or head movements, may be associated with flashing lights.	**Refer** to exclude retinal detachment, retinal breaks or vitreous haemorrhage. the likelihood of having retinal break increases when the floaters are associated with flashing lights. Posterior vitreous detachment is untreatable condition and rarely cause severe visual problems.
Posterior uveitis	Vitritis is associated with vitreous white cells and possibly cells in the anterior chamber too	**Refer** to make a diagnosis and treat if needed.
Vitreous haemorrhage	Variable degrees of visual loss depending on the severity of the haemorrhage, loss of the red reflex.	in the absence of diabetic retinopathy and retinal vascular diseases, vitreous haemorrhage should be considered to be caused by retinal break until proved otherwise. **Refer** to exclude retinal breaks and vascular retinal diseases.
Vitreous degenerative conditions (asteroid hyalosis)	small refractile opacities, of no clinical significant.	No need to refer.
Migraine	floaters and flashing lights are often transient, associated with seeing zig-zag lines, headache may or may not be associated with the floaters and flashing lights.	This diagnosis is often made by exclusion, no need to refer if confident of the diagnosis.

Anisocoria
(unequal pupils)

Anisocoria more marked in the dim light
(do the 10% cocaine eye drops test)

Disease	Main manifestations	What to do?
Physiological anisocoria	the small pupil dilates with 10% cocaine eye drops.	no need to refer.
Horner syndrome	ptosis, miosis, with or without anhidrosis, no dilatation after 10% cocaine eye drops. more	do the 1 % Hydroxyamphetamine test to differentiate preganglionic (the pupil dilates), and postganglionic (the pupil does not dilate) causes. **Refer** for further investigations (e.g. CXR and carotid arteries) especially in recent onset cases.

Anisocoria more marked in the bright light
(do the 0.1% pilocarpine eye drops test)

Disease	Main manifestations	What to do?
Traumatic iris damage	torn iris sphincter on microscopic examination, slow near pupil reaction	No need to refer.
Third nerve palsy	no constriction with 0.1% pilocarpine, constricts with 1% pilocarpine, may be exodeviation and ptosis.	**Refer** for further investigations
Adie's pupil	pupil constricts with 0.1% pilocarpine, sector iris palsy, tonic near reaction.	No need to refer.
Pharmacological dilatation.	the pupil constricts with 1% pilocarpine drops.	No need to refer.

The cocaine and the Hydroxyamphetamine test

- Put one drop of cocaine 10% in each eye and then examine the pupils after 15 minutes. If nothing happens repeat the drops and examine again in 15 minutes. In case of 1 % Hydroxyamphetamine test, examine the pupils after 30 minutes.
- Hydroxyamphetamine should not be used within 24 hours of using the cocaine drops.

Ptosis
"droopy upper lid" more

Causes of ptosis

1. Levator muscle dehiscence e.g. old age (the commonest cause), postoperative, or post-trauma
2. Congenital
3. Myasthenia gravis
4. Third nerve palsy
5. Horner syndrome more
6. Chronic progressive ophthalmoplegia
7. Prolonged use of topical steroids

Differential diagnosis

Disease	Main manifestations	What to do?
Levator muscle dehiscence	the upper lid skin crease is typically raised, good levator muscle function,	**Refer** for surgical treatment.
Congenital	onset since birth, the skin crease is typically normal, poor levator function	**Refer** soon (if there is a risk of visual deprivation) for vision evaluation, amblyopia treatment and surgical treatment if indicated.
Myasthenia gravis	may be double vision, worse towards the end of the day, weakness of other facial or swallowing muscles.	**Refer** to an ophthalmologist or a neurologist for confirmation by acetyl-choline receptors antibodies and Tensilon test. more
Third nerve palsy	pupil may be dilated, the eye may be deviated outwards, no diurnal variation.	**Refer**. Sudden onset of painful third nerve palsy with pupil involvement is a real emergency to role out the possibility of intracranial aneurysm.
Chronic progressive ophthalmoplegia	gradual onset, ocular misalignment and limited ocular movements, may be other muscles weakness, no diurnal variation, normal pupils, may be family history.	**Refer** for fundus examination, and ECG to exclude Kearns-Sayre syndrome, abetalipoproteinaemia, and Refsum's disease, may need a neurological opinion.

Kearns-Sayre syndrome	onset before 20 years of age, retinal pigmentary changes, heart block, hearing loss, mental retardation.
Abetalipoproteinaemia	retinal pigmentary changes, diarrhoea, ataxia, CNS signs, acanthocytosis of red blood cells.
Refsum's disease	retinitis pigmentosa-like picture, increased blood phytanic acid, other neurological signs.

- **The Tensilon test**: inject 0.2 ml IV of Edrophonium chloride, if an improvement in the lid position is noticed the test is considered positive. If no improvement occurs, inject 0.4 ml and notice the lid margin position again. If no improvement occurs inject another 0.4 ml and notice the lid margin and any side effects.
- Be prepared with Atropine (0.4 mg IV) and resuscitation equipment.

Proptosis

Proptosis is the hallmark of orbital diseases. Almost all the orbital diseases present with these typical presentations:

- Proptosis or exophthalmos
- Pain
- Restriction of ocular movements and double vision
- Blurred vision
- Resistance to retropulsion of the globe.

Before diagnosing proptosis, care should be taken to exclude causes of pseudo-proptosis e.g. high myopia and contralateral enophthalmos. Radio-imaging plays a very important part in the diagnosis and **all patients with proptosis should be referred to an ophthalmologist for a CAT or MRI scan .**

Common causes of proptosis

1. Thyroid eye disease (the most common cause)
2. Orbital pseudo-tumours
3. Orbital cellulitis
4. Orbital tumours
5. Trauma
6. Varix
7. Arteriovenous fistula

Differential diagnosis

Disease	Main manifestations	Radio-imaging
Thyroid eye disease	may be unilateral or bilateral, may have a gradual or rapid onset, upper lid retraction, lid lag. T3, T4, TSH.	thickening of the extraocular muscles without involvement of their tendons.
Orbital pseudo-tumours	often painful, healthy patient with normal white count and no pyrexia, dramatic response to systemic steroids.	thickened muscles with involvement of their tendons, the scleral orbital fat or the lacrimal glands may also be involved.
Orbital cellulitis	pyrexia, high white count. Patients should be followed up daily to watch out for improvement or the possible development of cavernous sinus thrombosis (*drowsiness, with nausea and vomiting, decreased sensation of the fifth cranial nerve, dilated and sluggish pupils, weakness of the third, fourth, and sixth cranial nerves*), or peri-orbital abscess.	sinusitis, peri-orbital abscess.
Orbital tumours	mass, globe displacement according to the location of the mass, there may be a primary in the breast or the bronchus.	a mass is shown
Trauma	trauma and foreign body may be followed by a retrobulbar haemorrhage.	

Varix	due to a large dilated orbital vein by a thrombus, proptosis increases with Valsalva manoeuvre.	Dilated vein may be shown with an enhanced CAT scan during Valsalva manoeuvre
Arteriovenous fistula	may follow trauma or may be spontaneous, a bruit may be heard, prominent conjunctival vessels and chemosis.	enlarged superior ophthalmic vein, the extraocular muscles may also be enlarged, reversed blood flow may be noticed by ultrasound Doppler.

Differential diagnosis of the common orbital tumours in adults

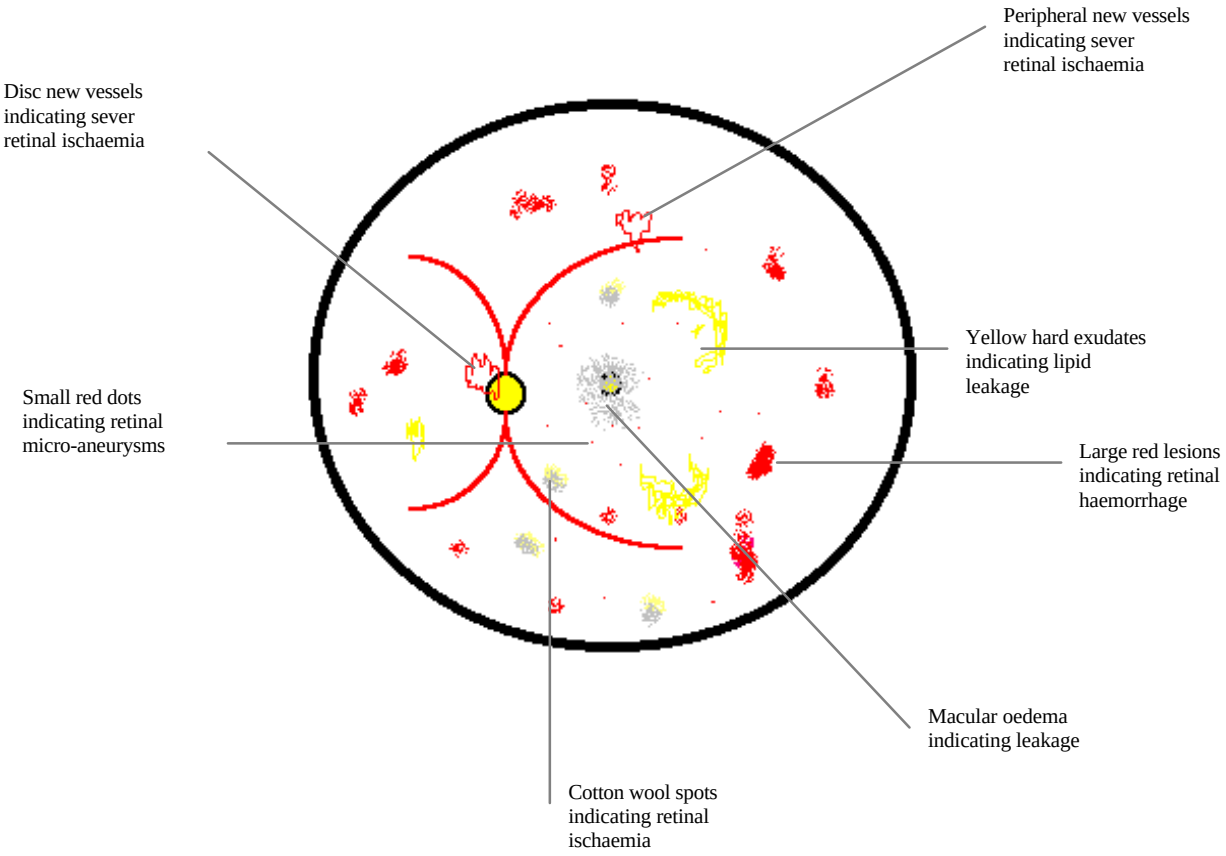
Tumour	Ophthalmic features	Radio-imaging
Secondary tumours	the most common cause of orbital mass, common primary sites include breast, lung, prostate, and GIT,	poorly defined mass, bone destruction.
Cavernous haemangioma	young adults, slow onset,	well defined mass often within the muscle cone, high amplitude internal echo by ultrasound.
Optic nerve sheath meningioma	middle aged women, slowly progressive visual loss with mild proptosis and RAPD, optic nerve swelling or atrophy with opticociliary shunt vessels, may be a temporal fossa mass.	tubular enlargement of the optic nerve,
Lymphoid tumours	middle age to elderly patients, slow progression and onset, may be associated with lymphoid tumours of the anterior segment, not necessarily associated with systemic disease,	irregular mass, no bony erosions,
Mucocele	frontal headache with a history of sinusitis.	frontal or ethmoid sinus swelling with bone erosions.

Differential diagnosis of the common orbital tumours in children

Tumour	Ophthalmic features	Radio-imaging
Dermoid and epidermoid cyst	present since birth, slow progress, often develops in the outer upper quadrant, smooth round and non-tender.	well-defined mass.
capillary haemangioma	from birth till early infancy, slow progress, may enlarge during the first year but often regresses afterwards, may present a s bluish-red mass seen through the lid, proptosis may increase with crying.	irregular mass.
Rhabdomyosarcoma	often around the age of 7, rapid onset and progression, malignant and may metastasise, history of nose bleeding, **urgent biopsy** is mandatory if this tumour is suspected, needs **referral** to a paediatric oncologist.	bone destruction, may be well-demarcated mass.
optic nerve glioma	at the age of 2-6 years old, RAPD and	fusiform swelling of

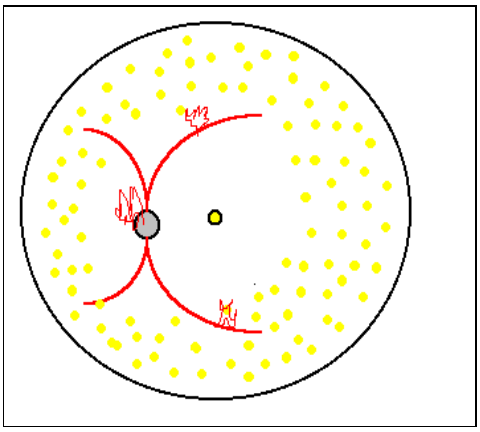
	decreased vision, optic nerve swelling or atrophy, may be associated with neurofibromatosis.	the optic nerve, the chiasm may also be involved.
Leukaemia	often in the first decade of life, rapid progression, may be bilateral, may precede blood or bone marrow changes (acute myelogenous leukaemia).	irregular mass, temporal fossa mass may be present.
Lymphangioma	in the first decade of life, slowly progressive, rapid growth if bleeds, may be increased in size with infections, may be other lymphoid tumours elsewhere.	non-capsulated irregular mass, with cystic multiloculated areas.

Diabetic retinopathy: ophthalmic features

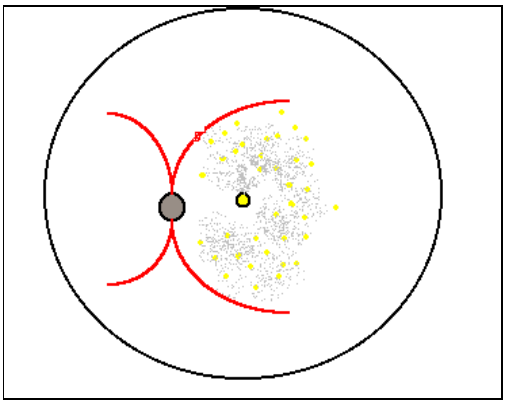


ophthalmic feature	what it means and what to do?
Micro-aneurysms	no treatment unless leaking and threatening fixation by macular oedema
Retinal haemorrhage	no treatment needed
Yellow hard exudates	indicates lipids and macrophages leakage, should be **refereed** and treated if threatening fixation
Macular thickening	indicates macular oedema, may affect vision, should be **refereed**, treated if near enough to fixation
Cotton wool spots	indicate ischaemia, needs **referral** for close observation
Disc or peripheral new vessels	indicate severe retinal ischaemia, high risk of vitreous haemorrhage and retinal detachment and poor visual outcome, needs urgent **referral** for laser treatment
Vitreous haemorrhage	indicates poor visual outcome, needs urgent **referral** to exclude retinal detachment, may need vitrectomy.
Acute disc oedema	occurs mainly in juvenile diabetics, mild visual loss, no RAPD, often resolves in a few months, no need for treatment .

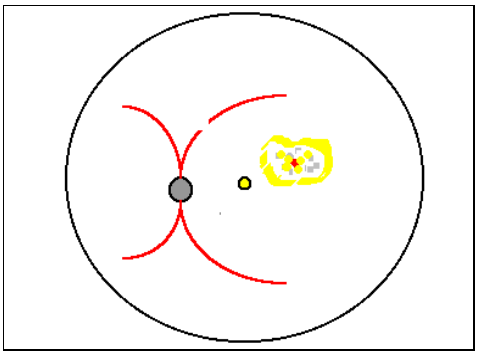
Diabetic retinopathy: types of laser treatment



1. Panretinal photocoagulation
(several hundreds to few thousands burns)
indicated in disc and/or peripheral new vessels



2. Grid laser photocoagulation
(few hundreds burns)
indicated in diffuse macular oedema



3. Focal laser photocoagulation
(several burns)
indicated in focal leakage threatening fixation

Ophthalmic features of AIDS

Anterior segment features

Molluscum contagiosum	dome-shaped umblicated shiny nodule on the lid margin or the lid, may be multiple, may be associated with chronic follicular conjunctivitis and keratitis.
Kaposi sarcoma	malignant sub-conjunctival red nodule, occurs in about 30% of patients.
Severe herpes simplex or herpes zoster infection	in young patients often suspect aids, corneal dendritic ulcers may be peripheral.
Microsporidial keratitis.	fine to coarse diffuse chronic keratitis.

Posterior segment features

Retinal micro-angiopathy	asymptomatic, cotton wool spots, may be retinal haemorrhage, micro-aneurysms.
CMV retinitis	peripheral opacification of the retina with/without haemorrhage, often progressive, dense white well demarcated confluent opacities of the retina, mild vitritis. **more**
Pneumocystis carinii choroiditis	yellow round choroidal lesions, often bilateral, no vitritis.
Toxoplasmosis	**more**
PORN	**more**

Strabismus

Squint may be convergent (esodeviation) when the two eyes are looking towards each other, or divergent (exodeviation) when the two eyes are looking away from each other.

You must, first of all, exclude pseudo-esotropia (the eye appear to be turning in but they do not actually show and deviation with the cover test).

Causes of pseudo-esotropia:
1. Wide nasal bridge
2. Prominent epicanthus fold
3. Small inter-pupillary distance

You must differentiate between the main two type of squint:

Concomitant squint	Incomitant squint
manifest deviation of the eye where the deviation angle is nearly the same in all direction of gaze, the ocular movement seems to normal in this case.	the measured angle of squint varies depending on the patient 's direction of gaze. This is mainly due to a paralytic cause.

Common causes of concomitant esodeviation

Disease	Main manifestations
Congenital	often positive family history, appears in the first few months, the angle of deviation if often large, little or no refractive errors, may be associated with nystagmus, amblyopia may or may not be present. Refer the patient to treat amblyopia if present and also to align the eyes with surgery.
Accommodative refractive	often appears at the age of 2-3 years old, children often have high hyperopia, moderate to small angle of deviation with is equal to near and far vision, the deviation disappears on wearing the corrective glasses. Refer for refraction and treatment of amblyopia if present.
Accommodative non-refractive	the refractive error is not significantly higher than normal, the angle of deviation is larger for near vision than for distant vision. Refer to treat amblyopia and surgery if needed.
Partial accommodative	the angle of deviation is decreased but not completely eliminated by wearing the corrective glasses. Refer to correct amblyopia and to align the eyes surgically.
Sensory deprivation	as in congenital cataract, corneal opacity, optic nerve diseases or intraocular tumours. Refer to diagnose and treat the cause.
Divergence insufficiency	diagnosis of exclusion.

Common causes of incomitant esodeviation

1. Neurological diseases e.g. Tumours, hydrocephalus.
2. Thyroid eye disease
3. Orbital trauma
4. Isolated sixth nerve palsy

Common causes of exodeviation

Disease	Main manifestations
Intermittent exodeviation	the most common type in children, often occur at the age of 4, often progressive from intermittent deviation on distant vision to constant deviation on near and far vision. **Refer** for surgical treatment.
Sensory deprivation	blind eyes, from any cause, tends to diverge. **Refer** for cosmetic surgery if the patient is interested.
Duane syndrome type 2	limitation of adduction of the eye with retraction of the globe on attempted adduction. **Refer** for consideration of surgical treatment.
Third nerve palsy	pupil may be dilated, the eye may be deviated outwards, no diurnal variation. Sudden onset of painful third nerve palsy with pupil involvement is a real emergency to role out the possibility of intracranial aneurysm. **Refer**.
Orbital diseases	proptosis and ocular motility restriction. Refer for MRI.
Myasthenia gravis	may be double vision, worse towards the end of the day, weakness of other facial or swallowing muscles. **Refer** to an ophthalmologist or a neurologist for confirmation by acetyl-choline receptors antibodies and Tensilon test.
Convergence insufficiency	blurred near vision and headache when reading, straight eyes for distance but exodeviation for near. **Refer** for convergence exercises.

The cover test

- Ask the patient to look at a distant object. Cover the right eye and see what happens to the left the eye when it is forced to take up fixation, then cover the left eye and see what happens to the right eye when it is forced to take up fixation.
- If the right eye turns inward, when the left eye is covered, this means that the right the was turning out when both eye were open and then had to turn in to take up fixation. This means that the patient has a right divergent squint.
- If the right eye turns outward when the left eye is covered, this means that the patient has a right convergent squint.

Diplopia
double vision

Care should be taken to differentiate between monocular and binocular diplopia. In monocular diplopia patients complain of double vision even if one eye is covered. In binocular diplopia double vision is present only if both eyes are open.

Common causes of binocular diplopia	Common causes of monocular diplopia
1. Isolated third nerve palsy 2. Isolated sixth nerve palsy 3. Isolated fourth nerve palsy 4. Giant cell arteritis 5. Myasthenia gravis 6. Thyroid eye disease 7. Chronic progressive external ophthalmoplegia 8. Orbital tumours or pseudo-tumours 9. Orbital trauma and blow out fracture.	1. Error of refraction 2. Lens or corneal opacities

Differential diagnosis of diplopia

The disease	features	Tests	What to do?
De-compensated phoria	common, history of difficulty and eye strain for close fine work, may be intermittent first, symptoms may be more severe if the patient become ill or debilitated.	**Refer** to an optician for refraction and ocular muscle balance.	If symptoms persist despite proper glasses **Refer** for orthoptic assessment.
Cranial nerves palsy	*see next table.*		
Myasthenia gravis	worse towards the end of the day, weakness of other facial or swallowing muscles, normal pupil most of the time, weak orbicularis muscle..	Ice or Tensilon test	**Refer** to an ophthalmologist or a neurologist for confirmation by acetyl-choline receptors antibodies and Tensilon test.
Thyroid eye disease	may be unilateral or bilateral, may have a gradual or rapid onset, upper lid retraction, lid lag. T3, T4, TSH.	thickening of the extraocular muscles without involvement of their tendons.	**Refer** to an ophthalmologist for medical treatment or surgical treatment of proptosis or associated lid or extraocular muscles disorders.
Chronic progressive external ophthalmoplegia	gradual onset, ocular misalignment and limited ocular movements, may be other muscles		**Refer** for fundus examination, and ECG to exclude Kearns-Sayre syndrome, abetalipoproteinaemia, and

	weakness, no diurnal variation, normal pupils, may be family history.		Refsum's disease, may need a neurological opinion.
Giant cell arteritis	sudden loss of vision in a 50 or older patient with RAPD, severe headache and temporal tenderness, no temporal artery pulsation, severely ill patient, no pain with ocular movements, pale optic nerve head with flame shaped haemorrhage,	high ESR and CRP.	**Refer** immediately for IV and oral steroids (80-100 mg of prednisolone daily) and confirmation with a blood test and/or temporal artery biopsy. Medical referral is also advisable.
Orbital tumours or pseudo-tumours	often painful, healthy patient with normal white count and no pyrexia, dramatic response to systemic steroids.	thickened muscles with involvement of their tendons, the scleral orbital fat or the lacrimal glands may also be involved.	**Refer** for MRI diagnosis and possible steroids treatment.

Differential diagnosis of the isolated cranial nerve palsy

The nerve	Features	Causes	what to do?
Third nerve Palsy	diplopia and ptosis, may be complete or incomplete, in complete palsy all eye movements will be lost except outward gaze. In partial palsy inward, upward or downward gaze will be affected depending on which branch of the nerve is involved. The pupil may be dilated and fixed, or may be normal.	pupil sparing is often caused by vascular lesion e.g. diabetes, hypertension or giant cell arteritis. Pupil-involving palsy is likely to be caused by a compressive lesion e.g. aneurysm, tumour or trauma, it may also be caused by a vascular lesion.	occlusion patch to prevent diplopia and Refer to diagnose the cause. Sudden onset of painful third nerve palsy with pupil involvement is a real neuro-ophthalmic emergency to exclude intracranial aneurysm. MRI scan in all pupil-involving lesion, young patients with no vascular cause, incomplete palsy, and patients with no recovery in 3 months
Sixth nerve Palsy	horizontal diplopia worse for distance than for near mainly in the direction of action of the involved muscle.	vascular causes e.g. diabetes, hypertension and atherosclerosis, trauma, idiopathic. May also be caused by raised intracranial pressure. In children post-viral palsy is common and often have a benign course.	occlusion patch to prevent diplopia and Refer for diagnosis of the cause. MRI in young patients and children, if not resolved in no better in 3-4 months or if there is a primary cancer.

Fourth nerve Palsy	vertical or oblique diplopia, difficulty reading, the involved eye if typically higher than the other eye.	congenital, trauma, vascular lesions, demyelinating disease, idiopathic.	occlusion patch to prevent diplopia and refer to diagnose and treat the cause if possible. MRI scan if there is other suspected neurological lesion and in young patients.

If there is multiple ocular motor deficiencies, consider the following:

1. Cavernous sinus syndrome or superior orbital fissure syndrome
2. Myasthenia gravis
3. Chronic progressive ophthalmoplegia
4. Orbital lesions e.g. tumours or pseudo-tumours.
5. Thyroid eye disease

Cavernous sinus/superior orbital fissure syndrome

Ocular features	Causes
limitation of ocular motility for any combination of different cranial nerve palsies, facial pain and numbness corresponding to the trigeminal nerve distribution, may be a Horner syndrome, the pupil may be dilated if a complete third nerve palsy is present, proptosis may be present.	1. Arteriovenous fistula, 2. intra-cavernous aneurysm or tumours 3. fungal infection (mucormycosis) in diabetics 4. pituitary apoplexy 5. herpes zoster 6. cavernous sinus thrombosis

Leukocoria (White pupil)

Common causes and differential diagnosis of Leukocoria

Disease	Ophthalmic features	What to do?
Congenital cataract	congenital cataract may be unilateral or bilateral, it may also be an isolated ocular abnormality or may be secondary to a local ophthalmic (persistent hyperplastic primary vitreous, trauma, infections, tumours) or systemic (Galactosaemia, Rubella, Lowe's syndrome) disease.	**Refer** urgently to an ophthalmologist and a paediatrician for investigations and surgical treatment. Surgical treatment of a unilateral congenital cataract should be carried out as soon as possible. The question about IOL is still controversial but more surgeons are implanting IOL at the time of primary surgery to avoid the postoperative problem about correcting the aphakia and avoiding amblyopia.
Retinoblastoma	A white nodular retinal mass extending into the vitreous or underneath the retina causing retinal detachment, often present between 12 and 24 months of age, iris neovascularisation, cataract and pseudo-hypopyon may occur.	**Refer** to establish the diagnosis, and treat. Most cases can now be treated with chemotherapy and radiotherapy, enucleation may also be needed in advanced case.
Toxocara	A history of contact with puppies and eating dirty things. May appear a s a localised white elevated granuloma in the posterior pole, as a peripheral granuloma with macular traction, or as a diffuse endophthalmitis. Rarely bilateral, often diagnosed between the ages of 6 months and 10 years.	**Refer** for ELISA test to confirm the diagnosis, and also possible steroids treatment or vitrectomy.
Persistent hyperplastic primary vitreous	A developmental ophthalmic abnormality. Present at birth, rarely bilateral often associated with microphthalmos, a fibrovascular membrane behind the lens and cataract.	**Refer** for possible cataract surgery or vitrectomy.
Coats disease	A retinal vascular abnormality. Exudative retinal detachment, mainly in boys, in the first two decades of life, rarely bilateral, may lead to severe glaucoma .	**Refer** for possible laser treatment, or retinal detachment surgery.
Retinopathy of prematurity	ROP predominantly occurs in premature children (less than 32 weeks of gestation and less than 1500 grams) who have had oxygen treatment. more	**Refer**, if not already been refereed by the obstetrician, for follow up and possible laser or cryotherapy treatment (in stage 3) and possible surgical treatment of the retinal detachment (in stages 4 and 5).

Eyelid lumps

Causes of eyelid lumps and swellings

1. Chalazion
2. Basal cell carcinoma
3. Squamous cell carcinoma
4. Sebaceous gland carcinoma
5. Keratoacanthoma
6. Molluscum contagiosum
7. Squamous papilloma
8. Actinic keratosis
9. Seborrheic keratosis

Differential diagnosis of eyelid lumps

Disease	features	What to do?
Chalazion	chronic obstruction of the meibomian glands, painful and tender, may also be painless, may also be associated with lid inflammation resembling preseptal cellulitis.	Treat with topical antibiotics and warm compresses, it persistent **Refer** for incision and curettage.
Basal cell carcinoma	The most common eyelid tumour, may present with a lump, ulcer or diffuse indistinct skin mass.	**Refer** for incision or excision biopsy and lid reconstruction.
Squamous cell carcinoma	Squamous cell carcinoma may present as basal cell carcinoma, this tumour, however, can metastasise to distant organs in the body.	**Refer** for incision or excision biopsy and lid reconstruction.
Sebaceous gland carcinoma	Must be considered in recurrent chalazion, or in persistent blepharitis in elderly population, the tumour may also be multifocal involving both the upper and the lower lids.	**Refer** for incision biopsy, excision and lid reconstruction.
Keratoacanthoma	A mass resembling basal cell and squamous cell carcinoma with a central ulcer crater, rapid growth, followed by a slow shrinkage and spontaneous resolution.	**Refer** for surgical excision.
Molluscum contagiosum	Often multiple lesions, umbilicated centre, may be associated with chronic follicular conjunctivitis.	**Refer** for surgical excision.
Squamous papilloma	Soft elevated or flat sessile lesions, spontaneous resolution, some lesion may be a squamous carcinoma.	**Refer** for excision biopsy.
Actinic keratosis	Round, pre-malignant, scaly surface, found in the exposed areas.	**Refer** for excision biopsy.
Seborrheic keratosis	Middle age or elderly patients, brown-black well-demarcated crust-like lesion.	May be excision by a shave biopsy if needed.

It is suggested that all lid lesions should be sent for histopathology after removal as clinical diagnosis is not often enough to exclude malignancy.

Other eyelid problems

Entropion	inward rotation of the lid margin, the lid margin and the eye lashes rubs on the eye causing corneal irritations, gritty eyes, discomfort and watering	**Refer** for surgical treatment. more
Ectropion	outward rotation of the lid margin, watery eye due to irritation and lacrimal punctum eversion.	**Refer** for surgical treatment
Ptosis	droopy upper lid, may cover part of the visual field, may cause fatigue when reading.	**Refer** for diagnosis of the cause and treatment . more
In-growing eye lashes	irritation and watering eyes.	If one or two lashes you can remove them, if more or recurrent **Refer** for electrolysis, cryotherapy or surgical treatment.

Epiphora
watery eyes

Common causes and differential diagnosis

The disease	Features
Congenital nasolacrimal duct obstruction	in babies and children, due to failure of canalisation of the lacrimal duct, spontaneously improves in the majority of cases within the first year. Most ophthalmologists wait for spontaneous improvement unless there is a recurrent conjunctivitis or dacryocystitis when the baby should be **referred** for probing with or without closed intubation. more
Acquired Nasolacrimal duct obstruction	may be complicated with recurrent conjunctivitis and dacryocystitis and orbital cellulitis. **Refer** for DCR operation. more
Eyelid abnormalities	e.g. ectropion, entropion, lid notches and in-growing eyelashes. **Refer** for surgical treatment.
Dry eye syndrome	excessive drying of the corneal leads to irritation and burning sensation with reflex lacrimation mainly at the end of the day. may be diagnosed by the Schirmer's test. Treated with artificial tear drops. **Refer** if drops need to be used too frequently for punctal plugs insertion. more
Blepharitis	itching, burning and crusting of the lid margin. Treated with artificial tear drops with lid hygiene and sometimes with a short course of topical antibiotics and steroids. May need a long course of tetracycline treatment if rosacea is suspected. **Refer** if complicated with marginal corneal ulceration.

Conjunctival pigmentation

Conjunctival pigmentation may be due to local or general causes:

General causes	Local causes
1. Ochronosis with Alkaptonuria (due to enzymatic deficiency, often in young adults, associated with dark urine and arthritis). 2. Addison's disease. 3. Agyrosis (history of using silver nitrate drops) 4. Haemochromatosis. 5. Adrenochrome deposits (history of using Adrenaline or Propine drops). 5. Mascara deposits. 6. Chlorpromazine treatment.	1. Ocular or oculo-dermal melanosis. 2. Primary acquired melanosis. 3. Naevi. 4. Malignant melanoma. 5. Racial pigmentation.

Differential diagnosis of the local causes

Disease	Ophthalmic features	What to do?
Ocular or oculo-dermal melanosis	congenital, it is mainly an episcleral lesion (i.e. you can see the conjunctiva moving on top of the lesion), the lesion is often unilateral, is often associated with darker ipsilateral iris and choroid, the skin on the ipsilateral lid may also be pigmented (naevus of Ota).	**Refer** to exclude other uveal melanomas as this condition predisposes to uveal tract malignancy.
Primary acquired melanosis	appears in the middle age, flat and brown patches, may be pre-malignant.	**Refer** for observation and detection of malignant changes (extension, modularity, increased vascularity of the lesion).
Naevi	commonly develop at puberty, well demarcated, the degree of pigmentation may change with time, may have cystic lesions, rare in the palpebral conjunctiva, may undergo malignant transformation.	watch closely, **Refer** if there is a suspicion of malignant transformation.
Malignant melanoma	in middle aged to elderly population, the lesion is often nodular, well vascularised, with a large conjunctival feeding blood vessel.	**Refer** to detect for any other associated intraocular malignant tumours and to consider excision biopsy or other surgical or chemical treatment. more

Contact lens-Related problems

Disease	Ophthalmic features	What to do?
Corneal infiltrate or ulceration	white corneal lesion which may stain with fluorescein , central lesions are more likely to be due to infection than peripheral lesions, severe pain indicate possible infection.	all cases must be considered as infectious until proved otherwise, **Refer** for compete microbiological work out.
Giant papillary conjunctivitis	itching, mucous, lens intolerance.	stop contact lens wear in severe cases, use cromolyn sodium or Alomide, replace the lens, more thorough cleaning, consider daily wear lenses.
Corneal vascularisation	often asymptomatic early in the disease.	discontinue lens wear, consider steroid treatment, refit with highly gas permeable lens when it is better.
Tight lens syndrome	severe discomfort and pain one or two days after poor fitting of soft contact lens. the lens does not move with blinking, may lead to corneal oedema and iritis with or without hypopyon, conjunctival marks may occur at the edges of the tight lens.	discontinue wear, may need cycloplegic drops, refit with a flatter lens.
Corneal warpage	in long term PMMA contact lens wearers, good vision with contact lens but blurred vision with glasses, blurred vision then occur with both contact lens and glasses, discomfort, may or may not be punctate keratopathy.	discontinue lens wear, refit with gas permeable contact lens when refraction and keratometry is stable.
Contact lens deposits	these may lead to corneal and conjunctival irritation,	change the lens
Superior limbal kerato-conjunctivitis	hyperaemia and fluorescein staining of he upper limbal conjunctiva, infiltrate and irregularity at the upper cornea, no corneal filaments, no papillary conjunctivitis.	consider changing the cleaning solutions, may need topical steroids if severe.
Displaced contact lens	may be displaced outside the eye or in the superior fornix.	evert or double evert the lid to find the lens and examine it for damage or lost pieces, refit if needed.
Hypersensitivity reaction	irritation and conjunctival injection shortly after lens cleaning after using a new type of cleaning solution, SPK, conjunctival follicles, corneal infiltrates.	discontinue wear, use preservative-free artificial tears, new contact lens and new preservative-free solutions.

External Eye Diseases

Infections

bacterial infection

Severe infectious keratitis is a major cause of ocular morbidity in temperate and tropical regions. **Predisposing factors** for central corneal ulceration in these areas include ocular surface disease, contact lens wear (even without corneal epithelium disruption), previous trauma, cocaine abuse, and the use of traditional eye medicines. Ulcerative keratitis also develops in 4.7% of patients with prolonged bullous keratopathy. Steroid drops and bandage soft contact lens are risk factor for microbial ulcers in these patients. Prophylactic antibiotic use does not seem to prevent ulcer development. Conditions associated with systemic immune suppression should also be considered among the disease that constitute higher risk factor for patients with infectious keratitis.

Microbial keratitis is a serious complication of **contact lens wear**. In certain communities in the USA, contact lens wear was found to be the most significant risk factor for developing ulcerative keratitis. Contact lens and also contact lens cases are major sources for corneal infections in contact lenses wearers. A study of 178 asymptomatic wearers found microbial contamination in 53% of the cases. **Cases hygiene** is as important as lenses hygiene, frequent and regular changes of the cases may prove to be a necessary measure to prevent contamination.

Among the various types of contact lenses, extended wear soft contact lenses seem to carry the greatest risks for causing corneal problems. **Overnight** extended wear is the most important risk factor for developing ulcerative keratitis even with disposable contact lenses and good hygienic measures. Previous reports found that the relative risk of developing ulcerative keratitis for overnight wear is 21 for soft lenses and 3.6 for daily wear soft lens when compared with gas permeable hard lenses. 49% to 74% of contact lenses related ulcerative keratitis could be prevented by not wearing the lenses over night. Corneal hypoxia, caused by overnight wear with the accumulation of deposits and contamination of the lens, lead to higher risk of complications and corneal infection.

Daily disposable contact lenses have many advantages over extended wear contact lenses e.g. minimal handling and less need for hygienic compliance. It had been hoped that this theoretical advantages might eliminate the incidence of ulcerative keratitis with this type of contact lenses, but higher rate of **complications** may also occur with extended wear of daily disposable contact lens. The main complications associated with extended wear of disposable contact lens are, however, sterile

corneal infiltrates. It seems that frequent and regular disposing of lenses does not completely eliminate complications.

Large **central** corneal ulceration is more often associated with positive culture and anterior chamber activity than peripheral ulcers. There has been some controversy regarding the need for complete work-up in suspected microbial keratitis. 3 different strategies for management have previously been proposed:

- Complete laboratory work-up for all cases.
- Complete laboratory work-up only for unusual or severe corneal ulcers.
- Work up, only, if treatment with the common antibiotics fails.

Most authorities consider that complete work-up should be carried out in **all** suspicious microbial keratitis. Corneal scrapings should be taken from all lesions not including the visual axis. The scrapings should be cultured on blood agar, chocolate agar, Sabouraud, and Thioglycate medium. Corneal specimens should also be stained with gram and Giemsa stains as a routine. Optional culture media and special stains for specific infections can also be carried out in suspected cases. Corneal biopsy may also be needed in chronically progressive lesions.

Confocal in vivo slit scanning video-microscope is a new confocal microscope which offer a **non-invasive** and non-contact imaging of the corneal layers with good lateral and axial resolution and also good contrast even in the presence of corneal opacities, without the need for histological staining. The technique has been shown to give results that are consistent with histopathological and biochemical techniques. This technique is, however not as sensitive as biomicroscopy in some conditions. Microbiologic evaluation of a diagnostic **corneal biopsy** may be used in the diagnosis and treatment of patients with progressive infectious keratitis.

fluoroquinolones

There are several topical fluoroquinolone eye drops available now on the market. The main preparations are:

- Ciprofloxacin.
- Norfloxacin.
- Ofloxacin.

The three preparations have similar antibiotic spectrum of activity but ciprofloxacin seems to be more potent than the other two. The greater potency of ciprofloxacin seems to offset the superior corneal penetration ability of Ofloxacin. The combination of fluoroquinolone e.g. ciprofloxacin, norfloxacin, or ofloxacin is superior to any of the fluoroquinolone alone.

Fluoroquinolone preparations should be used with caution in patient with a history of convulsions, **epilepsy**, or liver or kidney failure. Frequent application of ciprofloxacin or norfloxacin drops, especially in patients with dry eyes or eyes with corneal ulcers may cause a white **precipitate** on the ulcerated corneal surface which may lead to the formation of a firmly adherent plaque which might delay corneal healing.

Ciprofloxacin or ofloxacin is effective as **single** agent in the treatment of ulcerative keratitis. They seems to be as effective as, or even better than, fortified topical antibiotics drops (e.g. Cefazolin and Gentamicin). Mono-therapy with ciprofloxacin has the advantage of being easier to prepare, more cost effective, and also being less toxic to the cornea. The use of fluoroquinolone as a monotherapy may, however, lead to serious complications (e.g. corneal perforation) especially in deep corneal ulcers in the elderly patients. Topical ciprofloxacin may also be effective in cases with non-tuberculous **mycobacterium** keratitis that does not respond to amikacin treatment.

Continued use of the drug has lead to the emergence of increasing resistance among gram positive and gram negative bacteria including Staphylococci aureus, Streptococci, Pseudomonas and Neisseria gonorrhoea. It is estimated that about 30.7% of the pathogens causing bacterial keratitis is developing **resistance** to the drug. Care should be taken when using fluoroquinolone as a monotherapy in bacterial keratitis because of these emerging resistance among many pathogenic bacteria. Resistant cases may be treated with cefazolin in gram positive infection, or gentamycin in gram negative infections.

Sparfloxacin is a new member of the fluoroquinolone family of antibiotics. The drug is particularly active against microbial infections against which the fluoroquinolone drugs in general have low activity (e.g. streptococci, mycoplasma, and chlamydia).

chlamydial infection-trachoma

Trachoma is still thought to be the second most common cause for **blindness** in the world. It is estimated that there are about 5.9 million cases of blindness from corneal scarring caused by the disease world-wide. The disease is mainly confined to poor and crowded areas in the developing countries. The world health organisation designed a simple **grading** scheme for the disease:

- **TF**, trachoma inflammation-follicles: 5 or more follicles in the upper tarsal conjunctiva.
- **TI**, trachoma inflammation-intense: pronounced inflammatory thickening of the tarsal conjunctiva that obscures more than half of the normal deep tarsal vessels.
- **TS**, trachoma scarring: presence of visible scarring in the upper tarsal conjunctiva.
- **TT**, trachoma trichiasis: at least one eye lash on the eye ball.
- **CO**, corneal opacity: easily visible corneal opacity over the pupil obscuring pupil margin.

The pathogenesis of the disease is not completely known. Tissue damage may result from **immunological** and metabolic mechanisms. Anti-chlamydial antibodies in tears are seen significantly more often in patients with conjunctivitis than in those with urethritis. Anti-chlamydial Ig G is found only in tears of patients with conjunctivitis. The detection of anti-chlamydial Ig G in the tears might be helpful for diagnosis in patients with suspected chlamydial conjunctivitis who have antigen-negative conjunctival swabs. The polymerase chain reaction test is likely to play an increasing role in the diagnosis of ocular C-trachomatis infection because of its excellent sensitivity and specificity.

There is also evidence that there is an increase in the local production of **cytokines** in the conjunctiva in eyes with trachoma. The cytokines may promote conjunctival scarring. Anti-cytokines treatment may be useful in the treatment of this disease.

Increased collagen content in the conjunctiva is also a feature of the inflammatory process. Type V **collagen**, increased type I, III, and IV collagen have been demonstrated in the conjunctiva in eyes with trachoma. Increased levels of the enzyme gelatinase B may also play a role in the pathogenesis of the disease.

Control of the disease may also carried out by using the **SAFE** strategy:

community based **S**urgery
Antibiotics treatment
Face cleanliness
Environmental improvement

Lack of compliance is a major problem in treating trachoma in endemic areas. Treatment of trachoma, in endemic areas, needs to be simple, effective and inexpensive. The world health organisation has recommended mass treatment of children in trachoma endemic areas with the drug azithromycin. **Azithromycin** is a relatively new antibiotic derived from erythromycin. The drug can be administered once a day. A single dose of oral Azithromycin (20 mg/kg) gives blood level that reaches the minimum inhibitory concentration of the drug for 6 days. Prolonged high concentration has been demonstrated in ocular tissue after a single oral dose of one gram. It is also as effective as a 6 weeks course of topical tetracycline ointment in managing active trachoma in endemic areas. The drug has also been found effective in the treatment of other chlamydial genital infections.

fungal infection

Fungus infection is often caused by fungi that are considered saprophytic. Candida typically affects compromised corneas. The chronic use of **topical anaesthesia** can cause severe morbidity to the eye due to it's direct toxic effect on the corneal epithelium and also due to delaying corneal wound healing. Polymerase chain reaction test may be used in the diagnosis of some types of fungal keratitis. Endogenous fungal keratitis may occur after the treatment of fungal endophthalmitis. Fungal organisms may not be completely eradicated with treatment. Patients should be monitored for a long period after the treatment of endophthalmitis. The incidence of ocular involvement (mainly chorioretinitis) in patients with **candidaemia** seems to be clinically significant (26%). It is recommended that ophthalmic follow up should be undertaken in all patients with candidaemia for at least 2 weeks after an initial negative ophthalmic examination.

Antifungal drugs (e.g. natamycin 5%, flucytosine, and amphotericin B drops and ointment), are expensive, and not often readily available. Treatment with these medications may also be needed for long periods of time. The treatment of fungal keratitis in developing tropical countries may be difficult due to the lack of specific anti-fungal medications, and also lack of appropriate microbiological facilities. **Chlorhexidine 0.2%** may be used as the first line of treatment in some cases. The drug is cheap, readily available, and may be superior to natamycin in the treatment of filamentary fungus infection.

herpes simplex virus infection

Herpes simplex virus infection can mimic varicella-zoster virus infection. The differential diagnosis is specially important because incorrect treatment may aggravate the disease. DNA specific herpes simplex virus can be detected from the tears of patients by the **polymerase chain reaction** when the diagnosis is in doubt.

The typical features of herpes virus infection is by **dendritic** corneal epithelial ulceration. Herpes simplex virus **iridocyclitis** in the absence of keratitis is thought to be rare and self limited. Chronic iridocyclitis with iris atrophy may also occur as the primary manifestation of herpes simplex virus infection without corneal involvement. Unilateral anterior uveitis with **sector atrophy** of the iris without associated, or previous, keratitis may also occur in herpetic eye diseases. Typical feature of this entity is rise of the intraocular pressure during intraocular inflammation. Recurrent unilateral anterior uveitis with iris atrophy and/or elevated intraocular pressure may indicate a herpes simplex virus infection.

Posner-Schlossman (recurrent attacks of unilateral raised IOP with mild iridocyclitis) has also been linked to varicella-zoster virus, cytomegalovirus, and herpes simplex virus. Herpes simplex virus may play a role in the pathogenesis of this syndrome. herpes simplex virus DNA has been detected in the aqueous of patients with **Fuchs heterochromic iridocyclitis**. Herpes simplex infection may play a role in the pathogenesis of the disease.

Herpes simplex virus keratitis may also affect **immunosuppressed** patients e.g. patients with HIV. The incidence and clinical course of HSV keratitis do not seem to be different among patients positive for HIV except for the recurrence rate. The recurrence rate is about 2.48 times more frequent among patients positive for HIV.

Acyclovir is the drug of choice in treating herpes simplex virus keratitis in Europe. Topical steroids in active herpes simplex virus stromal keratitis are significantly better than placebo when administered with topical antiviral medication. The role of systemic antiviral medications in the treatment of herpes simplex virus keratitis has been controversial. **Oral Acyclovir** has recently been shown to reduces the number of recurrences of herpetic genital and labial infections. Long-term oral Acyclovir treatment (800 mg / day) is also associated with a reduced rate and duration of recurrences of herpes simplex virus stromal Keratitis. Oral acyclovir also appears to be beneficial, in treating epithelial disease and in providing prophylaxis and preventing recurrences, in the paediatric patients.

Continued use of Acyclovir lead to the emergence of acyclovir resistant strains of herpes simplex virus. **Ganciclovir** ophthalmic gel 0.15%, is a new drugs that may be used in the treatment herpes simplex virus

infection. It is reported to be equally effective to acyclovir ophthalmic ointment 3% in treating herpes simplex virus keratitis without significant side effects. It has the added advantage of having less effect on the vision being a watery gel rather than an ointment.

Cidofovir eye drops, and **Penciclovir** eye ointment have also been successfully tried in the treatment of the epithelial disease in animals and may prove useful and effective in humans. Cidofovir is highly effective against epithelial disease when used twice a day. it can also be used to prevent stromal disease. The drug is not, however, able to treat already established stromal disease. **Carbocyclic Oxetanocin G** is a new antiviral drug that is active against herpes simplex virus, varicella-zoster virus, CMV, Epstein-Barr virus and HIV virus. Eye drops containing 0.1% Carbocyclic Oxetanocin seems to be excellent and safe in the treatment of herpes simplex virus corneal ulcers. The average healing time is about four days. The drug does not seem to be associated with significant side effects.

Corneal **graft failure** after herpes simplex virus keratitis is known to be associated with the recurrence of herpetic corneal disease within the first year. Herpes simplex virus infection of the corneal endothelium may contribute to graft failure in recurrent infection. Postoperative systemic acyclovir therapy after penetrating keratoplasty for HSV keratitis is associated with a reduced rate of recurrent HSV dendritic keratitis and possible graft failure at 1 year of follow-up.

varicella-zoster virus infection

The clinical presentation of herpes zoster ophthalmic infection varies considerably. About 40% of patients are affected by some form of anterior segment intraocular inflammation. Many of the iris changes, associated with disease, are believed to be due to an ischaemic occlusive vasculitis. Iridoplegic granulomatous iridocyclitis is another newly described, acute, fulminant uveitis probably caused by varicella-zoster virus. Acute secondary glaucoma may also be seen in 15% to 43% of the patients. The glaucoma is often dramatic and difficult to control.

Cases with ocular Zoster without skin rash have been well documented, this condition has been termed (*Zoster Sine Herpete)*. Accurate diagnosis of the infection is important as anti-inflammatory treatment may be required as well as antiviral treatment. Polymerase chain reaction tests can detect varicella-zoster virus DNA in intraocular material and confirms the diagnosis when the typical skin rash is absent.

Herpes zoster virus may cause **chronic** epithelial keratitis in patients with AIDS. The keratitis is characterised by dendritic lesions, long duration, and extreme pain. The disease may also occur without skin lesion. Herpes Zoster infection in young Africans with HIV infection has a poor visual prognosis. 40% of these patients have visual outcome of light perception or no light perception only. Severe keratouveitis and perforation are common and responsible for most cases with poor visual outcome.

Topical and **systemic** acyclovir is regarded as the drug of choice in patients with varicella-zoster infection. The role played by the drug is not, however completely understood. Topical use, when compared with systemic use, is associated with more complications and more frequent anterior uveitis recurrences. The uveitis and corneal hypothesia also appear to be more severe in patients taking topical treatment. Topical Acyclovir does not appear to have a prophylactic value in spite of its better ocular penetration. A retrospective case control study also showed that oral acyclovir (800 mg 5 times a day, starting within 3 days of the onset of the rash and taken for 7 days) does not appear to affect the rate of ocular complication in immune competent patients after Herpes Zoster eye infection

acanthamoeba keratitis

Acanthamoeba keratitis is often associated with contact lens wear in the Western world. In the UK the disease is associated with contact lens wear in 85% of cases. All types of contact lenses may be associated with the disease. The strongest association is thought to be with **daily** wear soft disposable contact lens. In the tropics the disease has been reported after **trauma** and mud splashing. Chronic eye disease (e.g. trachoma) may also compromise the corneal surface and predispose the cornea to infection without a history of contact lens wear or trauma. Corneal abrasion seems to be needed for the organism to penetrate the cornea. Diagnosis of Acanthamoeba keratitis is often made later in non-contact lens wearers than in contact lens wearers.

Severe pain and photophobia out of proportion to the physical signs is a characteristic feature of the disease (often due to the accompanying scleritis and neuritis). Superficial corneal ulceration with perineural keratitis is the main corneal features. Ring infiltration with stromal ulceration may also occur. Significant decrease in the corneal sensation is also a frequent finding in the disease. Acanthamoeba keratitis may also masquerade as herpetic, or adenoviral keratitis. Acanthamoeba keratitis may also occur as a secondary or opportunistic infection in patients with **herpetic keratitis**.

Current methods of **investigations** for Acanthamoeba keratitis includes:

- Staining of corneal material with Calcofluor white stain in addition to gram and Giemsa stains.
- Cultures of corneal scrapings and contact lens and contact lens containers on non-nutrient agar with E coli overlay. Buffered charcoal-yeast extract agar is another excellent culture medium that is readily available.
- Corneal biopsy is also needed if the gram stain and cultures are negative.
- Confocal microscopy can also be a useful non-invasive method of examination in patients with suspected Acanthamoeba keratitis. High contrast round bodies suggestive of Acanthamoeba cysts, and irregular forms suggestive of Acanthamoeba trophozoites are seen. Occasionally the *confocal microscope* can also reveal the characteristic double walled structure of the Acanthamoeba ectocyst. Radial kerato-neuritis may also be seen. Confocal microscopy diagnosis may be confirmed by histological examination and PCR analysis of epithelial biopsy.

Acanthamoeba **scleritis** is rare, it may be associated with a poor prognosis, even with intensive medical and surgical treatment. Acanthamoeba infection should also be considered in the differential diagnosis of uveitis and endophthalmitis in AIDS patients. Diagnosis may be confirmed by finding the Acanthamoeba cysts in aqueous and vitreous

samples. Topical treatment with anti-amoeba drugs does not seem to be effective.

treatment

The prognosis of Acanthamoeba keratitis has improved due to increased **awareness** and early diagnosis of the disease, and also due to the improvement of treatment. A high level of suspicion (especially in contact lens wearers) is needed to achieve early diagnosis and effective treatment. Prompt diagnosis and medical treatment, and avoiding topical steroids can lead to cure in most cases of Acanthamoeba keratitis with excellent prognosis for vision. 79% of all eyes and 70% of culture positive eyes may achieve a final visual acuity of 6/12.

Most patients with Acanthamoeba keratitis can expect a good visual prognosis and cure by medical treatment alone if diagnosed early. The current topical anti-amoebic used at present are:

1. Diamidine derivatives e.g. Brolene, and Desomedine.
2. Biguanide derivative e.g. polyhexanide (PHMB), and chlorhexidine. The most commonly used medical treatment in the UK is polyhexamethylene biguanide (PHMB) which is non-toxic and effective against trophozite and cysts forms.
3. Propamide may also be used in combination with the PHMB. The combination of chlorhexidine and propamidine seems to have an effective amoebicidal action within the cornea. The use of this combination may shorten the period and reduce the frequency of using anti-Acanthamoeba medications and consequently reduce their toxic side effects and also reduce the development of resistance to these drugs.
4. Neomycin. The role of Neomycin in the treatment of the disease is controversial. Neomycin is known to be a poor cysticidal agent but a good trophozoicidal agent. The addition of Polyhexamethylene biguanide to neomycin and propamidine may dramatically improve the clinical response in eyes with Acanthamoeba keratitis.

Medical treatment needs to be used for a **long time**, recurrences may occur if the treatment is discontinued after a short period. Corneal epithelial toxicity seems to be common with all drugs (probably with the exception of PHMB). Topical **steroids** are useful in cases with deep corneal involvement with limbitis and uveitis. Steroids should not, however not be started till the disease seems to be under control with the anti-amoebic drugs.

Regular cleaning and replacement of **contact lens containers** and the use of sterile commercial cleaning, disinfecting and rinsing solution may be important and effective in removing the Acanthamoeba from the contact lenses. Disinfection for more than 3 hours in H_2O_2 is recommended. Tap water should not be used in the cleaning process of

the lenses. Sodium salicylate may successfully reduced amoebal trophozoite attachment to hydrogel lenses. This effect may be due to inhibition of biofilm formation, direct effect on the amoebae, or due to alteration in the biofilm–amoebal attachment resulting modification of the hydrogel lens surface.

About 39% of patients may need therapeutic penetrating **keratoplasty**, most of these eyes are associated with delayed diagnosis. Penetrating keratoplasty is often indicated in quite eyes with gross corneal scarring or in acute eyes impending perforation. The outcome of surgery is much better in eyes medically controlled before surgery. Cataract, Intumescent cataract and glaucoma, graft rejection are the main complications after surgery. Penetrating keratoplasty have good results in quiet eyes but in inflamed eyes the results are often compromised by complications .

Others Infections

cat scratch disease

Cat scratch disease is a systemic disease characterised by lymphadenopathy, fever, and malaise. The disease is probably caused by **Bartonella henselae** infection (a gram negative bacilli belonging to the order Rickettsiales). Transmission from cats to patients often occurs via flea bites. The disease can also be transmitted by bites from an infected animal (often a cat or a dog).

Patients often develop an erythematous papule or pastule followed by a systemic rash within days or weeks. The typical ocular features are painful regional lymphadenopathy and follicular conjunctivitis. The disease may also be associated with serous retinal detachment of the macula, neuroretinitis, a retinal white spot syndrome, intermediate uveitis and retinal vasculitis, unifocal choroiditis, inflammatory mass of the optic nerve head producing acute loss of vision and focal choroiditis. An unusual, well-defined retinal opacification with features of both multiple retinal arteriolar occlusions and a low-grade retinitis has also been described.

Rochalimaea henselae infection should be considered in intraocular anterior and posterior inflammation with optic nerve swellings even in the absence of a history of cat scratch or lymphadenopathy. Improvement in the inflammation and in the visual acuity can be achieved by **oral ciprofloxacin**, Rifampicin or Doxycycline and steroids. Diagnosis of this disease can be confirmed by specific enzyme-linked immuno-assay (**ELISA**) serologic tests, as well as lymph nodes, conjunctival or skin biopsy.

mycobacterium keratitis

Non-tuberculous mycobacterium are now recognised as an important cause of microbial keratitis. Several reports of Mycobacterium fortuitum and Mycobacterium chelonae keratitis have been published. Corneal ulcers often develop after foreign body injuries (metallic foreign bodies), after surgical procedures or after contact lens wear. Clinical features include satellite or ring infiltrates, crystalline keratopathy and hypopyon. Mycobacterium keratitis is generally difficult to treat. **Amikacin** remains the main line of treatment of mycobacterium keratitis, however, failure of treatment or resistance may develop. Topical clarithromycin, ciprofloxacin and combined amikacin and vancomycin may all be clinically useful in the treatment of this infection. **Ciprofloxacin** is effective in the treatment of Mycobacterium keratitis, but the drug appears to be less effective against M. chelonae than M. fortuitum in vivo studies. Topical ciprofloxacin may be effective even in cases that does not respond to amikacin treatment. Lamellar keratectomy should be considered in medically resistant cases, and also for corneal involvement of 80%

thickness or more. This method of treatment can help to obtain a specimen for biopsy, eradicate the micro-organism, and facilitate drugs penetration

Allergic Diseases

atopic keratoconjunctivitis

Atopic keratoconjunctivitis is the **most serious**, sight-threatening allergic manifestation of atopic diseases in the eye. Atopy should be considered in the differential diagnosis of severe keratoconjunctivitis even in the absence of systemic findings of atopy. About 70% of patients have some type of keratopathy, 60% have corneal neovascularisation, and 20% have symblepharon. Conjunctival biopsy and serum Ig E are valuable measures in making the diagnosis. The **impression cytology** technique may also be used. Loss of goblet cells and conjunctival squamous metaplasia have been previously demonstrated. Cataract, rhegmatogenous retinal detachment, and keratoconus, may also be associated with the disease. Higher levels of aqueous flare caused by the breakdown of blood-aqueous barrier may contribute to the formation of cataract in patients with atopic dermatitis.

Successful long-term control of symptoms can be achieved with medical treatment by mast cell stabilisers, antihistamines, and ocular lubrication (with unpreserved saline solution). Short-term topical or systemic steroid therapy may be needed during exacerbation. Topical **cyclosporin 2%** eye drops may also be used, the drug seems to reduce the severity of symptoms. The mechanism of action may be due to inhibition of CD 4 T-lymphocytes. Systemic cyclosporin A may also be an alternative therapy in severe cases. Some food antigens may contribute to the pathogenesis of severe atopic dermatitis and its ocular complications.

vernal disease

Vernal keratoconjunctivitis is a chronic eosinophilic disease of the ocular surface involving Ig E, no-Ig E-mediated mechanisms. The disease often has a good prognosis. **Severe visual impairments** may, however, result from long-standing inflammation. Large giant papillae indicates poor prognosis for the persistence of the disease and its evolution into a chronic, perennial condition. A reduction of visual acuity may result from corneal scarring, or steroid-induced glaucoma.

Multiple mechanisms have been implicated in the pathogenesis of vernal disease. **Histamine** is the most significant mediator in this disease. Histamine is secreted by mast cells and activated basophils. Increased tear histamine levels is due to increased production by the mast cells and their de-granulation. Decreased histamine degradation by the enzyme histaminase in tears and plasma has also been shown in patients with vernal diseases. Alteration in the ratio between collagen and proteoglycan and between the different types of collagen also seems to play a role in the development of the morphological abnormalities associated with this disease. There is also accumulation of CD 4+ cells, plasma cells, eosinophils, Ig E cells irrespective of the atopic status of the patient. The role of the allergen-specific Ig E sensitisation in the pathogenesis is not clear. Increased expression of adhesion molecules also play an important role. Adhesion molecules play a key role in the selective recruitment of different leucocytes population to inflammatory sites.

Conjunctival **eosinophils** are considered the histological hallmark of vernal kerato-conjunctivitis. There seem to be a significant correlation between eosinophils cationic proteins value, and disease severity in all conditions. Serum, and tear levels of eosinophils cationic proteins (a product secreted by activated eosinophils) are significantly higher in vernal disease patients, and may be used as a marker for ocular inflammation. Extra-cellular deposition of eosinophils granules major basic protein has also been found in the conjunctiva in patients with vernal keratoconjunctivitis. The success of superficial keratectomy in some forms of vernal keratopathy could be explained in part by the removal of this protein deposits.

In vernal keratoconjunctivitis patients, the tarsal and bulbar conjunctival epithelium and sub-epithelium contain more **oestrogen** and **progesterone receptors** than in non atopic controls. Most of the cells positive for the oestrogen and the progesterone receptors are eosinophils. Sex hormones through their receptors may influence the activity of eosinophils. This may explain the natural history of the disease with the usual spontaneous resolution of activity by the age of about 30 years of age.

clinical features

Patients typically present with redness and itching. Patients with vernal disease, may also present with **acute hydrops** as the presenting sign of keratoconus. Corneal hydrops may indicate undiagnosed keratoconus especially if associated vernal conjunctivitis. Impression cytology is a simple, cheap and non-invasive technique that can be used in studying cellular reaction in eyes with vernal conjunctivitis. In vernal conjunctivitis the mean number of goblet cells is significantly higher than in controls and the diameter of the goblet cells seem to be smaller. The disease can be classified into **palpebral** and a **limbal** types. In temperate regions limbal inflammation is severe, but the palpebral manifestations predominates.

treatment

Mast cell stabilisers and antihistamines have been used successfully for many years to reduce the ocular signs and symptoms of the disease. **Cromolyn** sodium is the classical treatment of vernal eye disease. Cromolyn is thought to act by reducing calcium transport across the mast cells membrane and subsequently inhibiting histamine release. A new theory hypothesise that cromolyn interferes with protein synthesis and therefore, with receptors mediated changes in the mast cells.

Nedocromil sodium is a recent inhibitor of activated inflammatory cells (e.g. eosinophils and mast cells), that seems to be more efficient in inhibiting activated inflammatory cells than sodium cromoglycate. Unlike sodium cromoglycate, which appears to stabilise only connective tissue type mast cells, nedocromil sodium also stabilises mucosal mast cells which is the predominant type of mast cells in vernal disease. A double masked comparative study of four times daily 2% Nedocromil sodium, 2% sodium cromoglycate and placebo found that both drugs are effective in controlling vernal keratoconjunctivitis. The Nedocromil sodium, however had a more pronounced overall therapeutic effect.

Levocabastine (Livostin) is a newly synthesised histamine H1 receptor antagonist. A single dose of 0.05% Levocabastine seems to be more superior than cromolyn 4 times / a day for treating allergic conjunctivitis, it also has a duration of action of at least 4 hours.

Lodoxamide (Alomide) is a new drug that has been shown to reduce the ocular signs and symptoms in vernal conjunctivitis, presumably by inhibiting mast cell de-granulation and the toxic effects of eosinophils-derived products on corneal epithelium. In a recent study the drug significantly reduced eosinophils activation and seemed to be more effective than sodium cromoglycate in reducing clinical signs and symptoms. Patients treated with lodoxamide seem to have a better symptoms and signs score than those who are treated with over cromolyn sodium. **Clinical superiority of lodoxamide** over cromolyn sodium may be linked to its greater effect on the $CD4^+$ cells, because

$CD4^+$ cells plays a pivotal role in the pathogenesis of vernal keratoconjunctivitis.

Topical **Cyclosporin** eye drops 2% has recently been shown to be effective in the treatment of vernal kerato-conjunctivitis without significant side effects. The clinical improvement after Cyclosporin treatment may result from its immune modulator effects on the components of cell-mediated and humoural immune response. Within the first month of treatment, both the symptoms and signs of the disease improve significantly (particularly papillary proliferation). The drug does not seem to have an effect on the mast cell or the Ig E-mediated allergic response.

Supra-tarsal injection of steroids may be associated with dramatic relieve of symptoms and signs in patients with refractive vernal keratoconjunctivitis. Short acting steroids (Dexamethasone) and long acting steroids (Triamcinolone) are equally effective but short acting steroids do not seem to be associated with raised IOP. The steroid is injected by a 30 gauge needle in the space between the conjunctiva and the Muller muscle about 1 millimetre above the superior tarsal margin after a small amount of local anaesthesia.

Olopotadine is a new anti-allergic drug that has a double antihistamine and mast cell stabiliser action. The drug, in concentrations of 0.05% and 0.1%, has a rapid and prolonged anti-allergic action that may last for up to 8 hours.

Low dose (0.01%) topical **Mitomycin C** may be useful in the treatment of resistant cases with vernal disease. The effect of the drug seems to be due to its anti-proliferative effects on the conjunctival mast cells.

In vernal keratoconjunctivitis patients, **shield corneal ulcers** or plaque, that do not re-epithelialise after controlling the disease activity, should be treated surgically. A simple scraping of the base and margins of the ulcer with removal of the inflamed material results in rapid re-epithelialisation. Complications of delayed corneal healing include bacterial infection, amblyopia, corneal scarring, vascularisation and possibly perforation.

Corneal Dystrophies

lattice dystrophy

Lattice corneal dystrophy is characterised by the presence of refractile dots and fine lines in the anterior corneal stroma. The stromal lines gradually become larger and thicker. The intervening cornea typically stays clear. There are three clinically and histopathologically distinct types of lattice dystrophy:

1. Type (I) and type (II) which are autosomal dominant.
2. Type (III) which is autosomal recessive.

Type I tends to have more numerous deep and more central lines into the stroma than type II, it also progresses more rapidly. Type II manifests by the age of 20 and rarely needs corneal transplantation, it is often suspected by the typical facial features of the patient (droopy lids and protruding lips). Only type II is known to be associated with systemic Familial Amyloidosis Finnish type (FAF), also called (Meretoja) syndrome. In lattice dystrophy Type II (Meretoja Syndrome), the corneal lines are less numerous but thicker than in Type I. The lines are also radial and extend from the corneal periphery to the centre of the cornea. Visual acuity are often normal until later years. The vast majority of families with this disorder originate from Finland. Recently a genetic defect underlying Meretoja Syndrome has been discovered. The anti-FAF antiserum should prove useful for rapidly screening corneal buttons to determine whether there is any evidence of FAF in lattice type II. Recurrent corneal erosions may occur and patients may be particularly susceptible to microbial keratitis as a result of repeated epithelial disturbances and ophthalmologists should remain alert to the possibility of sight-threatening infective complications.

macular corneal dystrophy

Macular corneal dystrophy is the **least** frequent types of stromal dystrophies. It is characterised by the presence of cloudy corneal stroma in both eyes with superimposed discrete white opacities that enlarge and merge together with time. The basic metabolic abnormality in macular corneal dystrophy is an abnormal synthesis of corneal **glycosaminoglycans**. Macular corneal dystrophy may be classified into:

1. **Type I** (no antigenic keratan sulphate activity in the serum and in the cornea). Type I A, is characterised by the lack of detectable antigenic keratan sulphate in the serum, and a corneal stroma that does not react with the keratan sulphate monoclonal antibody but in which corneal fibroblasts react with keratan sulphate monoclonal antibody.
2. **Type II** (detectable and normal of serum and corneal levels of antigenic keratan sulphate activity).

Macular dystrophy is a genetically determined disease. The gene for type I dystrophy has been located to chromosome 16q22 and it is presumed that type II is also liked to this location. Both types may occur together in a single patient. The finding of both type in the same sibling in a family provides an evidence to the hypothesis that both diseases are localise din the same chromosome.

avellino corneal dystrophy

Avellino corneal dystrophy is a relatively new type of stromal corneal dystrophy which was originally described in patients originating from the Italian province of Avellino. Avellino dystrophy is characterised by anterior stromal deposits and deep fusiform stromal deposits. The corneal deposits have been shown to be **amyloid** material. There is a substantial phenotype variation in patients with this dystrophy. Granular, lattice type I and Avellino dystrophies have been independently linked to the same region on chromosome 5q. Histological evidence also suggests that these dystrophies are caused by mutation within the same gene. The three diseases may be phenotypic variations caused by mutation in the same gene.

schnyder corneal dystrophy

Schnyder dystrophy is an autosomal dominant, bilateral, symmetrical stromal dystrophy that often affect the anterior 1/3 of the corneal stroma. It is characterised by the deposition of needle shaped polychromatic cholesterol crystals. Visual acuity is often not affected. Schnyder dystrophy is thought to be due to a primary abnormality of the **corneal lipid** metabolism resulting in opacification secondary to lipids accumulation. Phospholipids, unesterfied cholesterol and cholesterol esters are the main lipids involved. Disturbance in the corneal metabolism sphingomyelin has also been shown. The severity of the primary corneal lipids metabolism abnormality may be altered by **systemic hyperlipidaemia**.

Only 51% of patients with Schnyder corneal dystrophy actually have clinical evidence of corneal crystalline deposits. The name (**Schnyder crystalline dystrophy sine crystals**) has been proposed for patients who do not demonstrate these typical corneal crystalline deposits. The corneal crystalline deposits may disappear in stromal areas underlying areas of epithelial corneal erosions. In patients with superficial stromal opacities (without stromal haze) epithelial debridement or excimer photo-therapeutic keratectomy may be an alternative treatment to penetrating keratoplasty. The dystrophy may recur after penetrating keratoplasty.

keratoconus

basic science

keratoconus is characterised by corneal ectasia. The anterior and the posterior corneal curvature are affected in the disease. Electron microscopy studies show that the earliest stages of the disease occurs in the corneal epithelium layer. The pathological process in keratoconus results from enhanced **matrix metalloproteinase** activity. In vitro and vivo analysis show that a gelatinase of molecular weight 65000 is the major protease secreted by normal keratocytes, whereas keratocytes from keratoconus cornea and traumatised corneas secrete an additional types of gelatinase with a molecular weight 61000. The enzymatic abnormalities are mainly seen in the corneal epithelial layer. It has also been shown that the conjunctival epithelium may be altered in patients with keratoconus in a manner similar to the corneal epithelium.

clinical features

Keratoconus is often diagnosed at adolescence. In patients with **vernal** disease acute hydrops may be the presenting sign of keratoconus. The presence of corneal **hydrops** may indicate undiagnosed keratoconus especially if associated with vernal conjunctivitis. Acute hydrops may also occur in Down's Syndrome, and in congenital rubella presumably due to eye rubbing. It is often caused by a rupture of the corneal endothelium and the Descemet's membrane, resulting in corneal oedema and opacification. Intra-stromal clefts formation have also been described in some eyes. These clefts seem to close with time but corneal neovascularisation commonly develop, compromising the results of future possible penetrating keratoplasty operations.

The use of **Botulinum ptosis**, topical and sub-conjunctival steroids may achieve a quick recovery and resolution of hydrops in Down's Syndrome patients. Topical steroids may reduce inflammation and subsequent corneal scarring. **Contact lens** wear in patients with corneal hydrops may lead to infectious keratitis and corneal perforations and should not be worn during the acute phase of the disease. Corneal perforation is uncommon in uncomplicated disease. Black race and young age at presentation are also significant risk factors for the progression of the disease. Sex, laterality, systemic atopic diseases and family history do not seem to be statistically related to the outcome.

The incidence of "**unilateral**" keratoconus appears to be very low. Patients initially diagnosed with unilateral keratoconus, when observed for a sufficient period of time, commonly had signs of keratoconus developing in the opposite eye. Videokeratography is useful in detecting early sub-clinical cases of keratoconus. Videokeratography in most patients shows an inferior corneal steepening in the fellow eyes. The possibility that all cases of unilateral keratoconus may eventually become **bilateral** should be considered.

Three dimension scanning electron microscopy shows alterations in the Bowman's membrane layer **specific** to keratoconus (lattice like

configuration and collagen scar tissue). Fragmentation of Bowman's membrane layer may be an early sign of keratoconus.

treatment

irregular astigmatism is a major problem in the disease. One method of correcting the irregular astigmatism is by the **Piggyback** contact lens. Piggyback contact lens is a PMMA hard contact lens placed on a soft contact lens base obtaining better fitting and centration with the soft lens and better optical correction with the hard lens. Animal studies showed that the oxygen pressure under Piggyback lenses is higher than under PMMA lenses when used alone.

Corneal grafts in keratoconus patients stabilise quickly and usually achieve good visual results. **Recurrence** of keratoconus is a rare cause of corneal graft failure. Keratoconus recurrence is believed to be due to either incomplete initial excision of the corneal cone, or due to abnormal host keratocytes or epithelial cells infiltrating the donor tissue and causing the pathological changes to recur. A graft in the second eye seems to increase the risk of failure to the graft in the first eye. Surgery to the second eye should be delayed as much as possible if there was a rejection episode affecting the first eye. Prophylactic treatment to the first eye could be considered at the time of surgery to the second eye. The overall survival of corneal grafts in the second eye is better than in the first eye unless there was a history of rejection in the first eye which increases the risk of rejection in the second eye as well.

posterior keratoconus

Posterior keratoconus is an abnormal variation of the posterior corneal curvature. This uncommon non-inflammatory disorder is generally considered a developmental anomaly, although acquired and post-traumatic varieties also have been described. The distinct topographic patterns seen probably warrant a further classification of localised posterior keratoconus into central-paracentral and peripheral varieties.

Dry eye syndrome (KCS)

The **prevalence** of dry eyes is not exactly known, it varies between different studies, because studies use different signs or tests in making the diagnosis. The diagnosis and the grading of dry eye disease is not often easy. **The Ocular surface Disease Index** is a 12 item questionnaire developed by Allergan Inc to provide a rapid assessment of the symptoms of the disease and the impact of the disease on the visual function. The index has a good reliability, validity, sensitivity and specificity. The index could also be used for comparison and assessment of treatment for this condition.

The disease may be caused by two main mechanisms:

1. Tear **deficiency** which may be due to Sjogren's or non-Sjogren's syndrome causes.
2. Excessive **evaporation**, which may be due to oil deficiency , lid retraction, contact lens wear, or surfaces changes. Evaporation of tears is higher in patients with dry eyes than in patients with normal eyes and this increased evaporation seem to account for the majority of tear loss in these eyes. Lipid secretion from the meibomian glands are important in reducing the ocular surface water evaporation and preventing dry eyes.

Conjunctival squamous metaplasia is often observed in the conjunctival epithelium in eyes with keratoconjunctivitis sicca. The expression of type-1 **growth factor receptors** is greatly increased in the conjunctival epithelium of these eyes. This may explain the conjunctival changes seen in this disease.

tests

This is a summery of some of the tests used in the study of dry eyes:

Test	comment
Tear turn over	Tear turn over is the percentage decrease per minute of fluorescein concentration in tears after the instillation of fluorescein drops. Tear turn over can be determined by fluoro-photometry. The tear clearance rate test is a simple and useful method to estimate basal tear turn over and tear flow, it can also indirectly measure the tear drainage.
Tear function index	Tear function index is the combined values of both tear secretion and tear drainage tests. It is the value obtained from dividing the value of Schirmer's test with local anaesthesia by the tear clearance rate. This index is more specific and more sensitive in diagnosing dry eyes associated with Sjogren's syndrome than the Schirmer's or the tear clearance rate test alone. Tear function index below 96 are consistent with dry eyes and those below 34 are seen

	mainly in patients with Sjogren's syndrome. Meibomian gland secretions are important in reducing tear evaporation and preventing dry eye
Rose Bengal staining	Rose Bengal stain is inversely correlated with bulbar conjunctival goblet cell densities and with the absence of bulbar conjunctival mucous membrane mucin expression. Preferential distribution of rose bengal staining in the non-exposed parts of the ocular surface characterise lipid tear deficiency dry eye and may helps to differentiate it from liquid tear deficiency. Rose Bengal stain is thought to stain only the degenerated conjunctival cells and mucous
Lissamine green staining	Lissamine green is a synthetic organic acid dye that is used as a food dye. It has been shown to have the same staining profile as Rose Bengal with better tolerance by patients.
Meibography	Meibography can objectively assess meibomian gland dysfunction. Patients with meibomian gland drop out have an increased risk of developing dry eye due to increased tear evaporation, even if the tear production by the Schirmer's test is moderately reduced because the evaporation rate in these patients is very high.
Infra-red ocular thermogram	This test can be used in the objective assessment of dry eyes. The evaporation of tears reduces the temperature of the cornea. The mean ocular surface temperature of dry eyes is greater than normal. There is also a greater variation of temperature across the ocular surface in dry eyes. The tear lipid layer pattern is highly correlated with dry eye severity. Dry eyes are characterised by non-uniform distribution of the tear lipid interface or by partial exposure of the corneal surface.
The tear lipid layer interference pattern	this tear pattern can be observed by a special non-invasive and non-contact specular reflection video-recording system. The study of the tear lipid layer may lead to useful and reproducible information in the diagnosis of dry eyes. There is an association between blink rate, maximum blink interval and ocular surface conditions.
Abnormal pattern of blinking	Abnormal pattern of blinking is often considered to be due to a psychological or emotional disorder. External eye diseases can also significantly affect patients pattern of blinking. The use of artificial tear drops may in some patients normalise the pattern of blinking. The blink rate and the maximum blink interval, are significantly different in dry eye patients compared with healthy eyes. An automated non-invasive blink monitor that allows quantitative analysis of blinking has described.
H185 monoclonal antibodies	These antibodies have been linked to a mucin like glycoprotein produced by the epithelial cells of the ocular surface. The binding of H185 monoclonal antibodies to the epithelial cells seem to be absent or severely reduced in keratinised ocular surface epithelium. Changes in mucous

	contents of tears may occur in various types of external eye diseases, and dry eyes.
Impression cytology	Impression cytology with ELISA and the tumour marker CA 19-9 may be used in the measuring glycoproteins of the mucin.

management

Ocular surface area and evaporation is greater on looking up than on looking ahead or down. Increased tear evaporation is thought to be the main cause of ocular fatigue in **VDTs** users since they have a greater exposed ocular surface area and reduced rate of blinking. It is recommended that VDTs to be placed at a lower level to allow a lesser exposed surface area and lesser tear evaporation, and also that VDTs users to keep their eyes partially closed and to blink frequently.

Dry eyes with decreased BUT time may be associated with **allergic** conjunctivitis and papillary reaction, raised serum Ig E and history of allergic diseases. The decreased BUT time seems to be due to a decrease in the conjunctival goblet cells due to the papillary conjunctival reaction. A combination of anti-histamine and low dose of steroids may used if the conventional methods of treatment fail.

Animal studies in dogs showed significant increase in the tear production in dogs with dry eyes after the administration of topical Cyclosporin. Patients with renal allograft recipients who are treated with systemic Cyclosporin, show a significant increase in the tear production. **Systemic Cyclosporin** appears to increase tear flow even when no lacrimal auto-immune disease exists. **Topical cyclosporin** 0.05% and 0.1% significantly improve the ocular signs and symptoms of moderate-to-severe dry eye disease, and decreased the effect of the disease on vision-related functioning. Cyclosporin A 0.05% and 0.1% appear to be safe and well tolerated. Administration of 5-mg **pilocarpine** tablets 4 times daily (20 mg/d) may produce a significant improvement in symptoms of dry eyes and other xeroses in patients with Sjögren Syndrome.

Bicarbonate containing solutions are valuable in patients with severe dry eyes, not only for the comfort of the eyes, but also to promote the recovery of the ocular surface. Carbomer gel is a water-soluble polymeric resin that has been reported to maintain the tear film in contact with the eye for an extended period. The drug appears to be more efficacious than placebo in improving a number of subjective and objective symptoms of moderate-to-severe dry eye syndrome. Sodium hyaluronate, when used 6 times a day dose not appear to offer subjective advantages to patients more than the conventional tear drops, but it may have a role in maintaining a healthy corneal epithelium, promotes corneal epithelial wound healing and protects the corneal epithelium.

Hyaluronan, Fermavisc, (sodium hyaluronate) is a polymer of acetyl glucosamine and glucuronic acid that is widely distributed in the connective tissue and vitreous. Topical application of the drug has been shown to be more beneficial than normal saline in the subjective and objective improvement in dry eyes.

surgical treatment

Punctal and / or canalicular occlusion may be used in patients with KCS. A trial of temporary occlusion with collagen plugs may be used. Permanent closure of the punctum may be accomplished by cautery, or argon laser. **Punctal occlusion** by thermal cautery seems to give a longer lasting effect than occlusion by argon laser. This might be due to the ability of the thermal cautery to penetrate and coagulate deeper in the canaliculus than the laser technique. Silicone plugs are a reversible means of punctal occlusion that can be effective for long term treatment. Migration of plugs into the lacrimal drainage system requiring surgical removal has been reported. Permanent occlusion can be complicated by very symptomatic epiphora.

Transplantation of autologous **submandibular** gland is a new method that may be useful in the treatment of severe cases of KCS. It is associated with a significant increase in the basal tear secretion and relief of symptoms in patients with KCS.

The orbicularis muscle plays an important role in the pump mechanism of the lower canaliculus and in tear drainage. It has recently been described that injection of **botulinum** into the medial part of the eye lid may decrease lacrimal drainage (as measured by the drop test) by interfering with the orbicularis muscle function. This method may have potential in treating dry eyes and improving patient's comfort.

vitamin a deficiency and xerophthalmia

Vitamin A deficiency may be associated with protein calorie malnutrition, with chronic hepatic or biliary disease, cystic fibrosis, and intestinal disease. Breast feeding appears to be highly protective against this condition. Vitamin A deficiency is a major cause of morbidity and mortality among pre-school children in many parts of the world. It is also a leading preventable causes of **childhood blindness** in the world. Vitamin A deficiency may lead to Xerophthalmia which is often associated with corneal xerosis, Bitot's spots and corneal ulceration.

Impression cytology is useful technique in the evaluation of vitamin A deficiency. The test may show alteration in the external eye that is not seen by fluorescein or rose bengal staining. Diagnosis on the basis of impression conjunctival cytology should, however, be made with caution in areas endemic with trachoma, as children with trachoma are likely to have an abnormal result on impression conjunctival cytology.

The current World Health Organisation protocol for treating children 1 year of age and older with vitamin A is **200,000 IU oral dose every 3 to 6 months** for prophylaxis and 3 times of this dose for the treatment of xerophthalmia. Approximately 8% of children treated prophylactically with vitamin A have side effects (e.g. nausea, vomiting and fever). Although these side effects are transient, they may decrease community compliance with the treatment. The most important factor in predicting response to treatment is base line serum retinol concentration. Children with lower pre treatment concentrations are more likely to have responsive lesions.

Cicatricial diseases

ocular cicatricial pemphigoid

Ocular cicatricial pemphigoid is characterised by conjunctival inflammation associated with scarring in the form of symblepharon, and shortening of the inferior fornix. Poor tear film and lid margin disorders, may then lead to corneal ulceration, infection and ultimately loss of vision. The disease is believed to be caused by the deposition of sub-epidermis **auto-immune deposits** of anti-epithelial basement membrane zone antibodies. It often affects both eyes, may be asymmetric and very rarely may be unilateral. Most of the disorders leading to conjunctival and mucous membrane scarring have an acute phase of activity followed by scar formation. A chronic form of the disease can also be found in some patients. The majority of patients with cicatricial pemphigoid have ocular involvement and about 50% of them develop systemic manifestations. **Systemic** manifestations of the disease include mouth, pharynx and oesophagus lesions as well as nose, sinus and skin involvement. There is no association between the ocular and system manifestations. Chronic progressive cicatrising conjunctivitis may also occurs as a part of **paraneoplastic** syndromes and also in association with some systemic and topical medications (pseudo pemphigoid).

Circulating Ig A and Ig G auto-antibodies have been recognised. Macrophages may also play an important role in the mechanism of the disease by secreting fibrogenic cytokines (e.g. TGF-B). Blockers of the fibrogenic cytokines may be of therapeutic importance. In ocular cicatricial pemphigoid the conjunctiva is infiltrated with neutrophils, macrophages, Langerhans cells, CD 8+, and CD 4+ in the acute stage, and mainly by CD 8+ T-cells in the chronic stage. The mechanism of fibrosis is not known but it may be due to an increased amount of fibrogenic growth factors. Blister formation and tissue damage may be caused by the release of eosinophilic granule proteins which may play a role in the acute phase of the disease.

treatment

The need for treatment depends on disease activity. Super-added bacterial or toxic conjunctivitis should be excluded and treated**.** Systemic **immunosuppression** treatment is regarded to be the treatment of choice of the disease. Broad spectrum medication (e.g. steroids) may be more effective in the treatment of this disease than specific immuno-suppressant drugs (e.g. cyclosporin). High doses topical steroids alone is often ineffective in controlling the conjunctival inflammation. Cylclophosphamide and short term high dose steroid is often effective in treating severe ocular pemphigoid but may not completely prevent ocular scarring.

Dapsone is the most effective initial agent for active disease, it is also a safer treatment in the elderly than steroids. Dapsone commonly induces significant haemolytic anaemia (more commonly in patients deficient in the enzyme glucose 6-phosphatase dehydrogenase). Patients are also at higher risk of agranulocytosis. Dapsone-induced neutropenia may not be dose dependent and routine white blood cells monitoring (specially 8 to 10 weeks after treatment) in needed. A taste disturbance and tingling sensation in the mouth and lips has been reported as a side effect of Dapsone.

Suggested system for treatment of mucous membrane pemphigoid:

severity	drug	follow up
mild	• topical steroids	IOP
moderate	• sulphapyridine • dapsone	• Full blood count. • urea and electrolytes. • G6PD screening.
severe	• systemic prednisolone • cyclophospham (in older patients) • azathioprine • methotrexate • cyclosporin (in younger patients)	• Full blood count. • urea and electrolytes. • blood pressure. • chest X ray. • liver function tests. • urine analysis.

Intravenous immunoglobulin treatment may also be effective in arresting progress in cicatricial ocular pemphigoid in resistant cases. The treatment consists of cycles which can be repeated every 2 to 6 weeks. Each cycle involve administration of 2 to 3 g/Kg body weight of the immunoglobulin over a 3 days. Other drugs that has been used include Sulphapyridine and Interferon Alfa-2

In patients with cicatricial obliteration of the conjunctival fornices, surgical lysis of the adhesion followed by intraoperative application of 0.4 mg **Mitomycin** C / ml in saline for 3-5 minutes seems to be useful in preventing fornices shrinkage. Sub-conjunctival injections of Mitomycin C might be effective in preventing progression of the disease.

Conjunctival **surgery** and opening the conjunctiva should be avoided in the acute stages of the disease when possible**.** Ocular pemphigoid and Sjogren's syndrome have always been difficult to treat because of the immediate recurrence of the adhesions. Mucous membrane **grafts** can successfully protect the corneal surface without provoking the conjunctiva inflammation in most cases, but in the long term complications eventually develop in a large number of patient. Mucous membrane grafts should not be performed in severe keratoconjunctivitis sicca, very advanced ocular cicatricial pemphigoid or active conjunctiva inflammation without proper immunosuppressive treatment.

Penetrating keratoplasty in patients with advanced cicatricial conjunctivitis disease can be performed for tectonic reasons. Visual restoration is often limited even after intensive medical treatment. The major causes of failure of the penetrating keratoplasty are epithelial defects, stromal ulceration, perforation, and infections .

stevens-johnson syndrome

Stevens-Johnson Syndrome is associated with severe purulent conjunctivitis which often leads to severe conjunctival cicatrization resulting in trichiasis, symblepharon conjunctival and corneal scarring and ultimately blindness. Steven-Johnson Syndrome may be caused by an autoimmune mechanism. The disease has been associated with certain **HLA tissue types** (e.g. HLA-BW 44, and HLA-DQB 10601). Patients with this tissue types may be at higher risk of developing ocular complications. Drugs (e.g. sulphonamides) are the most frequent identified aetiological factor in the cicatricial eye diseases

Systemic steroids during the acute phase of the disease appears to have **no effect** on the development of ocular manifestations. Topical antibiotics, steroids, lubricants and symblepharon lysis are required. Autologous conjunctival transplantation to promote normal trans-differentiation of the corneal cells has been tried in unilateral cases. In bilateral cases affecting the conjunctiva and the cornea, transplantation of the conjunctiva and the cornea from a cadaver eye has also been suggested. **Amniotic membrane transplantation** restores adequate bulbar surface and fornices depth and prevents recurrence of symblepharon in severe cases of Stevens-Johnson Syndrome. **A combination** of allograft limbal transplantation, amniotic membrane transplantation and tarsorrhaphy followed by the use of serum derived tear drops may reconstruct the ocular surface and lead to significant improvement in vision.

Surgery Of The Cornea

Penetrating keratoplasty

The indications for penetrating keratoplasty have changed over the past 20 years. Keratoconus, endothelial failure, corneal scarring secondary to corneal infection, aphakic bullous keratopathy and interstitial keratitis are currently the main indications for penetrating keratoplasty in the UK. Failed grafts are increasing as an indication for penetrating keratoplasty. Graft clarity and visual acuity results, after repeat transplantation, appear to be very good.

Preoperative considerations

The most commonly used storage media for donor corneas are the **Optisol** medium and **organ culture** medium. Corneas can be stored in the Optisol medium for up to 2 weeks (or 21 days in the Optisol GS medium). Organ culture media have the advantages of longer storage time, and the ability to detect infection in the donor cornea prior to transplantation. Penetrating keratoplasty using donor corneas stored (for up to 11 days) by either method seem to have the same results for up to 2 years after surgery.

Transmission of the donor disease to the recipient, through corneal transplantation, is a very rare complication after penetrating keratoplasty. The Eye Bank Association of America has developed certain **contraindications** for donor corneal use. These contraindications include:

1. Death of unknown cause.
2. Certain CNS disease of unknown nature and certain CNS infectious disease (e.g. Creutzfeldt-Jakob disease and subacute sclerosing pan-encephalitis).
3. Systemic infections (e.g. Septicaemia, endocarditis, AIDS, syphilis and viral hepatitis).
4. Intrinsic congenital or acquired eye diseases.
5. Prior anterior segment surgery.
6. Choroid malignant melanoma has traditionally been considered as a contraindication for donor corneal use. Recent studies, however, showed that corneas transmitted from eyes with primary choroid malignant melanoma have similar outcome to corneas transmitted from healthy eyes, as long as the tumour has not spread to the ciliary body or the iris.

Hepatitis B, and C, **HIV**-1 virus, and **Creutzfeldt-Jakob** disease can be transmitted through corneal grafts. In HIV patients, serological testing for HIV does not guarantee against infection, because patients may not test HIV positive for as long as 6 months after infection. In these diseases, the polymerase chain reaction may be able to detected the virus DNA in donors tears and aqueous humour samples.

VZV and HSV-1 may infect the cornea. **HSV** in a donor cornea may cause endothelial destruction and both primary graft failure and ulcerative keratitis after transplantation. PCR and immuno-histochemistry are both sensitive for the detection of HSV-1 in the cornea. A combination of PCR and immuno-histochemistry increases the specificity for the diagnosis to 97%.

Other **microbial** contamination may also be transmitted through corneal grafts. Immersion of donor corneas in 5 mg / ml solution of povidone-iodine for 2 minutes significantly reduces microbial contamination without significantly affecting the corneal structure.

Penetrating keratoplasty is often unsuccessful in patients with severe ocular surface abnormalities (e.g. chemical burns, ocular cicatricial pemphigoid or limbal stem cell deficiency). **Impression cytology** can be used to diagnose and monitor corneal diseases with limbal stem cell deficiency. Limbal allograft transplantation (see later sections in this chapters) and intensive immune-suppression and steroid therapy may be used for the reconstruction and preparation of corneas affected by these diseases before corneal grafts are carried out.

Penetrating keratoplasty in **children** presents special problems. Postoperative amblyopia often results in poor vision despite good surgical results. Corneal grafting for congenital opacities In infants should be performed as early as possible for unilateral as well as bilateral involvement. Corneal neovascularisation is, however, a recognised problem in penetrating keratoplasty surgery in children under 2 years of age. This necessitates early removal of suture with its accompanying problems. The postoperative course in children may be complex and patients may require re-grafting.

Late endothelial failure is the commonest cause of graft failure 5 years after surgery. The most important risk factor for late endothelial failure is the low endothelial cell count in the donor cornea before surgery or immediately after the operation. Taking care in choosing the donor material may play a role in reducing the incidence of late graft failure.

In considering donor materials, it may be difficult to detect eyes that had undergone previous **PRK surgery** even with microscopic examination. Transplantation of corneas after PRK may be associated with high postoperative hyperopia. Corneal topography by Videokeratography may be used in detecting eyes that had undergone PRK. Confocal microscopy

may also be used to study corneas after PRK. Stromal changes can be detected many months after surgery.

Surgical techniques

Astigmatism is a major problem after penetrating keratoplasty. Different **suturing techniques** have been devised to reduce postoperative astigmatism. Corneal grafts may be sutured by a single running suture, interrupted sutures, or a combination of interrupted and running sutures.

A single running suture often results in more rapid visual rehabilitation and less early astigmatism compared with the combined interrupted and running single technique. In using a 24 bites single running sutures technique, with postoperative sutures adjustment, the postoperative mean astigmatism is reported to be about 2.7 +/- 2.2 D, compared to 3.9 +/- 2.5 D in the combined running and interrupted sutures technique. Sutures adjustment can be made on the basis of retinoscopy, and keratometry. The sutures should be tightened in the flat meridian and loosened in the steep meridian. Suture adjustment may be done at 2 to 6 weeks after the operation. Continuos suture can also be adjusted during surgery by using a keratoscope fixed to the microscope (**Pollack keratoscope**). This technique allows quicker visual rehabilitation. The long term benefits of this technique is not known.

The difference between the results of single running suture technique, and combined running and interrupted technique is **insignificant** when all the sutures are removed. **Removal of continuos sutures** after penetrating keratoplasty may have unpredictable outcome. Corneal astigmatism can change unpredictably, and by large degrees when sutures are removed even up to 6 years after the operation.

The relationship between the donor cornea and the recipient bed seems to be the most important factor in controlling postoperative astigmatism. Malposition of the recipient and the donor cornea is a main cause for postoperative astigmatism. The donor cornea is often cut about 0.5 mm larger than the recipient corneal bed. It is suggested, however, that the use of he **same size trephine** for cutting both the donor and the recipient cornea may give less astigmatism, and better visual results. It has also been suggested that **cauterisation** of the central cornea may improve the postoperative refractive results of keratoconus patients.

Discrepancy in the corneal wound between donor and recipient cornea, when cut by mechanical trephine, is one of the major factors influencing the optical results of penetrating keratoplasty. Excimer and YAG laser can be used for non-mechanical trephination of donor corneas. **Laser trephination** has the advantages of reducing vertical tilt that is often noticed with the traditional mechanical methods. Orientation notches can also be produced with the laser which helps in the placing and orientation of the donor cornea.

Non-mechanical trephination in penetrating keratoplasty with the excimer laser is associated with less postoperative disruption of the blood aqueous barriers than the conventional mechanical methods. Postoperative non-randomised studies showed that laser trephination produces lower keratometric astigmatism, high regularity of the cornea surface and better corrected visual acuity. Non-mechanical trephination with excimer laser for tectonic penetrating keratoplasty can also be used.

Graft failure and rejection

After penetrating keratoplasty the corneal **endothelial cell density** decreases rapidly during the first three years after surgery. The mean endothelial cell density continues to decrease by a 7.8% per year for 3-5 years after surgery compared to a rate of 0.5% in the fellow eyes. The recipient peripheral cornea may also be affected in graft rejection. Eyes with IOLs loose more endothelial cells with time.

The main **risk factors** for non-immune mediated graft failure includes:

1. Prior glaucoma or uveitis.
2. Vitreous surgery in the same time with the graft surgery.
3. Repeat graft surgery.

Allograft rejection accounts for at least 33% of all graft failure. It often follows an inflammatory event (e.g. loose suture, suture track infection or recurrent HSV infection). Patients with corneal transplantation may suffer from recurrent episodes of unilateral or bilateral corneal grafts rejection during periods of **pregnancy** and child birth, or after vaccination. Rejection often occurs in the endothelial cells but may also rarely occur in the epithelial layer or the stroma.

There are conflicting results regarding the role of human leukocyte antigen **(HLA)** matching and A, B, O compatibility in corneal graft rejection for low and high risk patients. The main antigenic stimulus for allograft rejection is the major HLA system. There is a large number of studies indicating that **HLA class I** matching offers a survival advantages in high risk corneal grafts, while **HLA-DR** compatibility may lead to graft rejection. The relative risk of graft rejection also seems to increase with increasing mismatch in the HLA-A and B system. Currently it is recommended that matching for class I (HLA-A and HLA-B) should be carried out in high risk corneal transplants. The high incidence of graft rejection in matched grafts indicate that several other histocompatibility complex genes may play a role in graft rejection.

Steroids are the main drug for treating corneal graft rejections. The role of systemic versus intensive topical steroids is not completely understood. Some reports showed that, in cases with severe rejection, topical steroids is not enough and systemic or intravenous pulse

treatment (500 mg prednisolone) may be needed. Other studies showed that a single pulse treatment may be more effective than oral treatment. Some recent reports demonstrated that systemic steroids treatment does not appear to have any additional benefits over intensive topical steroids in the treatment of graft rejection in patients with no risk factors. The difference in the results in these studies may be due to different degrees of rejection.

In high risk corneas, steroids treatment alone seems to be insufficient in providing enough immunosuppression. Systemic and topical **cyclosporin** may be needed. A 12 months course of the cyclosporin is needed for maximal effects. **Combined** IV pulse methylprednisolone and oral cyclosporin treatment may also be used.

Other drugs that showed beneficial effects in the treatment of graft rejection include:

The anti-lymphocytes monoclonal antibodies CAMPATH-1H.
FK 506.
Rapamycin.
Mycophenolate.
Interleukin-1 receptors antagonists.

Mycophenolate is an immuno-suppressant that has been used in the treatment of renal transplant rejection. The drug acts by inhibiting the formation of guanosine nucleosides and consecutively purine synthesis. Combined therapy with Mycophenolate and cyclosporin A seems to have a marginal benefit, over mycophenolate alone, with no major complications. The drug has also been shown to be effective and safe for the treatment of corneal graft rejection (when used in combination with a short course of steroid).

It has also been shown that topical treatment with **interleukin-1 receptors antagonists** suppresses corneal graft rejection in animal corneas. The drug seems to reduce graft rejection by preventing activity of recipient Langerhans cells. The drug may prove to be useful in clinical practice.

Postoperative glaucoma

IOP increase in the early postoperative period occurs in about 12 % of all patients undergoing penetrating keratoplasty. The measurement of IOP is often difficult with the Goldmann applanation tonometer because of the graft irregularities. **Tono-Pen** and pneumotonometer seem to be associated with slight overestimation of the IOP. The **minified Goldmann** applanation tonometer (in which the front of the prism is reduced from 7 mm to 4 mm) seems to be as accurate as the pneumotonometer and the Tono-Pen in measuring IOP after penetrating keratoplasty.

Penetrating keratoplasty, cataract and pseudophakia

There is some controversy about the best approach in patients with co-exiting lens and corneal opacities needing cataract surgery and penetrating keratoplasty (e.g. Fuchs endothelial dystrophy). Some authorities argue that triple penetrating keratoplasty, cataract extraction and IOL implantation is better than consequential penetrating keratoplasty followed by cataract surgery. The following table summarises the different advantages and disadvantages for each approach:

Triple procedure	cataract surgery followed by penetrating keratoplasty
Rapid visual rehabilitation. In consequential surgery you need to wait until all sutures are removed in order to get a stable and accurate keratometry readings.	Cataract extraction with the open sky technique is unsafe as the eye is at greater risk of expulsive haemorrhage during the period after removing the cornea.
Good refractive and visual outcome can be achieved by analysing the surgeon own results and by using regression formulae to determine the anticipated keratometry readings and consequently the IOL power. Some studies showed that, in the absence of a keratometry value, a keratometry value of 7.49 mm can be used for calculation of the power of the implant as shown in. Videokeratoscopic data of the peripheral recipient cornea may result in improved postoperative refractive outcomes.	Despite using regression formulae to determine the individual surgeon own keratometry results, postoperative refractive results are still more accurate in consequential surgery when accurate biometry can be carried out.
Penetrating keratoplasty may hasten the progression of lens opacities, and cataract surgery often leads to more endothelial cell loss.	ECCE is associated with increased risk of posterior capsule rupture and vitreous loss than small incision phacoemulsification surgery.
There is no doubt that the triple procedure is beneficial in some patients who need rapid visual recovery (single eye patients), or in patients for whom two operations might be undesirable.	Other alternative approaches include performing the penetrating keratoplasty with ECCE followed later by accurate biometry and secondary IOL implantation.

Deep lamellar keratoplasty

Previous studies demonstrated a progressive endothelial cellular loss after penetrating keratoplasty surgery. Deep lamellar keratoplasty is a new procedure in which pathological corneal stroma is completely excised as far down as Descemet's membrane, at least in the pupillary region. The operation **may reduce the risk of corneal graft rejection**, and may lead to a marked improvement in postoperative visual acuity in certain selected conditions e.g. keratoconus. Compared with penetrating keratoplasty, deep lamellar keratoplasty allows endothelial cell counts to be maintained for a longer period. In deep lamellar keratoplasty, the postoperative endothelial density appears to be normal in most cases. Difficult surgical technique is the main drawback of this procedure.

The difficulty in this technique is in determining, accurately, the depth of the graft in the donor and the recipient cornea. Air injection has been used to facilitate corneal dissection down to the level of Bowman's membrane. **Balanced salt solution** has recently been injected in the corneal stroma to facilitate dissection. Fluid injection transfer the cornea into a solid and opaque tissue that can be easily dissected. Fluid deep lamellar keratoplasty has recently been reported to be a safe and effective procedure, especially in bilateral keratoconus. The technique is difficult and has a slow visual rehabilitation course.

Posterior lamellar keratoplasty

This is a new technique of corneal grafts that has recently been described in patients with pseudophakic bullous keratopathy and Fuchs' endothelial dystrophy. The technique involves transplanting the posterior corneal stroma Descemet's membrane and the corneal endothelium in the pupillary area. A micro-keratome is used to create a 9 mm corneal flap with a 350 micron thickness. A 7 mm trephination of the posterior lamella is then fashioned. The donor posterior lamella is then transplanted and sutured to the recipient bed. The corneal flap is sutured with a continuos suture. It is thought that this procedure may have a place and some advantages in diseases of the corneal endothelium. The preservation of the anterior corneal layers preserves the refractive surface and the refractive power of the eye. If the operation fails, a penetrating keratoplasty can then be carried out.

Corneal Refractive Surgery

Laser In Situ Keratomileusis (LASIK)

Laser in situ keratomileusis (LASIK) is gaining popularity as a reliable method for correcting **medium and high myopia**. The operation involves excimer laser photoablation of the corneal stroma under a partial thickness corneal flap, which may be hinged at one point or completely removed. Flap complications are relatively common but rarely lead to a permanent decrease in visual acuity. Flapped corneal buttons are more likely to cause loss of visual acuity than free flaps.

The operation seems to be safe. Intraoperative or postoperative complications does not appear to lead to serious visual loss in the majority of patients. There is, however, a concern that Laser in situ keratomileusis (LASIK) may be associated with so much thinning of the central corneal stroma which may lead to corneal ectasia and iatrogenic keratoconus.

Complexity of instruments and surgical technique is a main drawback of Laser in situ keratomileusis (LASIK) surgery. **Picosecond** laser Myopic keratomileusis is a new technique that allows laser application to the corneal stroma without affecting the epithelium of the Bowman's membrane and also without the need for micro-keratome. It has been shown, in animal model studies, that is possible to cut the corneal stromal lenticule by the laser without the need for a micro-keratome. The laser produces plasma formation, shock wave and gas cavitation within the corneal stroma without affecting the epithelium or the Bowman's membrane. The lenticule can then be removed manually through a very small flap. It has also been shown that this method can produce good refractive results. The results appear to depend on the corneal thickness, and may not last for longer than 6 months.

History of **contact lens wear** is very important in patient candidates of refractive surgery. There is great individual variation in contact lens-induced corneal changes among patients. Contact lens wear may lead to an increase or a decrease in the corneal thickness. A recent study showed that long-term contact lens wear results in a decrease in the entire corneal thickness and an increase in the central curvature and in the corneal surface irregularities.

Precise measurement of the corneal thickness is of great importance in refractive surgery. Corneal thickness measurements with conventional pachymetry, and computerised Videokeratography correlate poorly with the refractive results of lamellar corneal surgery. **Partial coherence** laser Doppler interferometer technique measures the central and peripheral corneal thickness with high precision. This new technique does not seem to be associated with significant inter-observer variability and is likely to be more superior to the currently used ultrasound and the conventional

optical pachymetry technique. Very high frequency ultrasound is another new promising method for studying the micro-anatomy of the cornea before and after PRK surgery.

The **results** of LASIK is better for low to moderate myopia than for higher myopia. Most studies show stability of refraction and adequate uncorrected visual acuity in a large percentage of patients with myopia up to 15.00 D. Laser in situ keratomileusis (LASIK) can also be used to correct higher levels of myopia that cannot be successfully corrected by PRK or RK procedures. It can also be used to reduce astigmatism and myopia **after penetrating keratoplasty**. For myopia greater than 15.00 D, accuracy and patient satisfaction are poor. LASIK for high myopia may be associated with early regression. Stabilisation often occur between 3 and 6 months. However, patients with high myopia show more improvement in the visual acuity mainly due to the increase in the size of images after surgery. Optical coherence tomography studies showed that corrections of higher degrees of ametropia runs a high risk of producing a thinner than expected central cornea, particularly, corrections greater than 12 D.

It has been suggested that deep application of laser may have a detrimental effect on the corneal **endothelium**. Recent reports, however showed that LASIK surgery for up to 14.5D is not associated with clinically significant corneal endothelial loss for up to 12 weeks after surgery.

Optical complications (e.g. glare, halo, and monocular diplopia) may occur in some patients after both PRK and LASIK for moderate to high myopia. In a randomised prospective, **comparative study,** between Laser in situ keratomileusis and PRK, for myopia between 2.5D and 8.00D, both operations achieved a successful refractive outcome. Laser in situ keratomileusis (LASIK) was, however, associated with better correction, quicker recovery of vision, more regular postoperative corneal topography, and less pain. A recent study showed that, for myopia between 1 and 9.5 D, laser in situ keratomileusis (LASIK), however, appears to be associated with more postoperative haloes. Corneal sensitivity at the ablated zone may be more reduced after laser in situ keratomileusis than after photorefractive keratectomy during the first 3 months after surgery, but it appear to be similar 6 months after either surgery. Another recent study indicated that PRK patients show an increase in halo and diplopia symptoms, but not glare, after surgery, and LASIK patients show an increase in diplopia, but not glare and halo symptoms. The study also showed that there is a lesser tendency toward postoperative optical symptoms in LASIK compared with PRK treated eyes.

The operation appears to be effective and safe, but about 5% of patients may develop **complications**. These complications are often mild and rarely lead to loss of more than two lines of visual acuity. The most

common complication after this procedure is under-correction. The mean refractive **regression** after Laser in situ keratomileusis (LASIK), in one study, was -1.07D (7.6%) from the first week to the third month. Early regression of refraction after LASIK appears to be a consequence of an increase in corneal thickness associated with central corneal steepening. Re-treatment of residual myopia is possible and predictable, but epithelial in-growth and flap melting are more likely to occur in re-treatment than in first time treatment. The surgical technique of re-treatment may be more demanding.

There are conflicting reports on the suitability of refractive laser corneal surgery in patient with a previous history of **herpes simplex** virus corneal infection. Recent reports indicate that reactivation of latent herpes simplex virus may be triggered by the application of laser treatment.

Diffuse lamellar keratitis is relatively new non-infectious condition that may complicate surgery. Several different names have been given to this condition and similar conditions (e.g. **interface keratitis, Fine lattice lines and Sands of the Sahara syndrome**). The condition is characterised by the presence of corneal infiltrate at the interface of the corneal flap, that typically present 2 to 6 days after surgery. Patient often present with pain, photophobia, and redness of the eye. The conjunctiva and the anterior chamber are typically quiet. The cause and the mechanism of this condition is not completely known. Causes may include povidone iodine, balanced salt solution, metal particles, or contamination from the meibomian gland. There is also a theory that this condition may be caused by contamination, of the surgical interface, by bacterial cell wall from the instruments or from the irrigating solutions. It may also be related to endotoxin released from gram-negative biofilm in sterilizer reservoirs. Intraoperative intra-stromal steroid application, and intensive topical steroids treatment immediately after the diagnosis is a safe and effective way to reduce the incidence and severity of this condition.

Increased intraocular pressure associated with the micro-keratome vacuum ring used during laser in situ keratomileusis (to stabilise the eye) may precipitate optic nerve head ischaemia and visual field defect. **IOP** monitoring is a very important part in postoperative follow up as many patients need steroids treatment after surgery. The measurement of the IOP by a chlorine-disinfected applanation tonometer may be associated with corneal epithelial changes. It is suggested that non-contact tonometry is better used in these patients.

Serious vitreoretinal complications after Laser in situ keratomileusis (LASIK) procedure appear to be rare. Some investigators, however, reported **retinal breaks** and asymptomatic retinal detachment after Laser in situ keratomileusis (LASIK), PRK, and RK surgery. Patients, however, should be warned about these complications.

Photorefractive Keratotomy (PRK)

PRK is often performed by the argon fluoride **excimer laser** (193 nm) which produces a pulsed far-ultraviolet laser which can ablate the corneal surface with sub-micron accuracy. The excimer laser, however, has many disadvantages (e.g. the extremely toxic fluoride gas, the apparatus is heavy, bulky and complicated). Neodymium YAG laser, and ER-YAG laser have also been used. The neodymium YAG laser has the advantage of being solid and compact, more cost effective and without the potential safety hazards of the toxic fluorine gas in the excimer laser. The ER-YAG is a solid state laser that is easier to handle, less expensive, and can also be fitted on a slit lamp or an operating microscope.

Photorefractive keratectomy causes significant refractive changes in **the anterior as well as the posterior corneal surface**. It is also associated with forward shift of the cornea. The thinner, ablated cornea may slightly bulge forward to steepen both anterior and posterior curvatures. This may account for the regression toward myopia that is typically found in the first few days post-treatment. The forward bulging is similar to the corneal relaxation effects observed after radial keratotomy

Removal of the corneal epithelium is an important part of PRK surgery before laser ablation to the stroma. **Corneal de-epithelialisation** may be carried out by mechanical or chemical (ethanol) methods, or by laser trans-epithelial debridement. In a rabbit experiment all methods of de-epithelialisation produced a significant decrease in the stromal keratocytes associated with acute inflammation. The use of topical metabolic nutrients (e.g. storage media) after de-epithelialisation may reduce this effect and increase the re-epithelialisation rate. The postoperative re-population of the anterior stromal keratocytes seems to be associated with collagen production which can lead to the formation of sub-epithelial haze and unpredictable outcome after surgery.

In a recent study, a single intraoperative application of **Mitomycin C** (0.02%) for 2 minutes was carried out, after epithelial debridement, followed by saline irrigation. The eyes were then patched, or a bandage contact lens placed until epithelial healing was complete. The study showed that, topical application of Mitomycin C (0.02%) may be a useful method of preventing recurrence of sub-epithelial fibrosis after epithelial debridement.

Optical zone **centration** is critical in corneal refractive surgery. Visual outcome may be reduced due to poor centration of the ablation zone. Patients with de-centration of the ablation zone can be retreated with a repeat, photorefractive keratectomy. Theoretically, the smaller the diameter of ablation zone the higher the dioptric correction for a given ablation depth. Some studies showed that The use of large zones in high myopia (more than 5 mm and depending on the degree of myopia), is

recommended as it gives more precise and stable refractive results. Other studies showed that photorefractive keratectomy with a 6-mm zone may be associated with reduction in vision. A multiple zone technique can also be used to reduce the total depth of ablation necessary to correct high myopia.

The autonomous technologies corporation (ATC) LADARVISION excimer laser is a new laser system that combines a small shaping beam with an eye **tracker system**. The tracker system detects eye movements and either stops the laser delivery or guide the laser system to follow the eye movements without stopping laser delivery to ensure proper centration of laser ablation. Recent studies showed that treatment, with this new system, of 1-10D of myopia with or without astigmatism, is associated with early refractive stability, excellent uncorrected visual acuity, no loss of best corrected visual acuity and low levels of corneal haze. An active eye-tracking system alone cannot, however, ensure good centration. Patient co-operation and fixation are important.

wound healing and corneal haze

Wound healing plays an important part in the visual outcome and in the visual predictability of PRK surgery. Exposure to Ultraviolet-B during post-PRK stromal healing exacerbates and prolongs the stromal healing response. Excessive ocular **Ultraviolet**-B exposure should be avoided during the period of postoperative period. PRK does not seem to be associated with detectable changes in the central corneal **endothelial cells**. Previous studies showed that there might be slight increase in the corneal endothelial cells after surgery, presumably due stopping wearing contact lenses.

Untreated **allergic** conjunctivitis seems to be associated with increased corneal haze after PRK surgery. Treatment of allergic conjunctivitis before surgery is recommended. Caution should also be taken in performing PRK in patients with a long history of **tranquilliser** use. A long history of tranquilliser intake (e.g. Chlorpromazine) may be associated with corneal endothelial cells abnormalities, and stromal haze.

Mild anterior corneal stromal haze is often seen after PRK. It usually appears within 4 weeks after the procedure. A new type of **corneal haze**, starting relatively late (4 to 12 months) after PRK, has been reported in about 1.8% of patients. Although glare and halos appear to be reduced with the 6 mm treatment, a small number of patients still report substantial glare or halo after the procedure.

Several distinct patterns of **corneal topography** have been identified after PRK. Central islands, and key-hole semicircular patterns are often noticed in the postoperative period. Central island are areas of higher refractive power. They can be observed in the cornea several months after treatment, and represent areas of irregular corneal astigmatism

which may lead to loss of best corrected visual acuity during the early or late postoperative period.

Although some of the central islands resolve with time due to the healing response of the cornea, the presence of central islands has been shown to correlate with poor visual rehabilitation because of the inhomogeneous refraction across the pupil. The cause of these islands is not known. It is hypothesised that they are due to local defects in the optics of the laser machine, resulting in colder spots and less ablation centrally, or may be due to differences in the hydration between the deep and superficial layers of the cornea.

Topical steroids, and non-steroidal anti-inflammatory drugs are the main treatment against excessive haze formation. **Gene transfer** is a new technique to modulate wound healing after PRK in order to reduce postoperative corneal haze. In this technique the keratocytes are genetically transduced with a herpes simplex virus vector, which makes these cells more sensitive to ganciclovir. Topical application of ganciclovir would be highly selective to these cells with causing any damage to other corneal cells. In an experimental study on rabbits eyes, eyes which were treated with ganciclovir after transduction developed significantly less corneal haze than eyes that were not transduced. The use of an antioxidant to reduce tissue damage may also help minimise postoperative stromal opacification.

results

Most patients (86%) seek PRK treatment to be able to have good vision without spectacles or contact lenses. 73% of patients seek treatment because of difficulties with contact lens use. The procedure is highly effective, safe and reliable in treating myopia of **up to 5.00 D** spherical equivalent. Individual variation in the refractive outcome after PRK is noticed in many patients, specially patients with high myopia. A recent study showed that, the operation increases the ocular aberrations and impairs the visual performance of the treated eyes. Scotopic visual measures such as low-contrast visual acuity and glare visual acuity suffer most from the myopia correction.

Age may play a role in the outcome of refractive surgery. In patients younger than 50 years of age, age does not significantly affect visual outcome or predictability after myopic photorefractive keratectomy. There is a significant difference between patients older than 50 and patients younger than 50 years of age in predictability of the refractive outcome at 3, 6, and 12 months.

Some patients are disappointed even after achieving good visual acuity due to **glare** and distortion. **Refraction** may continue to change for up to 20 months after surgery. It is essential that patients should be counselled properly before surgery. The accuracy of correction diminishes

significantly with myopia greater than 10 D spherical equivalent and the potential for loss of best corrected visual acuity is also increased with increasing pre treatment myopia. Recent studies demonstrated that good predictable results may also be achieved in myopic eyes up to 9 D. PRK in myopia higher than 9.5D is associated with more corneal scarring and refractive regression than in smaller degrees of myopia. Perception of halos, and night driving problems may be noted by some patients with high myopia.

Complications of PRK are few and not often vision threatening. A significant number of patients show refraction **regression** after PRK. The risk of regression is higher in patients with higher myopia, patients who had small diameter treatment area, female patients taking contraceptive pills, and also in patients who had regression after treatment of the other eye. The cause of postoperative myopic regression after PRK is not very clear. It appears to be dependant on the epithelial and stromal healing process. It may be related epithelial hyperplasia and stromal re-modelling. The most significant shift in refraction seems to occur in the first one or two months. Small degrees of refractive changes may also continue to occur for up to 12 months. It is not known when refraction stabilises after surgery.

Repeated PRK can be used successfully to improve visual acuity in cases with refractive regression. Deliberate over-correction may also reduce the chance of further regression. A second PRK operation can be carried out six months after the primary operation in patients with regression. When corneal haze is present, re-treatment is less predictable with about 40% of patients having over-correction. Patient with high myopia and those who regressed beyond -3.5 D should be treated with caution as the risk of further regression is high.

Post-PRK **hyperopia** is a major problem that is caused mainly by epithelial hyperplasia and collagen deposition adding to the corneal thickness. Over-correction of more than 1.0 D of hyperopia occurs in about 1% of eyes. The over-correction tends not to persist. There does not seem to be any significant association between over-correction and age, gender, surgical treatment or the simultaneous correction of astigmatism.

The effect of **topical steroids** on the postoperative refraction is not known. Some studies showed that Dexamethasone may have an initial effect in reducing myopia after PRK operations when compared with placebo. The difference between steroids and placebo after discontinuing the steroids three months after surgery, in these studies was not significant. Other studies, on the other hand, showed that postoperative topical steroids play a crucial role in the development of the refractive results. Steroids may have a beneficial modulating effect on keratocytes activity during wound healing. This effect may limit the extent of the new collagen synthesis in the treated cornea and possibly reduce stromal re-

modelling during the healing process. Caution should be taken in using postoperative steroids because reactivation of viruses may occur after laser ablation.

Other postoperative complications include IOP rise, epithelial changes, recurrent corneal erosions. Unlike radial keratotomy, PRK does not appear to result in diurnal variation in visual acuity, spherical equivalent, or keratometry readings.

PRK and IOP

Corneal **thickness** is significantly reduced in patients with normal pressure glaucoma as compared with patient with primary open angle glaucoma and individuals with healthy corneas. Underestimation of the IOP in patients with primary open angle glaucoma who have thin corneas may lead to a misdiagnosis of NTG, while overestimation of the IOP in normal subjects who have thick corneas may lead to a misdiagnosis of ocular hypertension. The measurement of IOP with Goldman tonometry and non-contact tonometry, after PRK for myopia may be underestimated (by up to 2.4 +/- 1.23 mm Hg.) because of changes in the corneal thickness. The decrease in the IOP seems to be related to the degree of myopia treated. Pneumotonometry can reliably measure the IOP in all parts of the cornea after surgery, and may be a more accurate method of measuring the IOP in theses eyes.

Radial keratotomy (RK)

Radial keratotomy usually achieves partial improvement in uncorrected visual acuity in patients with non-progressive low and moderate amounts of myopia. Under-correction occurs commonly, and the amount of correction cannot be predicted accurately for an individual patient. Many surgeons recommend intentional under-correction followed by repeated surgery to augment the results.

In eyes with RK, a significant increase in the spherical equivalent (hyperopic shift) and in the keratometric value is noticed at **high altitudes** (12000 to 17000 feet). Patients travelling to high altitudes may benefit from taking multiple spectacles with increasing plus power lenses. A higher myopic correction can also be expected in patients who have the operation at high altitude compared with those at sea level if the same technique and the same nomogram is used. The mechanism of the hyperopic shift may be mechanical due to the change in the barometric pressure, or due to a slower metabolic process in the cornea. **Hypoxic** corneal expansion at high altitude with central flattening may also explain this phenomena. Some patients may also show small diurnal variation in refraction and visual acuity after surgery. The technique and nomogram used in RK surgery should take in consideration the height at which the surgery is carried out.

RK surgery makes the cornea susceptible to trauma and may be associated with corneal rupture after minor blunt trauma up to 91 months after surgery. Globe rupture often involves the RK wounds sites. **Mini radial keratotomy** refers to a radial keratotomy procedure with the corneal radial incision limited to within 3.5 millimetres from the centre of the central clear zone. The corneal integrity is still reduced with mini radial keratotomy, but corneas with mini radial keratotomy incisions appear to rupture at a significantly higher pressure than cornea with conventional radial keratotomy incisions. Mini radial keratotomy may have an advantage to patients at high risk of minor ocular trauma.

Micro-corneal perforation, corneal ulcer and early onset keratitis following radial keratotomy are relatively infrequent. Diamond knife contamination from the eye lashes is an important source of infection during this procedure. Severe bacterial endophthalmitis and cellulitis have also been reported. Patients should be informed about this small but potentially blinding complication.

Intra-stromal Corneal Ring *"intacs"*

Intra-stromal corneal rings and Intra-stromal corneal ring segments are a relatively new technique designed to treat **low to moderate** myopia (1-3 D) by flattening the anterior corneal curvature by inserting corneal rings into the peripheral corneal stroma. The rings are made of polymethylmethacrylate. The thickness of the rings seems to be crucial in determining the amount of myopia corrected. The procedure involves making corneal incisions, creating stromal channels by a special suction device and then implantation of the rings in the peripheral corneal stroma. The rings can be removed from the cornea, if needed, to reverse the refractive effect of the procedure with minimal disruption to the corneal stroma. The ring segments can also be exchanged with segments of different thickness to correct over- and under-correction in the initial surgery. Clinical studies showed that this technique is safe, effective and predictable in reducing myopia. Intra-corneal ring segments are also not associated with clinically significant diurnal variation in visual acuity or manifest refraction. The technique may be a promising alternative to current kerato-refractive surgical procedures.

Lens refractive surgery

Several strategies have been used to correct high myopia. Changing the curvature of the cornea by radial keratotomy, PRK, or by Laser in situ keratomileusis (LASIK) have been tried with varying degree of predictability and stability. Another approach for correcting myopia is by **clear lens extraction**. This approach carries the same risk as any other intraocular procedure. It also leads to loss of accommodation. The incidence of retinal detachment after clear lens extraction, for axial myopia, is about 7.5%. There is a strong association between the incidence of the detachment and postoperative laser or surgical capsulotomy but, apparently, not with primary intraoperative capsulotomy. The presence of vitreoretinal degeneration should be considered as a contraindication for this procedure.

A third approach is by **implanting a minus power IOL** without removing the clear crystalline lens. Preservation of accommodation is a main advantage of this technique. The predictability of this approach is good, but visual acuity and refractive outcomes with clear lensectomy appear to be associated with more favourable results. Anterior chamber as well as posterior chamber IOLs have been implanted in phakic myopic eyes. AC IOL implantation, has been reported to have good safety and good visual results. Posterior chamber silicon IOL may is associated with a high incidence of cataract formation.

The procedure may be complicated by:

- Lens rotation.
- Cataract.
- Oval pupil.
- Endothelial cell loss.
- Retinal detachments (in about 4.8% of patients). The time between implanting surgery and retinal detachment ranges between 1 and 44 months. Conventional scleral surgery is successful in most cases, but it may be associated with significant increase in the myopic spherical equivalent.

Pterygium surgery

The pathogenesis of pterygium is not completely known. Sun exposure and ultraviolet light seem to play an important role in its development. Protective **sun glasses** may reduce pterygium formation in sunny areas. Surgical treatment is often indicated when the pterygium threatens vision by encroaching on or near to the visual axis, or when it causes a significant dellen effect.

Several methods of treatment have tried in the treatment of pterygium with varying degrees of success. The traditional method of treatment in vision threatening pterygium is by surgical excision. Recurrence is common and also more aggressive in some cases after surgical excision. The rate of recurrence varies considerably depending on the method of treatment employed. These methods include:

Excision with bare sclera technique
Excision with mitomycin c
Excision with beta irradiation
Excision with conjunctival flaps
Excision with buccal mucosal grafts
Excision with amniotic membrane

The use of a **bare sclera** technique is better avoided in the treatment of primary pterygium as the possibility of recurrence is high if no conjunctival graft is carried out, or if Mitomycin C treatment is not applied. Intraoperative application of **Mitomycin C** (0.02 mg/ml) for two to three minutes after pterygium excision seems to be effective in reducing recurrence rate. The midterm results of this procedure is also encouraging. Mitomycin C may also be applied postoperatively in the form of eye drops. A recent study showed that intraoperative administration of 0.04% mitomycin C is **more effective** than irradiation as an adjunctive treatment for pterygium surgery. Excision of pterygia with the use of Mitomycin C or **beta irradiation** may, however, be associated with some complications e.g. infectious scleritis associated with scleral abscesses formation. Pseudomonas infection seems to be common in this type of scleritis. Early diagnosis and prolonged treatment with topical as well as systemic antibiotics is needed in these cases

Sliding conjunctival **flaps** may also be used with pterygium excision. This technique may, however be limited in cases with repeated surgery due to shortening of the conjunctiva in this area. The use of conjunctival free grafts is also effective and safe. Advanced recurrent pterygia may be treated by limbal autograft transplantation, which could be included in the procedure of conjunctival transplantation.

When it is not possible to obtain enough conjunctiva from the superior bulbar conjunctiva or from the other eye, the conjunctiva covering the pterygium may be used instead. After dissecting the pterygium, the

conjunctiva is freed from the underlying tissue. It can then be used to cover the bare scleral area after rotating the graft so that the leading apex of the conjunctiva is facing towards the fornix. Intraoperative use of mitomycin C with conjunctival autograft reduces the rate of recurrence of severe pterygia compared with use of conjunctival autograft alone.

Recurrent pterygia may be aggressive and repeated conjunctival excisions may result in conjunctiva scarring and shortening. Repeated conjunctival grafts may therefore not be possible. In recurrent, and aggressive cases, excision of the pterygium may be repaired by full thickness or partial thickness **buccal mucosal grafts**, and postoperative beta irradiation. The advantages of using buccal mucous membrane is that it is often available in sufficient quantities. Mucous membrane covering may also delay any re-growth of the pterygium. Partial thickness mucosal grafts may have some advantages over full thickness grafts, resulting in a better cosmetic appearance. Transplantation of human **amniotic membrane** with a limbal autograft may also be used in patients with recurrent pterygium associated with conjunctival shortening and symblepharon.

Limbal transplants, and amniotic membrane transplantation

Epithelial stem cells in the cornea are located in the basal layer of the limbal epithelium. Limbal basal cells contain 4-5 folds higher levels of epidermal growth factor receptors than the central corneal cells. This higher level of growth factor may help to maintain the limbal basal cells in an undifferentiated stem cell state. The stem cells are responsible for the repopulating of the rest of the corneal cells.

Limbal transplantation is a surgical procedure used in conditions associated with **stem cell deficiency** (e.g. aniridia keratopathy, chronic contact lens epitheliopathy, chemical burns, Steven Johnson syndrome and corneal intraepithelial dysplasia). Absence of progressive epithelialisation, with 2 to 3 weeks of corneal lesions, should alert the surgeon to the possibility of poor stem cell function and also to the possibility of needing a limbal transplantation to promote corneal healing. Limbal **auto-transplantation** is used in the treatment of unilateral conditions, while allograft transplantation is used for bilateral conditions. The procedure may be carried out either in acute or the chronic phase of the disease, and also in preparation for penetrating keratoplasty in severe external surface and corneal diseases. Close monitoring of the conjunctival epithelium to ensure that it does not cross to the corneal surface, in the immediate postoperative period, will ensure that the corneal surface will re-epithelialise mainly from the epithelial limbal cells which may improve the success rate of the operation.

In the reconstruction of the ocular surface disease, three factors are considered; limbal cells restoration, basement membrane replacement, and tear substitution. **Amniotic membrane** may be used if the limbal epithelial cells are available for further repair (e.g. in persistent epithelial defects as in aniridia). If no stem cells or conjunctival cells are available, limbal autograft or allograft is then needed (e.g. chemical burns, and Steven-Johnson syndrome). If tear secretion is also involved, artificial tear drops with serum drops may also be needed. Limbal cells function seems to depend on the extra-cellular environment. The use of Amniotic membrane in situation of damaged or diseased stroma seems to be rational.

Amniotic membrane have been used for the repair of skin and mucosal wounds. They have also been used in the eye for the treatment of persistent corneal epithelial defects, ocular surface reconstruction, and in the treatment of pterygia. Repeated transplantation of amniotic membrane may be associated with a **hypopyon** iritis. Immunological, toxic, and hypersensitivity may be responsible for this reaction.

The Amniotic membrane is separated from the chorion and cut into the appropriate size and then stored at -80 degrees. The membrane is often sutured in the damaged area with 10/0 nylon sutures. The transplanted

membrane dissolves with several months of application. Transplantation with preserved amniotic membrane when combined with limbal allograft may be used effectively in patients with severe cicatricial diseases and also in patients with persistent epithelial defects and ulceration. Oral cyclosporin may be used to prevent rejection.

Advantages of using Amniotic membrane include:

1. They are non-antigenic
2. Easy to manipulate surgically
3. They have a strong and a stable connective tissue substrate

Cataract Surgery

Anaesthesia

Local anaesthesia is used in about 70% of intraocular operations in the UK. Routine **medical assessment** does not appear to be necessary for patients having cataract surgery under local anaesthesia. A recent report indicated that preoperative medical assessment does not lead to any significant reduction in the operative or postoperative complication and does not increase the safety of the patients.

The majority of cataract operations are carried out under peribulbar anaesthesia. Retrobulbar, sub-conjunctival, sub-Tenon and topical anaesthesia are also used. Lignocaine, marcaine and prilocaine are commonly used as anaesthetic agents. **Prilocaine** is the least toxic of the commonly used local anaesthetics. The drug has a longer duration of action than lignocaine, greater tissue diffusion, no requirement for adrenaline and slower systemic absorption. The main disadvantage of prilocaine is the production of methaemoglobinaemia (and falling oxygen saturation) when used even in small volumes. **Warming** the local anaesthetic solution, in peribulbar anaesthesia, to body temperature, is associated with less pain sensation by patients. An increase in the temperature tends to raise the pH of the solution and increase its lipid solubility which also increase its potency. Warming the solution may also cause a change in its pH resulting in more rapid onset blockade.

Peribulbar anaesthesia is supposed to be safer than retrobulbar anaesthesia regarding brain stem anaesthesia, orbital haemorrhage and scleral perforations. **Serious systemic and local complications** may, however, occur with any type of anaesthesia. Some of the complications may be life or sight threatening. The rate of local anaesthesia related complications seems to be higher than previously thought. Retrobulbar **haemorrhage** is the most common complication of retrobulbar anaesthetic. Visual loss has been reported following retrobulbar haemorrhage from retrobulbar and peribulbar anaesthesia. Sub-periosteal orbital haemorrhage, following a retrobulbar injection, may also result in permanent and severe visual loss.

Inadvertent **globe penetration** and dense vitreous haemorrhage may also occur after local anaesthesia injections. In a study of 50000 injections, it was found that the only significant factor for scleral perforation, during peribulbar or retrobulbar injection, is the presence of a posterior staphyloma. In theses cases, prompt referral for early vitrectomy is recommended. Early vitrectomy may lead to a good visual outcome by preventing retinal detachment. Some other studies documented a spontaneous improvement in visual acuity in some eyes

after this complication. In an experimental study in rabbits eyes, Intravitreal injection of 0.2 ml of lidocaine (2% to 0.25%), bupivacaine (0.75% to 0.25%) and a mixture of 2% lidocaine and 0.75% bupivacaine was found to be non toxic to the animal's retina.

Peribulbar anaesthesia may be associated with impairment of the **retinal circulation**. The effects of peribulbar anaesthesia on ocular blood flow may be caused by elevations in intraocular pressure or direct pharmacological action on the vascular tone. Drug-induced vasoconstriction may occur after peribulbar anaesthesia, and visual loss may occur in patients with compromised retinal or choroidal circulation.

The effect of covering the patient's head with the surgical drapes is controversial. **Carbon dioxide** may accumulate under the surgical drapes. Oxygen breathing via nasal intubation had been thought to prevent increased levels of carbon dioxide in patient's breathing air. A recent study, however, reported that nasal intubation is beneficial in preventing hypoxic effects but it does not seem to be effective in preventing increased carbon dioxide levels in breathing air. Elimination of accumulated carbon dioxide by a suction machine appears to be the only effective method.

Monitored anaesthesia is preferred in cataract surgery, even with pure local anaesthesia, as a high percentage of patients need some kind of intervention during the operation. The intervention may only be verbal reassurance or active intervention to deal with respiratory and blood pressure problems.

Topical local anaesthesia (with or without IV sedation) is a new technique that allows rapid visual rehabilitation and also avoids the complications and side effects associated with peribulbar and retrobulbar injections e.g. diplopia, amaurosis, ptosis, lid ecchymosis, and pain associated with injection anaesthesia. Topical anaesthesia for cataract surgery can, however, damage the ocular surface in older patients with dry eye and blepharitis. This technique seems to be as effective as either of these two methods in cataract surgery. However, eye movements and lid squeezing are more common with topical anaesthesia, but do not seem to cause major problems. Topical anaesthesia with a van Lint block may be used in cases with severe lid squeezing. Patients selection and preparation are the keys to using topical anaesthesia. Iris manipulations, irrigation-aspiration, and IOL implantation may also be associated with some discomfort. Topical anaesthetic drops are used in **both eyes** prior to surgery in order to reduce the blinking reflex. Patients having topical or retrobulbar anaesthesia may have different **visual experiences** during their operation. Some patients may be able to see the surgeon's hand and the instruments. Some of these visual sensation may also frightening to some patients. patients should be counselled about these visual sensations.

Most surgeons consider supplementing the topical block during cataract surgery with additional drops, or with **intracameral lidocaine** anaesthesia, if needed. Some drops may Inadvertently enter the eye and may cause clinically and statistically significant corneal thickening and opacification. Intracameral injection of lidocaine 1% during surgery may alternatively be used to increases patient's comfort. On the other hand, a recent double-masked, prospective, randomised, controlled trial showed that there was no significant reduction in intraoperative pain when intracameral 1% lidocaine was used during phacoemulsification under topical anaesthesia.

lidocaine 1% may cause a transient **endothelial cells oedema** to in-vitro perfused endothelium of human and animal corneas. Short term exposure, however, seems to be harmless. Non-preserved bupivacaine 0.5% is as effective, clinically, as lidocaine 1.0% for intracameral anaesthesia during surgery. However, experimental studies in rabbits showed that perfusion of bupivacaine 0.5% can damage the corneal endothelium except when the drug was diluted 1:1 with glutathione bicarbonate Ringer solution. Electrophysiological studies showed that ERG amplitudes are not significantly reduced after 0.15-ml intracameral lidocaine half an hour after surgery.

Sub-Tenon anaesthesia may also be used. The technique is very comfortable to administer with good pain relief and good akinesia. A small opening is made in the conjunctiva in the inferior nasal quadrant after injecting a small amount of anaesthetic solution in the conjunctiva. A sub-Tenon curved cannula is then passed in the sub-Tenon space around the eyeball and a further 2-3 ml of the anaesthetic solution is then injected. The addition of **Hyaluronidase** to the anaesthetic solution appears to increase the akinesia effect, but not the sensory effect, of the block. The technique is reported to be superior to topical anaesthesia in ensuring patient comfort, and better akinesia during phacoemulsification cataract surgery. A significant number of patients experience a sever pain at the time of acetylcholine intracameral injection with this technique. The obvious advantages of topical anaesthesia over sub-Tenon infiltration are time saving and shorter duration of action which allows the patient to regain visual acuity rapidly after surgery.

Recent progress in cataract surgery technology has diminished the need for complete ocular akinesia during phacoemulsification cataract surgery. **Rand-Stein Analgesia Protocol** for Cataract Surgery is a new technique that produces ocular analgesia while eliminating the risks and side effects associated with general, local, topical, and intracameral anaesthesia. In this technique a very low-dose, titrated, intravenous **alfentanil** (125 mcg in 0.5 ml) is used to achieve ocular analgesia. Alfentanil is a potent synthetic opioid that has an intense rapid-onset analgesia and a short action. It produces a significant generalised body analgesia that is effective in relieving chronic back and neck pain, which can induce unwanted patient movements during surgery. Complete control of lid

squeezing and ocular and general body movements, can be achieved, whenever necessary, by using very low-dose, titrated, intravenous **methohexital** (10 mg), which is an ultra–short-acting barbiturate. The technique allows for an immediate postoperative recovery with instantaneous vision restoration. **Midazolam** (short-acting benzodiazepine, a central nervous system depressant) may also be used for preoperative anxiety.

Intraocular implants

- **foldable implants**

Foldable IOLs with small corneal section technique is gaining popularity because of the **rapid postoperative visual recovery** associated with the small incision. Foldable IOLs are thought to provide superior visual results than rigid IOLs. However, in some studies foldable acrylic IOLs did not provide any visual advantages than rigid PMMA IOLs in the early postoperative period. Long term visual outcome may depend on the degree and rate of posterior capsule opacification associated with the IOL.

There is some controversy about the best foldable IOL that can be used. The current popular foldable IOLs are made of the following material:

Silicon
Hydrogel
Soft acrylic

Postoperative inflammation and posterior capsule opacification depend, among other factors, on the design and the biocompatibility of the lens material. **Heparin surface modification** of the IOL seem to reduces postoperative inflammatory features after phacoemulsification.

Posterior capsule opacification is caused by proliferation, migration and transformation of the lens epithelial cells that remain in the capsular bag. The **hydrogel IOLs**, when compared with the PMMA and the silicon IOLs, are very bio-compatible. They are associated with reduced number of inflammatory cells on the lens surface. They are also, on the other hand, associated with great number of lens epithelial cells growing on the posterior capsule, and higher rates of posterior capsule opacification. A recent study showed that intraocular lenses made of hydrogel are associated with a significantly higher degree of posterior capsular opacification and more laser capsulotomies than polymethylmethacrylate and silicone intraocular lenses over a period of two years.

Acrylic foldable IOLs seem to adhere to the posterior capsule more than PMMA IOLs, and also seem to be associated with considerably less proliferation of the lens epithelial cells on its surface. Silicon IOLs, on the other hand do not seem to show any adhesiveness to the posterior capsule. The presence of lens epithelial cells on the posterior capsule is considerably less with polyacrylic IOLs than with PMMA or silicon IOLs. The regression of the epithelial cells also appears to be quicker with the polyacrylic IOLs. Silicon IOL with large positioning holes seem to be more fixed to the capsule than IOL with small holes. The increased fixation is due to regeneration and fibrous tissue in-growth through the holes. IOL with large holes may be useful in preventing IOL de-centration.

Foldable **silicon** IOLs are now recognised to be associated with these main complications:

1. Lens de-centration
2. Moisture condensation during fluid gas exchange in vitreoretinal surgery. Heating the anterior segment by warmed irrigation fluid is a cheap, non-invasive, and safe means to prevent condensation on IOL materials.
3. Silicon oil-silicon IOL interaction
4. Accumulation of pigmented cellular membrane on the anterior surface of the IOL
5. Intraoperative deposition of crystalline materials have also been reported with some implants, mainly silicon implants. The crystalline deposits are thought to be due to the use of BSS +, as a source of the calcium deposits. Exchange of the implant, and anterior chamber wash out with simple BSS may be needed.
6. There is also some reports that, the use of three piece foldable silicon polypropylene IOL may be associated with an increased risk of postoperative endophthalmitis.
7. Discoloration of silicon IOL have been described before. Recent report described similar complication in acrylic IOLs during surgery and also several months afterwards. Some cases may improve spontaneously while others may need explantation. The cause of this phenomena is not completely understood. It is thought that temperature change (e.g. warming of the IOL prior to implantation) may play a role in the development of these transient changes.
8. Adherence of S. epidermidis to IOLs may play a role in the pathogenesis of some forms of endophthalmitis after cataract surgery. A recent study showed that S. epidermidis can adhere, in vitro, to Acrysof IOLs more readily than PMMA IOLs.

Silicon material has been used in ocular and other surgeries for some time. It has been suggested that patients receiving silicon implants or prosthesis might have a specific anti-polymer **immune response** which might lead to severe immunological symptoms, as in patient who receive breast silicon implants. In a study of 49 patients who had retinal and cataract surgery using silicon material, the frequency of enhanced serum Ig G binding to silicon was very low, making the correlation to surgical complications difficult. The results of the study did not suggest any change in the clinical use of this material in eye surgery.

In-the-bag implantation of the IOL which achieve a strong contact between the posterior capsule and the IOLs may play a role in preventing posterior capsule opacification and wrinkling, by acting as a barrier against the migration of the proliferating lens epithelium along the surface of the IOL.

- **multifocal lenses**

Multifocal IOLs are relatively new. They are mainly used to provide **less spectacle dependency** than with the monofocal lenses. The overall patients satisfaction with these lenses is generally good. Most patients suffer from mild haloes due to the blurring effect of the near vision rings. Mild reduction in the contrast sensitivity is also common. Patient's **selection** is very important in the indications of these lenses. patient's motivation, lack of other macular diseases, less than 1 D of astigmatism, are important factors that should be considered in selecting patients.

There are two main **types** of multifocal implants:

1. Diffractive lenses
2. Refractive lenses

Both types of lenses provide patients with sufficient unaided distance and near vision. The diffractive lenses have 20-30 concentric rings superimposed on its posterior surface providing a theoretical power add.

The main multifocal intraocular lenses currently in practice are:

- The AMO ARRAY silicon IOL.
- The tripod M F4 multifocal hydrophilic IOL.

The lens, in the **ARRAY IOL**, has a concentric zones of progressive aspheric power on its anterior surfaces to provide a repeatable power distribution for near and distance. Some loss of contrast sensitivity may occur. Some patients also complain of seeing haloes. Night haloes and glare disabilities may occur after monofocal as well as multifocal IOL implantation. Patient's age, corneal surface abnormalities, and the design of the IOL may all play part in the pathogenesis of these symptoms. It has been thought that mono-focal IOLs achieve a better functional performance than multifocal IOLs outside standard conditions of vision (e.g. low contrast and illuminations). A recent study showed that there is high **patient satisfaction** with the ARRAY multifocal IOL. It also showed a greater functional independence from spectacle wear, by objective and subjective patient measures, than with the monofocal IOL. The ARRAY multifocal IOL has also been shown to produced distance visual outcomes comparable to monofocal IOL in patients with concurrent eye disease. Management of associated eye disease does not seem to be compromised by the nature of the IOL.

The **M F4 multifocal IOL** has 4 refractive zones with a + 4 add in the central zone for reading (unlike the ARRAY lens which has a distance refraction in the central zone). Patients may notice some reduction in the visual acuity in bright light due to pupil constriction. The lens has a tripod shape and needs a 3.7 mm incision.

Bilateral implantation of **asymmetrical diffractive IOLs** may be used for restoring simultaneous distance and near vision with a potential for

improved contrast sensitivity compared with conventional multifocal IOLs. Distance vision would be better for distant-dominant IOL while near vision would be better for the near-dominant lens. This regime leads to improved binocular visual performance, and more spectacle independence.

- **the Artisan IOL**

The artisan IOL is an anterior chamber IOL that can be used for the correction of myopia or hyperopia. It can also be used as piggy back IOL for high myopia and hyperopia. The lens is fixated to the iris tissue by a pair of claws. A new **Toric Artisan IOL** has also been recently described for the correction of high astigmatism. Two types have been described, in the first type the cylinder axis is in the same direction as the axis connecting the claws haptics. In the second type the cylinder axis is at a right angle to the axis connecting the claws. Preliminary results indicate that these lenses may be useful in correcting high astigmatism in aphakic or phakic eyes.

Biometry

Biometry has traditionally been carried out by ultrasound A scan for measuring the axial length of the eye. **Partial coherence interferometry** biometry is a new non-invasive method for measuring the axial length. The method does not need any contact with the eye, and no local anaesthesia is required. A recent study compared this method to standard A-ultrasound axial length measurement in the evaluation of biometry with the SRK II formula. Precision of the partial coherence interferometry was estimated to be ten times more accurate than the ultrasound. This could result in a 27% improvement in the mean absolute error for postoperative refraction.

IOL power measurement and biometry is not often accurate in eyes with **high myopia or high hyperopia**. The use of third generation formulae e.g. Holladay I, SRK/T and Hoffer may provide more accurate results. IOL power measurement in eyes that had undergone corneal **refractive surgery** is also inaccurate and may result in postoperative refractive surprises. Standard calculations in these eye may result in underestimation of the IOL power with a postoperative hyperopia. The use of automated corneal topography to measure the corneal power may be useful in achieving better results. The measured corneal power must be corrected. The modified corneal power can be calculated by subtracting the spherical equivalent change in the corneal plane induced by the PRK from the average corneal power measured before the PRK. The use of pre-refractive surgery readings about corneal power and axial length, as well as over refraction with a hard gas permeable contact lens may also be used.

Axial length measurement may decrease after a successful **trabeculectomy** operation. Biometry in phakic eyes with a history of trabeculectomy may result in unexpected postoperative refractive results (they tend to be more myopic). Measurement of axial length before the trabeculectomy operations is recommended, as many of these patients may need to have cataract surgery following the trabeculectomy operation. Many patients with a history of vitreoretinal surgery and **silicon oil** develop postoperative cataract. Combined removal of the silicon oil and phacoemulsification surgery may be carried out in the same operation. The speed of sound is different in silicon oil compared with vitreous. Echography of an oil-filled eye may overestimate the axial length of the eye. Unexpected postoperative refractive errors may occur if biometry is calculated using the same formula as in eyes with no silicon oil. A **conversion factor** (0.71 with a range of 0.70-0.73) has been developed to allow for this difference in the sped of sound. The factor will allow an accurate IOL power calculation, when used with the SRK / T formula, in patients undergoing a combined phacoemulsification and silicon oil removal.

Phacoemulsification surgery

Phacoemulsification surgery is gaining popularity world-wide. One of the main advantages of phacoemulsification surgery is that it allows surgery through a small incision. Recovery and visual rehabilitation is often quicker in small incision surgery. Routine ocular examination on the **first postoperative day** does not seem to be necessary after uncomplicated phacoemulsification surgery. Current data indicates that 80% of patients, in the UK, achieve visual acuity of 6/12 or better after phacoemulsification surgery. Patients with macular degeneration also benefit from cataract surgery, regardless of the technique of cataract extraction. **Second eye** cataract extraction is often associated with better visual acuity, contrast sensitivity, stereo-acuity, and also better binocular visual field. Second eye cataract surgery improve the visual outcome more than single eye surgery. Patients who opt for second eye surgery are often relatively younger and have poor visual acuity in the second eye.

Phacoemulsification surgery has many advantages over ECCE surgery. It gives much better control of the anterior chamber depth throughout cataract operation, as well as the benefits of the small wound postoperatively. Phacoemulsification technique is thought to be more beneficial in reducing **postoperative astigmatism** and achieving a better visual outcome in the early postoperative period than ECCE. However, no difference in the outcome or in the rate of postoperative complications is found between ECCE and phacoemulsification surgery four months after cataract surgery.

The **incision** can be fashioned either by scleral tunnel or by clear corneal approach. Temporal clear corneal incision is particularly useful in eyes with against the rule astigmatism. In the immediate postoperative period, clear corneal incision is associated with less disruption of blood-aqueous barriers than scleral tunnel incisions. **Corneal wound burns** are serious complication that may result in wound leak and high postoperative astigmatism. Ultrasound energy is created by the forward and backward vibration of the hand piece needle. There are two sources of heat generation: heat transmitted from the machine to the needle tip, and heat produced from friction between the needle and the sleeve. Corneal wound burns occur mainly when the wound compresses down on the phacoemulsification tip sleeve creating contact with the needle. Risk factors of wound burn:

1. Hard nucleus
2. Tight incision
3. Irrigating tube occlusion
4. High power phacoemulsification for a long time
5. it may also occurs in the absence of all these factors.
6. Blockage of the incision by viscoelastics in the anterior chamber.

Phacoemulsification tips with dual sleeves seem to be very effective in protecting the corneal wound from the needle tip heat. The position of the phacoemulsification tip, in relation to the incision, seems to be important.

Determination of **lens hardness** is important in evaluating patients for phacoemulsification surgery. Previous studies demonstrated a relationship between the lens hardness and the degree of nuclear sclerosis as measured by lens colouration. Age of the patients was also significantly related to hardness.

There are several techniques for phacoemulsification depending on the degree of hardness of the cataract. these techniques include:

Divide and conquer
Chip and flip
Crack and flip
Phaco-chop

Phacoemulsification is often carried out in the capsular bag. In previous techniques the emulsification of the lens was carried out in the anterior chamber, this was associated with higher rates of corneal de-compensation. Recently a **supra-capsular technique** has been described, in which the emulsification of the lens is done at the iris plane. It is thought that this technique is more suitable to soft lenses.

Phacoemulsification surgery can safely be carried out in **white mature cataract**. The procedure is thought to be more difficult in cases with intumescent cataract with cortical liquefaction and high ultrasound internal acoustic reflections, due to high rate of capsulorhexis failure. Capsulorhexis is not often successful in these eyes due to a sudden leak of milky cortex and poor visibility as well as irregular opening of the capsulorhexis and tendency to extend outward. Cases with fibrosed anterior capsule and low ultrasound internal acoustic reflection are also thought to carry higher risks for failure of capsulorhexis. It may be advisable to avoid the phacoemulsification technique in white cataract if the endothelium is not very healthy.

instrumentation

Phacoemulsification of the lens is produced by the movements of the ultrasound instrument tip. Most machines use piezo electric crystals. Increasing the power increases the ultrasound frequency as well as the distance travelled by the tip. The emulsification power of the machine is due to a combination of mechanical, ultrasound acoustic wave shock, and cavitation effect.

Phacoemulsification pumps are either of the **peristaltic** (most common), **venturi**, or **concenterix** type. In the venturi and the concenterix types

occlusion of the tip is needed to build up vacuum. In the peristaltic type, on the other hand, vacuum may be build without occluding the tip.

Laser phacoemulsification machine have been emerging on the market. (**YAG laser Photolysis**). Erbium: YAG laser machine have been developed. YAG laser has recently been used for the removal of cataract in animal and human studies. The laser energy can be transmitted to a titanium target within the probe tip. The laser pulsating energy impact the target leading to the formation of a shock wave and disruption of the cataract. Recent multicentre prospective study in human eyes showed that this method is safe and effective. It also offers the advantage of lower intraocular energy and heat release as well as using a 1.5 mm corneal incision. The phacoemulsification effect of the Erbium: YAG laser seems to occur only at the tip of the hand piece which enable emulsification of the lens in a very small area within the bag. Erbium laser phacoemulsification may be effective for mild to moderate nuclear sclerosis, but not for severer nuclear sclerosis lenses.

capsulorhexis

Capsulorhexis is an important part in modern phacoemulsification surgery. The procedure has many **advantages** e.g. less traction on the zonule, more secure border preventing radial tears extending to the posterior capsule, safer hydrodissection and also better placement of the IOL. The **disadvantages** of capsulorhexis include the capsule block syndrome, disruption of blood-aqueous barriers, and phymosis of the capsular opening. A new complication (The Liquefied After Cataract) has recently been described. The after cataract, in this condition is characterised by the presence of milky white substance between the lens optic and the posterior capsule when the anterior capsule opening becomes occluded by the lens optic.

For the creation of a safe capsulorhexis, it is important to maintain a **deep anterior chamber** throughout the procedure. The **size** of the capsular opening is also crucial. Large capsulorhexis enables outside the bag, posterior chamber phacoemulsification technique. A contact between the capsulorhexis ring and the posterior capsule, beyond the lens optic, is also thought to form a barrier against the migration of lens epithelial cells and may reduce the incidence of posterior capsule opacification. It has recently been demonstrated that large capsulorhexis (one that lie completely off the lens optic) are associated with significantly more wrinkling of the posterior capsule and worse posterior capsular opacification, and visual acuity than small capsulorhexis (one that lie completely on the intraocular lens optic).

When performing capsulorhexis, It is important to stay within the central 6.86 mm of the anterior capsule as this area is often **zonule-free zone** (the position of the zonule fibre insertion in the crystalline lens seems to be influenced by many factors e.g. age).

Capsulorhexis is often difficult to perform in eyes with **mature white cataract** because of the absence of a good red reflex. A new effective and safe method of performing capsulorhexis in eyes with white cataract has been described. A few drops of **indocyanine green or vision blue dye** can be instilled in the anterior chamber to stain the anterior chamber to improve visualisation of the anterior capsule edge. The use of **air bubble** in the anterior chamber is also thought to improve visibility in these cases. Capsulorhexis can also be carried out by the Kloti diathermy instrument. Diathermy capsulorhexis has the advantage of that it does not rely on the presence of red reflex, can be done in children when the capsule is too tough to tear manually. The mean capsulorhexis elasticity is however significantly greater with the manual technique than with the diathermy technique due to the difference in the morphology of the cut edge of the capsulorhexis. The diathermy capsulorhexis also has a more unpredictable behaviour if it tears under stress which make it less suitable for extra-capsular cataract extraction operations.

Some surgeons advocate performing a **posterior capsulorhexis** in cataract surgery routinely. The theoretical advantage of this technique is that it removes the support for lens epithelial cell migration and proliferation, in the central visual axis, and reduce posterior capsule opacification. The incidence of retinal detachment also appears to be less with primary posterior capsulorhexis than with postoperative YAG laser capsulotomy. Loss of control of the posterior capsulorhexis has a low incidence but can lead to serious problems during surgery.

hydrodissection

Hydrodissection enhances the general safety and efficiency of cortical cleanup, especially at 12 o'clock. Thorough **cortical cleanup** and to the cortical cleaving hydrodissection step are important for significant reduction in incidence or the elimination of posterior capsule opacification. The barrier effect of the IOL optic also appears to be of critical importance in retarding in-growth of cells, functioning as a second line of defence when cortical cleanup is incomplete.

The complications of hydrodissection is not well documented. During vigorous hydrodissection posterior **capsule rupture** may occur and may be associated with a sudden marked pupillary constriction (The pupil snap sign). This complication may be related to strong equatorial cortical adhesions in the lens which causes a build up of fluid and pressure until such time when the adhesion break or the posterior capsule breaks. It has rarely been reported that the **lens nucleus may be dislocated** during the hydrodissection procedure. This complications appears to be related to eyes with longer axial length or eyes with pseudo-exfoliation syndrome mainly in elderly patients. It is thought that this complications may be due to weakness in the posterior capsule. Hydrodissection should be carried out with care in these situations.

The use of **Mitomycin C** in the solution used for hydrodissection, may be effective in preventing posterior capsule opacification in rabbits eyes. Heparin does not seem to have this effect

intraoperative vitreous loss and loss of nuclear fragments

It is estimated that the incidence of posterior capsule rupture during phacoemulsification surgery ranges from 0.4% to 3.9%. Posterior dislocation of nuclear fragments is a serious complication in cataract surgery. All eyes with posteriorly dislocated nuclear fragment or cortical material will have raised intraocular pressure; 63% will have corneal oedema; 67% will have marked uveitis and 26% will have retinal tear or detachment. The main reason for poor visual outcome in these cases is retinal detachment.

If the **nucleus is dropped in the vitreous** during the operation, surgeons should be discouraged from attempting to retrieve it from the vitreous. The surgeon should, on the other hand, clear the vitreous from the wound, implant PC or AC IOL (or leave the eye aphakic), close the wound and then refer the patient to a vitreoretinal surgeon for pars plana vitrectomy (or conservative treatment if the nucleus fragment is small enough). Aggressive attempts at intravitreal lens fragment retrieval from a cataract section should be avoided because this may result in serious retinal complications, such as giant retinal tear.

Vitrectomy and removal of the nuclear fragments can achieve good visual results in about 61% of patients. The timing of vitrectomy is, however still controversial with most ophthalmologists advising early intervention, while other reports showed that a better outcome is not statistically significant with early intervention. The rationale from waiting include the possible development of spontaneous posterior vitreous detachment, and softening of the nuclear fragment.

Some studies showed that early removal of retained lens fragments (within one week) is associated with significantly less inflammation and less IOP elevation, while other studies showed no statistically significant differences between early (less than 7 days) and delayed (8 days or more) vitrectomy when increased IOP, corneal oedema, choroidal effusions, cystoid macular oedema and visual acuity are considered. Perfluorocarbon liquid may be used as an aid during pars plana vitrectomy to remove dislocated lens fragments from the vitreous cavity. Perfluorocarbon liquid allows easier and safer removal of dislocated lens fragments, it also provide protection to the macula during the procedure.

Postoperative Complications

- **endophthalmitis**

Endophthalmitis may have drastic effects on the visual prognosis. Postoperative **streptococcal** pneumonia endophthalmitis may also be complicated with meningitis. Awareness of this complication and aggressive treatment is needed to reduce mortality. The incidence of endophthalmitis seems to depend on the type of surgery. Endophthalmitis is estimated to occur in 0.07% to 0.12% after phacoemulsification or ECCE, and in about 0.3% after secondary IOL implantation. 93% of bacterial endophthalmitis are due to gram positive, and 7% are due to gram negative organisms.

The endophthalmitis-vitrectomy study demonstrated that **gram positive, coagulase negative** micrococci are the main causative organisms in post-cataract extraction endophthalmitis. The visual prognosis seems to be strongly associated with the type of infecting organism. Gram positive coagulase negative cocci is associated with the best prognosis while streptococci and enterococci seem to be associated with the worst prognosis. Presenting visual acuity is, however, a more powerful predictor of visual outcome than the microbiological factors.

Microbiological investigation may fail in demonstrating infecting organisms in cases of suspected endophthalmitis. The **polymerase chain reaction** may be useful in the diagnosis of endophthalmitis when applied to the aqueous and vitreous. PCR technique seems to have a higher rate of positive identification of the causative organism than microscopy or diagnostic culture.

It is widely believed that endophthalmitis is often due to entry of micro-organisms, that are present on the ocular surface, into the eye during surgery. The application of **povidone–iodine** on the conjunctival surface appears to significantly reduced the relative risk of postoperative endophthalmitis. IOLs may also attract micro-organisms from the ocular surface. IOLs are normally electrically charged, they are therefore able of attracting any particulate matter form the air or from the external surface of the eye. **Washing** the IOL before its implantation is likely to reduce its surface charge and contamination. Washing the IOL leads to the removal, or neutralisation of the electrical charge on the IOL surface.

It has been thought that phacoemulsification surgery may be associated with less risk of postoperative endophthalmitis due to the small incision and also the high IOP during surgery. Some reports show that phacoemulsification surgery is associated with less anterior chamber contamination than with ECCE but the difference does not appear to be significant. It is also believed that superior incisions may invite infection more readily than temporal incisions due to the rubbing action of the eye lids especially in sutureless incisions. Patients with retained lens

fragments after cataract operations may develop severe endophthalmitis without evidence of infection. Concomitant infection may also be present in some of these patients.

The classic presentation of postoperative endophthalmitis includes reduced vision, conjunctival hyperaemia, pain, hypopyon, and lid swelling within days after cataract surgery. Physicians should be aware that pain and hypopyon may not always present. There is commonly an asymptomatic **latent period** after cataract surgery before patients develop postoperative endophthalmitis. This period is often about 7 days, however certain percentage of patients develop endophthalmitis one month after the operation. 10% of these patients do not suffer with pain. Ophthalmologists should be aware of the concept of delayed onset chronic and often painless endophthalmitis in which the coagulase negative Staphylococci also plays a prominent role, delayed onset endophthalmitis may also be caused by indolent organisms e.g. Propionibacterium acne, Candida and other organisms.

Chronic endophthalmitis often present by recurrent low grade uveitis with partial response to topical antibiotics. **Chronic** pseudophakic endophthalmitis is likely to be caused by pathogens of low virulence e.g. Propionobacterium acne, staphylococci epidermidis, and candida organisms. Fungal infection is typically associated with chronic indolent inflammation associated with relatively mild symptoms and vitreous snowballs opacities. Single dose administration of intra-vitreous amphotericin B is inadequate in the treatment of some fungal endophthalmitis. Vitrectomy with repeated intraocular injection of anti-fungal drugs may be necessary to eradicate the infection.

Propionibacterium infection is also associated with low grade chronic, delayed and recurrent infection. Propionibacterium acne is an anaerobic, gram positive bacillus with very low growth characteristics on culture media. Postoperative Propionibacterium endophthalmitis is characterised by:

- The presence of white intracapsular plaque (which is a sequestrated organism inside the capsular bag).
- Low grade iritis .
- High rate of recurrence after topical steroids treatment.

In some studies half of all patients with Propionibacterium acne endophthalmitis have been successfully treated initially with non-surgical or limited surgical intervention. Definite treatment of Propionibacterium infection is often achieved with pars plana vitrectomy, total or partial capsulotomy with removal of the capsular bag, and intraocular antibiotics injection (vancomycin). IOL removal or exchange may be needed in resistant or recurrent cases.

anti-microbial treatment

Gram positive organisms are often sensitive to vancomycin while gram negative ones are sensitive to gentamicin, amikacin or ceftazidime. Macular retinal toxicity has been reported after the injection of 0.4 mg of **intraocular gentamicin**. A toxic effect from the drugs can occur even with smaller doses. Gravitational effects and positioning seem to contribute to the location of gentamicin induced retinal toxicity in vitrectomised eyes. It would be advisable to position patients in such a way to make their maculae not dependent in the immediate period following intraocular gentamicin injection. The interval between repeated intravitreal injection should be considered to avoid this complication.

Vancomycin and **aminoglycosides** (including amikacin) are the drugs of choice in gram positive and gram negative infection respectively. **Amikacin and ceftazidime** are thought to be better in gram negative infections than gentamicin. However, some reports described retinal toxicity with amikacin. Many surgeons, therefore, prefer to use ceftazidime instead of amikacin for gram negative infection. It must be remembered, however, that due to the pharmacological properties of both drugs that **vancomycin and ceftazidime are incompatible** and should not be mixed together or given at the same time in the same eye. Mixing the two drugs often results in the formation of micro-precipitates in the vitreous. These micro-precipitates often disappear within a period of two months.

Studies have shown that Amikacin, when combined with a **beta-lactam**, acts synergistically against many clinically important micro organisms. In inflamed aphakic eyes and aphakic vitrectomised eyes; the vitreous drug level is equal to or below the minimal drug inhibitory concentration for most organisms considered sensitive to the Amikacin after 24 hours of administration. Supplementation of the intravitreal antibiotic is therefore required in clinical practice.

The effect of adding **antibiotics in the infusion fluid**, on preventing postoperative endophthalmitis, in cataract surgery is controversial. Some studies demonstrated a very low incidence of postoperative endophthalmitis when either gentamycin or vancomycin was added to the irrigating solution, and no incidence of endophthalmitis when both added to the solution. Most studies showed, however, that the addition of antibiotics (e.g. vancomycin or gentamicin) to the infusion fluid during cataract surgery does not seem to have significant effects on the organism commonly responsible for postoperative endophthalmitis. It seems that longer periods of exposure of these organisms to the antibiotics is needed for the antibiotics to have a significant effect. A higher incidence of postoperative **cystoid macular oedema** and lower final visual acuity may, however, be associated with intracameral vancomycin. Care and restrain should be taken in using vancomycin as a prophylactic antibiotics in the infusion fluid in order to avoid developing resistant strains.

Oral ciprofloxacin may have a role in the treatment and prevention of postoperative endophthalmitis. Some reports demonstrated good intraocular level of ciprofloxacin after oral and IV administration. Ciprofloxacin levels in the aqueous humour seems to be the same after oral or topical application. The vitreous level of the drug is, on the other hand, significantly higher after oral administration. Vitreous level of Ciprofloxacin (750 mg orally 17.5 and 5.5 hours before the operation) exceeds the minimal inhibitory concentration of Staphylococcus epidermidis, Propionibacterium, Pseudomonas aeruginosa, Proteus organisms, and Haemophilus influenza as well as Staphylococcus aureus and Bacillus.

Ofloxacin has also been reported to have a high bio-availability and high tissue penetration to the aqueous, vitreous and subretinal fluid. Ofloxacin levels in the aqueous humour reaches four time higher levels than ciprofloxacin levels after topical application. Its bio-availability to the subretinal fluid appears to be increased after combined oral and topical administration compared with topical administration alone.

Levofloxacin is a new fluoroquinolone. The drug can be administered orally and also intravenously. It is reported to be more potent and to have a lower inhibitory concentration to most of the ocular pathogens, in the aqueous and in the vitreous, than ofloxacin. Trovafloxacin is another new antibiotic that may have a potential role, when given orally, in the treatment of endophthalmitis. The drug has a great activity against gram positive cocci, and also gram negative organisms.

The role of oral or intravitreal **steroids** in the treatment is controversial. In a recent study, oral and intravitreal dexamethasone was reported to produce less inflammation in postoperative and post-traumatic endophthalmitis. Reduction of inflammation might help reducing the elimination of intravitreal antibiotics and might, therefore, enhance its effect. A recent report, however, showed that visual results in eyes that have intravitreal steroid injection are worse than eyes that does not have steroids.

The endophthalmitis-vitrectomy study showed that there is no difference in the final visual acuity or in media clarity with or without the use of **systemic antibiotics** (ceftazidime + amikacin). A recent study showed that vitreous vancomycin concentrations after intravenous administration does not reach therapeutic levels. Therapeutic level are, on the other hand, achieved after intravitreal administration. The endophthalmitis-vitrectomy study also showed that, in patients with initial visual acuity of HM or better, there is no difference in the final outcome whether or not immediate vitrectomy is performed. However, vitrectomy is associated with a better visual prognosis, in patients with initial visual acuity of PL, than vitreous tap only.

This is a recommended regime for treatment of post-cataract endophthalmitis:

1. Aqueous and vitreous **tap** if the visual acuity is better than hand movements or by aqueous tap and **vitrectomy** if the vision is less than hand movements. Vitrectomy may be carried out if vitreous tap was not enough and repeat intravitreal injection may also be carried out.
2. **Intravitreal antibiotics** *(vancomycin 1.0 mg + ceftazidime 2.25 mg or amikacin 0.4 mg).* A single intravitreal antibiotic injection may not be sufficient to cure some cases of bacterial endophthalmitis. Resistant organism may include Staphylococcal, Streptococcal, Propionobacterium and fungal species. A second injection of amikacin may produce more retinal toxicity than a second injection of vancomycin. **Teicoplanin** is a new antibiotic that has the same spectrum of activity to vancomycin. Animal studies showed that the drug can penetrate ocular tissues after IV, and topical administration. The drug does not seem to penetrate readily into the vitreous in human eyes when applied systemically, and not detected in the vitreous at all when given topically. Vancomycin (50 mg/ml) may also be applied **locally** to the eye either in the conjunctival sac or into the medial canthus with closed lids with good therapeutic concentrations in the aqueous.
3. Topical hourly **Ofloxacin**
4. **Systemic Ofloxacin** (200 mg twice a day and imipenem 500 mg three times a day).
5. The antibiotics may be adjusted according to the culture and sensitivity results.
6. The use of preoperative **Povidone iodine** has also been proved to reduced the incidence of endophthalmitis. The value of sub-conjunctival antibiotics injection at the end of surgery is controversial.

- **posterior capsule opacification**

The most common complication after cataract surgery is opacification of the posterior capsule. Posterior capsule opacification is the second most common cause of reversible visual loss in the world. Visually significant posterior capsule opacification develops in more than 25% of patients undergoing standard extracapsular cataract extraction or phacoemulsification with posterior chamber intraocular lens implantation over the first 5 years after surgery. It has been thought, therefore, that implantation of anterior chamber IOLs after intracapsular cataract extraction may be a valid alternative option in poor developing countries where resources are not readily available.

The opacification of the posterior capsule can be quantified by using the technique of densitometry with the Scheimpflug photography system. Densitometry measures appears to be correlated with patients symptoms and visual acuity.

The design and the material of the IOL have an important effect on the degree of opacification. IOLs made of polyacrylic material are associated with less posterior capsule opacification than PMMA, and silicon IOL. The cause of reduced posterior capsule opacification with the polyacrylic IOLs is not known but it thought that it might be due to stronger adhesions between the IOL and the posterior capsule. **Heparin** surface-modified IOLs does not seem to provide any significant advantages regarding the amount of cellular deposits in patients with previous uveitis or diabetes. The use of **Mitomycin C** in the solution used for hydrodissection, has also been shown to be effective in preventing posterior capsule opacification in rabbits eyes.

It has also been shown, in animal experiments that, **transforming growth factor-beta** plays an important factor in the genesis of posterior capsule opacification. Regulation of Transforming growth factor-beta may be useful in inhibiting the opacification. In patients with postoperative fibrinous uveitis the fibrinous reaction may lead to posterior synechiae formation, and posterior capsule opacification. The use of **intracameral plasminogen activator** may be associated with less posterior capsule opacification. This technique does not seem to be associated with significant ocular side effects.

Tranilast is an anti-allergic drug that also has an effect on wound healing and granulation tissue formation. Tranilast eye drops also appears to be effective in preventing fibrous posterior capsule opacification in the early postoperative stage. The possible mechanism of this drug's action may be prevention of collagen synthesis by minimising transforming growth factor type â released during lens epithelial cell metaplasia.

- **anterior capsule opacification and phymosis of the capsular opening**

Anterior capsule opacification and fibrosis often occurs much earlier than posterior capsule opacification. The rate of anterior capsule opacification depends on the IOL material and design being relatively higher with plate-haptic silicon IOL than with three piece acrylic optic-PMMA haptic IOL. Contraction of the capsule opening (**phymosis**), and IOL tilt is a known complications of capsulorhexis in some conditions associated with zonule weakness e.g.:

Diabetes.
Old age.
Retinitis pigmentosa.
Pseudoexfoliation syndrome.

The maximum rate of capsule contraction seems to occur in the first 6 weeks after surgery. **Silicon** IOLs seem to be associated with more phymosis of the capsulotomy than PMMA IOL. Phymosis may be complete leading to a complete occlusion of the capsular opening. It may

also be complicated with traction ciliary detachment, choroidal effusion and ocular **hypotony**. Capsule contraction may be caused by excessive shrinkage of the capsule by actin filaments in the residual epithelial cells, as well as proliferation of the lens epithelial cells. Weakness of lens zonule may also play a part in its development. Implantation of a **capsular tension ring** might help in preventing this complication in high risk patients. Clinically significant phymosis may be divided by YAG laser treatment. Caution should be taken as delayed dislocation of silicon implants may occur after this treatment.

- **capsular bag distension syndrome**

Capsular bag distension syndrome is a newly described complication of capsulorhexis that may present with:

Shallowing of the anterior chamber.
Anterior displacement of the IOL.
Unexpected postoperative high myopia.

In this syndrome, the capsule opening is occluded by the IOL optic, distension of the capsular bag then occurs due to the high osmotic pressure of its contents (e.g. viscoelastics, soft lens matter or epithelial cells). Capsular bag distension syndrome often occur 1 to 2 days after surgery. It has also been reported about 5 years after uncomplicated cataract surgery. The syndrome has often been reported with PC IOL implantation in the capsular bag. Rarely it may also occur with IOL implantation in the ciliary sulcus.

YAG laser peripheral anterior capsulotomy has been successfully performed in cases of slowly resolving myopia. Surgical removal of the **viscoelastics** from behind the IOL may be needed if the condition persists and if laser treatment is not possible. Care should be taken in making the capsulorhexis opening adequate and in ensuring that the viscoelastic is removed from behind the implant at the end of surgery. Entrapment of the viscoelastic material may also result in unexpected myopic shift, without increase in the IOP, due to the forward displacement of the IOL. Removal of the viscoelastic material at the end of surgery is, there, very important.

- **retinal detachment**

The risk of developing postoperative retinal detachment 2 years after cataract surgery is 0.18%. About 75% of post-cataract surgery retinal detachments occur within the first year. Some studies shows no difference in the incidence rate of retinal detachment between phacoemulsification and ECCE.

YAG laser capsulotomy seems to be associated with a significantly raised risk of retinal detachment. The relative **risk** of developing retinal

detachment after YAG laser capsulotomy is 4.9, this risk is changed by a factor of 1.3 with an increase of axial length of 1 millimetre and by a factor of 0.94 for each added year of the patients age. The time between cataract surgery and YAG laser capsulotomy does not seem to affect the risk of retinal detachment development.

Atrophic retinal **holes** may play a role in the pathogenesis of post-YAG laser retinal detachment. Identification and prophylactic treatment may reduce the incidence of retinal detachment after YAG laser capsulotomy. Pseudophakic retinal detachment may be treated with conventional scleral buckling surgery, pneumatic retinopexy or by pars plana vitrectomy without scleral buckling. Primary pars plana vitrectomy with fluid–gas exchange and laser appears to be safe, and effective in repairing primary pseudophakic retinal detachments.

- **retinal phototoxicity**

The incidence rate of induced retinal injury by the use of the surgical microscope varies considerably among ophthalmologists. Retinal lesions caused by the operating microscope are often found in the lower part of the macula, they typically have a horizontal oval shape or a round shape. Prevention of retinal lesion during surgery may be achieved by reducing the light power, using filters, avoiding foveal exposure by tilting the microscope towards the surgeon, and also by using an air bubble if possible to defocus the light. Decreasing the temperature of the irrigation fluids, and decreasing the oxygen tension of inspired air may also reduce the risk of light injury. Surgeons should also be aware of the agents that cause **photo-sensitisation** (phenothiazine, allopurinol, haematoporphyrin, and hydroxychloroquine.

- **cystoid macular oedema (CMO)**

Macular oedema is a major complication after cataract surgery. The disease may occur as a result of vitreo-macular traction or due to liberation of prostaglandins from the anterior segment. The incidence of CMO after routine phacoemulsification is **19%.** A recent study showed that patients with CMO at day 60, after surgery, had significantly worse visual acuity, than those who did not. The study also showed that more postoperative inflammation may be associated with more CMO at day 60.

Treatment is often possible with topical, peribulbar, sub-conjunctival injection, orbital floor injections or systemic steroids, with or without carbonic anhydrase inhibitors. It must be remembered that **Peribulbar steroids** injection may result in serum steroids levels comparable to those achieved by a high oral dose. After a peribulbar injection of 5 mg of dexamethasone, an average intravitreal dexamethasone concentration is reached with a 75 times greater anti-inflammatory potency than physiological levels. Dexamethasone concentration in the serum is also several times higher than physiological levels. Sub-conjunctival injection

of 1 mg of dexamethasone results in a higher vitreous concentration than after peribulbar injection of 5 mg or after oral administration of 7.5 mg of dexamethasone. Systemic absorption after sub-conjunctival injection may also be high.

A new method of an **intraocular biodegradable** polymer dexamethasone drug delivery system has been described in the treatment of postoperative inflammation after uncomplicated cataract surgery. The system appears to be safe and effective in suppressing postoperative inflammation with no additional topical anti-inflammatory drops needed for most patients.

A meta-analysis of previous published reports about medical prophylaxis for cystoid macular oedema indicated that **medical prophylaxis** with cyclo-oxygenase inhibitors and steroids are effective in aphakic and pseudophakic angiographic and clinical cystoid macular oedema. Treatment with topical non-steroidal anti-inflammatory drugs (e.g. ketorolac) may also be effective in chronic cases identified more than 24 months after cataract surgery. The treatment may be needed for a long time. It has also been suggested that treatment with no-steroidal medications may only ask the CMO, and that the oedema may recur after cessation of the treatment. The commonly used anti-inflammatory ophthalmic drops currently available are:

- Flurbiprofen (Ocufen)
- Diclofenac (Voltarol)
- Ketorolac (Acular)

Some cases are, however, resistant to these traditional methods of treatment. **Macular grid laser photocoagulation** (yellow dye, and medium intensity burns) may be beneficial in the treatment of macular oedema caused by Irvine-Gas syndrome or uveitis. The treatment may be associated with angiographic as well as clinical improvement. **Pars plana vitrectomy** may also be needed in resistant cases of CMO. The technique may improve visual acuity, in patients with chronic CMO, that is not responding to medical treatment especially when there is vitreous adhesions to the anterior segment structures. Improvement in the macular oedema and visual acuity may also occur even in eyes with no apparent vitreous abnormalities.

- **other complications**

Retained **nuclear fragments** in the anterior chamber may cause postoperative iritis, raised IOP and mechanical damage to the corneal endothelium, and corneal oedema. Gonioscopic examination may be needed to exclude the presence of such fragments in resistant iritis and corneal oedema. Surgical removal of the nuclear fragment may be needed. Iris bubbles in the anterior chamber is a common occurrence during phacoemulsification surgery. **Air bubbles** in the intraocular fluids

with a high surface tension may cause a ring shaped damage to the corneal endothelium. Severe damage to the corneal endothelium may occur after a contact with the air bubbles for as little as 20 seconds. The mechanism that cause this damage seems to be due to surface tension of the bubbles.

Operative **suprachoroidal haemorrhage** may be associated with devastating visual results. Longer axial length, old age, and higher preoperative IOP are associated with increased risk of acute operative suprachoroidal haemorrhage. Poor visual results often occur in the following conditions:

- Retinal detachment,
- Four quadrant haemorrhage,
- Eyes with spontaneous nuclear expression,
- ECCE “rather than phacoemulsification surgery”,
- Visual acuity of perception of light or worse on the first postoperative day.

Cataract surgery in the future

It is thought that cataract surgery in the future will be carried out by removing the lens via a small capsular opening and then filling the capsular bag by injecting a polymer that solidifies and offers some degree of accommodation range. Re-filling of the lens capsule after endocapsular phacoemulsification through a mini capsular opening and sealing the opening with a silicone plug has been shown to provide a small degree of accommodation in monkey's eye [1]. An inflatable endocapsular balloon has also been used to fill the lens capsular bag in animals eyes. A mixture of two silicon oils polymers which can polymerise in about two hours is then injected in the balloon to refill the capsular bag.

Glaucoma

Basic science

Glaucoma is the second leading cause of visual loss in the world. It is estimated that there is about 66.8 million people with primary glaucoma in the world, 6.7 million of them are suffering from bilateral blindness.

The pathogenesis and aetiology of primary open angle glaucoma is unknown. Raised **IOP** is the main risk factor in the development of glaucoma. A recent study showed that some cells exhibit morphological and cytoskeletal changes as well as alteration in their intracellular adenylyl cyclase activity when exposed to increased levels of hydrostatic pressure. **Myopic** individuals have a twofold to threefold increased risk of developing glaucoma compared with that of non-myopic subjects.

Sleep apnoea syndrome is a disease characterised by recurrent complete or partial upper airway obstructions during sleep. These obstructive respiratory disturbances may last from 10 seconds up to 2 minutes, leading to severe hypoxia and hypercapnia. Other ophthalmologic findings in patients with Sleep apnoea syndrome include:

1. *Floppy eyelid syndrome.*
2. *Keratoconus.*
3. *Optic disc oedema.*
4. *Recently, Hayreh described patients with anterior ischaemic optic neuropathy with a high prevalence of Sleep apnoea syndrome.*
5. *Sleep apnea syndrome has also, recently, been described as a risk factor for open angle glaucoma (7.2% of patients with the syndrome are reported to have glaucoma). The syndrome is characterised by episodes of upper airway obstruction during sleep, causing hypoxia with risks of cardiovascular and neurological disorders.*

Hereditary factors also play an important role in the pathogenesis of glaucoma, and a positive family history is a major risk of developing the disease. Glaucoma may be inherited as autosomal dominant, recessive, or X-linked disorder. The disease has been mapped to the **chromosomes 2** cen-2q 13 region, 3q 21-q 24 region, 8q 23 region, and also to the 10p15-p14 region. Juvenile open angle glaucoma, on the other hand, has been located to chromosome 1q 21-q 31. The **Gln368stop mutation** has recently been found in several cases of late-onset primary open-angle glaucoma. The penetrance of glaucoma increases with age in Gln368stop carriers. The myocilin Gln368stop mutation shows a good genotype-phenotype

correlation and should be investigated in all familiar cases of chronic primary open angle glaucoma . This may be important for early diagnosis and periodical check-ups of pre-symptomatic individuals belonging to these families.

Abnormal blood perfusion of the optic nerve head appears to play an important part in the pathogenesis of glaucomatous optic neuropathy. **Vasospasm** and cardiovascular disease have been identified as risk factors for some patients with glaucoma irrespective of the level of IOP. Vasospasm appears to be more prevalent in patients with focal ischaemic discs, while patients with senile sclerotic discs have a higher prevalence of cardiovascular diseases. There is also a positive correlation between **systemic blood pressure** and IOP. Lower diastolic perfusion pressure appears to be associated with a marked increase in the frequency of hypertensive glaucoma.

There are conflicting reports about the state of **ocular blood flow** in patients with glaucoma or ocular hypertension. Some studies found no significant difference between normal eyes and eyes with ocular hypertensive, while other studies demonstrated impaired circulation and ocular blood flow in eyes with ocular hypertension and glaucoma. It is not known whether these changes in the blood flow are a cause or a consequence to the raised IOP, the vascular insufficiency may be primary or secondary to raised IOP.

Abnormalities in the enzymatic activities in the **red blood cells** walls are common in patients with primary open angle glaucoma compared with normal subjects. These enzymatic abnormalities may interfere with blood flow and oxygen transport in retinal and disc micro-circulation. It is not known if these abnormalities play any significant role in the optic nerve head blood perfusion.

There is also some evidence that some patients with normal tension glaucoma may have an **autoimmune** component to the disease that is not related to the level of IOP. HLA-DR3, HLA-B8, HLA-DRB and HLA-DQB and HLA-DQA1 have all been associated with glaucoma in different populations. A subgroup of normal tension glaucoma patients have a high level of serum immune reactivity to bacterial heat shock protein 60. Immune responses to heat shock protein are implicated in the development of human autoimmune diseases. A recent study showed an increased immuno-staining of **heat shock proteins** in the retina and optic head of normal and glaucomatous eyes suggesting that immune-regulation plays an important part in the pathogenesis of glaucomatous optic neuropathy. High levels of serum immune-reactivity may also be associated with **anti-Sjogren's Syndrome** A and B antigen which are non-organ specific auto-antibodies. Some glaucoma patients also have increased levels of **auto-antibodies to glycosaminoglycans** of the optic nerve head. These auto-antibodies play important part in immune mediated diseases. They may increase the

susceptibility of the optic nerve head to damage by changing the functional structure of the lamina cribrosa.

A recent study described some patients with normal tension glaucoma who have increased serum immuno-reactivity to retinal protein. In some of these patients the immuno-reactivity regress and visual field improves after a course of **methotrexate** treatment.

Optic nerve damage in glaucoma may be caused by direct traumatic effect of the increased IOP or by IOP rise-mediated optic nerve head ischaemia. **Nitric oxide** (NO) and **endothelin** are cellular mediators that act as hormones or neuro-transmitter. Nitric oxide produces relaxation of the smooth muscle cells, by stimulating the production of cGMP. Endothelin, on the other hand, is a potent vasoconstrictor. Vascular endothelial cells can produce Nitric oxide. Nitric oxide synthase enzyme has also been identified in the lamina cribrosa of normal eyes. Eyes with ocular hypertension and eyes with primary open angle glaucoma seem to have more cells which stain positive for the enzyme. It has recently been shown that higher levels of **hydraulic pressure** enhanced basal production of nitric oxide in human trabecular cells. Nitric oxide may be a physiological mediator in the regulation of intraocular pressure.

It has been shown that Nitric oxide and endothelin are involved in the regulation of IOP and ocular blood flow. Trabecular meshwork has contractile elements that can be relaxed or contracted by Nitric oxide or endothelin respectively. Nitric oxide and endothelin can thus play an important part in controlling the IOP by changing the resistance of the trabecular meshwork.

Nitric oxide is also involved in the control of retinal ganglion cell apoptosis by interacting with glutamate. Experimental studies in animal models showed that reduction of nitric oxide by nitric oxide synthase inhibitors provide significant protection against the effect of anoxia and excitatory amino acids on the animal ganglion cells.

The amino acid glutamate has been found in large quantities in the vitreous body of glaucoma patients. Increased **glutamate** production may be initiated by an increase in the IOP. Glutamate can produce apoptosis and ganglion cell death by activating some enzymes with simultaneous production of Nitric oxide in larger quantities than its physiological levels. This process also results in the production of the free radicals super-oxide which reacts with Nitric oxide resulting in the formation of toxic the agent peroxynitrite that can trigger apoptosis. Pharmacological inhibition of the Nitric oxide system, and blocking the excito-toxic effect of glutamate may protect against cell death and may prove useful in the treatment of glaucoma.

Glaucoma is associated with morphological as well as metabolic and structural changes in the **lamina cribrosa**. The lamina cribrosa is normally consisted of a lattice-like structure composed of connective tissue sheets and channels through which the retinal ganglion cell fibres pass. The lamina's structure consists of various collagen types e.g. elastin, proteoglycan, fibronectin and glycoproteins. The changes associated with glaucoma include compression of the cribriform plates, posterior rotation of the peripheral lamina, and elongation of its pores. An increase in the total **collagen content** of the lamina cribrosa and a decrease in the percentage of type III collagen to type I collagen have also been previously described. The elastin component of the lamina seems to decrease with age. it's mechanical compliance and the resilience also decrease with age. Such metabolic and physical changes may be implicated in the pathogenesis of optic nerve head changes in raised IOP and glaucoma.

Clinical science

IOP Measurement

Goldman contact tonometry is the most common method of measuring the IOP. Variation in corneal thickness is a significant source of variation in IOP measurements between individuals. **Corneal thickness** is significantly reduced in patients with normal pressure glaucoma as compared with patient with primary open angle glaucoma and healthy controls. The reduced corneal thickness may lead to underestimation of IOP readings. Measurement of corneal thickness should be considered when assessing IOP. Goldman tonometry overestimates the IOP in cases with thick cornea, and underestimates the IOP in cases with thinner cornea. Measuring the central corneal thickness may be useful in determining the accuracy and the importance of elevated IOP in glaucoma suspect or the normal IOP in patients diagnosed as low tension glaucoma. A **single measurement** of central corneal thickness is sufficient when assessing patients with suspected glaucoma.

The role of **Tono-pen** in measuring the IOP, in corneas with abnormal thickness, is not known. In some studies the IOP measured by the Tono-Pen was significantly correlated to the central corneal thickness. The instrument seems to overestimate IOP readings in individuals with thicker central corneal. In other studies, it was suggested that the use of Tono-pen tonometer may be more accurate than Goldman tonometer, the instrument appeared to be less affected by changes in the corneal thickness than Goldman tonometry. Pneumotonometry is also thought to be more reliable, than Goldman applanation tonometry, in measuring the IOP after PRK in the peripheral as well the central cornea. The use of Goldman applanation tonometry, in these eyes, in the central cornea may underestimate the IOP.

IOP measurement may vary with **age**. Applanation tonometry markedly underestimates IOP readings in young patients eyes. The pneumotonometer method seems to be the best method for measuring the IOP clinically in all ages. It is thought that applanation tonometry is better reserved for patient of 10 years of age or older. Changes in blood circulation, (e.g. increase in the venous pressure in the Valsalva technique) may affect the IOP. These changes can be observed in measuring the IOP in **very obese patients,** due to the difficulty they encounter in positioning their heads on the slit lamp. Perkins tonometry in these situation may be more accurate than Goldman tonometry.

The sensation of light elicited by a non-photic stimulus is an entoptic phenomena called phosphene. Application of pressure on a closed eyelid gives rise to a phosphene sensation described as a glow, and perceived opposite to where the pressure is applied. The source of pressure phosphene is supposed to be the bipolar cells in the retina. A new

tonometer (**The Pressure Phosphene Tonometer**) has been described. The tonometer is applied with the eye close and the patient is instructed to indicate when the pressure phosphene is perceived, the IOP is then determined by reading the pressure on the dial. The IOP measured by the new instrument seems to be comparable to Goldmann tonometry results and may be used for home IOP self measurement.

The optic nerve head

Instrumentation

In glaucoma patients progressive optic nerve cupping may occur without causing recordable visual field loss. Evaluation of the optic nerve head is, therefore, an important part of glaucoma evaluation. The optic nerve head can be examined by direct and indirect ophthalmoscopy, slit lamp biomicroscopy and also by photography. These methods are, however, subjective and may not be reproducible.

Objective computerised image analysis methods with digital videographic image storage and processing techniques have recently bee used to avoid this problem. It is generally thought that none of these instruments is suitable for routine use in clinical diagnosis of glaucoma. **The main computerise image analysers** used at present are:

- The Rodenstock optic nerve head analyser.
- The Confocal Scanning laser Tomograph (The Heidelberg retina tomograph).
- The scanning laser polarimetry for the nerve fibre layer.
- Optical Coherence tomography.

The **Rodenstock** optic nerve head analyser uses a stereoscopic video camera to produce digitised image of the optic nerve head. The instrument is, however, technically difficult to operate, it also needs pupil dilatation and clear media.

The **Heidelberg** retina tomograph projects a diode laser beam on the retinal via a confocal system. The instrument has a high spatial resolution due to its confocal system. The depth of scanning ranges from 0.5 to 4.0 mm with a 0.5 mm increments. The instrument performs 32 scans within this depth. The computer then forms a three-dimensional image of the disc. The instrument has a better axial resolution than the Rodenstock optic nerve head analyser. The instruments also uses a low light intensity, and images can be obtained through undilated pupil. The main disadvantage of the instrument is that it needs a reference plane.

The **Optical Coherence tomography** operates by the same principle as ultrasound but by using optical, rather than, ultrasound beam. The instrument provides a very high resolution images without contact with the eye. It is not affected by the refractive status of the eye. Media opacities may, however, affect its results. Testing with this instrument also need pupil dilatation. Optical coherence tomography may be able to differentiate between normal, ocular hypertensive and glaucomatous eyes. A considerable overlap may, however, occur between all these three groups.

Measurements taken by the optical coherence tomography seem to correlate with scanning laser polarimetry measurements.

Morphological features

Normal optic nerve heads in the general population may **vary** significantly in the disc and neuro-retinal rim area. Age related changes may affect several parameters in the eye. However, age does not appear to be associated with significant disc characteristics.

Different patterns of disc damage have been described in glaucoma patients. Optic disc damage may be diffuse (in the majority of patients), localised, or undetectable. Patients with different disc appearances show differences in their demographic characteristics, prevalence of certain systemic risk factors, IOP levels and the patterns of their visual field loss. The presence of various disc appearances may represent different patients population with different mechanisms for the glaucoma. The 4 **different patterns** of glaucomatous discs are:

1. Focal ischaemic disc.
2. Myopic glaucomatous disc.
3. Senile sclerotic disc.
4. Generalised enlargement of the optic cup disc.

Disc and retinal imaging can be carried out by different imaging systems (e.g. fundus camera, infra-red scanning laser ophthalmoscope, and the Heidelberg retina tomograph). The size of the disc parameters depends on the **magnification** by the camera and by the eye. The use of a single magnification correction value for all these methods is not accurate, this may have significant implication in the calculation of disc and retinal lesions sizes.

The topography of the optic nerve head seem to be dependant of the level of the **IOP**. Increases in the IOP are associated with significant enlargement of the optic disc cupping in both emmetropic and myopic eyes. Lowering of the IOP, e.g. after trabeculectomy surgery, may be associated with improved optic nerve morphology (as demonstrated with Heidelberg retinal tomograph). The amount of improvement in the morphology of the optic nerve head seems to be correlated to the degree of IOP reduction. Recent studies, however, showed that there are no apparent differences between high tension and low tension glaucoma in the morphometric parameters as measured by scanning laser ophthalmoscopy.

Vertical cup/disc ratio has been used in the evaluation of disc cup in glaucoma patients. There is, however, a wide variation in the cup/disc ratio in normal population. **The cup/disc ratio relative to the disc size** is a new parameter that can be a useful in the evaluation of glaucomatous discs, especially in small discs.

The **neuro-retinal rim** is one of the main features in the diagnosis of glaucomatous optic neuropathy. Analysing the relation between the disc size and the neuro-retinal rim by the Laser scanning ophthalmoscope is a specific and sensitive method to differentiate between normal and glaucomatous discs. The system provides a high degree of reproducibility and can be used in the evaluation of the optic disc in glaucoma patients.

Glaucomatous neuro-retinal rim loss generally begins in the inferior temporal region and progresses to the superior temporal to temporal, inferior nasal, and finally the superior nasal region. Abnormally low inferior / temporal and superior / temporal ratio can be used to detect glaucomatous disc damage in some eyes with raised IOP. These ratios offer a method of neuro-retinal evaluation independent of disc size and magnification problems.

Measurement of the absolute rim area and the rim / disc area, is significantly larger with confocal laser ophthalmoscope than with planimetry or disc photos. This difference may be due to the fact that confocal laser ophthalmoscope measures the retinal vessel as a part of the retinal rim. It should be taken in consideration when comparing data.

Disc **haemorrhage** appears to be strongly associated with glaucoma (especially low tension glaucoma). The presence of disc haemorrhage is associated with localised damage of the nerve fibre layer in both NTG and primary open angle glaucoma and seems to increase the risk of further visual field deterioration. Most disc haemorrhages are present in patients with no other signs of glaucoma. They seems to be associated with larger vertical cupping and also with a history of migraine.

Acquired optic nerve head **pits** are known to be associated with the development of glaucoma, specially low tension glaucoma. They are often associated with an increased risk of developing progressive disc and visual field damage. The field changes associated with disc pits are deep and have a sharp margins scotoma which approaches or even involve fixation. Visual field loss within 1-3 degrees from fixation occurs in about 96.7% of cases. The presence of these pits constitutes a threat to central fixation vision specially if it is located in the inferior pole of the optic disc. 76% of the acquired optic nerve head pits occur in the inferior part while only 11% occur in the upper part.

The value of measuring the **peripapillary atrophy** in the diagnosis of glaucoma is uncertain. 38% of eyes with primary angle closure glaucoma and 68% of eyes with primary open angle glaucoma have peripapillary atrophy. The peripapillary atrophy in primary angle closure glaucoma has a different relationship to the structural and functional optic disc changes than that in primary open angle glaucoma. Different mechanisms seem to be involved in the development of the optic disc damage in the two types of

glaucoma. Beta zone (central peripapillary atrophy), and alpha zones (peripheral peripapillary atrophy) are found in 49% and 100% eyes with primary open angle glaucoma, respectively. It must also be remembered that the prevalence of zone beta seems to be higher in high myopic eyes. Both areas, especially beta zone, are associated with glaucomatous visual field loss when tested by standard automated perimetry and short-wavelength automated perimetry. It is suggested that clinical decision should not be based only on the presence or absence of these zones.

Nerve fibre layer polarimetry

Nerve fibre layer damage in glaucoma may be either diffuse or localised. The Nerve fibre layer can be visualised by direct ophthalmoscopy, slit-lamp biomicroscopy, high-resolution monochromatic photography, or by the more recent technique of scanning laser polarimetry.

The changes in the state of polarisation (**retardation**) of a light beam falling on the nerve fibre layer can be measured and quantified by the confocal laser ophthalmoscopy, a technique called **Scanning Laser Polarimetry**. The scanning laser polarimetry utilises the birefringent properties of the nerve fibre layer, and the principle of polarisation. The instrument measures the degree of retardation of the nerve fibre layer which is positively related to the degree of nerve fibre layer thickness. This method has the advantages of being independent of a reference plane, quick, sensitive, does not need pupil dilatation, and also independent of patient's refractive errors. Other polarising structures in the eye e.g. the cornea and the lens may, however, affect its readings.

The thickness of the retinal nerve fibre layer, as measured by polarimetry, seems to be correlated to its thickness as measured by **histological** methods. A quantitative differences, in retinal nerve fibre layer thickness, between age-matched ocular hypertensive, normal, and glaucomatous eyes has been recently reported. It should also be noted that there is **asymmetry** of the retinal nerve fibre layer thickness with respect to the horizontal midline and the vertical meridian between the two eyes in normal individuals. These findings should be taken in consideration when interpreting the results of polarimetry.

The value of retinal nerve fibre layer retardation seems to be less in **black** than in white subjects. Nerve fibre thickness also appears to decreases with **age** and in **myopic** individuals. The nerve fibre layer thickness, in myopic individuals, also seem to decrease with increasing myopia. **Retardation values** are greater in the superior and inferior quadrants of the peripapillary retinal nerve fibre layer compared with the nasal and temporal quadrants. The variation of retardation around the optic disk appears to be less than expected from the histological variation seen around the peripapillary area.

The effect of **age, optic disc size and neuro-retinal rim area** should be considered when interpreting the results of polarimetry. It should be noticed that the cross section area of retinal nerve fibre layer increases significantly with an increase in the **optic disc size**. In using the Nerve Fibre Analyser, the superior-nasal and inferior-nasal ratios of the retardation values appear to be more useful indices than individual values in discriminating patients with glaucoma. The results of scanning laser polarimetry measurement may also depend on the corneal refractive status. A new base measurement is recommended after Laser in situ keratomileusis **(LASIK) surgery**.

Optic nerve head measurements, as measured by the confocal scanning ophthalmoscope, correlate well with the optic nerve fibre layer measurements, and also with perimetry. The correlation of the two measurements around the disc margin, however, seems to be variable.

Assessment of the nerve fibre layer, by polarimetry can differentiate between patients with glaucomatous optic neuropathy from controls. Glaucoma suspects can also be differentiated from normal individuals by this method. The system might, however, fail in detecting a substantial number of subjects with severe damage, and it is not recommended for glaucoma screening at present. The use of a combination of more than one measurement by the instrument, improves the ability to differentiate between healthy eyes and eyes with early and moderate visual field loss. Retinal nerve fibre layer blood vessels may affect the results and the reproducibility of polarimetry measurements. The use of blood vessels removal algorithm seems to increase the reproducibility of scanning laser polarimetry, and enables an improvement in the ability of polarimeter to differentiate between normal and glaucomatous eyes.

Peripapillary retinal nerve fibre layer volume can be measured by various optic nerve head imaging techniques (e.g. confocal scanning polarimetry, optical coherent tomography and retinal thickness analyser) by using a special soft ware. Nerve fibre layer volume appears to be useful in the differentiation between normal individuals, patients with open angle glaucoma, patients with ocular hypertension or patients with normal tension glaucoma.

Perimetry

Large ganglion cells are more susceptible to damage in glaucoma patients. These cells project to the magnocellular layer and the lateral geniculate body. Damage to both the **magnocellular** and the **parvocellular** layers occurs in glaucoma patients. Ocular hypertension patients, on the other hand, have significant damage only in the magnocellular layer and only marginal damage in the parvocellular layers.

Few white patients become completely blind from glaucoma. The rate of visual field progression, in white patients, is not dependent on the level of IOP. Visual field progression seems to be similar in normal tension glaucoma and in primary open angle glaucoma. Visual field progression may continue despite a good IOP control. White patients with severe visual field loss in one eye are not at a high risk of having severe loss in the fellow eyes. The Advanced Glaucoma Intervention Study showed, on the other hand, that visual field defects are more severe in **black** patients than whites. Black patients also have fewer disc haemorrhages than whites.

Baseline perimetry should consists of more than one test. The learning effect of repeated perimetry should be taken in consideration in the evaluation of the progress of the disease. Wearing the proper refractive correction during perimetric testing is essential, refractive errors can produce refraction scotomas, spurious test results and increased variability. If patient's pupils are less than 3 mm in diameter, they should be dilated during the test.

Visual field testing should provide maximum amount of information with the least effort to the patients. Fast Pac, SITA standard, SITA fast have been compared against a full threshold Humphrey's test in a recent study. Both SITA programmes seem to provide a greater visual field defects than the Fast Pac, with a reduction in the test time to 53% in SITA standard, and 50% in SITA fast tests compared to full threshold Humphrey's test.

There are three statistical algorithms programmes commercially available to use with the Humphrey's visual field analyser to determine **true progression** of visual field loss :

1. The Linear Regression Analyser.
2. Glaucoma Change Probability Programme.
3. The Progressor Programme.

There is a high index of variability between the three programmes in determining visual field progression and non of them seem to correlate well with the clinical judgement. Glaucoma change probability test seems to be the most useful single test.

the FAST PAC programme

The standard threshold programme of the Humphrey visual field analyser uses steps of 4-2 dB and crosses the threshold twice when measuring retinal sensitivity in glaucoma patients. This programme often takes a long time to perform and might be tiring to some patients. Two time-saving visual field test strategies are being used. The FASTPAC and the supra-threshold screening programmes. The standard full threshold algorithm uses staircase bracketing logic. In contrast the FASTPAC uses 3 dB steps in bracketing the test points. It tests half of the test points with 1 dB higher than the test location and the other half with 2 dB below the test location threshold. The supra-threshold, on the other hand, uses 6 dB in bracketing the test points. In healthy subjects and in patients with early glaucoma FASTPAC strategy **saves 40%** of test time without significant deterioration in field defect detection.

blue on yellow perimetry

Visual damage in glaucoma affects either the parvocellular pathways (as detected by short-wavelength automated perimetry) or magnocellular pathways (as detected by motion automated perimetry). There might be an individual variation in which type of pathway is glaucoma damage first shown. Blue on yellow perimetry can isolate and measure the sensitivity of the **short** wavelength-sensitive S-cone pathway mechanism which seems to be affected centrally and peripherally early in glaucoma. This method is useful in detecting visual field defects in **early glaucoma** and also in glaucoma suspects with large disc cupping. Visual field defects detected by this method is highly associated with nerve fibre layer assessments, and may precede visual field defects detected by the Humphrey visual field analyser or the detection of nerve fibre layer defects by polarimetry. Clinically detectable structural abnormalities frequently coexist with blue-yellow visual field defects, in patients with ocular hypertension, are frequently associated with clinically detectable glaucomatous structural abnormalities. However, long and short term fluctuation and **variability** of blue-on yellow perimetry is greater than of that with white perimetry.

the oculo-kinetic perimeter test (OKP)

The Oculo-kinetic Perimeter test (OKP) is a simple, inexpensive and self-administered visual field screening test designed to make visual field screening possible. The test relies on eye movements to project a dark stimulus onto different areas of the visual field. The test is designed for **screening** purposes and lacks some sensitivity. The size and contrast of the target make this method effectively a supra-threshold method which make it less sensitive than humph perimetry.

dark stimuli on a bright background

Fields tests using dark stimuli on a bright background allows the differentiation between glaucomatous field loss and normal regions in central visual fields. Dark stimuli of lower contrast provided higher abnormal points detection rates. Visual field defects to the low contrast dark stimuli are more extensive than those to the luminous stimuli. These findings suggest that in glaucoma suspect eyes dark stimuli may diagnose visual fields abnormalities before they become evident equal sized deterioration on conventional positive contrast stimuli .

whole field scotopic sensitivity test

Whole field scotopic sensitivity test provide a high level of sensitivity and specificity in distinguishing patients with glaucoma from controls. The test assess the scotopic vision which is a function of the magnocellular retinal ganglion cells.

Miscellaneous

- **Frequency Doubling Tests**

Frequency doubling test is a new test that is based on detecting abnormalities in the **magnocellular** ganglion cells layer (other tests include Motion sensitivity testing, scotopic sensitivity). In this test, alternating light and black bars, that are rapidly reversed between white and dark, appear to have twice the actual number of bars. There is a theoretical and clinical evidence that the use of this phenomena may be useful in the diagnosis of early glaucoma.

The technique provides **high sensitivity and specificity** for detecting early, moderate and advanced glaucoma. Grading of glaucomatous visual field defects, in a clinically significant manner similar to that obtained by conventional visual field testing, is possible with this new psycho-physiological test. There is also a significant correlation between frequency doubling technique results and visual field defects. The test seems to be a promising method in **screening** for glaucoma. The test may be more sensitive than threshold perimetry in screening for glaucoma. visual field loss. It is simple, rapid and not affected by the patients refractive errors. Motion impairment may be used as a predictor for visual field loss in glaucoma patients. The period between motion impairment and visual field loss in not known.

- **The Retinal thickness analyser**

The Retinal Analyser test is useful in detecting retinal thickness alteration in macular diseases, and may provide multiple optical cross sections of the retina. The ganglion cell layer forms a significant part of the retinal thickness. Mapping the retinal thickness with the retinal thickness analyser may be helpful in the detection of ganglion cell layer abnormalities and may be useful in the diagnosis and follow up of glaucoma.

- **Fundus perimetry**

Fundus perimetry with scanning laser ophthalmoscope is new promising technique that allows correlation between the appearance of the fundus and visual field measurements. Visual fields obtained with this technique appear to be correlated with those obtained by computerised static perimetry. Increasing age may be associated with decrease in the light sensitivity and greater losses of fixation during the test.

- **Confocal tomographic angiography**

Blood supply to the optic nerve head is thought to play an important part in the pathogenesis of glaucomatous optic neuropathy. A new technique

(Confocal tomographic angiography) is developed to study the optic nerve head superficial and deep circulation by using both the scanning laser ophthalmoscope and indocyanine green angiography technique. Vascular filling abnormalities in the nerve head are noticed in patients with visual field loss.

Normal Tension Glaucoma

It is not known if the pathogenesis of low tension glaucoma is similar to that of the primary open angle glaucoma. Systemic cardiovascular and rheological factors have been implicated in the pathogenesis of this type of glaucoma. Pulsatile ocular blood flow is significantly lower in eyes with NTG than in normal eyes. Eyes with NTG, with visual field loss, are also associated with lower pulsatile blood flow indicating that blood flow difference may play an important role in the pathogenesis of this type of glaucoma.

A **histopathological** study of an eye with low tension glaucoma demonstrated optic nerve changes similar to that in eyes with raised tension glaucoma. The study also demonstrated deposition of serum immunoglobulin G and A in the ganglion cell and in the inner and outer retinal layers. Serum antibodies to retinal protein may play a role in the pathogenesis of low tension glaucoma.

In making the diagnosis of low tension glaucoma, the clinical differentiation between glaucomatous optic disc cupping and non-glaucomatous (compressive, traumatic, hereditary, or demyelinating) optic disc cupping is difficult. **Pallor** of the neuro-retinal rim is thought to be 94% specific for predicting a non-glaucomatous disc cupping, and focal or diffuse obliteration of the rim is thought to be 87% specific in predicting glaucomatous cupping. **Imaging** studies are often undertaken in patients with optic nerve head cupping with visual field loss and normal IOP. Imaging of the visual pathway rarely reveal compressive lesions in the evaluation of these patients. It is thought that the following factors may increase the likelihood of identifying intracranial mass lesion in this group of patients:

younger age.
lower levels of visual acuity.
vertically aligned visual field defects.
pallor of the neuro-retinal rim.

A recent study showed that chronic high-pressure glaucoma and normal-pressure glaucoma show **morphologic similarities in the appearance of the optic nerve head.** The study indicated that the lower frequencies of detected disc haemorrhages and rim notches in high-pressure glaucoma may be due to a smaller size of haemorrhages and localised retinal nerve fibre layer defects in high-pressure glaucoma. it seems that both glaucoma types have morphologic features in common, suggesting that they may possibly belong a spectrum of the same pathologic process.

Patients with normal tension glaucoma and **visual field loss** in one eye are at increasing risk of loosing visual field in the fellow eyes. The risk is increased if the visual field loss in the first eye is great and/or if the neuro-

retinal rim in the fellow eye is reduced. High IOP in normal pressure glaucoma, is associated with more damage to the optic nerve head and the neuro-retinal rim. Lowering the IOP may be useful in these eyes.

A multicentre randomised study in patients with low tension glaucoma demonstrated that a **30% reduction in the IOP** is associated with less progression of visual field loss. Some patients with low tension glaucoma do not progress whether IOP is reduced or not. Methods of treatment in low tension glaucoma is controversial. Medical treatment has always been disappointing. Recently it has been demonstrated that once a day **latanoprost** may be effective in lowering the IOP and increasing pulsatile ocular blood flow in these patients. **Filtration** surgery may also be needed in many patients to lower the IOP to very low levels. Trabeculectomy with adjunctive per-operative 5-FU should maintain a suitable target IOP without the additional sight threatening complications seen with adjunctive Mitomycin C. Filtration surgery may, however, be associated with an increase in lens opacities. The benefit of filtration surgery, on the visual function, is only significant after the effect of the increased cataract on the visual field is removed by cataract surgery.

Medical treatment

glaucoma, in the majority of patients, can be controlled by medical treatment only. However, about one third of white population with glaucomatous damage, at the time of diagnosis, needs filtration surgery. At present, reducing the **IOP** is still the main objective of the treatment. Some studies showed that reducing the IOP by 30% may be effective in reducing visual field loss progression even in normal tension glaucoma. A recent study, on the other hand, showed that there is no correlation between IOP and visual field loss progression.

The chronic use of glaucoma medications may be associated with drug-induced conjunctival scarring and ocular **cicatricial pemphigoid** which might affect the outcome of surgical treatment.. The clinical features of drug-induced and idiopathic ocular cicatricial pemphigoid seem to be very similar. Both conditions may respond to immunosuppression treatment. Conjunctiva biopsy may reveal a similar histopathological features in both conditions. Stopping the medication early in the disease may result in resolution of the conjunctival scarring.

Topical steroid drops are known to increase the IOP and cause glaucoma in susceptible patients. Physicians should be aware that systemic and inhaled steroids may also increase the IOP in susceptible patients and patients with a positive glaucoma family history.

Beta blockers

Beta blockers have been the most commonly prescribed medical treatment for open angle glaucoma. The main side effects of oral and topical beta antagonists medications are:

heart failure
hypotension
bronchospasm

Topical beta antagonist drugs have also been implicated as a major risk factor for **falls** in elderly glaucoma patients. Timolol also seems to adversely affects the high-density lipoprotein and total cholesterol / high-density lipoprotein ratio in women age 60 years and older with ocular hypertension or primary open-angle glaucoma, this may be due to its effect on the lipoprotein lipase enzyme. Carteolol, on the other hand, appears to be neutral in its effect on serum lipid levels.

Beta blockers medications should be used with caution in **African black** glaucoma patients. Recent studies showed that the IOP lowering effect of beta blocker drops, in this group of patients, is less than its effect in white Caucasian individuals. Rebound rise in the IOP may also occur in some

black individual after stopping the drops. A recent paper also showed that beta blockers may be less effective when used at **night** than during the day. The authors of the report suggested that this difference in action may be due to the circadian variation of the IOP, it is known that aqueous formation is less during the night.

Efficacy of topical timolol may also be reduced with the concurrent administration of **systemic ß-blockers**. Systemic side effects may also be increased. Ocular hypotensive agents other than ß-blockers, may be a more appropriate first-line therapy for ocular hypertension and glaucoma in patients concurrently taking systemic ß-blockers.

Beta blocker drops should be avoided in elderly patients because as many as 41% of elderly people have **airways disease**, most of these diseases are undiagnosed and unsuspected. Topical timolol application may be associated with mild bronchial obstruction even in patients with no pre-existing respiratory diseases. If there are no suitable alternatives cardioselective preparations are usually chosen. **Spirometry** studies (or at least a peak flow recording) should be performed before commencing beta antagonist therapy and should also be repeated at each outpatient visit. Most patients at risk of using beta blockers can be detected by performing spirometry at the start and then one month after starting the treatment.

Timolol **gellan** is a new preparation of Timolol 0.5% that is suspended in a polysaccharide derived from a gellan gum which forms a gel on application to the conjunctival surface. Once a day application of Timolol gellan is as effective as twice a day application of the aqueous solution with the added advantage of lesser systemic absorption. Both Timolol preparations reduce resting and peak heart rate but the reduction produced by the Timolol gellan is significantly less than with the aqueous solution even in peak exercise performance.

Topical **Metipranolol** may be associated with adverse reactions e.g. granulomatous anterior uveitis and blepharoconjunctivitis. Uveitis is often associated with large KPs, cells and flare and secondary glaucoma, when the drops are discontinued and topical steroids are started the uveitis often subside within 4 to 6 weeks. Beta blockers, with benzalkonium chloride, may also cause reduction in the mean basal tear turnover when compared with healthy controls. Non-preserved drug achieve better stability of the tear film which may be relevant when prescribing these drops for elderly patients with corneal surface diseases.

- **Beta blockers and the ocular blood flow**

The effect of systemic hypertension, and its treatment, and nocturnal hypotension on glaucoma patient is controversial. Some studies showed that glaucoma patients without systemic hypertension have lower optic

nerve blood flow than those with hypertension. It is thought that treatment of systemic hypertension may further decrease optic nerve blood flow in some glaucoma patients. Increase in **nocturnal hypotension** may be a potential risk for visual field deterioration in susceptible glaucomatous optic disc and anterior ischaemic optic neuropathy.

There has been some controversy about the role of beta blockers drugs on ocular and optic disc blood flow, (and consequently on visual fields), because beta adrenergic **receptors** have previously been identified in the human ciliary body, and in the anterior optic nerve and the optic nerve head in human eyes. The majority of these receptors seem to belong to the beta-2 subtype. Some beta blockers drops may be associated with significant drop in the nocturnal blood pressure and heart rate, and may thus increase the risk of further visual field loss in vulnerable discs. Previous studies, in glaucoma and ocular hypertensive patients, showed evidence that **betaxolol** as well as **metipranolol** might have a better protective effect than timolol, on the visual field, even if the IOP control with the two drug was similar, or even better with the timolol.

In a double masked, randomised, placebo-controlled study, the effect of betaxolol and timolol on the retinal blood flow was measured by laser Doppler velocimetry. Betaxolol was associated with a long term increase in the retinal blood flow, while timolol was associated with a short as well as long term decrease in the blood flow. It was concluded that betaxolol may have an additional vasodilator action to its IOP lowering effect. This action may be due to a calcium channel blocking action similar to that achieved by Verapamil.

Topical carbonic anhydrase inhibitors

Dorzolamide (Trusopt) is a topical carbonic anhydrase inhibitor that has been proved effective and safe as a monotherapy and also in combination with other glaucoma medications. Treatment with dorzolamide **reduces aqueous humour secretion** by about 13% during the day time, and by 9% during the night time. The drug also increases ocular pulse pressure in glaucoma patients and normal subjects, an action which may have a protective effects on the visual field in patients with high IOP.

The reduction in aqueous secretion seems to be less with dorzolamide than with the maximum dose of **oral acetazolamide**. The smaller effect of dorzolamide is due to insufficient inhibition of some of carbonic anhydrase inhibitors. Topical dorzolamide and oral acetazolamide (250 mg four times a day) do not seem to have an additive effect in lowering the IOP. Small doses of oral acetazolamide, when added to the dorzolamide does not reduce aqueous secretion any more. The use of both drugs in patients with glaucoma is not rational.

Dorzolamide has an **additive** hypotensive effect when added to timolol. When dorzolamide is combined with timolol eye drops, in a single drop, the IOP lowering effect of the combination, when used twice a day, is comparable to timolol twice a day and dorzolamide three time a day. The IOP lowering effect of the combination drops is greater than either of the timolol twice a day or of the dorzolamide three time a day.

The most common local adverse effects associated with dorzolamide use are burning, blurred vision, itching, tearing, foreign body sensation, stinging, eyelid discomfort, and non-specific conjunctival hyperaemia. Severe sterile **purulent conjunctivitis** may also occur in patient s taking the drug. Cessation of the drops leads to immediate resolution of the conjunctivitis.

Concern about the adverse effect of topical application of dorzolamide on the corneal carbonic anhydrase has been raised because the corneal endothelium contains carbonic anhydrase enzymes types I and II, which play a role in the water pumping action of the endothelium. In a double masked randomised one year study comparing the corneal effects of timolol and dorzolamide, no significant changes in the **central endothelial density** were noticed between the two drugs. Other retrospective studies suggested that dorzolamide can cause irreversible corneal endothelium de-compensation and corneal oedema in some patients with compromised corneal endothelium.

Dorzolamide treatment may be associated with some systemic side effects. The use of the drug has been associated with the development of **renal stones** in some patients. Cessation of the treatment may lead to clinical improvement and disappearance of the stones.

Other topical carbonic anhydrase inhibitors include **Cosopt** and **Brinzolamide** (Azopt). Cosopt is a drug combination that consists of timolol and Trusopt. The us of this combination, in glaucoma patients, seems to be equivalent in its effect and safety to the concomitant administration of timolol and Trusopt, both twice a day. The use of the fixed combination drug might be useful in cases of poor compliance. Brinzolamide (Azopt) has a high inhibitory action against carbonic anhydrase type II which is the main iso-enzyme responsible for aqueous production. Topical application of brinzolamide 1.0%, twice daily, produces IOP lowering effect similar to that of dorzolamide 2.0% with less ocular discomfort.

Latanoprost

Latanoprost is a potent prostaglandin F 2-alpha analogue. Treatment with latanoprost reduces the IOP, in primary open angle glaucoma, chronic narrow angle glaucoma, and also in some cases of secondary glaucoma, mainly by **increasing the uveoscleral aqueous flow**. Some animal studies showed reduced collagen types I, III, and IV immuno-reactivity in the ciliary muscle and adjacent sclera following topical prostaglandin F2 isopropyl ester treatment. These changes may explain the increased uveoscleral outflow observed with topical prostaglandin treatment.

The drug appears to be more effective than timolol eye drops in primary open angle glaucoma and also in pigmentary glaucoma. Unlike beta blockers medications, latanoprost can be used in patients with glaucoma and concomitant bronchial **asthma**. Airway function and asthma symptoms do not appear to be affected by the drug. The initial IOP reducing effect of latanoprost declines to some extent during the first two weeks of treatment and then remains at the same level reducing the IOP with about 20%. A two years study of Latanoprost (0.005%) showed that the drug is effective and tolerable for the long term treatment od glaucoma and ocular hypertension. The drug may have an **additive** effect, in lowering the IOP, to timolol, dorzolamide and Propine. When timolol is added to latanoprost, once a day treatment in the morning may be effective in reducing the IOP.

Latanoprost treatment is not without side effects. The drug has been associated with the following side effects:

Increased iris pigmentation
Darkening of the eye lashes
Anterior uveitis
Cystoid macular oedema in pseudophakic eyes
Optic disc swelling
Increased risk of recurrent herpes simplex virus keratitis

The most significant side effect of latanoprost is increased **iris pigmentation**, which may occur as early as 4 weeks after starting the treatment. The colour change is mainly found in green-brown, grey-brown, and blue-brown iridis. These eyes become progressively more brown with the use of latanoprost. The mechanism of iris darkening is not known. Sympathetic innervation is needed for age related darkening of the iris in rabbits. Prostaglandins may play a part in compensating for sympathetic denervation to produce the darkening effect. A recent morphologic and histological study, on an iris of patient who had latanoprost treatment with change in his iris colour, showed that, there is little indication that proliferation or any pre-cancerous changes of melanocytes occurred.

Growth of eyelashes, in a patient with total loss of eyelashes for 5 years secondary to alopecia, has also been reported after treatment with latanoprost.

Latanoprost therapy also increases the breakdown of the blood-aqueous barrier. A significant incidence of anterior uveitis (6.4%) and angiographic, as well as, clinical **cystoid macular oedema** (2.1%) has been reported with the use of latanoprost in the early postoperative period after cataract surgery. Cystoid macular oedema has also been described in phakic patients. The cystoid oedema often resolves after stopping the treatment. The use of latanoprost in patients with active, or with a history of uveitis or cystoid macular oedema should be with great caution. The administration of non-steroidal eye drops such (e.g. diclofenac) seems to prevent the adverse effects of latanoprost therapy while maintaining its effect to lower intraocular pressure. It is suggested that the concurrent use of these drops with latanoprost may be useful in preventing the macular oedema. Bilateral optic disc swelling has also been reported after the use of latanoprost. The swelling appears to resolve after cessation of the treatment.

Prostaglandins are known to have effect on the multiplication of herpes simplex virus. Animal studies, in rabbits eyes, showed that latanoprost may worsen **acute herpetic keratitis**, and increase the risk of recurrences in latent infection. Some case reports, in human eyes, also indicate that the drug may be associated with the development of herpes simplex virus infection.

Brimonidine and Apraclonidine

Brimonidine is a highly effective Alpha-2 adrenergic receptor agonist. It is estimated to be 1000 more selective to Alpha-2 receptors than to Alpha-1 receptors. It is also a more potent Alpha agonist than either Apraclonidine or Clonidine. Brimonidine has been shown to be safe and effective in lowering the IOP when topically applied twice a day for 12 months. The efficacy of Brimonidine is comparable to that of timolol but without a significant effect on the heart. Some studies showed no statistically significant difference in the IOP lowering effect of Brimonidine and apraclonidine.

Brimonidine, unlike clonidine, does not have a significant CNS action (e.g. sedation and hypotension). Topical Brimonidine in **infants** may, however, result in CNS depression (hypotension, bradycardia, hypotonia and apnoea). The drug should not be used in this subgroup of patients.

Brimonidine lowers the IOP, initially, by decreasing the aqueous flow. After chronic treatment, the drug lowers the IOP by increasing the uveoscleral outflow. The drug is known to have a vasoconstrictor effect on the blood vessels in the anterior segment of the eye. However, the haemodynamics of the posterior segment of the eye and the **optic nerve head**, do not appear to be affected by the drug even after long term use. The drug does not appear to alter the retinal capillary blood flow in patients with ocular hypertension.

The incidence of ocular **allergy**, dry mouth and conjunctival follicles seem to be higher in patients receiving Brimonidine when compared to timolol, while the incidence of burning and heart rate is higher in patients taking timolol. The drug may have an additive IOP lowering action when added to timolol. Brimonidine and apraclonidine reduce intraocular pressure in timolol-treated eyes, by further suppressing aqueous flow. The chronic use of Apraclonidine may be associated with allergic manifestation in many patients. It is generally safe as well as efficacious to administer Brimonidine to patients with apraclonidine allergy.

Calcium channel blockers

Vasospasm has been suggested to play a role in the pathogenesis of low tension glaucoma. Calcium channel blockers block membrane-bound calcium channels and inhibit calcium influx causing a relaxation of smooth muscle cells in the vascular wall and a decrease in the vascular tone and an improvement in the **blood flow**. Systemic administration of Calcium channel blockers is associated with a mild or no reduction in the IOP while **topical** administration of Verapamil eye drops is associated with a sustained reduction in the IOP and the episcleral venous pressure. The mechanism of action is not completely understood but it may be partially due to increase in the outflow facility. After two weeks administration of the topical drops the reduction of the IOP is estimated to be about 12% in the treated eye and by about 7% in the untreated eye.

Others

Marijuana, **Ticrynafen**, and **Citicoline** are new drugs that may have a potential in the treatment of glaucoma. Drugs containing cannabis and marijuana have been shown to cause a reduction in the IOP. Continuos use of marijuana, at high enough levels to control the IOP, may be associated with psychological problems. Ticrynafen (a drug similar to Ethacrynic acid) is another drug that has also been shown to increase the aqueous outflow and decrease the IOP in monkeys. The hypotensive effect is believed to be due to the sulphhydryl group. Ticrynafen and Ethacrynic acid may have potential for clinical use in humans. Citicoline is an intermediate substance for the synthesises of phosphatidyl-choline which is a major phospholipids in the neural cell membranes. The substance is thought to increase the neural metabolism and also inhibits phospholipids degradation. In randomised clinical study Citicoline produced a significant improvement in the VEP and PERG in patients with primary open angle glaucoma. The drug may have a potential in the treatment of glaucomatous optic neuropathy as a neuro-protective agent.

Laser treatment

Laser Peripheral Iridotomy

The initial treatment of acute closed angle glaucoma is often by medical treatment, followed by laser or surgical peripheral iridotomy. There does not seem to be any significant difference in visual acuity or intraocular pressure control 3 years after treatment of acute angle closure glaucoma with **surgical** or YAG peripheral iridotomy. Peripheral iridotomy is also beneficial in chronic narrow angle, or angle closure glaucoma. A recent study showed that laser peripheral iridotomy is successful in opening the anterior chamber angle in 73.4% of eyes with angle closure glaucoma.

Different types of lasers have been used in the treatment. **Picosecond lasers** use lower energy than nanosecond YAG laser, which result in considerably less disruptive effects in the treated eye. Picosecond lasers seem to be more suitable for peripheral iridotomy procedures, unlike nanosecond YAG laser which seem to be more suitable to capsulotomy procedures. When pilocarpine or Apraclonidine eye drops are applied peri-operatively significant IOP rise after the peripheral iridotomy is very uncommon. Routine post-peripheral iridotomy check of the IOP may, therefore, not be necessary.

Argon Laser Peripheral Iridoplasty

When systemic and topical anti-glaucoma treatment fail to control the high IOP, and when peripheral iridotomy is not possible (e.g. in cases of severe corneal oedema), the technique of Argon Laser Peripheral Iridoplasty may be effective in controlling the IOP and clearing the corneal oedema. The aim of this procedure is to, mechanically, **open the appositional closed angle**. In this technique a ring of low power, long duration, and a large size burns is applied to the iris periphery to contract the iris stroma and open the angle. This technique is often applied after controlling the IOP medically. Argon laser iridoplasty without medical treatment may also be used in cases with primary angle closure of duration less than 48 hours. A full 360 degree ring is often applied, but a more limited area of treatment may also be effective.

Laser Trabeculoplasty (ALT)

Argon, krypton, diode, and YAG laser trabeculoplasty, have all been used in the treatment of primary open angle glaucoma, pseudoexfoliation glaucoma, and pigmentary glaucoma. The **mechanism** by which Argon laser trabeculoplasty lower IOP is not completely understood. It is thought to be due to either displacement of the inner part of the trabecular meshwork pulling it from the outer wall and thus opening the Schlemm's canal or due to liberation of mediators released by the inflammatory response following the laser treatment that activate trabecular endothelial cells causing them to

multiply and thus improving the trabecular outflow. Failure of argon laser trabeculoplasty, in some patients, is often caused by a **membrane formation** in the anterior chamber angle.

Postoperative rise in the IOP may be reduced by preoperative use of **apraclonidine** or Brimonidine 0.2% drops. Pilocarpine 4% appears to be as effective as apraclonidine in preventing IOP rise. Apraclonidine does not seem to be very effective in patients on long term apraclonidine use. Pilocarpine may be more effective in these patients.

The Advanced Glaucoma Intervention Study examined 7 years result of two different **surgical intervention sequences** for black and white patients with advanced glaucoma. The two different sequences were:

1. Argon laser trabeculoplasty-Trabeculectomy-Trabeculectomy
2. Trabeculectomy- Argon laser trabeculoplasty-Trabeculectomy

The second and third intervention procedure were carried out after the failure of the preceding one. The mean decrease in the IOP was greater in second sequence more than in the first in both black and white patients. However, black patients were less likely to lose visual acuity and visual field if laser trabeculoplasty was carried out as a first intervention. In white patients visual acuity and visual field were more preserved when the first intervention was trabeculectomy rather than trabeculoplasty. The data from this study suggest that in advanced glaucoma the first surgical intervention should be trabeculectomy in white patients and trabeculoplasty in black patients.

Current methods of laser trabeculoplasty causes thermal scarring and damage to the trabecular meshwork. Some studies indicated that prior argon laser trabeculoplasty may lead to a higher rate of encapsulated trabeculectomy bleb afterwards. This may be due to damage of trabecular meshwork caused by the thermal coagulation of the argon laser.

Selective laser trabeculoplasty is a new technique in which the laser power is aimed at the pigmented trabecular meshwork without damage to the other structures in the meshwork. A prospective randomised clinical trial showed that selective laser trabeculoplasty with Q-switched 532 nm wave length YAG laser appears to be equivalent to ALT in lowering IOP during the first 6 months after treatment. In this technique about 50 non-overlapping 400 micron spots are used to treat an entire 180 degrees of the trabecular meshwork. Laser power is adjusted to level just below that level which causes cavitation bubbles. The technique is associated with a greater anterior chamber reaction 1 hour after treatment. Patients with previous failed ALT may have a significantly greater drop in IOP when treated with the selective technique. The lack of coagulation damage to the trabecular meshwork with this procedure makes it potentially a repeatable operation.

Some authorities believe that this technique can be used in association with, rather than instead of, argon laser trabeculoplasty.

Trabeculectomy

Trabeculectomy is the main surgical operation to control the IOP in patients with primary or secondary glaucoma. Reduction of IOP after trabeculectomy surgery may be associated with **reversal** of cup / disc ratio. A steady long-term **decline** in visual acuity and visual field have also been reported in some patients after surgery. The decline in visual acuity may lead to blindness. Estimated probability of retaining useful vision 15 years after surgery, is about 0.6. Eyes that have good preoperative visual acuity have a significantly better chance of retaining useful vision.

Success of trabeculectomy appears to be related to the **type** of glaucoma. Patients with neovascular, traumatic, paediatric or uveitic glaucoma often have the worst outcome after surgery. Trabeculectomy with adjunct chemotherapy is probably most needed in these patients. There is a high risk of surgical failure and complications after trabeculectomy for **acute primary angle closure glaucoma.**

Certain other conditions (e.g. previous **conjunctival surgery**, laser trabeculoplasty, and anti-glaucoma **medications**) are known to have a negative effect on the success rate of the operation. This may be due to an increase in the fibroblasts and inflammatory cells in the conjunctiva. Anti-glaucoma drugs may be associated with histological changes in the conjunctiva and in the trabecular meshwork. The conjunctival changes is believed to be mainly due to benzalkonium chloride preservative toxicity. Some authorities think that the use of anti-metabolites may be indicated in these situations. A high rate of **uric acid** in the aqueous in the anterior chamber has also been associated with increased risk of trabeculectomy failure, and thought to be a prognostic indicator for the success of surgery.

Episcleral, and Tenon capsule fibrosis are the most common cause of failure after trabeculectomy. Tenon capsule is inserted about 2 mm posterior to the limbus. **Micro-trabeculectomy** is a new technique that is reported to be safe and effectively in reducing the IOP, and also reducing the postoperative fibrosis rate. In micro-trabeculectomy a 2 by 2 mm scleral flap is fashioned and a 0.75 mm internal ostium is created using the Kelly Descemet's membrane punch. The procedure achieves a good IOP control in low risk eyes. This technique is also associated with smaller changes in the topographic and keratometric astigmatism than the conventional technique. Nasally sited micro-trabeculectomies seem to work better than temporally sited ones.

Shallow anterior chamber from excessive drainage is a main complication after trabeculectomy operations especially in chronic and acute narrow angle glaucoma. **Releasable scleral flap** technique reduces the incidence of shallow and flat anterior chamber without affecting the long-term result of the operation. The use of releasable sutures minimises the incidence of

postoperative hypotony and shallow anterior chamber and also maximises long term bleb formation and IOP control..

Complications

- **bleb failure**

Postoperative flattening of the bleb is often associated with failure of the trabeculectomy. Bleb failure in primary open angle glaucoma ranges from 67% to 94% of cases. Bleb **encapsulation** is a frequent cause of failure that is reported to occur in 13% of patients. It often occurs in the early postoperative period, due to adhesions and scar formation between the episcleral tissue and the Tenon capsule. Several factors have been associated with bleb encapsulation. These factors include glove powder, prior conjunctival surgery, prior treatment with sympathomimetic drugs, or prior argon laser treatment. Several methods have been used to reform the bleb and prevent failure. These methods include:

Early needling
Laser suture lysis
YAG laser opening of fistula
Sub-conjunctival Perfluoropropane gas bubble
Medical anti-glaucoma treatment
Ocular massage
Topical steroids
Surgical revision of the bleb

Early **needling** of the capsulated bleb is a relatively new method of treatment. A 30 gauge needle attached to an insulin syringe can be used. The needle is passed in the sub-conjunctival space, few centimetres away from the encapsulated bleb. Repeated punctures of the cyst is then tried till the bleb is inflated. Another needle with 5 FU (25 mg / ml), is then passes and the 5 FU is injected. This procedure seems to be safe and effective in treating encapsulated blebs. Sub-conjunctival injection of 5 FU may also be used in delayed bleb failure. Delayed sub-conjunctival injection of 5 FU reduces the IOP if ocular massage reduces the IOP prior to the injection. Injection of air bubbles under the conjunctiva may give only a transient formation of the bleb.

Laser treatment may be useful in failing blebs. The use of tight scleral flap sutures during trabeculectomy in conjunction with postoperative laser **suture lysis** has been reported to minimise hypotony and its associated complications. Suture lysis may be performed using either argon or YAG laser and Hoskin's lens The best results are obtained when lysis is done within the first two week after the operation. No benefit is expected if the suture lysis is done 4 weeks after the operation. When anti-metabolite is used with the trabeculectomy wound healing can be delayed so much that suture lysis can be beneficial even after as long as 21 weeks after the operation.

YAG laser may also be used to open failing filtering blebs, either by an internal gonioscopic approach or by an external approach. In the external approach, laser beam is focused on the bleb sub-conjunctival scar tissue. Multiple applications of medium power laser burns is then carried out till disruption of the scar tissue is achieved and the aqueous appears to percolate through the scar tissue. A new method to reform the bleb by sub-conjunctival injection of Perfluoropropane gas bubble has been described. The Perfluoropropane gas acts as a spacer in the sub-conjunctival space and may last for up to 2-4 weeks.

- **hypotony and bleb leak**

Hypotony may be caused by either decrease in the production of aqueous (due to inflammation, choroidal detachment, or medications), or due excessive filtration of aqueous (due to bleb leak, or cyclodialysis cleft). Postoperative bleb leak, and hypotony is a major problem after successful trabeculectomy surgery. Postoperative hypotony often resolves spontaneously within few days. Conservative treatment is, therefore, indicated in eyes with deep anterior chamber. Immediate anterior chamber re-formation is, however, needed in cases with **flat anterior chamber** (stage 3 shallow anterior chamber) to prevent rapid development of cataract and endothelial de-compensation. Chronic hypotony may cause poor visual acuity caused by cataract, choroidal effusion, supra-choroidal haemorrhage or maculopathy. Various methods has been used to treat leaking blebs. These methods include:

Intrableb autologous blood injection
Autologous fibrin tissue glue
Nd: YAG laser
Large contact lens wear

Autologous blood injection may be used to reduce filtration in an over-filtering bleb and hypotony. Under topical anaesthesia, about 0.1 or 0.2 ml of venous blood in injected with a 27 gauge needle about 6 mm away from the bleb. Inflammatory cells and serum protein from the injected blood accelerate the inflammatory and healing process. Laser-cured fibrinogen glue has also been used to close a leaking bleb in rabbit eyes. Fibrinogen may be taken from the patient own blood to prevent any blood transmitted diseases. The fibrinogen glue can be coagulated on the ocular surface by the diode laser.

The continuous wave **Nd: YAG laser** may also be effective in repairing bleb-related problems while maintaining successful filtration. The laser is applied to the large leaking bleb, after being painted with methylene blue dye, in a grid fashion. The laser beam is defocused so that the internal surface of the bleb is treated. The IOP may rise in the immediate postoperative period, but

it often drops again with time. Cataract formation, and pupillary abnormalities may also result after treatment. It has also been reported that **phacoemulsification** surgery may be associated with a statistically significant elevation in IOP in previously filtered eyes with hypotony.

- **blebitis, and endophthalmitis**

Bleb infection and late onset bleb infection are serious complications after trabeculectomy. The risk of bleb related infection is increased in **inferior** blebs, with the use of **anti-metabolites**, in younger age, and also in patients with late **bleb leak**. Blebitis may represent a limited form of endophthalmitis. Other risk factors that have been previously identified include blepharitis, ocular trauma, and nasolacrimal duct obstruction. Streptococcus, Haemophilus influenzae and Staphylococci organisms are currently recognised to be the most frequent organisms in bleb-related late endophthalmitis. The infection may also be recurrent.

Aggressive treatment is often needed by intravenous antibiotics (e.g. Cefazolin), and frequent topical antibiotics (e.g. Cefazolin and gentamicin). The incidence of post-trabeculectomy endophthalmitis, with or without anti-metabolites has been reported to range from 0.061% to 13.2%. Endophthalmitis after trabeculectomy operation is likely to result from infected thin avascular bleb especially if Mitomycin C has been used. Delayed-onset endophthalmitis is caused by a different spectrum of organisms than those in acute-onset, post-cataract surgery endophthalmitis.

Trabeculectomy with adjunct therapy

Adjunct therapy that has been used, with trabeculectomy, in the treatment of glaucoma include:

5 FU
Mitomycin C
Idarubicin
Suramin
Perfluoropropane
Beta irradiation
Photo-dynamic therapy
Electroporation

The use of cytotoxic drugs in glaucoma filtration surgery to prevent proliferation of fibroblasts of the human Tenon capsule has been established. **Mitomycin C and 5 FU** are currently the most commonly used drugs. The route of administration of 5 FU in glaucoma surgery has changed several times over the years. The exact amount of 5 FU applied to the sclera during trabeculectomy surgery is not often well determined. Application time, type of the sponge used, and the concentration of the drug are important factors that can significantly affect the amount of the drug applied. The effect of the drug appears to reach its maximum in about three minutes. There does not seem to any rationale in applying the drug for longer than three minutes. The intraoperative application of a single dose of 5 FU in high risk eye may not be enough to prevent trabeculectomy failure. Postoperative needling, with 5 FU, of failed blebs may be used in some cases.

Primary trabeculectomy may be carried out with Mitomycin C in **high risk patients.** When Mitomycin C is used the IOP is estimated to fall by about 30% in about 86% of eyes by the first year. Endophthalmitis has also been reported in about 2.2%, and hypotony in about 4.5% of eyes after Mitomycin C with primary trabeculectomy. Late leak after trabeculectomy is increases with the use of Mitomycin C, this complication is difficult to treat and may lead to sight threatening complications.

The optimum **dose** and duration of application of Mitomycin C with trabeculectomy in phakic eyes is not known. Mitomycin C is often applied to the sclera for few minutes during surgery, this may be associated with spread of the drug to the cornea and the conjunctiva. In a study of phakic eyes the application of Mitomycin C (0.5 mg/ml) for 0.5 to 1 minute was optimal for successful IOP control of primary trabeculectomy when compared with longer application and also with no Mitomycin C application.

Mitomycin C is often applied to the scleral surface before fashioning the scleral flap. It can also be applied under the scleral flap in high risk eyes. This method of application appears to be associated with a higher success

rate and lower complications rate than if the Mitomycin C is applied under the Tenon capsule. **Simultaneous** application of Mitomycin C to the scleral bed as well as to the conjunctiva may result in an additional IOP lowering effect. Mitomycin C application under the scleral flap, without sub-conjunctival application, may result in less avascular and healthier trabeculectomy blebs.

Idarubicin is a new drug that has the property of rapid entry into the cells. The drug has been shown to reduce cellular proliferation of human Tenon capsule after incubation for 0.5 minutes at a concentration of 0.3-1.00 microgram/ml. The short duration of application may be useful in reducing spread of the drug to neighbouring tissues.

The use of anti-metabolites in trabeculectomy surgery may be associated with serious side effects. Other techniques have been used to increase success rate in high risk eyes. **Suramin** is an anti-parasitic drug that can bind to growth factor receptors and inhibits binding of the growth factor to its target cells. It has been shown to delay wound healing in previous animal studies. In animal studies, Suramin was shown to be effective in preventing scarring after glaucoma filtration surgery with fewer side effects than other anti-metabolites. The drug may have a beneficial effect in glaucoma surgery in humans. Beta irradiation has also been used to reduce postoperative cellular proliferation. A single application of **beta irradiation** significantly inhibits Tenon capsule fibroblasts proliferation in vitro for a period of 28 days. This method may be beneficial in the management of eyes with high risk glaucoma. **Perfluoropropane gas bubble** may also be used in high risk eyes to reduce postoperative sub-conjunctival scarring. The gas bubble, with its long action, acts as a tamponade spacer between the conjunctiva and the episclera.

Photo-dynamic therapy has been described for the treatment of some ophthalmic and skin tumours as well as for the treatment of choroidal neovascular membrane. The technique may also be used to prevent or reduce postoperative fibrosis after glaucoma filtration surgery. Photo-ablation of the tissue cells has been achieved in animal eyes by using the fluorescent substance BCECF-AM. This substance can penetrate cellular membrane, and cause fluorescence upon cleavage by the intra-cellular enzymes. In an experimental study rabbits eyes were injected with the substance and then illuminated with a blue light for few minutes. Post-treatment histological studies confirmed the anti-fibrotic effect of the treatment. This treatment technique may be useful as an adjunct for drainage surgery in the future.

Electroporation is a promising new technique to increases the efficacy and safety of using anti-metabolites with trabeculectomy surgery. In this technique, application of short electrical pulses is made to increase cell membrane permeability in the area where the Mitomycin C applied.

Electroporation allows the use of smaller doses of anti-metabolites, and also minimise its local and systemic side effects.

Phacotrabeculectomy; one stage or two stage surgery?

There is controversy about whether patients with **cataract and glaucoma** should have a combined cataract and trabeculectomy operation or should have two separate operations. A recent study compared the intraocular pressure lowering effects of single-incision combined phacoemulsification and trabeculectomy with phacoemulsification done after previous trabeculectomy, both with an intraoperative dose of 5-fluorouracil. The study conclusion was that combined cataract and glaucoma surgery with intraoperative 5-FU is associated with good long-term IOP control similar to that after phacoemulsification with intraoperative 5-FU in eyes with previous trabeculectomy. In **patients who had had filtration surgery**, IOP appears to be better controlled by phacoemulsification than by ECCE.

Simple cataract extraction may be associated with a better IOP control in eyes with narrow angle glaucoma. The width and depth of the anterior chamber **angle** in eyes with Angle Closure Glaucoma increase significantly after cataract extraction and IOL implantation. This may lead to a better IOP control in the postoperative period.

Opinions vary regarding the benefit of a one stage phacoemulsification-trabeculectomy operation or a two stages procedure. The success rate of combined phacoemulsification-trabeculectomy surgery with or without anti-metabolite varies considerably. Phacoemulsification procedures with foldable IOLs seem to have better postoperative IOP results than with ECCE. Combined surgery may be carried out either by two sites or one site technique. **Two sites technique** seems to be associated with a slightly better IOP control.

Fornix-based and limbal-based **conjunctival incision** may be used. Both techniques appear to give the same IOP results. In a prospective, non-randomised comparative (fellow eyes) study, both, limbal and fornix based conjunctival flap techniques, were found equally effective in improving visual acuity and in lowering IOP. The fornix based is safe and effective with the use of Mitomycin C and may offer more advantages regarding the phacoemulsification surgery. In patients with no risk factors, the use of Mitomycin C does not seem to be justified.

The indication of a triple phacoemulsification with IOL implantation and trabeculectomy surgery with **Mitomycin C** should be based on the presence of major risk factors for glaucoma surgery failure (e.g. in black patients, high preoperative IOP, multiple drugs medical treatment). African American race, more than 2 preoperative medications, and intraocular pressure greater than 14 mm Hg in the first postoperative week are major independent risk factors for initial filtration failure during the first month after primary glaucoma triple procedure.

Previous failed trabeculectomy appears to be risk factor for failure of a combined trabeculectomy-cataract extraction surgery. The use of anti-metabolites may be associated with improved results in these cases. Intraoperative sub-conjunctival Mitomycin C application (0.5 mg/ml for 3 minutes) during combined glaucoma and cataract surgery has a beneficial effect of inhibiting posterior capsule opacification after combined surgery in patients with Primary open angle glaucoma. This observation indicates that aqueous Mitomycin C must reach great enough levels to inhibit the lens epithelial cell proliferation to result in a long-term decrease in posterior capsule opacification.

Cataract surgery after a previous trabeculectomy may result in failure of the bleb, and about 10-38% of eyes may need further medical or surgical treatment to control the IOP. Most **bleb failure** occur soon after cataract surgery. When cataract extraction is performed after trabeculectomy the following factors may be considered as risk factors for failure of the trabeculectomy bleb:

Age of 50 years or younger.
Preoperative IOP greater than 10 mm hg.
Intraoperative iris manipulation.
Early postoperative IOP greater than 25 mm Hg.

Other Surgical procedures

Deep sclerostomy with collagen implants

Deep sclerotomy with collagen implants is a **non-penetrating** glaucoma surgery which has recently been described for the treatment of open angle glaucoma. The operation controls the IOP by allowing aqueous filtration through a thin trabeculo-corneal membrane to the sub-conjunctival and supra-choroidal space. After opening the conjunctiva, a scleral flap is created, the thickness of the flap should be about 40%. A deep sclerotomy is then performed leaving a thin scleral layer over the choroid and the ciliary body. This sclerotomy can be created by using the **excimer laser**. Care should be taken to keep the sclerotomy site dry during laser application. The canal of Schlemm is then de-roofed and the corneal stroma is removed anteriorly down to the Descemet's membrane. A **collagen implant** is then secured to the deep sclera by 10/0 nylon suture. The implant prevent re-attachment of the scleral flap to the deeper scleral tissue (complete resorption of the collagen implants takes about 6 to 9 months). The scleral flap is then closed and sutured. Long term ultrasound studies showed filtration through the thin trabecular membrane to the area under the scleral flap, sub-conjunctival apace and then to the suprachoroidal space.

Trabecular aspiration

Trabecular aspiration is a new **non-penetrating** surgical procedure based on the hypothesis that removing fibrillar flake-like material, in patients with pseudoexfoliation glaucoma, from the trabecular meshwork may lead to lowering of the IOP. In this procedure an aspirator instrument is introduced in the anterior chamber via a paracentesis incision and directed to the trabecular meshwork. Another paracentesis incision is used to introduce an irrigating cannula to keep the anterior chamber formed. Suction pressure between 100-200 mm Hg is then applied to the anterior chamber angle. The aspirating and the irrigating cannula are then changed over, and more suction pressure is applied to another part of the trabecular meshwork.

The procedure appears to be safe and effective in decreasing IOP, in patients with pseudoexfoliation glaucoma, both with and without cataract extraction. There is, however some regression in its effect over time due to further liberation of pseudoexfoliation debris in the meshwork. Argon-laser trabeculoplasty before trabecular aspiration may reduce the IOP lowering effect of this procedure.

Trabecular aspiration in the glaucoma triple procedure could also be considered as a possible first-line treatment for pseudoexfoliative eyes with coexisting cataract and glaucoma. Although trabecular aspiration in the triple procedure does not achieve good pressure control in all patients, the risks

appear to be more favourable in the trabecular aspiration–treated eyes than in the filtering glaucoma triple procedure group.

Eyes with pigment dispersion syndrome and with pigmentary glaucoma also respond to trabecular aspiration but not as well as eyes with pseudoexfoliation syndrome. The response in these is better in eyes with pigment dispersion syndrome than eyes with pigmentary glaucoma. The response in these eyes, however, seems to be of short duration.

Gonioscopic curettage

It is proved that the main resistance to the aqueous humour outflow in open angle glaucoma lies in the trabecular meshwork. Gonioscopic curettage is an Ab interno non-fistula procedure designed to remove the trabecular meshwork and open a communication between the anterior chamber and the canal of Schlemm's. The procedure is carried out under the microscope by using a gonio lens and a micro-curette similar to that used in chalazion surgery. The micro-curette is used to scrape away the trabecular tissue without causing any damage to surrounding tissues. Morphological analysis of treated post-mortem eyes confirmed that gonioscopic curettage completely remove the trabecular meshwork and open Schlemm's canal, ensuring direct access into the anterior chamber. The main advantages of the operation is that the conjunctiva is not disturbed. The procedure should be more attractive in cases with severely damaged conjunctiva from previous surgery or previous medications or diseases. The reduction in the IOP is not, however, great. Level of IOP in the high teens is considered success. This might not be appropriate in some patients with severe disease when IOP in the low teens is required. Minimal to moderate and, rarely, severe hyphaema may also occur in some cases. Injury to the Descemet's membrane may also occur in some cases. Gonioscopic curettage in the presence of opaque cornea is difficult. The use of ophthalmic micro-endoscope is safe and effective in these situations.

Viscocanalostomy

Viscocanalostomy started in South Africa where black patients often have poor results after conventional trabeculectomy operations. In this procedure a parabola-shaped superficial and a deep sclerostomy flaps are fashioned. The deep flap in then dissected to the plan of Schlemm's canal. An window in the Descemet's membrane is then created by a gentle pressure. This window enables the aqueous to flow out to the space under the deep scleral flap. The Schlemm's canal is then un-roofed and high viscosity viscoelastics is passed to the right and to the left in the two ends of the canal. The deeper scleral flap is then excised and the superficial flap sutured. More high viscosity viscoelastics is injected under the flap to prevent fibrinogen migration and to keep the sub-scleral lake formed. The earlier results of this procedure is encouraging.

Enzymatic Sclerotomy

Proteolytic enzymes and bacterial extracts have been used for tissue modifications. Clostridium histolyticum is a bacterial enzyme that hydrolyses collagen under physiological conditions. Clostridial collagenase enzyme has been used in animal model to produce a localised thinning and an increase in the scleral permeability which result in a significant decrease in the IOP. this technique may prove useful in the treatment of human eyes with glaucoma.

Neuroprotection in glaucoma

Visual damage in glaucoma is mainly due to damage of the retinal ganglion cells layer. Neuroprotection means treating the disease by preventing neuronal death. Factors that are important for the neuronal survival are called neurotrophins. Several neurotrophins have been identified e.g. brain derived neurotrophins factor (BDNF) and ciliary neurotrophins factor (CNTF).

Different mechanisms may be involved in the process on neuroprotection. These include the delivery of neurotrophins, blockage of receptors mediating excitotoxins (one example of these toxins is glutamate), and scavenging of reactive oxygen species. Injection of BDNF in the vitreous is known to protect retinal ganglion cells from death as result of severing the cell axon. Blocking the receptors may be achieved by pharmacological antagonists to the excitotoxins. Examples of scavengers that can be delivered to reduce the levels of reactive oxygen species include super-oxide dismutases, catalases, glutathione peroxidase. The drug betaxolol has a calcium channel blocking function as well as an IOP lowering effect. By blocking calcium transport, the drug may be able to prevent retinal ganglion cell death and thus it may have a neuroprotective function.

Gene therapy in glaucoma

It has been shown that herpes simplex virus may be used in the transfer of foreign genes to the ciliary muscles and the trabecular meshwork system in the living cats. The transfer of genes may enable us to regulate the aqueous outflow thorough the trabecular meshwork and uveoscleral outflow. It may also affect the outflow by modulating prostaglandins secretion. Gene transfer in the retinal ganglion cells may also facilitate investigation of the process of apoptosis.

Treatment of intractable glaucoma

The two main techniques used in treating intractable glaucoma are:

1. Glaucoma implants
2. Cyclodestructive procedure

Cyclodestructive procedures need to be repeated more often than glaucoma implants. Glaucoma implants are often associated with a better IOP control but they are also 3.8 times more likely to develop postoperative complications. Some reports demonstrated superior results with trabeculectomy with Mitomycin C in some cases of intractable glaucoma.

Cyclodestructive procedures

Transscleral cyclophotocoagulation, with diode or YAG lasers, has been used for the treatment of refractory glaucoma. The semiconductor Diode laser wavelength is transmitted through the sclera less effectively, but they are better absorbed by the melanin than the YAG laser. Diode laser appears to have the same IOP lowering effect as the YAG laser. The hypotensive response varies among patients because the ciliary process can not be visualised directly during treatment. During trans-scleral cyclo-photocoagulation, about 3-5% of the laser energy reaches the posterior pole. The clinical significance of this finding is not known. Contact diode laser cyclo-photocoagulation may be associated with the development of neurotrophic corneal ulceration especially in eyes with external surface diseases. This may be due to the effect of the laser treatment on the limbal corneal innervation.

Glaucoma implants

The material of the glaucoma implants is very important in reducing adherence of fibroblasts and macrophages and increasing the rate of aqueous flow through them. New material for coating the implants may offer promise in improving drainage. The main types of glaucoma implants are:

Valved implants	Non-valved implants
1. Ahmed implant	1. Optimed
	2. Krupin
	3. Molteno implants
	4. Baerveldt

The optimed and the Krupin implants offer resistance to aqueous outflow which stays relatively stable independent on the IOP, thus increasing the IOP when the outflow increases. The **Ahmed implant**, on the other hand, functions as a true valve that regulate the pressure with a certain range by

decreasing or increasing the level of resistance in the valve depending on the aqueous outflow, thus avoiding hypotony and increases in the IOP. The majority of patients show increases in the IOP after valved implants (e.g. Ahmed implants) that peaks after one month of surgery, with gradual stabilisation over a six months period. One third of patients, however needs a second surgical operation to better the IOP. The incidence of hypotony and flat anterior chamber appears to be low after the implantation of these implants. **Occlusion** of Ahmed valved implant may occur in the early or in the late postoperative period. Early occlusion is mainly due to blood, vitreous or due to Tenon capsule thickenings. The cause of late occlusion is not completely understood. treatment of early occlusion can be achieved by irrigation of the tube. Late occlusion, on the other hand, is better treated by exchanging the tube with particular attention to careful handling of the no touch zone over the valve area.

Previous In vitro testing showed that non of the implants manage to maintain the advertised pressure level while being perfused at a rate close to the rate expected in human eyes. In vivo, however, it seems that the surrounding conjunctiva contribute to the measurable resistance to aqueous humour outflow.

Shunt failure is a common problem. The main cause of shunt failure is fibrosis and tube encapsulation. When the tube fails, as additional tube may offer a better IOP control than revision of the failed tube. All of the major complications of non-valved tubes drainage operations is due to **hypotony**. Postoperative hypotony is associated with suprachoroidal haemorrhage and visual deterioration. Older patients with hypertension and atherosclerosis are more likely to develop suprachoroidal haemorrhage after the insertion of non-valved tubes (e.g. Baerveldt implants 350-mm^2 and 500 mm^2). A number of techniques has been developed to reduce the aqueous outflow in the immediate postoperative period to avoid hypotony after the insertion of non-valved implants. The placement of a an absorbable suture just anterior to the implant plate followed by a through-and-through penetration of the tube by anterior to the ligature suture is a new technique that is reported to provide an adequate IOP control after non-valved implants.

Extraocular **motility disturbances** also commonly occur after double-plate Molteno surgery. Muscle palsies, acquired Brown syndromes, and generalised restrictions occurred in similar proportions. Patients should be counselled before Molteno surgery concerning the risk of strabismus and diplopia.

Corneal endothelial touch by the implant anterior chamber tube may also lead to **endothelial injury** especially in eyes with shallow anterior chamber, pars plana insertion of the tube following a pars plana vitrectomy can be considered as an alternative technique for tube implantation in some eyes.

Secondary glaucoma

Malignant glaucoma

The exact cause and mechanism of malignant glaucoma is not well understood. It is widely believed that the rise in the IOP is mainly due to misdirection of the aqueous. In a study of six eyes with postoperative malignant glaucoma, high resolution ultrasound examination showed annular ciliary body detachment in all of them. Resolution of the condition and deepening of the anterior chamber was also associated with the spontaneous resolution of the detachment, or with the surgical drainage of the fluid. Malignant glaucoma may be due to either aqueous misdirection, or in some patients, may be due to ciliary body detachment. High resolution ultrasound examination may be very useful tool in examining these eyes.

Pseudoexfoliation syndrome

Pseudoexfoliation is a specific lens epithelium disorder that may be associated with secondary open angle (or rarely closed angle) glaucoma. A distinct type of corneal endothelial cells changes may also occur in these eyes. This endothelium changes may lead to an early corneal endothelial de-compensation after cataract surgery.

There are certain difference in the clinical features, and in the prognosis between primary open angle glaucoma and pseudoexfoliation glaucoma. The optic discs seem to be more vulnerable to IOP rise in the pseudoexfoliation syndrome than in primary open angle glaucoma. The correlation between IOP rise and visual field defects also seem to be stronger in the pseudoexfoliation glaucoma than in primary open angle glaucoma.

Cataract surgery is often associated with a higher rate of complications in pseudoexfoliation syndrome due to zonular weakness. A recent study showed that a shallow anterior chamber, as shown by an A ultrasound scan, may indicate zonule weakness and should alert surgeons to the possibility of complications.

It has been thought that the disease may be associated with higher risks of **cardiovascular** abnormalities and early death. Recent reports, however, showed that, there is no increased risk of mortality or cardiovascular morbidity associated with the disease.

Pigmentary glaucoma

It has recently been shown that the **number** of melanin granules in the anterior chamber is strongly correlated to with the level of IOP and also with

the visual field loss. quantification of aqueous melanin by the flare-cell metre may be useful in the evaluation of cases with pigmentary glaucoma.

Raised IOP in pigmentary glaucoma is thought to be due to a **reversed pupil block mechanism**. 60% of patients with pigmentary glaucoma have posterior iris bowing, and **irido-lenticular contact**. Factors that have been shown to increase the IOP gradient between the anterior and the posterior chamber are accommodation and blinking. The iris-lens diaphragm has been shown by the micro-bubble ultrasound technique to act as a one way valve, allowing the aqueous to pass from the posterior chamber to the anterior chamber. An increases in the IOP in the anterior chamber may result in increasing the concavity of the iris. Laser iridotomy can restore the normal iris shape and decrease the irido-lenticular contact in these patients.

Eyes with pigmentary glaucoma do not show any differences in the appearance of the optic disc from eyes with primary open angle glaucoma. Aqueous melanin granules are essential in the mechanism of raised IOP in this condition. Quantification of the granules by the laser flare-cell meter is possible and reproducible, it shows increased number of granules in the anterior chamber especially after pupillary dilatation. This method may be useful in the assessment and treatment of this condition.

Neovascular Glaucoma

IOP rise in neovascular glaucoma may be due to increased permeability of newly formed vessels or angle closure by PAS formation. Another factor which may be responsible for IOP elevation is neovascular tissues which can be found in the trabecular spaces in some eyes. Patients with neovascular glaucoma have increased levels of vascular endothelial growth factor VEGF in the aqueous humour. VEGF may play a role in the development of neovascularisation in these patients. it thought that the ciliary body as well as the retina may take part in the production of this factor.

Medical Diseases Of The Retina

Central and branch retinal vein occlusion

pathogenesis

The pathogenesis of central retinal vein occlusion is not completely understood. Venous thrombus formation, venous stasis and inflammation play varying roles in the development of central and branch retinal vein occlusion. Local as well as systemic factors play parts in the pathogenesis of the disease, local factors are considered to be more important than systemic factors. Different pathogenic mechanism may be involved in first and second order branch retinal vein occlusion. **Anatomical factors** appear to be more crucial in second order branch retinal vein occlusion than in more peripheral occlusions. Narrowing of retinal veins at the A/V crossing may induce haemodynamics changes that lead to thrombus formation and venous occlusion. Among the other anatomical factors that play a role in the mechanism of the disease, is the axial length of the eye. The axial length in eyes with central or branch retinal vein occlusion appear to be shorter than controls.

Chemical mediators also play important roles in the pathogenesis of the disease. **Vascular endothelial growth factor (VEGF)** has been detected in higher levels in animal eyes with central retinal vein occlusion. Hypoxia-induced VEGF in human eyes is also likely to be the linking factor between retinal ischaemia and iris and retinal neovascularisation. Plasma **endothelin-1** (a vaso-active peptide that is released by endothelial cells) has also been shown to be raised in patients with retinal vein occlusion. The plasma levels seem to be higher in cases with ischaemic type of the disease. The exact role played by this peptide in the pathogenesis of the disease is not yet known.

aetiology

Retinal vein occlusions is a major cause of unilateral visual loss. The prevalence of this condition is estimated to be 0.7% in patients younger than 60 years of age and, 4.6% in patients older than 80 years. Central and branch retinal vein occlusion are **multifactorial** conditions. Patients presenting with branch, hemispheric or central retinal vein occlusion should be evaluated for:

- diabetes
- glaucoma
- cardiovascular diseases

In young patients, the disease may also occur secondary to retinal **congenital arteriovenous communication**. It is proposed that a turbulent flow, high intra-vascular volume and arteriolar pressure in the venous side of the malformation may lead to vessel wall damage, thrombosis and occlusion of the blood vessel. Recent reports indicate that the incidence of retinal vascular diseases may also be slightly increased in recent **contraceptive pills** users.

Antiphospholipid antibodies syndrome is a rare syndrome characterised by:

1. Recurrent venous and / or arterial thrombosis.
2. Recurrent spontaneous abortion.
3. Thrombocytopenia.

The main Antiphospholipid antibodies are the lupus anticoagulant and the anticardiolipin antibodies. Antiphospholipid antibodies may be primary, or secondary to other disease (e.g. SLE, lymphoma, dysglobulinaemia and some infections such as Q-fever). Patients with occlusive retinal diseases have a significantly high prevalence of antiphospholipids antibodies. Screening of these antibodies is indicated in patients who do not have any of the common risk factors e.g. hypertension, cardiovascular diseases or diabetes.

A recent study of 39 patients with primary antiphospholipids syndrome demonstrated that permanent pathological ocular features are rare. The study also demonstrated that, there is a high prevalence of **visual disturbances** among patients. Most of these disturbances are transient and mainly caused by central nervous system ischaemia.

Recurrent thrombosis appears to be significantly reduced with treatment with **warfarin** as compared with systemic **prednisolone** or with no treatment at all. A prothrombin ratio of 1.5 / 2.0 is recommend. It is also recommended that treatment should be continued for at least 6 months after the disappearance of the antibodies. Recurrent branch artery occlusion has, however, been reported in some patients after the disappearance of the antibodies, despite treatment with aspirin and steroids.

Retinal vein occlusion may also be associated with abnormalities in the coagulation system. **Resistance to activated protein C** has been associated with retinal vein occlusion in some younger patients. More than 90% of resistance to protein C is caused by a mutation in factor V (R 506Q), which renders activated factor V relatively resistant to its degradation by activated protein C. The prevalence of this mutation is high in white patients but very rare in blacks. Mutation of factor V has been identified in many patients with retinal vein occlusions as well as deep venous thrombosis. Screening for this mutation, in patients with

retinal vein occlusion, is recommended by some authorities in order to identify patients at risk of developing deep vein thrombosis.

Patients with central retinal vein occlusion and **family history of thrombotic diseases** should be investigated for a possible hypercoagulability conditions. **Hyper-homocysteinemia** is a risk factor for central retinal vein occlusion and may suggest a poor prognosis in patients with central retinal vein occlusion. **Thrombophilia**, **hypofibrinolysis** and raised **thrombin-anti-thrombin III complex** are other abnormalities with the coagulation system that have been reported with retinal vein occlusion. These abnormalities may be more important in retinal vein occlusion near the main vein trunk rather than in the retinal periphery.

management

The clinical course of the disease is determined by the location of the venous occlusion with relation to the fovea and the formation of collateral blood vessels. The prognosis of central retinal vein occlusion is highly unpredictable because non-ischaemic types may become ischaemic. About 54% of initially non-ischaemic eyes progress to ischaemia over one year period.

Neovascular glaucoma is a major complication after central retinal vein occlusion. Eyes with a large amounts of retinal haemorrhage obscuring capillary details of fluorescein angiography need to be monitored closely for iris, or / and angle neovascularisation. Angle neovascularisation may occur in the absence of pupil margin rubeosis. **Gonioscopic** examination should be a routine examination procedure in these patients.

- **medical treatment**

Medical treatment, in this disease, seems to be limited. Intravenous thrombolysis by **streptokinase infusion** has rarely been reported to produce dramatic improvement in the visual and angiographic features of acute central retinal vein occlusion. Treatment is, however, associated with increased risk of **life threatening bleeding** elsewhere (e.g. cerebral bleeding) and patients should be properly counselled about this risk. The risk of such life threatening bleeding is high enough to make this method of treatment unacceptable in a such non-life threatening condition as retinal vein occlusion. In a recent experimental animal study, smaller dose of streptokinase was successful in opening all the retinal vessels, which had laser-induced thrombosis, when associated with low energy ultrasound application to the animal eye. This approach may be useful in using lower safer doses of the drug.

Central retinal vein occlusion may also be associated with thrombosis at the level of the lamina cribrosa. Experimental studies showed that, by inserting a cannula in the blocked vein and injecting **tissue plasminogen**

activator, visual and angiographic improvement may be achieved. The effects of **intravitreal tissue plasminogen activator** in recent onset central retinal vein occlusion has recently been studied. Intravitreal tPA treatment (75-100 µg)for central retinal vein occlusion appears to be simple and safe, but did not significantly modify the course of the occlusion in our patients immediately after treatment.

- **laser treatment**

Laser photocoagulation in retinal vein occlusion is indicated for proliferative changes as well as for **macular oedema** in cases of branch retinal vein occlusion. In branch retinal vein occlusion with macular oedema, improved central visual function in treated eyes seems to be due to the movement of scotoma away from fixation. Scotoma size does not appear to be correlated to the improvement in the visual acuity.

Laser photocoagulation to the Bruch's membrane may also stimulate **anastomosis** between the choroidal and the retinal circulation and may be helpful in the treatment of non-ischaemic central retinal vein occlusion and in preventing ischaemic complications. The mechanism of action of this method of treatment in not completely known. The laser anastomosis seems to work by diverting part of the venous drainage away from the compromised area. Visual improvement of 6 or more lines has been reported in some patients. However the general results of this procedure are still very guarded.

Laser applications are often placed about three disc diameters nasal to the optic disc head in eyes with central retinal vein occlusion and, within one disc diameter peripheral to the occlusion site in branch vein occlusion. Avoiding the posterior ciliary artery and staying about three disc diameters away from the disc is recommended to avoid, but not guaranteed to prevent, complications. Successful cases may not be associated with any special signs. Asymmetry of the venous diameter at the disc margin and a hyper-fluorescent spindle sign one week after treatment are observed in many successful cases.

One of the major **complication** of this procedure is retinal neovascularisation at the site of treatment due to retinal ischaemia. Laser treatment to the ischaemic retina may reduce the risk of this complication. This procedure may also result in severe vitreous haemorrhage and macular scarring which might affect the final visual outcome even when the procedure is successful. Vitreous haemorrhage may need vitrectomy in some patients. Anterior segment neovascularisation may also occur after a successful treatment.

- **surgical treatment**

Retinal vascular surgery in eyes with retinal vein occlusion has become more feasible and is gaining popularity. A recent paper described a new technique for surgical **decompression** of the arteriovenous sheath via a pars plana approach. The technique appears to improve the retinal perfusion and may improve vision in some patients.

Surgical chorioretinal anastomosis has also been tried in **ischaemic** central retinal vein occlusion. In a recent study five eyes with ischaemic disease had pars plana vitrectomy, a slit like incision in the retinal veins in each quadrant of the retina, and insertion of a Mersilene suture to promote vascularisation and then pan retinal photocoagulation. the results of the study was fairly encouraging regarding a low incidence of iris neovascularisation in the treated eyes.

Branch retinal vein occlusion is occasionally complicated by retinal holes without vitreous traction or retinal traction tears, that may lead to a rhegmatogenous **retinal detachment**. In eyes with traction retinal detachment, following central retinal vein occlusion, better surgical results can be achieved in eyes without disc new vessels than in eyes with disc new vessels. The degree of retinal perfusion, the presence of angiographic factors and the distance of the site of occlusion may affect the visual and the surgical outcome.

Retinal vein occlusion in young patients

Central retinal vein occlusion in young patients is rare. The disease is rarely associated with systemic disease. It often undergoes a slow spontaneous resolution over a period of 4-6 months. Good visual recovery often occurs in most patients. Some studies on the other hand demonstrated poor visual outcome. The final visual results largely depend on the degree of retinal ischaemia as well as the presence of complications e.g. cystoid macular oedema.

The **cause** and pathogenesis of the disease is unknown. It is thought that the disease, in most cases, is caused by a mild non-specific vasculitis of the retinal or disc capillary vessels. Other investigators believe that vitreous traction may play an important role in the pathogenesis of the disease.

Routine examination should be directed at excluding **possible causes**. The following systemic and local conditions have previously been described in association with central retinal vein occlusion in young adults:

Systemic causes	Local causes
1. Hypertension	1. Glaucoma

2. Diabetes 3. Hyperlipidaemia 4. Hypercoagulability conditions (e.g. smoking, abnormal platelets function and blood diseases associated with increased viscosity) 5. Migraine 6. Mitral valve prolapse (it is thought to be due to abnormal platelets function) 7. Collagen vascular diseases 8. AIDS 9. Carotid artery disease (possibly due to the presence of atherosclerotic vascular changes in both the carotid and the retinal vessels) 10. Medications (e.g. oral contraceptives, diuretics)	2. Congenital arteriovenous malformation 3. Anterior and posterior uveitis 4. Optic nerve disease (e.g. drusen and papilloedema) 5. Trauma

treatment

Systemic **steroids** may be used in cases with other local or systemic features of inflammation. **Anticoagulants** have also been suggested by some clinician in order to promote collateral development. **Plasmapheresis** and haemodilution may also be effective in causing regression in the clinical findings and improvement in the visual acuity in some patients with mixed connective tissue diseases. **Vitrectomy** may also be indicated to relieve vitreous traction or to treat vitreous haemorrhage or traction retinal detachment.

There is a controversy about the role played by **contraceptive pills** in the risk of developing cardiovascular diseases. Case control and cohort studies suggest that taking norethisterone or levonorgestrel-containing pills (second generation pills) increases risk of developing venous thromboembolism from 5 cases per 100,000 per year to about 15 cases per 100,000 per year. Taking pills containing a desogestrel or gestodene (third generation pills) increases the risk, on the other hand, from 5 to 25 cases per 100,000 per year. There does not appear to be any data to show that the risk of having myocardial infarction is increased with any of these medications.

It is thought that the use of **HRT** is not associated with any significant cardiovascular risks, or retinal vascular occlusion. However, there are recent reports and case presentations, that highlights the possibility of an association between retinal vein occlusion and the use of HRT. Central retinal vein occlusion may be associated with celioretinal artery occlusion.

The mechanism of this condition is not completely understood. a recent case report documented this condition in a patients who had started hormone replacement therapy 6 weeks previously. The authors believe that the celioretinal artery occlusion followed the central retinal vein occlusion.

Central and Branch Retinal Artery Occlusion

aetiology

Significant carotid artery stenosis is a major cause for transient monocular blindness, retinal artery occlusion and ocular ischaemic syndrome. The presence of **emboli** does not appear to be necessary for the pathogenesis of these conditions. Embolic acute retinal artery occlusion has, however, a higher mortality rate than non-embolic disease. The presence of a retinal embolus does not necessarily indicate the presence of a significant carotid stenosis, but their presence has a 39% sensitivity and 68% specificity for the presence of a significant carotid artery stenosis. Patients with retinal emboli, even if asymptomatic, are at increased risk of having strokes, hypertension, and cardiovascular disease. Medical referral for assessment may be beneficial.

Patient with retinal artery disease, at any age, should have carotid ultrasound examination to investigate the status of the carotid artery. Selection for treatment should be based on the morphology of the lesion as well as the degree of stenosis. **Complex heterogeneous** carotid lesions are known to be associated with more vascular lesions than simple heterogeneous or homogenous lesions. In patients with severe carotid artery stenosis (70-99% reduction in carotid artery diameter), associated with symptoms (e.g. amaurosis fugax, transient ischaemic attacks, or minor ischaemic strokes), carotid endarterectomy appears to be beneficial in reducing subsequent stroke rate. Carotid endarterectomy may also change the haemodynamics in the circulation of the ophthalmic artery, central retinal artery, and some posterior ciliary vessels.

Amaurosis fugax is typically associated with carotid artery diseases. Abnormal **haematological factors** may also cause occlusive retinal vascular diseases, and amaurosis fugax. Amaurosis fugax may also be associated with intra-orbital mass lesions in young patients. Gazed evoked amaurosis has been previously described in patients with cavernous haemangiomas, optic nerve sheath meningiomas, osteoma, and neurofibroma.

Central retinal artery occlusion is rare in young adults. Systemic evaluation is necessary to rule out any life threatening conditions. **Cardiac valve diseases** are the most commonly diagnosed cause in this age group. The prevalence of cardiac valve diseases in patients presenting with occlusive vascular retinal diseases is about 25%. Investigations to rule out the presence of emboli (e.g. by trans-thoracic or by, the even better, approach of **trans-oesophageal echocardiography**) is recommended for the evaluation of the heart condition in these patients, even in the absence of retinal emboli. Tailoring the investigations according to the type of emboli (calcific, cholesterol, or platelets) does not seem to be reliable as there is inter-

and intra-observer disagreement in the diagnosis of the type of the embolus.

Other diseases causing **hyper-coagulation** or systemic emboli (e.g. atrial myxoma, subacute bacterial endocarditis, smoking, internal carotid artery disease, oral contraceptives and leukaemia) may also cause the disease. Trauma, sickle cell haemoglobinopathy (even if not associated with any contributing factors), intravenous drug abuse, SLE, varicella-zoster infection and T cell lymphoma may also cause retinal artery occlusion in children. Activated protein C resistance should also be considered in patients with retinal arterial occlusion when the usual embolic or thrombotic diseases are ruled out.

Hyper-homocysteinaemia has been identified as a general vascular risk factor. Homocysteinaemia, has a toxic effect on the vascular endothelium which may result in arteriosclerosis and arterial and venous thrombo-embolism at a younger age. Patients with Hyper- homocysteinaemia have increased risk of vascular occlusive diseases, strokes and myocardial infarction. The disease may also lead to the development of retinal artery and retinal vein occlusion and also non-arteritic anterior ischaemic optic neuropathy in young patients. This condition should be excluded in these patients who are otherwise healthy, or patients with bilateral or recurrent disease. Diagnosis is important as the high serum level of homocysteine can be lowered by high doses of vitamin B6, folic acid or betaine.

management

Patient with central retinal artery occlusion, central retinal vein occlusion, or anterior ischaemic optic neuropathy are at increased risk of developing **macro-vascular diseases** (e.g. myocardial infarction and cerebrovascular accidents). Hypertension, hypercholesterolaemia and hypertriglyceridaemia appear to be associated with vascular retinal diseases e.g. central and branch retinal artery occlusion and anterior ischaemic optic neuropathy.

Many studies demonstrated clinical benefit from treating blood pressure, higher than 160 systolic and 95 diastolic, in patients under the age of 65 with vascular retinal diseases, other studies proved this benefit in older patients as well. It is suggested that the combined treatment of hypertension, hypercholesterolaemia and the use of anti-platelets drugs would reduce recurrence in the fellow eyes. In high risk patients it has also been shown that anti-platelets therapy (aspirin 75-325 mg daily) reduces the risk of vascular death, myocardial infarction and stroke. In view of the increased mortality noticed in patient with central retinal vein or artery occlusion it seems appropriate to treat patients with anti-platelets drugs.

It is also recommended that patient taking **combined oral contraceptive pills** should discontinue the treatment if they develop retinal artery or retinal vein occlusion to avoid recurrence in the fellow eye. Patients with retinal artery or retinal vein occlusion, on the other hand, should continue treatment with **HRT** to avoid macro-vascular diseases.

Re-breathing into a bag produces hypercapnea (which increases the retinal blood flow) and hypoxia (which causes vasodilatation). Both hypercapnea and hypoxia increases the cardiac output, systemic blood pressure and also increases the ocular perfusion pressure and produce a large increase in the macular leukocyte velocity. Re-breathing into a bag might be useful in the immediate treatment of retinal arterial obstructive diseases, but they should be used with caution in elderly patients with cardiovascular diseases.

Age related maculopathy

Age related maculopathy is the leading cause of legal blindness among older people in the Western countries. Blind and partially sighted registration rates, in the UK, because of cataract, glaucoma and optic atrophy have decreased during the past 50 years. However, the incidence of registration due to age related maculopathy seems to be increasing in the order of 30-40%.

Age related maculopathy patients have greater difficulties with daily activities than patients with cataract who have the same visual acuity. The visual difficulties of these patients are better assessed using either the DLTV (Daily Living Tasks Dependant On Vision) index or the NEIVFQ (National Eye Institute Visual Function Questionnaire) index. These systems are based on several questions asked to patients about routine daily activities.

26% of eyes with age related macular degeneration (with unilateral extra-foveal choroidal neovascular membrane) develop choroidal neovascular membrane in the **fellow eyes** 5 years after presentation and are associated with poor visual acuity at the end of the 5 years period. In patients with a unilateral visual loss, the risk of visual loss in the second eye is between 7-10%. Significant risk factors for the development of exudative or non-exudative lesions include the degree of confluence of drusen within 1600 mm of the centre of the fovea, focal hyper-pigmentation, slow choroidal filling, and focal extra foveal areas of atrophy of the retina pigment epithelium.

risk factors

Some of the risk factors that has been associated with age related maculopathy include:

Drusen
Hyperopia
High body mass index in men
Decreased stromal iris pigmentation
Serum high density lipoprotein
Alcohol consumption
Tobacco smoking

Drusen are subretinal pigment epithelium hyaline deposits that may be associated with age related maculopathy. Choroidal neovascular membrane may develop in eyes with drusen and good visual acuity. Up to 40% of patients with drusen and good visual acuity, and up to 87% of fellow eyes may develop choroidal neovascular membrane in a period of 5 years. The risk of developing choroidal neovascular membrane in eyes

with drusen depends on the health status of the macula as well as on the presence or absence of hypertension. Drusen may be classified depending on their morphology into:

- Hard drusen
- Soft drusen
- Drusen of the basal lamina

Large and confluent soft drusen are thought to be clinical marker and predisposing factor for choroidal neovascular membrane. Drusen may gradually disappear spontaneously. Its disappearance may be associated with retinal pigment epithelium atrophy. The pathogenesis of drusen is not known. There are three main theories to explain the pathogenesis of the disease:

1. Transformation theory of Donders
2. Deposition theory of Muller
3. Vascular theory of Friedman

Donders proposed that drusen are directly transformed from unhealthy pigment epithelium. Muller, on the other hand, thought that drusen are deposited by an intact retinal pigment epithelium. Friedman proposed that drusen originate from blood constituents. Other workers also postulated that certain genetic mutation may result in drusen formation e.g. in Malattia Leventinese and Best disease.

Alcohol consumption (with the exception of beer), does not seem to be a risk factor for the incidence of age related maculopathy. Beer consumption, especially in men, appears to be associated with a slightly higher incidence of age related maculopathy and soft drusen development. Tobacco smoking also seems to have adverse effect on age related maculopathy. Previous smokers appear to remain at higher risk. A slower recovery from glare and more extensive fundus changes in the affected eye also appear to be risk factors for the fellow eyes involvement. A slower foveal ERG implicit time may also be an indicator of early stage choroidal neovascular membrane development because of outer retina ischaemia.

clinical features

Patients with good visual acuity may have symptoms of poor vision in dim light, and central scotoma in the dark. These symptoms reflect changes in the scotopic sensitivity and alteration in the dark adaptation mechanism. Visual loss in geographic age related maculopathy is nearly always perceived by patients as slow and gradual even when considerable decrease in visual acuity occur. This can be explained by having a transitional period during which patients switch between foveal and extra-foveal site for fixation. The complaint of sudden loss of vision

should raise the suspicion of choroidal neovascularisation which may be occult and difficult to detect.

Macular perimetry, with the scanning laser microscope, provides considerable information on the functional status of the macula. Patients with central scotoma usually develop a single **preferred retinal locus** (PRL) for fixation and reading. The preferred locus is often located in the lower and left part of the visual field. It has recently been shown that the number of preferred loci may be more than one depending on the size and the degree of illumination of the target. Patient may also use certain eye movements to maintain fixation.

The natural history of sub-foveal choroidal neovascular membrane does not necessarily lead to profound visual loss. 95% of patients have stable or improved visual acuity over a median follow up period of 87 months. The size of the choroidal neovascular membrane seems to be the only variable associated with long term visual acuity.

In age related macular degeneration, **choroidal neovascular membrane** can be classified, according to fluorescein angiography, into two types, classic and occult:

Classic	Occult
The typical features of classic choroidal neovascular membrane are: • Areas of bright hyper-fluorescence, • Well demarcated • Identified in the early stages of fluorescein angiography • Progressive pooling of the dye in the later stages of the angiogram. • The fibrovascular tissue grows in subretinal space in classic membranes.	Occult choroidal neovascular membrane, on the other hand, include lesions with the following characteristics: • A fibrovascular pigment epithelium detachment with hyper-fluorescence, (not as bright as with the classic choroidal neovascular membrane), within 1 to 2 minutes after the fluorescein injection with staining or leaking of the dye later on, or • The presence of areas of late leaking of undetermined origin, or • The presence of both features. • The location and the extent of occult subretinal membrane is difficult to delineate with fluorescein angiography. • The fibrovascular tissue grows on the choroidal side of the retinal pigment epithelium in occult membranes.

Peripapillary membranes accounts for less than 10% of choroidal neovascular membranes. Their rate of growth is very unpredictable and treatment is only recommended if the fovea is threatened. Small symptomatic peripapillary choroidal neovascular membrane can be completely treated by laser, but massive lesions (3.5 disc diameter or bigger) only need partial laser treatment. In these massive lesions, treatment is often applied to the active edge of the membrane that

threatens the fovea. Patients under 40 years of age often have a unilateral disease and seem to have a better prognosis. Early and aggressive laser treatment is recommended in older patients, while conservative treatment is needed in younger patients. Aggressive treatment may result in ischaemic optic neuropathy.

retinal angiography

Fluorescein angiography is the main diagnostic tool used in age related maculopathy. Indocyanine Green is, however, considered more superior when used with confocal scanning laser ophthalmoscopy, because of its biophysical properties:

1. Indocyanine dye has a better penetration through blood and overlying pigments.
2. It is also highly protein bound (98%), which account for its relatively slow and limited leakage through fenestrated blood vessels compared with fluorescein. About 11% of patients, however, demonstrate intraretinal leakage of the dye between 14 and 34 minutes after injection.

Fluorescein angiography should be performed in all patients with suspected choroidal neovascular membrane membranes as it is more useful in identifying **classic** membranes than the Indocyanine Green angiography technique. It might not be possible to administer fluorescein intravenously in some patients (e.g. children). **Oral fluorescein,** when used with confocal scanning laser ophthalmoscopy, appears to produce good enough images to enable diagnosis of most retinal disease. Oral fluorescein angiography might also be associated with less side effects than intravenous administration.

Indocyanine green angiography is beneficial in demonstrating choroidal neovascular membrane under haemorrhagic retinal pigment epithelium detachment. The angiographic features of Indocyanine green angiography in age related maculopathy varies in the size of the changes as well as in the degree of fluorescence and the presence or absence of late leak. Choroidal neovascular membrane can be classified into three types, based on the size of their Indocyanine green angiographic features:

Plaques (commonest, poor visual outcome).
Focal spots.
Combined type(rare).

Plaque choroidal neovascular membrane tends to become larger with time. The resulting loss of visual acuity, however, is not significant, and is slightly correlated with the extension of the lesion. Patients with the plaque type choroidal neovascular membrane are generally considered untreatable, whereas patients with the spot type may benefit from laser

treatment. Eyes with the focal spot on the edge of the plaque (marginal spot) may also benefit from laser treatment and may show improvement in the visual acuity after treatment.

Indocyanine Green angiography is useful in demonstrating well demarcated choroidal neovascular membrane in about 50% of eyes diagnosed of having occult choroidal neovascular membrane and in about 80% of eyes diagnosed of having pigment epithelium detachment. Indocyanine green angiography may be useful in **predicting** the visual outcome in eyes with choroidal neovascular membrane. In a study of 89 eyes, the angiograms were classified into 4 types based on the whether the choroidal neovascular membrane is well or poorly demarcated and also on the presence or absence of late leak. Well demarcated choroidal neovascular membranes with late indocyanine green leak were associated with the highest risk of visual loss.

Indocyanine Green angiography can also delineate occult choroidal neovascular membrane, choroidal neovascular membrane with overlying subretinal fluid or haemorrhage and also choroidal neovascular membrane with retinal pigment epithelium detachment. Although ICG angiography may enhance visualisation of choroidal neovascular membrane associated with serous retinal pigment epithelium detachment in age related maculopathy, **ICG-directed laser treatment** does not appear to improve visual acuity when compared with no treatment. Indocyanine green angiography-guided laser photocoagulation may temporarily stabilise visual acuity in some eyes with occult choroidal neovascular membrane, and choroidal neovascularisation associated with pigment epithelial detachments. Final visual acuity, however, seems to decrease with time.

Retinal-choroidal anastomosis can present as a primary manifestation of the exudative process in age-related macular degeneration. Specific clinical and angiographic features have been identified that can aid in the diagnosis of these vascular anomalies. Their presence represents a poor prognostic sign for successful ICG-guided laser treatment. Clinical evidence of pre-retinal and intraretinal haemorrhage and cystic oedema coupled with angiographic evidence of intraretinal dye leakage were key features of retinal choroidal anastomosis.

The prevalence rate of serious **side effects** after fluorescein angiography is estimated to be about 0.7%. Photo-toxic or photo-allergic reactions to fluorescein in humans have been reported only rarely. Patients may experience marked cutaneous erythema, oedema and pain to sun-exposed areas within 1 hour of exposure. Drug **incompatibility** has been noticed when promethazine and fluorescein are mixed together in the syringe because of the formation of microscopic precipitates. This precipitation reaction may result in delayed and ineffective treatment of the allergic response as well as causing more complications if the precipitates are injected.

Indocyanine green angiography seems to be as safe as fluorescein angiography. Adverse reactions are reported in only 0.34%, most of these are mild reactions (e.g. nausea, rash, urticaria and urgency to defecate). Treatment for shock may be needed for patients with severe hypotension.

optical coherence tomography

Optical coherence tomography is a new non-contact, non-invasive imaging technique that is similar to ultrasound but with using light rays, instead of acoustic waves, to provide a cross-sectional image of the posterior segment with micrometer scale resolution. It has a high depth of resolution (10 micro-meter), compared to (150 micro-meter) with the standard ultrasound technique and (20 to 40 micro-meter) with the high frequency ultrasound and (300 micro-meter) with the scanning laser tomography. The technique is useful in the quantitative evaluating of subretinal and intraretinal fluid, assessing subfoveal involvement and also in monitoring response to laser treatment. Optical coherence tomography does not seem to be able to detect choroidal neovascular membrane beneath serous detachment.

scanning laser ophthalmoscopy

The Heidelberg confocal laser ophthalmoscopy can be used to study retinal and macular diseases. It provides non-invasive quantitative measurements of the neuro-sensory retinal detachment. It is also useful in the examination of the vitreoretinal interface for conditions e.g. epiretinal membranes. The technique has a good reproducibility for measuring the height of retinal lesions especially when used with dilated pupils. In scanning laser tomography the Z profile signal width analysis offer a non-invasive objective topographic index of macular retinal thickness. The peak intensity of this signal is assumed to indicate the depth of the vitreous internal limiting membrane interface.

Treatment of choroidal neovascular membrane

Idiopathic choroidal neovascular membrane is an uncommon condition that affect patients younger than 50 years of age with no other ocular pathology. It is an important cause of visual loss in young Japanese patients. The prognosis of this condition is thought to be better than age related choroidal neovascular membrane, with many eyes retaining useful vision many years after presentation. Conventional fluorescein angiography is often unhelpful in the evaluation of these eyes. Choroidal vascular anomalies, as shown by Indocyanine Green Angiography appear to predispose to the formation of these membranes. Regression may be indicated by the finding of a dark rim surrounding the choroidal neovascular membrane in Indocyanine Green Angiography. Laser photocoagulation of these idiopathic membranes has been

recommended by previous studies. Current opinion, on the other hand, recommends conservative treatment based on the often good prognosis of the condition.

- **laser photocoagulation**

About 87% of primary choroidal neovascular membrane, in age related maculopathy, are **ill-defined** by fluorescein angiography and can not be treated adequately by laser. Persistence and recurrence of age related choroidal neovascular membrane is another big problem that may lead to further visual loss. Recurrent membranes are often poorly defined by the fluorescein angiography. Indocyanine green angiography can achieve a better imaging in about 30-40% of ill-defined membranes, and can also achieve a better definition of recurrent and persistent membranes. It does not however seems to be beneficial in well defined recurrent membranes, or in cases where fluorescein angiography does not reveal any recurrent choroidal neovascular membrane.

In age related **subfoveal** choroidal neovascular membrane, direct laser photocoagulation is often associated with a sudden and a dramatic decreases in visual acuity. Photocoagulation of the **feeder vessels**, as detected by fluorescein angiography, has been successfully tried in these cases. Some studies demonstrated 70% reduction in macular exudate, and 68% stabilisation or improvement in visual acuity. Good prognostic factors for the treatment include small vessels, larger distance of laser burns from the fovea, and the absence of fibrous tissue. Dynamic indocyanine green angiography can detect smaller feeder vessels and can also detect incomplete treatment in some cases. The success or failure of treatment seems to be related to the width, length, and number of the feeder vessels.

Soft confluent drusen are major risk factor in the development of choroidal neovascular membrane especially in fellow eyes with age related maculopathy. There are conflicting reports regarding whether laser photocoagulation might prevent neovascular complications and blindness in these cases. Some studies showed evidence of decreased risk of exudative age related maculopathy development and improvement in the visual acuity after treatment. Other studies, on the other hand, showed that laser treatment in high risk fellow eyes may increase the short term incidence of choroidal neovascular membrane. Choroidal neovascular membrane associated with laser photocoagulation to soft drusen often develop at the site of treatment, and are often occult. Surgical excision of these choroidal neovascular membrane may be associated with good visual prognosis because the membranes are often extra-foveal, and the degree of cell damage is often focal.

More than 50% of treated eyes with choroidal neovascular membrane develop resistant or **recurrent** choroidal neovascular membrane within 3 years after treatment. Additional damage to the visual function may result

from the persistence or the recurrence of neovascularisation. Clinical examination probably cannot replace fluorescein angiography in detecting all recurrent choroidal neovascular membrane after laser treatment. The protocol used in the macular photocoagulation study to detect recurrent lesions recommend repeat fluorescein angiography at 3 and 6 weeks and then at 3, 6, 9 and 12 months after treatment. A definite recurrence is indicated by the leaking of fluorescein dye at the periphery of the treated areas at late stages of fluorescein angiography, the area of leakage is often preceded by intense hyper-fluorescence early in the course of the angiogram. Other features of recurrence are Focal staining along the edges of the laser lesions, blocked fluorescence from subretinal haemorrhage that was not documented previously, and speckled hyper-fluorescence noted beyond the edges of the laser lesions.

- **Sub-threshold laser retinal photocoagulation**

Sub-threshold laser retinal photocoagulation is a new technique that uses Nd:YLF non-visible retinal laser photocoagulation to reduce the side effects of the conventional laser photocoagulation methods. The technique involves using short laser pulses that remains confined to the retinal pigment epithelium layer, with little or no thermal effect on the photo-receptors layer. Recent experimental studies showed that this technique is useful in many retinal conditions e.g. diabetes, drusen, and central serous retinopathy. A recent multicentre randomised study also showed that infra-red diode laser photocoagulation, with sub-threshold laser burns, to macular drusen in non-exudative age related maculopathy reduces macular drusen and improve visual acuity. Long term effects in the fellow eyes is not known.

- **teletherapy**

Laser photocoagulation of subfoveal choroidal neovascular membrane results in the destruction of the overlying retina with sudden and dramatic visual loss. The rationale of radiation therapy is based on the fact that **growing blood vessels are more sensitive to radiation** damage than mature vessels. Ionising radiation, unlike laser photocoagulation, has been shown to induce regression of choroidal haemangioma and choroidal neovascular membrane without thermal damage to the overlying retina. Radiotherapy also appears to have a favourable treatment effect in eyes with subfoveal neovascular membranes and haemorrhage associated with **pathological myopia**.

Low dose of radiation has been reported to cause regression of the subretinal vessels and maintain the central vision in a significant number of patients. In some studies low dose of radiation (1000 c Gy in 5 fractions) has been reported to cause **significant regression** of the choroidal neovascular membrane, and maintained the central vision in about 77% of eyes after 12 months. Some other studies, on the other

hand, showed that external beam radiotherapy, when using this dose, is not effective. The long term benefit of radiotherapy on the anatomical and visual outcome has been described in a recent study. The visual acuity, in this study, improved by 2 or more lines in 34% of patients after 12 months, in 31% of cases after 18 months, and in 32% of cases in two years. Long term complications may include radiation neuropathy, retinopathy, branch retinal vein occlusion and choroidal vasculitis.

After radiotherapy for age related maculopathy, a subgroup of patients may experience **extensive growth** of choroidal neovascular membrane after radiation, causing greater functional damage than occurs spontaneously. The crystalline lens may also shows **pre-cataractous** changes, in some patients, six months following radiotherapy. Most of these changes disappear after 12 months. A recent report also showed that radiation therapy to subfoveal choroidal neovascular membrane may be associated with an **unusual pattern of choroidal neovascular membrane**, characterised by the presence of round vascular blebs at the end on the neovascular membrane. This unusual pattern appears to be associated with a poor prognosis for vision.

The usual method of treatment often require a CAT scan and a face mask for the delivery of the radiation. A new method of delivery that does not require a CAT scanning has been described in a pilot study. This technique would significantly reduce the cost of treatment.

Ophthalmic **plaque radiotherapy** can also be used to treat neovascular age-related macular degeneration. The advantage of this technique is that it is a unilateral treatment, which allows a larger dose to be delivered to the macula with less irradiation of normal ocular structures. The technique does not seem to be associated with sight threatening complications e.g. radiation retinopathy, optic neuropathy, or cataract.

- **medical treatment**

VEGF and other growth factors play a role in the pathogenesis of the disease and the development of choroidal neovascular membrane. Anti-angiogenic medications have been tried for the treatment of the disease with varying results. These medications include:

Steroids
Interferon-alpha
Thalidomide (in non-pregnant patients!)
Pentoxifylline
Isotretinoin

Choroidal neovascular membrane may develop in young patients with posterior segment inflammatory conditions (e.g. punctate inner choroidopathy, and multifocal inner choroidopathy). In these conditions when no other cause for the choroidal neovascular membrane is found, a

course of **oral steroids** (60-80 mg per day for about 3,5 days, then reduced gradually over a period of 6-8 weeks) may reduce leakage and stabilise vision.

Interferon has an anti-proliferative effect on the vascular endothelium. In clinical studies, Interferon provided no benefit as a treatment for choroidal neovascularisation secondary to age-related macular degeneration. It may also associated with marked side effects which include flu-like symptoms, leucopaenia, thrombocytopenia, increase liver enzymes, alopecia, nausea, fever and suicidal depression. Treatment with interferon alpha may also be associated with Interferon-associated retinopathy. Two weeks to three months after the start of interferon therapy retinal haemorrhage and cotton wool spots appear. The incidence of retinopathy depends on the initial dose of the drug.

Pentoxifylline is a methyl xanthine derivative that has been used in the treatment of vascular insufficiency diseases because of it's ability to improve the blood flow. The drug can produce a vasodilatation effect in rats muscles. It can also increase the blood flow because of its vasodilatation effect, decreasing the blood viscosity and also because of its ability to improve the deformability of the red and white blood cells. Oral administration of Pentoxifylline in healthy volunteers produces a significant improvement in the retinal capillary blood flow velocity and viscosity but not in the filterability of the whole blood. Pentoxifylline might be useful in the treatment of age related maculopathy. A three months course of Pentoxifylline increases the choroidal, but not the retinal, blood flow in patients with age related maculopathy.

- **surgical excision of the choroidal neovascular membrane**

About 80% of choroidal neovascular membrane are not treatable with laser photocoagulation because they lie under the fovea, and laser photocoagulation is associated with dramatic visual loss after the treatment. Surgical excision of the choroidal neovascular membrane is a relatively new method of treating subfoveal choroidal neovascular membrane.

It is now known that **choroidal neovascular membrane** may be classified into two types, type 1 and type 2. Age of the patient, and clinical features of the fundus may help in the differentiation of the two types. Older patients seem to be more prone to type 1, while younger patients are to type 2. Type 2 is characteristically associated with subretinal pigmented halo or plaque in the area of the membrane, and also with a well defined border of the membrane.

Type 1	Type 2
located beneath the retinal pigment epithelium, some portion of the membrane enters the subretinal	located between the sensory retinal and the retinal pigment epithelium.

space.	
occurs mainly in older patients.	occurs mainly in younger patients e.g. POH and myopia and idiopathic.
can not be excised with removing the retinal pigment epithelium at the fovea.	Can be excised surgically.

Surgical removal of type 1 choroidal neovascular membrane is often associated with damage to RPE and disruption of the function of overlying retina. During surgical excision of age related choroidal neovascular membrane, the Bruch's membrane and the retinal pigment epithelial cells are damaged to varying degrees, resulting in poor visual outcome. The extent of the damage of the Bruch's membrane affect a the future growth of transplanted RPE cells. Injured Bruch's membrane does not allow growth or differentiation of the host or the transplanted RPE cells. Recurrence of choroidal neovascular membrane after surgical excision is often due to incomplete excision of an occult membrane. Re-surfacing of the membrane with by RPE and fibroblasts may play a part in limiting visual improvement after the surgical excision.

When there is **subretinal haemorrhage** affecting the macular region, the final visual acuity depends on the underlying cause and the duration of the haemorrhage. Sub-macular haemorrhage secondary to age related macular degeneration have a poor visual prognosis after surgical treatment. The addition of tissue plasminogen activator can assist clot lysis but it does not appear to improve the visual outcome from surgery. In sub-retinal haemorrhage, from different causes (e.g. trauma), pars plana vitrectomy with subretinal tissue plasminogen injections is possible and may be associated with improved visual acuity. It has been shown, in an animal experimental studies, that intravitreal injection of commercial tissue plasminogen activator solution results in dose-dependent retinal toxicity in cat eyes. Intravitreal injections of commercial tissue plasminogen activator in concentrations greater than 25 µg/0.1 mL may be potentially unsafe in human eyes.

non-age related choroidal neovascular membrane

The results of surgical excision of non-age related choroidal neovascular membrane are promising. It is controversial whether laser photocoagulation is useful in the treatment of myopic choroidal neovascular membrane. A recent study shoed that surgical excision of choroidal neovascular membrane in myopic patients may result in visual improvement in some patients.

Selected eyes of children with choroidal neovascular membrane may also benefit from surgical excision. Postoperative visual loss may be noticed in eyes with good preoperative visual acuity. The assessment of vision on the basis of Snellen visual acuity alone is misleading. Reduction

of visual distortion may be achieved even in the presence of the same visual acuity after surgery. Recurrences of the choroidal neovascular membrane may occur after surgery, especially in eyes with subfoveal haemorrhage. Repeat surgery does not seem to be associated with worsening of the visual acuity. RPE atrophy and older age may be associated with poorer outcome.

- **retinal pigment epithelium transplantation, and foveal trans-location**

Current experimental therapies, such as photoreceptor transplantation and implantation of a visual prosthesis, are based on the fact that some inner retinal neurones are preserved after death of photoreceptors as shown in patients with retinitis pigmentosa. Despite a statistically significant loss of cells in all retinal layers, a large percentage of the **inner retinal neurones** appear to remain histologically intact. A healthy Bruch's membrane appears to be important for the success of RPE transplantation. Macular trans-location in patients with subfoveal choroidal neovascularisation, from age-related macular degeneration, offers a potential for improving visual function. It may be associated with less loss of vision than the disease itself, if allowed to progress.

The technique of **foveal translocation** involves vitrectomy with or without lensectomy, creation of retinal detachment by a retinotomy, removal of the subfoveal membrane and retinal re-attachment with trans-location of the fovea. Trans-location of the fovea may also be achieved after performing scleral resection in the superior temporal or inferior temporal equatorial sclera, suturing the edges of the resected scleral will, subsequently, result in scleral shortening and foveal trans-location. Laser photocoagulation of the subfoveal choroidal neovascular membrane (which is now not subfoveal) would be possible. Surgical shortening of the sclera is useful in the management of several retinal disorders, but causes significant changes in axial length.

Foveal translocation may also be achieved by **redistribution and mobilisation of the neuro-sensory retina**. Relocation of the fovea is achieved by utilising the natural redundancy of the neuro-sensory retina. Stabilisation of the retina is then achieved by using perfluorocarbon liquid, intra-operatively, and silicon oil postoperatively. Vascular occlusion, RPE changes, macular hole formation, and epiretinal membrane formation are all possible complication after surgery.

This technique has also been used in choroidal neovascular membrane in **myopic** eyes. Visual acuity have been reported to improve from 20/200 pre-operatively to 20/20 postoperatively in some patients after this technique. The postoperative results of this technique, however, do not appear to be predictable. Oblique astigmatism, transient diplopia, torsional and micropsia may occur after surgery. These side effects may resolve with time due to the development of suppression. Other

complications may include development of epimacular proliferation, retinal detachment and neovascular glaucoma.

- **photodynamic therapy**

Photo-dynamic treatment is a new method for selective treatment of subfoveal choroidal neovascularisation secondary to age related maculopathy and also in selected cases with choroidal neovascular membrane secondary to pathologic myopia, ocular histoplasmosis syndrome, angioid streaks and idiopathic causes. The technique causes occlusion of the neovascular tissue with minimal damage to the healthy surrounding structures. This mode of treatment involves intravenous injection of a photosensitiser dye, followed by irradiation of the photosensitised tissue by a suitable light.

Photodynamic therapy has been applied successfully for experimental treatment of tumours as well as for photo-thrombosis therapy for normal and abnormal blood vessels. It is generally accepted that the dye binds to the endothelium lining of the choroidal neovascular membrane. Light induced activation of the dye generates oxygen radicals which would then starts a clotting mechanism inside these abnormal vessels. Release of free radicals from the sensitised tissue also leads to structural damage of cells membranes and cell death.

A liposomal preparation of benzoporphyrin derivative (**Verteporfin**) have been shown to be safe and effective for use in the treatment of choroidal neovascular membrane since the dye can easily be taken by the growing vessels. Effective occlusion of normal choroidal vessels can also be achieved by using the new photosensitiser **NPe6**, with minimal injury to overlying neuro-sensory retina. Both NPe6 and the benzoporphyrin have a strong far-red absorption and rapid skin clearance, but NPe6 differs from the benzoporphyrin in that it is hydrophilic and can be available in aqueous preparation. **Lutetium texaphyrin (Lu-Tex)** is a new agent that may be used in the treatment. Lutetium texaphyrin (Lu-Tex) is a water soluble agent that has the advantage of being used as a dye for diagnostic angiography, as well as for therapeutic causes in photodynamic therapy.

ATX-S10(Na) is a new Photosensitiser that has recently been shown to induces selective occlusion of choroidal neovascular membrane in non-human primate eyes. Occlusion of choroidal neovascular membrane without direct damage to the sensory retina is useful to preserve visual acuity The dye might have a therapeutic application in the clinical practice.

A new **hypothesis** has been put forward to explain few of the clinical and angiographic features of treatment that can not be explained by the traditional hypothesis. It is thought that light activation of the dye would lead to liberation of oxygen radicals, which act on the red blood cells, first

of all, to liberate haemoglobin which has a vasoconstriction effect. Flow reduction to the treated area may, thus be due to vasoconstriction of the vessels, followed by clotting of the slowed down blood.

Post-treatment fluorescein angiography shows significant **reduction in the filling of the choroidal neovascular membrane** and also reduction of the late phase leaking. An area of choroidal hypo-fluorescence is also noticed for about one week after treatment. A recent non-randomised, multicentre, open-label, clinical trial showed that photo-dynamic therapy achieves short-term cessation of fluorescein leakage from choroidal neovascular membrane without loss of vision or growth of classic choroidal neovascular membrane in some patients after a single treatment. Non-perfusion of neuro-sensory retinal vessels at high light dose (150 J/cm²) may occur in some patients. Fluorescein leakage from at least a portion of the membrane reappears by 4 to 12 weeks after treatment in almost all cases.

Multiple laser treatments appears to achieve repetitive, short-term cessation of fluorescein leakage without loss of visual acuity. There is concern, however, that re-treatment may result in progressive thinning of the neuro-sensory retina with loss of photoreceptor outer segments and nuclei in the rabbit eye. Animal studies showed that repeated applications is associated with limited damage to the retina when using 6 mg/ m² Verteporfin. High doses of the dye may, however, be associated with significant damage to the retina, choroid and the optic nerve.

The 12 months results of this treatment were recently reported in a multicentre, double-masked, placebo-controlled, randomised clinical trial. 61% of treated eyes, lost fewer than 15 letters of visual acuity, from baseline, compared with 46% of untreated at the end of a 12 months period examination. The visual results of the study were strikingly better in eyes with predominantly **classic** choroidal neovascular membrane (classic choroidal neovascular membrane was defined as a membrane with a classic component that is equal to or greater than 50% of the area of the entire lesion). There was no difference in visual outcome in patients demonstrating less than 50% classic choroidal neovascular membrane at the initial visit. Other reports showed that results may vary depending on intraocular pressure, region of fundus treated, ocular pigmentation, and the total time of exposure to the photosensitizer.

The **protocol** of treatment that was used in the recent trial includes:

1. Injection of 6 mg / square meter of body surface area of Verteporfin.
2. Fifteen minutes after the start of the infusion, a laser light at 689 nm delivered 50 J/cm^2 at an intensity of 600 mw/ cm^2 over 83 seconds.
3. A spot size with a diameter 1000 µm larger than the greatest linear dimension of the choroidal neovascular membrane lesion was used.
4. At follow-up examinations every 3 months, re-treatment with the same regimen was applied if angiography showed fluorescein leakage.

Possible **adverse** effects of the treatment include:

1. Transient visual disturbances
2. Injection-site adverse events
3. Infusion-related low back pain.
4. Transient photosensitivity reactions

- **trans-pupillary thermotherapy**

Trans-pupillary thermotherapy may provide an alternative method of treatment for subfoveal choroidal neovascular membrane. The technique has been used successfully in treating choroidal malignant melanoma. In this technique, heat is delivered to the choroid and retinal pigment epithelium with a modified diode laser. Near infrared radiation is ideal for this technique as tissue penetration is high and absorption by the ocular media is minimal. Thermal treatment for choroidal neovascular membrane needs less choroidal tumours, and damage to the surrounding retina is, thus, expected to be small. Earlier studies showed no significant side effects from this method of treatment.

- **optical methods**

The Implantable Miniaturised Telescope (IMT) is a new approach to aide vision in patients with dry age related maculopathy. The telescope consists of a 3X telescope that is contained in carrying device made of PMMA that can be implanted in the capsule bag under local anaesthesia. The IMP provide improvement of the central visual acuity in the implanted eye for reading, while the other eye cam be used for peripheral navigational vision. The implant has a universal power, fine adjustment of vision can be achieved by wearing low power plus or minus spectacles. 91% of patients tried with this device reported improvement in viewing television, and 66% reported improvement in reading vision. The advantages of the implant is that it provides magnification of vision without the need to hold the device by hand, which avoid the relative movements between the eye and the hand. Transient postoperative difficulty in orientation may be noticed by some patients.

- **genetics**

Determining the genetic locus of the disease and targeting it may provide an effective way of treatment. Studies are currently underway to investigate the relationship of age related maculopathy and the ABCR gene which code for the retinal photoreceptors, and which has been found to be altered in patients with Stargardt's disease.

Diabetic retinopathy

epidemiology and natural course

Diabetic retinopathy is an important cause of visual loss in relatively younger patients. The presence of severe diabetic retinopathy and poor vision is also considered as a risk factor for the development of ischaemic heart disease and death. The prevalence of diabetic retinopathy in newly diagnosed non-insulin dependant diabetics is estimated to be 39% in men and 35% in women. In a population based incidence study, of 634 insulin dependant diabetics, 14 years rate of progression of diabetic retinopathy was estimated to be 86%, regression 17%, and progression to proliferative diabetic retinopathy was 37%. The incidence of macular oedema was estimated to be 26%.

Male sex, higher glycosylated haemoglobin, higher diastolic blood pressure, and proteinuria are factors that may be associated with progression of diabetic retinopathy. A 10 mm Hg or more increase in the systolic **blood pressure** is associated with an increased incidence of diabetic retinopathy in younger onset diabetic patients. Reduction of hyperglycaemia and blood pressure may be associated with a decreases in the progression of diabetic retinopathy to proliferative diabetic retinopathy. The presence of gross **proteinuria** is associated with Increased risk of developing macular oedema. The risk of proliferative diabetic retinopathy in patients with gross proteinuria is also higher than in patients without proteinuria. Micro-albuminuria (between 0.03 and 0.29 g/l) is also associated with greater risk of developing retinopathy in diabetic patients and also with the presence of proliferative diabetic retinopathy in younger onset patients.

basic science

The pathogenesis of diabetic retinopathy is not completely understood. **Hyperglycaemia**, retinal blood flow, retinal capillary occlusion and non-perfusion, growth factors, hormonal factors, and dietary factors play important role in the pathogenesis of the disease. High concentrations of glucose can stimulate the transcription of genes coding for growth factors which may influence the glucose regulatory mechanisms of the retina, and consecutively, affect progression of diabetic retinopathy. Retinal blood flow and oxygen consumption appear to be increased during periods of acute hyperglycaemia. It has been suggested that increased retinal blood flow, and increased ocular perfusion pressure may play a role in the development of diabetic retinopathy and also a role in the progression of the disease to proliferative diabetic retinopathy in the younger onset groups.

Retinal capillary occlusion and non-perfusion is a common feature of diabetic retinopathy. **Haemodynamics** factors, increased blood viscosity and decreased red blood cells deformability are believed to be important

factors in causing capillary occlusion and retinal non-perfusion. Both increased and decreased blood flow have been described. In a recent study it was found that pulsatile choroidal blood flow, but not the retinal blood flow, increases with the progression of diabetic retinopathy.

Micro-displacement of the **RBC cell membrane** indicates the deformability of the cells, which is directly related to its ability to pass through small retinal blood vessels and retinal capillaries. The RBC cell membrane micro-displacement is reduced in eyes with advanced diabetic retinopathy. This indicates that the RBC are unable to pass through small vessels causing capillary occlusion and areas of retinal non-perfusion.

Renin is a major vaso-active agent that is thought to play an important role in diabetic retinopathy. There are evidences that there is an intraocular **Renin-Angiotensin** system independent of that in the circulation. Vitreous levels of pro-renin in diabetic patients is higher than that in non-diabetic patients suggesting an activation of the Renin Angiotensin system in diabetics. Intraocular synthesis of angiotensin II may be involved in the blood supply and also in the pathogenesis of vascular processes e.g. neovascularisation in diabetic retinopathy. Serum total renin concentration is elevated in patients with active diabetic retinopathy, irrespective of the renal and the autonomic system functions. Diabetic retinopathy appears to be the most important determinant of serum renin in patients with insulin dependent diabetes. It is possible that serum total renin concentration could be used as a marker for activity in diabetic retinopathy in patients with insulin dependent diabetes.

Growth factors are likely to be involved in the pathogenesis of Proliferative diabetic retinopathy. Vascular endothelial growth factor (VEGF) is a glycoprotein that is secreted by the endothelial cells and pericytes in the retinal blood vessels. It plays an important role in the regulation of Angiogenesis in the developing eye and also in many pathological conditions (e.g. diabetic retinopathy, central retinal vein occlusion, choroidal neovascular membrane, ROP, corneal neovascularisation and wound healing, and iris neovascularisation). Vascular endothelial growth factor is also believed to be the most likely factor responsible for the development of diabetic retinopathy, and proliferative diabetic retinopathy.

Hypoxia increases VEGF levels in the retina, and vitreous. The vitreous levels of vascular endothelial growth factors is significantly higher in patient with proliferative diabetic retinopathy than in eyes without proliferative diabetic retinopathy. Systemic hyperoxia can lower retinal VEGF gene expression and re-oxygenate ischaemic retina. Other growth factors (e.g. Insulin-like growth factor 1 and fibroblast growth factor), and chemical mediators, (e.g. Interleukin 8, and interferon-induced protein) are present in the vitreous in eyes with active proliferative diabetic retinopathy more than controls, and may also play an important part in the pathogenesis of the disease.

High levels of serum **Laminin** (a glycoprotein) have been reported in patients with proliferative diabetic retinopathy. It is thought that a substantial amount of this chemical is secreted by the retinal basement membrane. Laminin levels reflect changes in the basement membrane in diabetic retinopathy. It has also been proposed that Laminin may be considered as an indicator for diabetic retinopathy. It is not however an early indicator of the disease. It should be mentioned that this chemical may be reduced after panretinal laser photocoagulation.

Diabetic retinopathy rarely occurs before puberty suggesting that **sex hormones** may play a role in its pathogenesis. The blood retinal barrier appears to remain stable until puberty and then progressively declines afterwards. There seems to be an association between puberty, decline of the blood retinal barrier and the development of diabetic retinopathy. Increased androgen activity may also be associated with progression of retinopathy in male subjects with type 1 diabetes.

The effects of **dietary factors** on diabetic retinopathy are not completely known. In one study of 387 patients with type 2 diabetes, antioxidants nutrients (vitamin C, E and beta-carotene) had no protective effects on diabetic retinopathy. It also appears that these nutrients may be associated with worsening of the diabetic retinopathy in some patients depending on their insulin use.

screening for diabetic retinopathy

Screening programs for diabetic retinopathy are proved to be **cost effective**. Screening reduces the risk of blindness in diabetic patients by 50%. There is no agreement, however, on the best method of screening for diabetic retinopathy. The prevalence of diabetic retinopathy seems to be higher when screening is carried out by photos and clinical examination than by either method alone. When screening sensitivity is high (e.g. by expert Ophthalmologists) the frequency of screening makes little difference to the years of sight saved, but when sensitivities are close to 50% the frequency of examination seems to be an important factor. Biannual, (rather than annual) screening may be considered when the screening sensitivity is high.

clinical features

Patients with diabetes, with or without diabetic retinopathy, may suffer from visual loss, loss of contrast sensitivity, and abnormalities in colour perception ((tritan-like defect). **Visual pathway dysfunction** may also occur in the absence of obvious diabetic retinopathy or hyperglycaemia. The mechanism underlying this abnormality is unknown. The visual loss may be caused by reversible changes in retinal function at the ganglion cell layer. Reduced retinal oxygenation seems to be contributing factor.

Senile **cataract** is commoner in diabetic patients. Diabetic patients are also more likely to develop cataract at an early age. Cataract surgery in patients with diabetic retinopathy is often associated with good visual results, especially if the retinopathy is well controlled by laser photocoagulation before hand. Patients with severe non-proliferative diabetic retinopathy or more advanced retinopathy have poor results. There are several advantages of **ECCE** in cataract surgery in diabetics; the technique allows a can opener capsulotomy technique which will avoid postoperative capsule phymosis and opacification of the anterior capsule, it also allows implantation of a large 7 mm IOL to make further fundus examination and laser photocoagulation easier. A recent study, however, showed that **phacoemulsification** surgery may be associated with a better visual acuity and less postoperative inflammation than ECCE. The visual results and rate of retinopathy progression after phacoemulsification surgery does not seem to differ significantly from those reported with other techniques.

The main causes of **poor results** in these patients are macular oedema or proliferative diabetic retinopathy. It is thought that clinically significant macular oedema found at the time of surgery is unlikely to resolve spontaneously and laser treatment should be carried out without delay. Macular oedema appearing after surgery may however regress spontaneously, and conservative treatment may be taken.

Diabetic retinopathy is occasionally very **asymmetrical** between the two eyes. Asymmetry of bilateral diabetic retinopathy may be related o the presence of carotid artery disease or to posterior vitreous detachment. Complete posterior vitreous detachment, optic atrophy, and high myopia are considered to be protective factors against the development of severe proliferative diabetic retinopathy.

Macular oedema is estimated to develop in 20.1 % of the younger onset diabetics, 25.4% in the older onset patient taking insulin, and 13.9% in non-insulin patient over a 10 years period. Macular oedema is an important cause of visual loss in diabetic retinopathy. Light sensitivity is reduced in oedematous areas. Recent studies showed that the correlation between the amount of oedema and visual function is not significant. Reduction in hyperglycaemia may result in reduction in the incidence of the macular oedema. Vitreous abnormalities and vitreo-macular adhesion may play a role in the pathogenesis of diabetic macular oedema in some eyes. Eyes with diabetic retinopathy are more likely to develop macular oedema if the posterior hyaloid membrane is attached to the macula. Vitreo-macular separation either spontaneously or by vitrectomy may result in reduced macular oedema and improved visual acuity after laser photocoagulation.

The assessment of retinal and macular thickness by slit lamp biomicroscopy is difficult and also subjective. **Retinal thickness analyser**, scanning laser ophthalmoscope and optical coherence

tomography are new tools that may be used in the diagnosis and evaluation of treatment of macular and retinal thickness in diabetic patients. Fundus perimetry with scanning laser ophthalmoscope allows the creation of exact maps of retinal dysfunction before and after laser treatment. It may help in making management decisions in diabetic and non-diabetic patients by offering a sensitive parameter in addition to visual acuity. Retinal Thickness Analyser gives quantitative, and objective measurement of the retinal thickness. The technique is based on angular delivery of a narrow green helium laser beam to the retina and detection of the intersection of the beam with the retinal structures. Evaluation of the macula by the scanning laser ophthalmoscope is also accurate, reliable and reproducible.

Optical coherence tomography has been shown to be more sensitive than scanning laser ophthalmoscopy in detecting early diabetic retinopathy. Recent optical coherence tomography studies shows three patterns of structural changes in diabetic macular oedema; a sponge-like retinal swelling (88%), cystoid macular oedema (47%), or serous retinal detachment (15%). Visual acuity with best correction moderately correlated with retinal thickness regardless of the different tomographic features.

Proliferative diabetic retinopathy is often associated with poorer visual prognosis, due to recurrent vitreous haemorrhage and also due to the higher incidence of thrombotic glaucoma. Spontaneous regression of new vessels in proliferative diabetic retinopathy may rarely occur. Spontaneous regression does not seem to be related to any improvement in the diabetic control, but it seems to be associated with improvement in the blood-retinal barrier. Iris new vessels occasionally develop in the anterior chamber angle before the pupil margin. Screening gonioscopy is valuable and important for the early detection of iris neovascularisation. Rubeosis iridis may develop rapidly in eyes with non-proliferative diabetic retinopathy in patients with IDDM or non-IDDM after ECCE with posterior camber IOL despite good diabetes control.

diabetic papillopathy

Diabetic papillopathy is a syndrome of a relatively benign optic disc swelling that occurs not only in young diabetics, but also in older patients with type 2 diabetes. Affected eyes often have macular oedema and retinal vascular changes that commonly affect the final visual outcome. Small physiological cup may represent an anatomical predisposition to this condition. The condition may be associated with rapid progression of the diabetic retinopathy and the development of disc neovascularisation. Patients with diabetic papillopathy should be monitored closely.

diabetic retinopathy in pregnancy

There is a significant decrease in the retinal venous diameter and blood flow in diabetic Pregnant women. This fall in retinal blood flow may exacerbate retinal ischaemia and hypoxia and thus may be associated with the progression of diabetic retinopathy. Pregnant women with moderate to severe retinopathy at conception are at greater risk of retinopathy progression. Retinopathy progression is increased in patients with poor diabetic control and higher systolic blood pressure. Women with diabetic retinopathy should have their diabetes and blood pressure well controlled when they consider conception. In those patients with moderate background retinopathy, fundus examination should be performed at each obstetric visit and if progression is detected the patient should be examined at 2 week intervals to detect any high risk characteristics. If high risk characteristics develop photocoagulation should be carried out.

Treatment

- **medical treatment**

Poor **glycaemic control** seems to be a cause of clinically significant macular oedema. The risk of developing clinically significant macular oedema, in patients with type 1 diabetes, increases with poorer blood glycaemic control. Some patients show progression of their diabetic retinopathy shortly after establishing a strict diabetic control, which may be due to the increase in blood flow of the retinal circulation, or to an increase in serum insulin-like growth factor. Metabolic control in the elderly diabetic patients with established diabetic retinopathy should be instituted **gradually**. Insulin appears to have a more marked effect on the choroidal blood flow more than on the retinal flow. Increased level of insulin significantly increase choroidal blood flow and mean blood flow velocity in the ophthalmic artery, but not the retinal blood flow.

Hypertension is now established as a major risk factor for the development and the progression of diabetic retinopathy. Increased retinal capillary perfusion is a major part in the pathogenesis of diabetic retinopathy. Factors that increases the retinal perfusion (e.g. hypertension, hyperglycaemia, and pregnancy), may worsen the retinopathy, while other factors that decreases it, (e.g. carotid stenosis and increased IOP), may protect the retina. Tight control on the blood pressure *(less than 150/85)* has been shown to reduce the risk of developing complications in diabetic retinopathy. In type 2 disease. In the **UK prospective diabetic study**, a 10 mm Hg reduction in systolic and a 5 mm Hg reduction in the diastolic blood pressure was associated with a 47% fall in the risk of doubling the visual angle in 9 years.

The UK prospective diabetic study also showed that reducing the pressure is the main factor, no matter what medications are used in achieving that. Anti-hypertension drugs, mainly the ACE inhibitor group, have a primary role in reducing retinal capillary leak and hypo-perfusion.

Reducing the blood pressure also appears to be associated with further benefits to the cardiovascular system and the kidneys. The evidence that tight blood pressure control is beneficial in type 1 diabetes is not as strong as in type 2 disease. The target blood pressure for patient with diabetic retinopathy is systolic and diastolic blood pressure equal or less than **130/80**.

In patients with diabetic retinopathy elevated **serum lipid** levels seems to be associated with increased risk of having retinal hard exudate. Lowering serum lipids may be associated with decreased risk of hard exudate development and visual loss. The association of lipid lowering agents with improvement of diabetic retinopathy, on the other hand, is not known. Some recent reports indicate that lowering serum lipids and cholesterol does not seem to affect the progression of retinopathy.

Pentoxifylline (a methyl xanthine derivative) that has been used in the treatment of vascular insufficiency diseases because of it's ability to improve the blood flow. Oral administration of Pentoxifylline in healthy volunteers produce a significant improvement in the retinal capillary blood flow velocity and viscosity. It may be useful in the treatment of diabetic retinopathy, and other vascular eye diseases.

- **laser treatment**

Laser photocoagulation is the main method of treatment of clinically significant diabetic macular oedema. It is not exactly known how laser photocoagulation works in reducing macular oedema. Reduction in macular oedema may result from post-laser vasoconstriction, which occur secondary to the improved retinal oxygenation caused by the laser treatment. Pre-treatment **fluorescein angiography** may improve the accuracy of laser treatment. Quantitative retinal thickness measurement provide an objective method of assessing and monitoring laser treatment in macula oedema.

Krypton, argon, and micro-pulsed diode lasers can be used in the treatment of diabetic macula oedema. The main advantage of krypton red over argon blue-green laser in diabetic retinopathy is the better penetration of the red light through red blood or yellow lens nuclear sclerosis. Diode laser has the advantage of being compact, portable, easy to connect the main electrical supply and easier to cool than Argon laser. Transscleral contact diode laser photocoagulation seems to induce less disruption of the blood-retinal barrier than the conventional cryotherapy in rabbits eyes.

Retinal laser photocoagulation is often carried out under topical anaesthesia. Occasionally peribulbar injection may be needed in extensive or very peripheral treatment. The use of topical **sodium diclofenac** 0.1% eye drops may help in relieving pain during the treatment.

Laser pulse of very short duration seems to affect the retinal pigment epithelium mainly with no or little damage to the neuro-sensory retina or the choriocapillaris due to the reduced thermal effect produced by this type of laser. The Iris Ocullight Micro-Pulse 810 nm diode laser is a new laser that has the advantage of a greater retinal pigment epithelium specificity and less damage to the inner retinal layers. Visual field, and colour vision loss appear to be reduced with this type of laser treatment. Recent studies showed that this laser is useful in the treatment of macular oedema in patients with diabetic retinopathy and vascular retinal occlusive diseases.

Diabetic patients with proliferative diabetic retinopathy should be treated aggressively with **panretinal photocoagulation** or cryotherapy or both. The mechanism of action is not completely understood. It has been suggested that panretinal photocoagulation is associated with a local increase in the retinal and the pre-retinal oxygen tension, in the treated areas, which causes vasoconstriction of the new vessels. Panretinal photocoagulation is also thought to be associated by vascular narrowing which might lead to the regression of the new vessels.

Regression of the proliferative diabetic retinopathy is known to occur in about 93% of all treated patients. Regression of proliferative diabetic retinopathy appears to be significantly related to the cumulative total number of laser burns applied to the retina. Renal disease and age (<50 years) are risk factors for non-regression of retinopathy after panretinal photocoagulation. Patients with diabetic nephropathy requires considerably more aggressive treatment than patients with no nephropathy. Hypertension, neuropathy, duration of disease and insulin dependence seem to have no significant effect on outcome.

Poor prognostic factors after panretinal photocoagulation include the presence of disc neovascularisation at base line, short interval between the diagnosis of diabetes and the need for panretinal photocoagulation, and earlier onset of diabetes. Patient with good visual acuity at presentation seem to maintain a good visual acuity after one year, while patients with poor visual acuity at onset seem to have poor visual outcome. Vitreous haemorrhage, traction retinal detachment may still occur after panretinal photocoagulation. Panretinal laser photocoagulation may be associated with loss of the visual field of vision. It may be possible to reduce the amount of visual field loss by altering the pattern of laser photocoagulation.

Premacular haemorrhage is common in patients with proliferative diabetic retinopathy. Most of these haemorrhages occur in association with partial posterior vitreous detachment. The haemorrhages are often slow to clear and may result in epimacular membrane or macular traction retinal detachment. Division of the posterior cortical face by the YAG laser has been used to achieve rapid intravitreal drainage of the premacular haemorrhage. Laser application allows the trapped blood to

enter the vitreous where it quickly gets absorbed. Complete intravitreal dispersion of the blood can be achieved in most eyes within one week. The technique can be used instead of vitrectomy to allows an early identification and treatment of any existing significant macular oedema.

- **vitrectomy**

Vitrectomy in diabetic patients has a valuable role in improving the patient's overall visual function, especially in patients with vitreous haemorrhage, and traction retinal detachment, and some eyes with intractable macular oedema. In eyes with diffuse diabetic **macular oedema** and no posterior vitreous detachment, vitrectomy and induction of posterior vitreous detachment may be effective in resolving the macular oedema with improvement of visual acuity for up to twelve months. Diabetic patients with **fibrovascular proliferation** affecting the macular (without macular detachment) suffer from visual loss even after full laser pan-photocoagulation. Pars plana vitrectomy in these cases may preserve useful vision in most of the patient.

Pars plana vitrectomy for proliferative diabetic retinopathy may be followed by vitreous haemorrhage. **Intraoperative fluorescein angiography** may be useful in disclosing unusual findings in the extreme peripheral retina and pars plana which might lead to vitreous haemorrhage. The technique may aid intraoperative evaluation and treatment of proliferative diabetic retinopathy. In eyes with persistent vitreous haemorrhage, peripheral retinal cryotherapy stabilises the peripheral retina and vitreous and also of the visual acuity in most patients. Trans-scleral cryotherapy is often possible even in eyes with opaque media.

Retina infection and AIDS related disorders

CMV retinitis

CMV retinitis is the most frequent opportunistic eye infection in patients with HIV infection. Low CD 4^+ T lymphocytes (**less than 50 x 10^6 / L**), is the most significant predictor for the development of CMV retinitis in AIDS patients. Patients with low CD 4 counts and positive urine cultures have a sevenfold increased risk of developing retinitis than patients who have negative urine cultures. Patients with CMV retinitis and positive blood or urine culture, during treatment, have greater mortality rates, and greater risk of involvement of the second eye. The diagnosis of CMV retinitis should also be considered in patients with immunosuppression (due to disease or drugs) as well as patients with low T-lymphocytes count due to HIV infection, cancer, or organ transplantation. The disease has also been reported in 14.6% of patients after cardiac transplantation.

CMV retinitis patient often present with painless loss of vision in one or both eyes. The diagnosis of CMV retinitis relies on the retinal appearance. The typical retinal features of the disease include the following:

1. The most common lesions are: micro-aneurysm (100% of patients), followed by cotton-wool patches (70-92% of patients) and retinal haemorrhages (12-40% of patients).
2. The eye is often white and quiet with little or no anterior chamber or vitreous cells.
3. The disease is characterised by multiple distinct areas of retinal opacification with irregular feathered borders.
4. The necrotic retinal areas often starts along the major vascular arcades and enlarge with time.

The retinitis may also be associated with serous retinal detachment, CMV papillitis, cystoid macular oedema and visual loss, and retinal detachment. In the early stages of disease and in patients with atypical features, it is difficult to differentiate between retinitis caused by CMV, and retinitis associated with the other herpes viruses. Polymerase chain reaction tests for CMV DNA in ocular fluids (e.g. aqueous humour) is a sensitive method to use in doubtful cases. **Cystoid macular oedema and epiretinal membranes** formation are major causes of poor visual acuity in patients with AIDS even in the absence of active retinitis. This maculopathy is often associated with mild vitritis. These macular changes and the associated vitritis may be caused by the methods of treatment of CMV retinitis.

Various changes in visual function have also been reported in the **absence of retinopathy** in HIV-positive patients. A significant

percentage of HIV-positive patients with visual acuity of 20/20 or better and no ophthalmologic evidence of retinitis have abnormal psycho-physical tests.

A newly described syndrome characterised by a stable or slowly progressive multifocal peripheral retinal infiltrates with mild uveitis and vitritis has recently been described in HIV patients. The retinal lesion are typically grey white, or yellow in colour, irregular in shape, and measure less than 200 micron in diameter. They are often located in the mid periphery or the anterior retina. The lesions may respond to treatment with zidovudine. The visual prognosis of this syndrome is often good.

Uveitis in AIDS patients is often caused by opportunistic infection, e.g. CMV, herpes simplex virus, herpes zoster virus, fungus or Toxoplasma infection. It must be remembered that HIV patients may present with vitritis as the only and initial manifestation of syphilis. Syphilis in these patients should be treated as neuro-syphilis with IV penicillin G. Transient intraocular inflammation may also be associated with anti-retroviral medications. The inflammatory response, in these cases, may be due to improvement in the immune mechanism. The inflammation seems to subside spontaneously in most patients, but topical steroid treatment may be needed in some cases. It should also be remembered that HIV infection may also be associated with uveitis in the absence of any other opportunistic infection. A trial of anti-retroviral treatment may be needed in the uveitis does not respond to steroids treatment.

CMV retinitis may be associated with **corneal endothelial deposits**, which are likely to represent a mild form of anterior uveitis rather than direct infection of the corneal endothelium with the virus. IOP is lower than normal in patients with HIV infection, with or without CMV retinitis, which is important in evaluating and treating HIV patients for glaucoma. the decrease in the IOP may be due to decreased aqueous production or increased outflow.

CMV retinitis may be associated with other **extraocular infections**. In patients with CMV retinitis, rising levels of CMV DNA in the blood may be an indication of extraocular extension of the disease. Reactivation of the infection may also occur in the absence of high CMV DNA levels. CMV **encephalitis** may be associated with retinitis, particularly when the retinitis involves the peripapillary region. In cases of suspected CMV encephalitis, a retinal examination may support the diagnosis if retinitis is present, if retinitis is absent other causes of encephalitis should be considered. CMV infection can also cause colitis, **oesophagitis**, encephalitis and pneumonia. The retinitis may follow extraocular infections in AIDS patients. Maintenance treatment with protease inhibitor drugs prolong the time interval between extraocular infection and ocular involvement. Maintenance treatment with protease inhibitor drugs is recommended in non-ocular infection.

The presence of a **positive blood culture** at the time of diagnosis of retinitis is associated with a greater mortality rate, and the occurrence of a positive blood or urine culture during follow-up is associated with the development of cytomegalovirus retinitis in the second eye of patients who initially had unilateral disease. Elevated CMV DNA blood levels may indicate the development of CMV disease, the reactivation of an already present disease, or the spread of CMV retinitis to extraocular sites. Reactivation of CMV retinitis may also occur without changes in the DNA blood levels.

treatment

The use of anti-retroviral agents (e.g. ganciclovir, foscarnet, and cidofovir), in AIDS patient has lead to increased patient survival. At present the main drugs available for the treatment of CMV retinitis are:

Anti-retroviral drugs	HAART therapy
The main anti-retroviral drugs are: • ganciclovir (causes myelo-suppression and may result in neutropenia and thrombocytopenia). • foscarnet (nephrotoxic and may result in electrolyte imbalance). • cidofovir (causes nephrotoxicity and uveitis).	HAART therapy includes: • Protease inhibitors e.g. ◊ saquinavir ◊ retonavir ◊ nelfinavir ◊ indinavir • Reverse transcriptase inhibitors e.g. ◊ zidovudine ◊ didanosine ◊ zalcitabine

Ganciclovir and foscarnet are often given intravenously with an induction dose for 2 to 3 weeks followed by a lower daily maintenance dose. Ganciclovir causes myelosuppression and may result in neutropenia and thrombocytopenia, while Foscarnet is nephrotoxic and may result in electrolyte imbalance.

Intraocular administration either by Intravitreal injection or by Ganciclovir ocular implants may also be used as an alternative to intravenous treatment in patients who cannot receive systemic treatment either due to intolerance or due to the development of side effects to the drug or to indwelling catheter. **Intravenous treatment** with ganciclovir or foscarnet is associated with a relatively short period of remission. It may also be associated with systemic complications, and complications related to the presence of indwelling catheter.

Ganciclovir **ocular implants**, on the other hand, are associated with longer remission periods (221 days compared to 71 days with IV treatment). Treatment with the ganciclovir implants may, however, be associated with involvement of the other eye, or with systemic dissemination of the disease. Ganciclovir implants may be associated

with posterior segment complications (e.g. rhegmatogenous retinal, vitreous haemorrhage, endophthalmitis, cystoid macular oedema) These complications occur in 12% of the ganciclovir implant procedures and may be associated with irreversible loss of vision. Ganciclovir implants is less successful in the treatment of cases that recur after or despite IV treatment. Longer treatment of preoperative IV ganciclovir or larger areas of CMV retinitis is associated with lower success rate of ganciclovir implants in recurrent cases. Treatment with potent anti-retroviral appears to be effective in those patients with recurrent disease when ganciclovir implants are used.

Cidofovir (HPMPC) is most potent and selective inhibitor of CMV in vitro. The drug has excellent anti-CMV activity when administered intravenously every 2 weeks. Nephrotoxicity, however, limits its dose. There is also a potential for haematological toxic effects. Treatment and maintenance with repeated intravitreal 20 microgram injection of Cidofovir every 5-6 weeks appears to be highly effective with only rare episodes of reactivation and progression of the disease. Acute intraocular inflammation may occur with or without hypotony after intravenous and intravitreal cidofovir therapy. The uveitis may be due to improvement in the immune state of the patient. It often respond to treatment and should not preclude the continuation of cidofovir treatment. Monitoring the IOP is important after starting treatment with cidofovir. Continued treatment with the drug is possible with the use of topical steroids and cycloplegic. Concomitant use of probenecid appears to decrease the frequency of the iritis from 71% to 18% after the first intravitreal injection. Probenecid inhibits anion transport across the epithelial barriers and reduce renal toxicity by decreasing renal tubular secretion of the cidofovir. Triple therapy with, foscarnet and cidofovir, seems to be associated with increase in the survival, decrease in relapses, and changes in the ocular features.

CMV **resistance** to Ganciclovir or Foscarnet at the time of diagnosis of CMV retinitis is uncommon. About 4% of patients, however, become resistance to Foscarnet, and about 2% are resistant to Ganciclovir. Clinical failure of intravitreal treatment with cidofovir for CMV retinitis may be related to cidofovir resistance caused by prior ganciclovir or cidofovir treatment. CMV isolates cultured from the blood and urine, may not represent the CMV population in the eye.

HAART (Highly Active Anti-Retroviral Therapy), is a relatively new approach for the treatment of CMV retinitis. It is characterised by using a combination of nucleoside reverse transcriptase inhibitor as well as a protease inhibitor. The current main protease inhibitors are saquinavir, retonavir, nelfinavir and indinavir. The protease inhibitors inhibit cleavage of the viral poly-proteins preventing HIV replication. HAART therapy improves patient's immune mechanism and is often associated with reconstitution of CD 4+ cells and dramatic fall in HIV serum virus load.

A new syndrome called **(immune recovery vitritis)** has been described in patients with CMV retinitis associated with the recovery of their immunity after anti-viral treatment with protease inhibitors. The syndrome consists of: vitritis, papillitis and cystoid macular oedema or epiretinal membrane. Optic nerve head neovascularisation may also occur. The syndrome is associated with visual morbidity and may respond to steroids treatment.

Zidovudine is a member of the nucleoside reverse transcriptase inhibitors drug that is used in the treatment of advanced AIDS disease. Different side effects have been reported with the anti AIDS drug Zidovudine e.g. anaemia, neutropenia, nausea, vomiting, myalgia, and abnormal liver function tests. Temporary colour vision abnormalities have also been reported with this drug. Tritan colour vision deficit is the main colour vision abnormality associated with the drug. Didanosine is a purine analogue drug. It may be associated with the drug include pancreatitis, peripheral neuropathy, and retinopathy characterised by multiple well circumscribed depigmented lesions in the mid retinal periphery.

The use of an HIV-1 protease inhibitors in the treatment of AIDS may lead to complete regression of cytomegalovirus retinitis. HAART therapy also increase the efficacy of anti-retroviral drug and delay the emergence of resistance of CMV isolates. The routine use of protease inhibitors has resulted in longer survival, higher CD $^{+}$4 T lymphocytes, and improved immune status in a large number of AIDS patients. AIDS patients with advanced CMV retinitis may be started on treatment with potent anti-retroviral drugs as well as intravenous anti-CMV drugs or ganciclovir implants. The role of the anti-CMV drugs is to control the disease till the potent drugs produce a sufficient improvement in the patient immune status. Anti-CMV drugs may also be used in patients taking HAART therapy if CMV retinitis develops or relapse or if there are signs of decreased immune status.

discontinuation of the treatment

After starting treatment with combination therapy, it might be possible, in some patients, to discontinue treatment for short periods of time. Discontinuation of maintenance therapy may be considered in the following patients:

- Patients with HAART-induced elevated CD 4^{+} counts above 100 cells/ul.
- Prolonged relapse-free intervals during the reconstitution period before CD 4^{+} counts rise above 100 cells/ul.
- Completely quiescent retinitis characterised by RPE scarring only.
- HIV-positive patients with CMV retinitis, who demonstrate a sustained HAART-induced elevation of CD 4 cell count on two consecutive counts 3 months apart and whose retinitis remains healed on anti-CMV

therapy for greater than 4 months, are likely to remain healed if the anti-CMV therapy is withdrawn.

Reduced risks of drug toxicity and drug-resistant organisms are potential benefits. Close observation for evidence of recurrent retinitis is indicated. It is important to monitor these patients with indirect ophthalmoscopy because HAART failure may occur and allow CMV retinitis reactivation.

retinal detachment in CMV retinitis

The incidence of retinal detachment in CMV retinitis is between 17% to 34% with a high frequency of bilateral involvement. Most of retinal detachments in theses eyes are of the rhegmatogenous type. The life time risk of developing retinal detachment in patients treated for CMV retinitis has been estimated to up to 50%. Eyes with peripheral retinal involvement greater than 25% have a five fold risk of retinal detachment compared to eyes with 10% involvement. If there is retinitis activity with more than 25% involvement the risk of retinal detachment is 24 fold. Vision is stabilised or improved in the majority of patient s after surgery. Cataract and optic atrophy may develop in 29% and 22% of cases after surgery.

Retinal detachment surgery in eyes with CMV retinitis is difficult because retinal breaks, in these eyes, are often multiple, posterior, and difficult to locate, through hazy vitreous, preoperatively as they are often present in areas of necrotic and atrophic retina. Posterior vitreous separation may also be incomplete and significant epiretinal membrane formation may be present. These features have made **vitrectomy and silicone oil tamponade** the treatment of choice for the majority of patients. Scleral buckling, alone, often fails to treat the detachment in these cases. Elimination of the scleral buckling procedure may reduce the time of surgery and also reduce possible morbidity associated with this procedure. The use of silicon oil in the retinal detachment repair in these patients is effective, safe and delays or prevents loss of vision. The use of silicone oil, rather than intraocular gas, as the retinal tamponade agents has the advantage that prolonged face down positioning is not required and visual rehabilitation is relatively rapid. Although the majority of patients recover macular vision in the first 1-2 months after vitrectomy, there is a gradual decline in acuity thereafter, sometimes without obvious cause. It may be reasonable to postpone surgery until the macula detaches and that patients whose fellow eye is free of retinitis with normal vision are unlikely to have their quality of life improved significantly by the surgery.

The use of laser photocoagulation alone may result in an excellent visual outcome in some cases with peripheral localised detachments. Localised retinal detachments involving less than quarter of the retina with less than 50% of the retina affected by the CMV retinopathy with macula sparing may benefit from laser photocoagulation treatment. Laser

photocoagulation (demarcation) is useful in delaying or avoiding vitrectomy with silicon oil surgery in some patients with CMV related retinal detachment. Laser treatment may ultimately fail in many patients but delaying vitreous surgery may be beneficial.

Progressive outer retinal necrosis (PORN)

Progressive outer retinal necrosis syndrome (PORN) is a recently recognised variant of necrotising herpetic retinopathy. The disease is characterised by the appearance of progressively enlarging multifocal deep white grey retinal opacities scattered throughout the periphery of the retina, with subsequent retinal vascular attenuation. Macular lesions may also be present in about 32% of patients at presentation.

A history of **cutaneous Zoster** may be documented in 67% of patients. Although the etiologic agent is reported to be VZV, **HSV-1** can be an etiologic agent in PORN. Patients often have less uveitis, vitritis, and vasculitis than is seen in typical acute retinal necrosis. There is also a tendency for the earliest visible lesions to occur in the posterior pole rather than in the periphery. Involvement of the fellow eye even with anti-viral treatment is over 70%. Patients with progressive outer retinal necrosis also have a higher risk of developing encephalitis. Progressive outer retinal necrosis can also affect immunocompromised patients due to other causes. This condition has also been describe in immune-competent patients with uniocular involvement. Treatment of progressive outer retinal necrosis syndrome by acyclovir or ganciclovir has been disappointed. **Sorivudine** is a new anti-viral with activity against varicella-zoster. The drug my represent an effective alternative treatment for this condition. The ability of sorivudine to inhibit VZV is about 1000 greater than acyclovir

Acute Retinal Necrosis

Acute retinal neurosis is characterised by diffuse uveitis, occlusive retinal arteritic, necrotising retinitis and vitritis. Acute retinal necrosis syndrome may also present with orbital inflammation, proptosis and optic nerve involvement. Some clinicians have restricted the use of the term acute retinal necrosis syndrome to otherwise healthy patients. Others believe that this restriction is unnecessarily. It is thought that if a patient has clinical findings consistent with the syndrome, that the diagnosis should be made regardless of the patient's systemic health.

Although most reported cases have been caused by **varicella-zoster** virus, others appear to be associated with **herpes simplex** virus, either types I or II. A recent report showed that Varicella-Zoster virus and herpes simplex virus type 1 cause acute retinal necrosis in patients older than 25 years of age, while herpes simplex virus type 2 causes the syndrome in patients younger than 25 years of age. Herpes simplex virus is also likely to be the causative agent if there is an associated CNS infection. ARN may also, rarly, occur in primary VZV infection (chickenpox). The mode of retinal infection is unclear. Possible routes include haematogenous or trans-neural spread to the retina.

The use of polymerase chain reaction based assay on vitreous specimen is proved to be a useful tool in making the diagnosis. Several previous reports have documented the association between acute retinal necrosis and chicken box in healthy or mildly immune compromised patients and also in patients with AIDS. The disease has been reported in pregnancy during the second trimester. Treatment with acyclovir and interferon lead to partial recovery of vision and no foetus abnormalities.

Miscellaneous retinal diseases

• Central serous retinopathy

Pathogenesis

The mechanism of central serous retinopathy is not completely known. Recent indocyanine green angiography and scanning laser ophthalmoscopy studies indicate that central serous retinopathy probably originates primarily in the choroid. **Hyper-permeability of the choriocapillaris** characterises all the stages of the disease and seem to be the primary alteration of he disease. Localised choroidal ischaemia can also be observed in other areas of the involved eye or in the other fellow eye in some patients with central serous retinopathy. Capillary or venous congestion after choroidal ischaemia may explain the choroidal hyper-permeability observed in central serous retinopathy patients. A new study suggested that some cases of presumed idiopathic CSR may be due to a thrombosis of the choroidal circulation secondary to the primary **Antiphospholipid antibody syndrome**.

A variety of risk factors have been associated with the development of central serous retinopathy. These include psychological stress, type A personality, hypochondria or hysteria, pregnancy, haemodialysis, Cushing syndrome and systemic or intra-muscular corticosteroid use.

Clinical features and Treatment

Central serous retinopathy typically affects patients between 30 to 50 years old. It is now believed that there is greater range of ages of the patients affected than previously though with a much lower male / female ratio. Older patients who have a lower visual acuity are more likely to have a diffuse retinal pigment epitheliopathy, have bilateral involvement and secondary choroidal neovascular membrane than young patients.

Central serous retinopathy have the same features in **women** as in men. it tends to develop in women in later age than in men. A significant number of women who develop central serous retinopathy take exogenous steroids, an observation which support the theory that steroids may play a role in the development of this condition. In women who take exogenous steroid, the central serous retinopathy is likely to be bilateral and associated with subretinal fibrin. Central serous retinopathy in pregnant women typically appear in the third trimester and spontaneously resolve 1-2 months after delivery.

Serous pigment epithelium detachment have been reported in **neonates** and also in premature babies. It is thought that the mechanism of his condition is a dysfunction of the retinal pigment epithelium cells due to an unknown lesion in the choriocapillaris. It is thought that the use of dilating

drops (e.g. phenylephrine) in premature neonates may induce changes in the choriocapillaris causing secondary retinal pigment detachment.

Fluorescein angiography, indocyanine green angiography and Ocular coherent tomography can be useful in the qualitative and quantitative evaluation of patients with central serous retinopathy. Central serous retinopathy may be associated with a **plaque** of sub-retinal hard exudate without any choroidal neovascular membrane. The sub-retinal plaque often overly an area of retinal pigment epithelium leak and often disappear before or with the resolution of the sensory retinal detachment. These exudates are believed to be fibrin in nature. When sub-retinal fibrin is present, early laser treatment is encouraged if the leak is not sub-foveal. The disease may also be followed by retinal vascular leak and cystoid macular oedema This may be due to accumulation of sub-retinal fluid leading to toxic breakdown of the retinal vessels or due to retinal vascular leak caused by the hypoxic detached retina.

The disease often resolves spontaneously, however **recurrence** may occur in up to 40% of patients. The disease may also become **chronic** with extensive lesions and a poor final visual acuity, visual field defects and sub-normal EOG. Central serous retinopathy may also present by a **bullous serous retinal detachment** with subretinal exudate. The detachment often resolves spontaneously with restoration of the visual acuity. It is important to recognise this variant of the disease to avoid unnecessary investigations and treatment. Central Serous Chorioretinopathy with persistent and / or recurrent exudation may also be difficult to differentiate from **idiopathic polypoidal choroidopathy**. In these cases ICG angiography is useful in differentiating between the two conditions.

The treatment of choice in patients with chronic central serous retinopathy is by **laser photocoagulation**. Direct laser photocoagulation of the leakage site(s) for CSR that persists for 4 months is safe and effective to shorten the duration of the serous detachment to improve final visual acuity and to decrease the incidence of recurrence. The duration of the disease and the recurrence rate may be reduced by laser photocoagulation. The lower recurrence rate associated with laser treatment appear to be maintained for up 10 years or more. Systemic steroids treatment is ineffective and dangerous as it may cause severe exacerbation of retinal detachment associated with lasting visual loss.

Central serous retinopathy and steroids

Early morning, late morning and 24 hours urine endogenous cortisone levels are increased in patients with central serous retinopathy when compared to controls. Diffuse retinal pigment epitheliopathy may develop in patients taking large doses of systemic steroids. The high levels of cortisone may be responsible for the RPE barrier damage and choriocapillaris changes that lead to this disease. In patients who are

susceptible, the periocular or systemic absorption of **inhaled** corticosteroid may be sufficient to produce central serous retinopathy. Patients in whom CSR develops while using corticosteroid inhalers or nasal sprays should be alerted to the possible relationship between CSR and these agents.

Central serous retinopathy has been associated with several other conditions characterised by increased exposure to and / or enhanced secretion of steroids. A high % of patients with endogenous **Cushing's** syndrome have one or more episodes of central serous retinopathy, in all cases the episodes occur during a period when there is an increase cortisone blood level.

Central serous retinopathy and beta blockers

Lesions similar to central serous retinopathy have been caused by epinephrine injection in monkeys and beta-blockers have been suggested as treatment. A prospective, randomised double-masked trial compared the beta blocker nadolol to placebo in 16 patients with central serous retinopathy. The data of the study suggested that nadolol may have an adverse effect on the rate of resolution of central serous retinopathy.

Central serous retinopathy and systemic disease

It is thought that choroidal vascular abnormality and secondary RPE dysfunction may be the common mechanism for a group of diseases (e.g. accelerated hypertension, pregnancy, haemodialysis, organ transplantation and hyper-secretion of corticosteroid) that may present with serous retinal detachment similar to central serous retinopathy. Most patients do well but chronic central serous retinopathy and visual loss may occur in some patients.

Systemic lupus erythematosus may rarely present with choroidopathy with serous detachment. Central serous retinopathy has also been described in patients with membrane-proliferative glomerulonephritis type 2.

• idiopathic polypoidal choroidal vasculopathy

Idiopathic polypoidal choroidal vasculopathy IPCV (also called **posterior uveal bleeding syndrome**), is a rare condition characterised by:

1. A juxta-papillary (macular or peripheral) branching choroidal vascular network with surrounding polypoidal aneurysmal dilatation.
2. Recurrent, multiple, and bilateral serous and haemorrhagic detachment of the neuro-sensory retina and the RPE.
3. No macular drusen or intraocular inflammation.

There is a high incidence (85%) of polypoidal choroidal lesions, on indocyanine green angiography, in white patients presenting with haemorrhagic or exudative PED. Diagnosis of this condition and differentiation from age related maculopathy is important as laser treatment in this condition is often associated with good results.

The condition is commoner in females and may be associated with systemic hypertension. Optical coherence tomographic images show that some of the polypoidal structures are anteriorly protruding lesions in the inner choroid. These lesions may cause detachment of the retinal pigment epithelium. Sub-macular haemorrhage may also occur in some patients. The differential diagnosis of this condition include various causes of choroidal neovascular membrane.

The **macular variant** of this disease is characterised by recurrent subretinal haemorrhage and exudates. It can be distinguished from other causes of macular choroidal neovascular membrane by indocyanine green or fluorescein angiography. Fluorescein and indocyanine angiography often show the choroidal vascular network and RPE detachment.

Laser photocoagulation may be used in cases with subretinal exudate or fluid. Surgical excision of the subretinal membrane may be beneficial in eyes with sub-macular haemorrhage associated with idiopathic polypoidal choroidal vasculopathy.

The orange-red lesions in eyes with idiopathic polypoidal choroidal vasculopathy have a more sharply peaked shape than serous retinal pigment epithelium detachment, suggesting polypoidal vascular lesions in eyes with idiopathic polypoidal choroidal vasculopathy are situated beneath the Bruch's membrane and covered anteriorly with both the retinal pigment epithelium and the Bruch's membrane.

Histological studies of removed tissues demonstrated fibrovascular tissue between the retina and retinal pigment epithelium (type 2 pattern). Visual prognosis is good, but vitreous haemorrhage and choroidal neovascular membrane may lead to visual deterioration in some patients.

• retinal macro-aneurysm

Retinal macro-aneurysm are commoner in women in their sixth to eighth decade. They are often located at the arteriovenous crossing or at arteriolar bifurcation. **Systemic hypertension**, and arteriosclerosis have been associated with the disease. Visual acuity may be compromised due to the presence of macular or sub-macular haemorrhage, macular oedema, or vitreous haemorrhage. The macro-aneurysm may be associated with bleeding at the pre-retinal, intra-retinal, sub-retinal space or in the vitreous. Indocyanine green angiography is useful in the diagnosis when fluorescein angiography is inconclusive because of pre-retinal, intraretinal, or subretinal haemorrhage.

The pathogenesis of retinal macro-aneurysm is not completely known. It is thought that weakening of the retinal arterioles by a **micro-emboli** may play a role in its pathogenesis. About 61% of patients with macro-aneurysm are associated with atheromatous plaques in the ipsilateral carotid artery. Carotid ultrasonography, and medical examination may be important in patients with retinal macro-aneurysm.

The treatment of this condition is controversial. Some authorities advise **conservative** treatment while others recommend laser photocoagulation in cases with macular oedema. The treatment of associated sub-macular haemorrhage may be difficult as the haemorrhage usually obscure the aneurysm. Disruption of the internal limiting membrane by the **YAG laser** may be useful in dispersing pre-retinal haemorrhage to the vitreous cavity. **Vitrectomy** may be used in cases with thick pre-retinal haemorrhage that may obscure a hidden intra-retinal or sub-retinal haemorrhage. The use of plasminogen activator-associated thrombolysis, and removal of the liquefied blood, in eyes with recent onset may achieve better visual results. **Pneumatic** displacement of the subretinal haemorrhage by injecting Perfluoropropane gas in the vitreous cavity may also be used to displace the subretinal haemorrhage. Macular haemorrhage secondary to retinal artery macro-aneurysms may also be managed by **observation** alone, good visual acuity outcomes can often be achieved.

• retinal vasculitis

Retinal vasculitis may occur as a manifestation of systemic disease (e.g. Behcet's disease, systemic lupus erythematosus syndrome, Wegener's granulomatosis, Ig A nephritis and sarcoidosis). It may also be a part of ocular inflammatory process (e.g. bird-shot choroidopathy or pars planitis). Infections (e.g. CMV retinitis, Lyme disease, syphilis and toxoplasmosis) may also be associated with retinal vasculitis. Less commonly retinal vasculitis may occur as an isolated primary condition.

In the absence of a medical history or systemic manifestation to suggest an underlying disease, few diagnostic tests should be ordered as full routine tests are likely to be costly and unrewarding and also because the positive predictive value of some of the most commonly ordered test is low. Potential false-positive results are also likely to cause confusion.

Idiopathic retinal vasculitis is an inflammatory condition of the retinal vessels which predominantly affects young adults and which can lead to blindness. Patients with primary retinal vasculitis represent a distinct entity and are unlikely to manifest a systemic disease.

Retinal vasculitis may be Ischaemic type, or Non-ischaemic (leaky). There is a high prevalence of thrombophilic abnormalities in retinal vasculitis patients. Smoking may play a role in the aetiology of the ischaemic type. Visual loss in retinal vasculitis is mainly due to CMO or vitreous haemorrhage secondary to neovascularisation.

Ischaemic retinal vasculitis is associated with a worse visual outcome than non-ischaemic cases (34% of patients compared to 6%). The ischaemic type is often due to localised thrombosis. Fluorescein angiography, full blood count and ESR, urine analysis, FTA-ABS test, rapid plasma reagent and chest X ray are indicated in patients with unremarkable medical history.

The significance of anticardiolipin antibodies in patients with isolated retinal vasculitis is not known, increased prevalence of raised anticardiolipin antibodies in patients with retinal vasculitis associated with other diseases have been previously reported. Measurements of anticardiolipin antibodies, in isolated retinal vasculitis, has no clinical or pathological importance and is generally of limited value in the management of these cases. Positive ANCA serology is found in a spectrum of vasculitis disease including polyarteritis nodosa, microscopic polyarteritis and Wegener's granulomatosis. Two main types are recognised: c-ANCA, which has a high positive predictive value for Wegener's granulomatosis, and p-ANCA, which is less specific but does suggest a vasculitis condition.

Systemic steroids, with or without cyclosporin A are the main treatment of retinal vasculitis. Azathioprine may also be used in combination with

systemic steroid. The drug seems to be useful in reducing relapses rate, but it does not seem to be useful in reducing the dose of systemic steroids. The drug does not appear to be associated with significant side effects

• paraneoplastic syndromes

Three autoimmune paraneoplastic syndromes have recently been described:

1. Carcinoma-associated retinopathy.
2. Melanoma-associated retinopathy.
3. Bilateral diffuse uveal melanocytic proliferation BDUMP (rare).

Cancer associated retinopathy is an uncommon paraneoplastic syndrome that often presents with visual loss, ring like scotoma, and night blindness as well as retinal phlebitis and vitritis. In carcinoma associated retinopathy there is degeneration of the retinal photo-receptor cells and antibodies to the retinal protein recoverin. The highest reported incidence of carcinoma associated retinopathy has been reported with small cell carcinoma of the lung. In epithelial cancers associated retinopathy (e.g. lung cancer) the onset is often gradual with progressive retinal degeneration which may lead to extinguished ERG similar to retinitis pigmentosa. Lung cancer associated retinopathy may present before the diagnosis of cancer is made, unlike melanoma associated retinopathy which often occur in already diagnosed patients.

Melanoma associated retinopathy MAR is a rare condition, distinct from lung cancer associated retinopathy. The disease has been described in cutaneous melanoma. Biological differences between the skin and the uvea may explain its rare occurrence with uveal melanomas. The disease is characterised by a sudden onset of night blindness and a central visual field loss, rather than ring scotoma. Patients may also present with bilateral central scotomas. ERG studies typically show dysfunction of the rods system and normal cones system. Circulating antibodies to the retinal bipolar cells are also often present. The disease occurs in patients with metastatic melanoma. It is often acute and non progressive. Treatment of this condition may be carried out by systemic steroids, plasmapheresis, or intravenous immunoglobulin.

• ophthalmic side effects of sildenafil (viagra)

Viagra is a new medication that is prescribed to stimulate and enhance penile erection. The drug acts by inhibiting phosphodiesterase-5 (PDE-5) in the corpus cavernosum. The drug also inhibits PDE-6, in the retinal photo-receptors, which controls the level of cyclic guanosine mono-phosphate in the retina and control the process of transduction. The drug may also have some vascular effects on the choroid and the retina. Animal studies showed that viagra changes ERG only when used in very high doses. Some patients receiving the drug may suffer from perception of bluish haze and increased light sensitivity.

Recent reports showed that, patients with micro-vascular disease, may develop third nerve palsy with pupil sparing with the use of the drug. The mechanism of this side effect is not known, but it is thought that the transient systemic hypotension associated with the use of the drug may cause hypo-perfusion of the third nerve. Anterior ischaemic optic neuropathy and transient changes in colour perception have also been described in association with viagra. No persistent visual abnormalities have been reported with using the drug. Patients should be counselled about these side effects of the drug, especially patients with pre-existing retinal or vascular diseases should be cautious in using the drug.

• congenital hypertrophy of the retinal pigment epithelium (CHRPE)

Congenital hypertrophy of the retinal pigment epithelium (CHRPE) is characterised by dark grey or black, flat round lesions at the level of retinal pigment epithelium. The lesions are typically surrounded by halo of de-pigmentation areas. CHRPE may rarely occur in the papillo-macular area. Lesions in this area may undergo progression and affect the visual acuity The retinal lesions may undergo progressive hypo-pigmentation, enlargement of the lesions or new pigmented areas or linear streak of pigment epithelium may appear adjacent to the old pigmented lesions. Congenital hypertrophy of the retinal pigment epithelium can also spawn a **nodular growth** that slowly enlarges, attains a retinal blood supply, and causes exudative retinopathy and chronic cystoid macular oedema. It is believed that the tumour probably represents either an acquired adenoma or a reactive proliferation of the retinal pigment epithelium.

Multiple patches of CHRPE have been described in association with familial adenomatous polyposis **(Gardner's syndrome)**. Familial adenomatous polyposis is an autosomal dominant condition characterised by the presence of thousands of polyps in the colon. The adenomas in this condition is typically pre-malignant. CHRPE is identified as a sensitive and useful marker of the disease. The CHRPE lesions in this disease are typically oval pigmented lesions with pale halos in the centre. Bilateral multiple patches of CHRPE is considered to be an early marker of the familial adenomatous polyposis coli gene (chromosome 5q 21). A positive criterion for **identifying the syndrome** include:

- At least four lesions whatever their size, or
- At least two lesions one of which is large.

By using this new positive diagnostic criterion, fundus examination allows early detection of children carrying the gene responsible for familial adenomatous polyposis.

Vitreoretinal Surgery

posterior vitreous detachment

Posterior vitreous detachment can be classified into four types:

1. Complete PVD with vitreous collapse (with age related changes and myopia).
2. Complete PVD without vitreous collapse (uveitis and central retinal vein occlusion).
3. Partial PVD with thickened posterior vitreous cortex (proliferative diabetic retinopathy).
4. Partial PVD without thickened posterior vitreous cortex (age related).

Posterior vitreous detachment is not limited to elderly patients only. In a study of 861 patients under the age of 30 years, a complete posterior vitreous detachment was found in 11%, and partial detachment in 17%. In the first and second decades of life, the detachment was associated with retinitis pigmentosa, non-diabetic retinal vascular diseases and history of trauma or surgery. In the third decade of life, the detachment was commonly associated with proliferative diabetic retinopathy. In high myopia the risk of developing posterior vitreous detachment increases with age and with the degree of myopia.

Detecting the posterior vitreous face by biomicroscopy is essential in making the diagnosis of posterior vitreous detachment regardless of the presence of Weiss ring or floaters. The presence of a **Weiss ring** or a detached posterior vitreous face (regardless of the presence of Weiss ring) is a definite sign of posterior vitreous detachment. Some eyes may have posterior vitreous detachment without the presence of a Weiss ring or floaters.

Prompt vitreoretinal examinations of patients presenting with floaters and / or light flashes is needed. The presence of both **floater and flashing lights** represent a higher risk of developing posterior vitreous detachment with retina breaks than patients presenting with either floaters alone or flashes alone. Patients with posterior vitreous detachment with vitreous **pigments** or **haemorrhage** are, also, at a higher risk of have a retinal tear compared with those who have normal vitreous examination. Aphakic eyes also have a higher risk of retinal tears associated with posterior vitreous detachment and also a greater risk of retinal detachments from such tears. **Asymptomatic retinal breaks** detected in phakic primary eyes do not often show significant tendency to develop retinal detachment. Posterior vitreous detachment, in phakic eyes, may occur in the presence of a pre-existing retinal break without provoking any further complications. Only a few of those cases

progress to sub-clinical retinal detachment. About 1% to 2% of all asymptomatic tears, may need treatment.

The need for follow up of phakic patients with posterior vitreous detachment is controversial. A recent study showed that in the absence of retinal breaks, on initial examination and retinal indentation, further follow up may not be necessary.

vitreo-macular traction syndrome

Vitreo-macular traction syndrome is characterised by incomplete posterior vitreous detachment associated with persisting vitreous traction on the macula. The syndrome represents a wide spectrum of vitreoretinal anatomical configuration that may cause visual symptoms.

Macular traction frequently causes cystoid macular oedema and decreased visual acuity, metamorphopsia, photopsia and micropsia. Spontaneous complete vitreo-macular separation may be followed by resolution of cystoid macular oedema and improvement in visual acuity. Vitreo-macular traction may also be associated with macular pucker, retinal blood vessels avulsion, retinal hole formation, and also traction macular detachment. **Vitreous surgery** to release the macular traction may result in an improvement of 2 or more lines of visual acuity in up to 75% of patients with about 40% of patients achieving a postoperative visual acuity of about 20/50 or better.

Vitreo-papillary traction may also cause trauma to the disc vessels causing intra-papillary and subretinal peripapillary haemorrhage, and elevation of the optic disc. Evaluation of the posterior hyaloid face should be an important part in the examination of patients with elevated optic nerve head. The optic nerve function is often preserved. Myopic discs may be particularly predisposed to this condition.

optic disc pit maculopathy

Optic nerve head pits are rare congenital anomalies that may be associated with **serous macular detachment** in many patients in the second or third decades of life. It has been thought that the origin of the subretinal fluid is either liquefied vitreous or CSF passing through the pit to the subretinal space. Recent indocyanine green angiography studies suggests that the fluid comes from the vitreous cavity.

Genetic defect may play a role in the pathogenesis of this condition. Congenital pits are often isolated, generally non-familial and unilateral malformations. Unilateral optic pits may also be inherited in an autosomal dominant fashion separate from mutations in the PAX2 gene which is responsible for the renal-optic coloboma syndrome.

Optic disc pits may be associated with macular detachment in about 30% to 45% of patients, especially if the pit is located at the temporal region of the optic disc. Optical coherence tomography studies showed that retinal detachment, that communicate with an optic disc pit, is most probably a **schisis-like** separation of the internal layer of the retina with **detachment of the outer layers** that occur later and is considered as a secondary phenomena. The outer layer detachment start in the macula without apparent communication with the pit. This explains the frequent failure of laser photocoagulation to create a barrier between the disc pit and the sub-retinal fluid. The dense central scotoma in optic nerve head maculopathy relates to the outer layer detachment.

Treatment of the macular detachment either by **pneumatic displacement** of the outer layer detachment from the posterior pole, or by macular buckling procedure results in an improvement in the visual acuity and may be associated with improvement in the central and peripheral visual field. The scotoma related to the inner layer separation may remain but it is often mild and consistent with relatively good visual acuity.

stickler syndrome

Stickler Syndrome is an autosomal dominant disease characterised by **ocular, articular, facial, auditory and oral abnormalities**. Ocular features of the syndrome include **myopia** (about -5 D) with **vitreous degeneration and retinal detachment often with giant tears**. Clinical overlap with Marshall syndrome (Marshall syndrome is similar to Stickler syndrome but without arthropathy), Wagner's syndrome (Patients infrequently have rhegmatogenous retinal detachment, but they often have traction retinal detachments, empty vitreous, choroidal atrophy, cataract and glaucoma.) and other hereditary vitreoretinal syndromes exists. Refractive errors, cataract and vitreoretinal abnormalities can be detected early in life in affected children.

Patients with Stickler syndrome are at higher risk of developing retinal detachment. Retinal detachment in these patients often have **poor surgical prognosis**. The reason for frequent "retinal detachments" in these patients is thought to be related to the vulnerability of the retina and the presence of lattice degeneration and retinal pigment epithelial thinning. Almost all the vitreous cavity in these patients is congenitally absent but a sheet of vitreous cortex exists and is often firmly attached to the weak retinal areas. If the vitreous cortex sheet remains intact, retinal tears might not lead to progressive retinal detachments, but if the vitreous cortex is broken, progressive bulbous retinal detachments will occur. Prophylactic laser photocoagulation has been used in patients with Stickler Syndrome in a 360 degree fashion between the pathological and the normal retinal or in a localised fashion to surround isolated lesions. It is reported, however, that the incidence of retinal detachment is significantly higher in the non-treated eyes than in the treated eyes. The

disease can be classified into two sub-types depending on the vitreoretinal phenotype:

- Type I denotes all patients with congenital vitreous anomalies.
- Type II are patients without the congenital vitreous anomaly.

The disease has been linked to the gene coding for type II procollagen **(COL2A1)** in about 2/3 of families. Type I patients show complete linkage to (COL 2A1). Type II patients are not necessarily linked to (COL 2A1). Type II disease is likely to be associated with other genes encoding other collagen. Mutation at (COL 11A2) and (COL 11A1) have also been linked to Stickler Syndrome without ocular manifestations. Mutation in the genes encoding collagen XI can give rise to manifestations of Stickler Syndrome but only mutation at (COL 11A1) seems to give rise to the full picture of the Syndrome. New data suggest that mutation involving exon 2 of the COL2A1 gene may lead to a predominantly ocular variant of the syndrome with a high risk of retinal detachment. these data may be useful in counselling patients.

Retinal detachment surgery

There is a high rate of satisfaction and improvement in the visual functions among patients who have vitreoretinal surgery even in the presence of good vision in the other eye. Preoperative visual acuity and the **duration** of retinal detachment are the most important factors associated with the return of central vision after surgery. If the macula is attached preoperatively, there is 82% to 87% chance of retaining a good postoperative visual acuity, whereas eyes with preoperative macular detachment have only a 20% to 37% chance of regaining the same visual acuity.

Death of retinal photoreceptors, in retinal detachment, is mainly due to retinal hypoxia caused by the separation of the outer retina from the retinal pigment epithelium. **Preoperative hyperoxia** may enhance retinal function after surgery. It may also reduce the proliferation of Muller cells and postoperative proliferative vitreoretinopathy.

Metamorphopsia is a sensitive indicator of previous macular detachment even in the presence of normal central vision and normal colour vision. Rhegmatogenous retinal detachment results in rapid and almost total loss in the blue cones. Significant loss in the rods also occur but the red-green cones, which are responsible for visual acuity, seems to be resistant to damage. These findings may explain the observed blue-yellow colours abnormalities in some patients, despite having a good visual acuity.

prophylactic treatment of retinal tears

The effect of prophylactic laser photocoagulation in fellow eyes with retinal tears and / or lattice degeneration has not be proved. Fellow eyes with or without posterior vitreous detachment and retinal tears may develop retinal detachment even after prophylactic laser treatment. Some authorities believe that laser photocoagulation might actually precipitate the formation of new retinal tears by increasing vitreous traction.

Prophylactic laser treatment is strongly recommended in **symptomatic flap tears**. There is no strong evidence, in the literature, to support prophylactic treatment in other types of tears. Prophylactic treatment has been carried out with **laser and / or cryotherapy**. Many retinal surgeons believe that cryotherapy may be associated with a greater incidence of macular epiretinal membrane formation than with laser photocoagulation. Recent reports showed that the incidence of epiretinal membrane after prophylactic treatment is 10% with laser treatment, 14% with cryotherapy and 18% with combined treatment. Argon laser retinopexy may also be associated with corneal complications e. g. corneal perforation. Corneal perforation may occur when a pigmented substance is present on the corneal surface.

The semiconductor diode laser, Erbium : YAG laser and argon fluoride laser have also been used in vitreoretinal surgery with promising results. The semiconductor **diode laser** has the following advantages:

1. It can be applied through silicon buckling material.
2. Is associated with reduced blood-ocular barriers breakdown (when compared to cryotherapy).
3. It can be applied in the presence of media opacities.
4. It does not seem to be associated with significant weakness of the sclera (unlike with diathermy).

Demarcation laser photocoagulation has also been shown to be useful in the treatment of acute or chronic, primary or recurrent shallow macula-sparing rhegmatogenous retinal detachments without proliferative vitreoretinopathy. A triple row of confluent laser burns should be applied.

The Erbium : YAG laser and argon fluoride laser are promising new lasers for the precise tissue cutting with minimal damage to adjacent tissues. The Erbium laser has the advantages of efficacy and precision of tissue cutting as well as coagulation of vascular tissues, and can be safely used in vitreoretinal procedures. Erbium:YAG appears to minimise intraoperative forces and movements of intraocular structures and may provide, therefore, a safer vitrectomy.

conventional scleral buckling technique

Uncomplicated retinal detachment is often treated with the scleral buckling technique. Scleral buckling technique involves a certain degree of surgical dissection and may have some limitations in patients with high myopia, patients with posterior staphyloma and in re-operations. Scleral indentation has been produced, in cadaver eyes, by using Holmium laser with a fibre-optic delivery system. **Holmium YAG laser** provides an infra-red light that is absorbed by the scleral causing shrinking the collagen tissues and causing a buckling effect to the sclera. The amount of the buckling effect can be controlled by controlling the laser setting. The main advantages of this technique is the creation of a small, localised and precise scleral buckling with minimum surgical dissection.

The surgical sequence during retinal detachment repair varies. The sequences **CDAE** involves: Cryotherapy-Drainage-Air-Explant, the sequences **CDE** involves: Cryotherapy-Drainage-Explant, while the sequence **D-ACE** involves: Drainage, Air injection, Cryotherapy, and Explant. In D-ACE retinal detachment surgery, it is important to obtain a single gas bubble in order to achieve good visualisation. This can be achieved by inserting the needle through the highest point of the pars plana. The speed of gas injection is very important in achieving a single gas bubble.

The two main types of retinal **explants** are silicon and hydrogel (MIRA) explants. Complications, e.g. infection or extrusion seem to be more common with silicon explants than with the hydrogel explants. Intra-scleral complications are, however, common with hydrogel implants too due to their expanding nature. Hydrogel explants have the advantages of having a smooth surface, being porous with hydrophilic properties enabling fluids and antibiotics to penetrate them. Progressive encapsulation may also occur with all types of materials. Some hydrogel explants may undergo microscopic breakdown inside the capsule associated with giant cell foreign body reaction. Long term follow up is recommended with both types.

Scleral buckling operations are known to cause postoperative **squint** in some patients (with incidence rate from 3% to 57% of patients). Restriction of eye movements are mainly due to adhesions between the globe and the muscles, the bulk effect of the explant under the muscle, disinsertion and retraction of a rectus muscle, or due to a direct injury to the muscle. Removing the explant may not lead to resolution of the muscle restriction. Vitrectomy with internal tamponade may be a better option in patients who are likely to develop diplopia (e.g. macula on detachments).

Scleral buckling may also be associated with postoperative **raised IOP** especially with retinal encirclement. Patients having extensive scleral buckling surgery for retinal detachment may benefit from prophylactic Diamox treatment. Scleral buckling, with encirclement bands, may also be associated with reduced retinal and choroidal **blood flow** on the buckle side.

Surgery may cause corneal shape changes and may lead to postoperative **astigmatism**. Encircling bands may be associated with up to 3D of myopic shift in some eyes. Vitrectomy and all types of circumferential scleral buckling surgery produce prolonged irregular and asymmetric corneal shape changes. The patterns of the changes differs depending on the buckling procedures used. Pneumatic retinopexy, on the other hand, does not produce significant corneal shape changes.

Scleral buckles **infection** may occur in about 3%-5% of cases. The most common organism identified has been staphylococci. Scleral buckling infection may also be caused by methicillin resistant S. aureus in patients with retinal detachment associated with atopic disease. Aggressive treatment by removing the buckle, and vancomycin with vitrectomy, in cases with endophthalmitis may be needed. Inadvertent scleral perforation at the time of buckle placement may be complicated by sympathetic ophthalmia.

Retinal detachment may be complicated with **choroidal detachment**. Surgery in eyes with choroidal detachment is associated with poor results because of the high incidence of postoperative proliferative

vitreoretinopathy. The postoperative proliferative vitreoretinopathy in these eyes is mainly due to the breakdown of the blood-retinal barriers. Aggressive perioperative treatment with oral steroids followed by pars plana vitrectomy and scleral buckling may be more superior than using a scleral buckling technique alone. Sympathetic ophthalmia may occur after retinal detachment surgery. It is important to recognise the significance of bilateral uveitis following surgery, since early diagnosis and vigorous treatment of sympathetic ophthalmia can be associated with a good visual prognosis.

pneumatic retinopexy

Pneumatic retinopexy is a relatively new technique for repairing uncomplicated retinal detachment. The technique appears to be gaining popularity during the last few years. Pneumatic retinopexy involves intravitreal injection of an expansile gas in association with cryotherapy or laser photocoagulation, without the use of scleral buckling. The classical indications of this technique has been:

- Retinal detachment due to a tear located in the upper two thirds of the retina.
- Retinal detachment due to several retinal breaks within one hour.
- Pneumatic retinopexy has also been described in the treatment of progressive rhegmatogenous retinoschisis.

The success of pneumatic retinopexy depends on proper case **selection**. In phakic eyes, this technique appears to be associated with higher complications rate than the scleral buckling procedure. A high incidence of **new inferior postoperative retinal tears** has been shown by some studies. The final anatomical and visual outcome, after repeated surgery, appears to be equal with both pneumatic retinopexy and scleral buckling techniques. The technique may also be complicated by **dehiscence** of clear corneal incisions after recent cataract surgery. Pneumatic retinopexy technique may be more economic than scleral buckling technique even in cases with repeated surgery.

pars plana vitrectomy

Conventional scleral buckling procedures in **pseudophakic** eyes are complicated by re-detachment and proliferative vitreoretinopathy. Pars plana vitrectomy (with or without scleral buckling) is an effective method for treating uncomplicated rhegmatogenous retinal detachments in these eyes. The technique is particularly useful when the retinal view is poor and also when internal tamponade is needed to close difficult tears. Vitrectomy in pseudophakic eyes has a better success rate (94%) than conventional surgery. Primary vitrectomy has the advantage of better viewing of the peripheral retina, better removal of vitreous traction and better application of endolaser treatment.

Posterior capsule opacification is about 400% greater in eyes containing foldable **silicon IOL** than in eyes containing PMMA IOL. If vitreoretinal surgery is anticipated, PMMA IOLs should initially be considered, in cataract surgery, instead of a silicon IOLs. When an eye contains silicon oil as well as a silicon IOL, posterior capsulotomy should be carried out at the end of the vitrectomy operation in anticipation of posterior capsule thickening.

Moisture condensation during fluid gas exchange may also occur on the posterior surface of PMMA and silicon IOL. The condensation is more marked in the presence of a posterior capsulotomy, it may limit the view of the retina during the operation, and may diminish the patient's visual acuity afterwards. **Heparin** coated IOL does not seem to prevent IOL adherence to silicon oil. It has been suggested that the use of a **pre-chilled balanced saline solution**, for the infusion fluid, may prevent the moisture droplets formation.

Pars plana vitrectomy may also be beneficial in other types of retinal detachment. In **children** with complicated retinal detachment, lens-sparing vitreoretinal surgery, with silicon oil tamponade, has been proposed as a treatment of choice for vitreoretinal disease in eyes with attached peripheral retina and non-extensive retina-lens adhesions. Retinal detachment secondary to choroidal **coloboma** is difficult to treat with conventional scleral buckle technique. Pars plana vitrectomy and silicon oil tamponade seems to be the treatment of choice. Gas tamponade seems to have a limited value in this condition.

surgical considerations

Poor pupillary dilatation is a major problem during vitreoretinal surgery. The adverse effects of mydriatic agents (to maintain mydriasis peri-operatively during prolonged vitreoretinal procedures) are well documented. They include severe hypertension subarachnoid haemorrhage, ventricular arrhythmia’s, and myocardial infarction. Suture fixation of the iris, iris retractors, or the use of a trans-pupillary continuos suture with a straight 16 millimetres needle mounted on a 10/0 Prolene

suture have been described. In the trans-pupillary continuos suture technique, the needle enters through the pars plana and exits through the corneal scleral limbus on the opposite side across the anterior chamber stretching the pupil in it's path. The needle is then passed in a similar way about 6 times to achieve complete pupillary dilatation.

Relieving vitreous traction is an important part of vitreoretinal surgery. Complete removal of the cortical vitreous from the retina surface is often difficult particularly in children. **Plasmin** has a fibrinolytic action that can hydrolyse a variety of glycoproteins. It can be used to produce a cleavage at the vitreoretinal interface between the posterior vitreous cortex and the internal limiting membrane.

At the end of pars plana vitrectomy the **sclerotomy** site is traditionally closed with 8/0 sutures. Water-tight wound closure is sometimes difficult. Maintenance of IOP during wound closure could also be difficult especially in inferior sclerotomy during the removal of the cannula. Pars plana vitrectomy can be performed through self-sealing sutureless sclerotomy. This technique allows wound closure with good IOP control. A half depth scleral tunnel incision is created for about 2 mm towards the limbus by a sharp crescent shape knife. Pars plana sclerotomy is considered to be a potential site for complications (e.g. peripheral traction retinal detachment, retinal tears and traction of the ciliary body causing hypotony and recurrent vitreous haemorrhage) in vitreoretinal surgery. These complications may be attributed to fibrovascular proliferation at the sclerotomy site High frequency ultrasound biomicroscopy may be used to evaluate entry sites after pars plana vitrectomy.

Internal retinal **tamponade** is often carried out by:

- Gases (air, SF6, C3F8).
- Silicon oil.
- Perfluorocarbon liquids.

The use of gas tamponade after fluid-gas exchange is an important part of modern vitreous surgery. Gases can be used in vitrectomised and non-vitrectomised eyes (e.g. in pneumatic retinopexy and in the D-ACE technique). Gas injection is also used with vitrectomy in order to flatten the retina and remove any subretinal fluid with the flute needle. The most commonly used gas is air. **Air** is rapidly absorbed (2-3 days). Sulphur hexafluoride SF6, and Perfluoropropane C3F8 are the other gases commonly used when more prolonged internal tamponade is required. The length of time that a gas remains in the eye depends on its concentration, and the volume injected. **SF6** can last for about 10 days inside the eye, while **C3F8** can last for about 28 days.

Postoperative posturing is needed after gas injection to place the gas bubble under the retinal tear. It has been thought that the use of **nitrous oxide anaesthesia** produces an increase in the size of the intraocular

gas (C3 F8) bubble, with a subsequent rise in intraocular pressure. This has led to the practice of discontinuing nitrous oxide at least 15 minutes before gas-fluid exchange in vitreous surgery to allow clearance of nitrous oxide from the body. Recent studies suggest that general anaesthesia using nitrous oxide does not adversely affect the size of the C3 F8 gas bubble 24 hours after surgery.

Silicone oil can also be used in retinal tamponade. The silicone oil study confirmed the superiority of **silicone oil** to Sulphur hexafluoride (S F6) gas as an intraocular tamponade for the management of retinal detachment complicated by advanced grades of proliferative vitreoretinopathy. Silicon oil injection may also be indicated in cases of giant tears, when postoperative posturing can not be achieved (e.g. children), in only eye patients as postoperative visual acuity is better with silicon more than with gas, and in CMV retinitis. Postoperative hypotony is also less common after silicon use.

Silicon oil may be complicated with intraoperative passage of the oil to the subretinal space or to the anterior chamber in aphakic eyes. Postoperative glaucoma, keratopathy, and corneal de-compensation may also occur. Postoperative **glaucoma**, due to oil in the anterior chamber, develops in 10% of patients even after several years. Postoperative gonioscopy may be helpful in identifying eyes at risk of developing oil related glaucoma. In vitrectomised eyes having long term retinal tamponade with silicone oil, inferior peripheral iridotomy can reduce the forward migration of the oil and help to prevent secondary keratopathy, and pupillary-block glaucoma. Retinal toxicity may also develop.

Silicon oil has a refractive index of 1.4 which is higher than that of the vitreous, and can cause a high **hyperopic shift** in phakic eyes which may lead to amblyopia and esotropia when used in young children.

There have been some concern about the stability of silicon material in the body. Some women developed **immunological** disorders after silicon breast implants. Highly purified silicon oil in the eye, on the other hand, seems to be chemically stable in cases with prolonged retinal tamponade.

Intraocular silicone oil may migrate out of the eye, along the intracranial portion of the optic nerve, and into the **lateral ventricles of the brain**. A case of a 42-year-old man with AIDS and a rhegmatogenous retinal detachment has recently been described. The patient developed peripheral neuropathy and MRI features of an intracranial shifting fluid that has the same imaging properties to the intraocular silicone oil.

It is strongly recommended that complete **removal** of the silicon oil should be attempted at least 8 weeks after injection to reduce the incidence of complications. In proliferative vitreoretinopathy re-detachment may occur in about 33% of eyes after the removal of the oil,

often within the first 3 postoperative months. The risk of re-detachment decreases with increasing time after oil removal. It is unlikely that the retina will re-detach 5 months after removing the oil. Prophylactic argon laser retinopexy 3-6 weeks before the removal of the oil seems to reduce the incidence of the re-detachment. Silicone oil removal can be combined with cataract surgery. Trans-pupillary drainage of silicone oil through a planned posterior capsulotomy is an alternative method for the removal of silicone oil to pars plana sclerotomy.

Perfluorocarbon liquids are clear fluids that have low viscosity, heavy specific gravity, and different refractive index to water. Perfluorodecalin is another substance used in vitreoretinal operations for giant retinal tears. Intraocular perfluorodecalin may be tolerated by the retina for up to 6 months. It may be used in combination with silicone to achieve retinal tamponade in retinal detachments with inferior and superior breaks. The two substances have different densities, perfluorocarbon liquids supports the inferior retina, while silicone oil supports the superior lesions. An intermediate area of the retina, between the two substances, may not get in contact with either substances and may develop proliferative vitreoretinopathy.

Proliferative vitreoretinopathy (PVR)

The most common cause of retinal detachment surgery failure is the development of proliferative vitreoretinopathy (it occurs in 7%-10% of eyes). The time interval between the onset of the PVR and the onset of the retinal disease ranges from 2 weeks to 45 months (average 2 months). Patients with proliferative vitreoretinopathy are at increased risk of developing vision threatening conditions in the fellow eyes e.g. acute retinal detachment, proliferative vitreoretinopathy and age related maculopathy. Significant risk factor for the development of proliferative vitreoretinopathy, after primary vitrectomy, are preoperative proliferative vitreoretinopathy, aphakia, and high vitreous protein levels.

Proliferative vitreoretinopathy results from cellular activities within the vitreous, e.g. dispersion or migration of certain cells within the vitreous cavity, proliferation of theses cells, synthesis of extra-cellular matrix and contraction of this matrix causing retinal detachments. MRI examination of the **blood-retinal barrier** shows that barrier breakdown is an important and early factor in the developing of proliferative vitreoretinopathy. Cryotherapy in eyes with giant retinal breaks is likely to enhance dispersion of retinal pigment epithelium cells in the vitreous..

Growth factors (fibroblast growth factor and platelets derived growth factors) play a major role in the pathogenesis of the formation of proliferative vitreoretinopathy. Growth factor blocking agents may pay a role in the treatment. There is also some evidence that an **immune response** may be involved. Adjunct treatment with steroids, and 5-FU, has been tried. Intra-vitreous injection of Triamcinolone in rabbits eyes reduces the barrier breakdown and proliferative vitreoretinopathy formation. Intravitreal injection of steroids at the end of vitreoretinal surgery may prove useful. Intravitreal 5-FU inhibits the progression of proliferative vitreoretinopathy in animal models, with no significant drug related corneal complications.

The **herpes simplex virus thymidine kinase gene** (suicide gene) is known to cause selective cell death by inhibiting DNA synthesis. The use of the virus gene with ganciclovir in animals with experimental proliferative vitreoretinopathy was associated with reduction in the proliferative vitreoretinopathy in some studies. A single short term exposure to thiotepa or 5 FU may be useful in inhibiting collagen contraction and RPE cells proliferation, and thus reducing proliferative vitreoretinopathy.

Postoperative use of **oral 13 cis-retinoic acid** (a potent inhibitor of the retinal pigment epithelium proliferation), appears to decrease proliferative vitreoretinopathy and increase the rate of retinal reattachment in vitreoretinal surgery.

Macular hole surgery

mechanism and natural course

Macular holes are often idiopathic. Other causes of macular holes include trauma, myopia, and solar maculopathy. The development of macular hole can be classified into 4 stages:

stage	features
stage 1	central yellow spot (**stage 1 A**), or a yellow ring (**stage 1 B**) at the fovea with loss of the foveolar depression.
stage 2	an eccentric crescent shape full thickness retinal defect with pseudo-operculum.
stage 3	a round central retinal defect with an overlying free pseudo-operculum.
stage 4	similar to stage 3 but with a posterior vitreous detachment.

The mechanism of macular hole formation is not completely understood. It has been hypothesised, by Gass, that shrinkage and **tangential** traction of the peri-foveal vitreous cortex induces traction detachment of the foveola and the fovea which may result in full thickness macular hole formation. It has therefore been thought that complete vitreous detachment may give protection against the development of full thickness macular holes. Tangential traction which causes macular holes appears to originate mainly in the premacular vitreous cortex that forms the posterior wall of a premacular liquefied pocket. Gass also hypothesised that **Muller cells** may possibly play an important role in the pathogenesis of the disease. He hypothesised that Muller cells layer is the primary structural support for the fovea, and may be the primary site of retinal changes causing the pathognomonic features of foveomacular schisis.

Recent optical coherence studies, on the other hand, showed that in fellow eyes posterior hyaloid detachment begins around the macula, but the hyaloid remains adherent to the foveolar centre, producing an **anteroposterior** traction forces. This anteroposterior traction forces results in an intraretinal split evolving into a cystic space, and then to the disruption of the outer retinal layer and the opening of the foveal floor, thus constituting a full-thickness macular hole.

Full thickness macular holes seem to be associated with few **systemic risk factors**. Some studies demonstrated some relationship of macular hole formation and changes in hormonal balance around the menopause period, and also relationship to previous hysterectomy and oophorectomy, and the use of oestrogen as HRT.

A recent study showed that approximately 34% of all eyes with macular holes have an increase in the **size** of the hole. During a follow up period of 3 years 84% of stage 2, 55% of stage 3 and 16% of stage 4 macular

hole undergo enlargement. Visual acuity also decreases by 2 or more lines in 30%, 68%, 29%, and 13% of macular hole stages 1, 2, 3, and 4 respectively. In the presence of posterior vitreous detachment, it is unlikely that stage 1 holes will progress to stage 2. Other studies showed that visual acuity remains stable in about 40.9% of eyes.

The rate of development of a **new** macular hole during follow-up in fellow eyes that are unaffected at baseline is about 4.3% for 3 or fewer years of follow-up, and 7.1% for 6 or more years of follow-up. Spontaneous regression may occur in 8.6% of patients in a follow-up period of 6 or more years. **Spontaneous closure** may occur due to a spontaneous release of vitreous traction, constriction of an epiretinal membrane or due to pigment epithelial hyperplasia. Closure or constriction of the macular hole may be associated with improvement of the visual acuity of the patient. Improvement in the visual acuity is greater in eyes in which macular holes disappear within 24 months.

Epiretinal membrane occur in about 65% of patients with macular hole. The prevalence is greater in pseudophakic than in phakic eyes. It also increases with increasing severity of the hole. The presence of membrane does not seem to be correlated with visual acuity.

The true nature of macular hole **operculae** is not completely understood. Analysing the vitreous in most patients after surgery does not show any evidence of cellular or fibro-cellular elements in the vitreous. This suggests that operculae rarely if ever contain retinal elements. Many investigators believe that operculae, in this disease, is better called pseudo-operculae. On the other hand, a recent study of stage 3 macular hole identified two distinct types of macular hole operculum:

1. Operculum containing **only glial tissue** (pseudo-operculum), that is thought to results from a failed attempt at macular hole formation. The presence of pseudo-operculum indicates evidence of vitreo-foveal separation and is considered a favourable prognostic sign with low risk of developing a macula hole.
2. Operculum containing **glial and foveal cones**, neurites and synaptic complexes (true operculum). Successful anatomical and functional results may occur in both type. Loss of macular tissue in the true operculum eyes may explain the worst success rate and the more modest visual improvement in these eyes even after complete anatomical success.

In another histopathological study of vitreous samples removed during macular hole surgery retinal and cellular membrane fragments were very rarely found. The absence of cellular membrane fragments in the majority of cases suggests that mechanisms, other than cellular proliferation, are important in the pathogenesis of macular holes. The study also found that operculae rarely contain retinal fragments, and the authors suggested that the term pseudo-operculum is better used.

fellow eyes

2% of the normal fellow eyes develop full thickness macular holes, and 25% of the eyes that have pre-macular holes changes develops full thickness macular hole. The macular hole in the fellow eyes often develop within 24 months. Fellow eyes with separation of the posterior hyaloid membrane in the foveal region appears to be protected from future macular hole development. Patients with attached hyaloid membrane in both eyes are at higher risk of developing macular hole in the fellow eyes. Patient with separated hyaloid membrane in the macular hole eyes only with attached membrane in the fellow eyes are at intermediate risks.

Ultrasound examination can be helpful in determining which of the fellow eyes is at higher risk. When the posterior hyaloid membrane is completely attached to the retina surface, it can not be seen ultrasonically, it becomes visible when it is separated from the retina surface by more than 500 micrometer. **Electrodiagnostic** and psycho-physical tests do not seem to be able to predict the outcome in the fellow eyes. A tritan colour contrast sensitivity loss at base line, in apparently normal eyes, may indicate sub-clinical foveal dysfunction.

management

The differentiation between true full thickness macular holes and pseudo-macular holes may be difficult. Fundus **auto-fluorescence** is known to arise from the retinal pigment epithelium. Auto-fluorescence imaging with confocal scanning laser ophthalmoscope is a non-invasive and rapid technique which can be used for the evaluation, staging, and the differential diagnosis of macular hole.

Idiopathic macular holes may be treated by **vitrectomy** with fluid gas exchange with or without the use of transforming growth factor-beta-2. In the absence of posterior vitreous detachment, as in traumatic macular holes in children, posterior vitreous detachment can be induced by the injection of autologous Plasmin. Surgical treatment may result is anatomical closure and improvement in the visual acuity even in **long-standing** macular holes.

The use of **recombinant TGF beta-2** does not seem to be necessary, similar results have been reported in patients who had TGF beta-2 and patients who received placebo. Injection of an autologous platelet concentrate over the macula during surgery for stage 3 and 4 macular holes of less than 3 years duration improve the anatomic success rate. The final visual acuity is, however, not better than without platelet.

Postoperative **positioning** of patients is very important in achieving good results. Peeling of the internal-limiting membrane is traditionally carried

out in cases of macular pucker. A recent retrospective study showed that routine peeling of the membrane in all cases may achieve good result with short postoperative periods of posturing. Air tamponade may also be enough in cases with internal-limiting membrane peeling. Silicon oil tamponade may be used with good anatomical results in patients who can not properly position after the surgery.

Surgery for **longstanding** macular hole may be beneficial in some patients even after 12 months of onset. The rate of anatomical success seems to be the same but visual acuity improvement is more likely in the recent onset holes. After surgery, complete closure of full thickness macular holes seems to result from proliferation of the Muller cell and fibrous astrocytes. This seems to occur whether adjuvant treatment is used or not. Histopathological studies show that the edges of the hole approximate after treatment and the remaining gap seems to be sealed with Muller cells.

Although overall anatomical closure success rates of macular holes is reported to be between 56% and 100%, a significant number of holes remain open after initial vitrectomy. **Re-treatment** with rigorous membranectomy and autologous serum administration is beneficial in most eyes in which initial macular hole surgery has failed. Final visual acuity improvement seems to be less than after successful primary closure, due to the longer duration of holes with failed primary surgery.

Re-opening of a successfully repaired macular hole may occur in about 5% of cases. In a recent study macular hole reopening occurred in 9.5% of cases. In most of the cases, no definite cause was evident. This phenomena does not appear to be related to cataract surgery. Re-operation in these cases results in good visual results similar to those obtained before the re-opening. Laser photocoagulation to the macular hole bed has also been described. Stimulation of the RPE is thought to release different cytokines that may promote healing. Persistent and re-opened macular hole after surgical treatment may also be treated with argon laser photocoagulation to the hole bed, and fluid-gas exchange.

Anatomical closure of macular holes can be achieved in a high percentage of patients. Smaller number of patients, on the other hand, demonstrate improvement in the **Snellen visual acuity**, as a high percentage of patients develop postoperative cataract and visual field loss. Visual loss in macular holes are thought to be due to loss of the retinal function in the area of neuro-sensory defect as well as reduction in the retinal function in the surrounding area. After surgery, patient may have some visual distortion and **metamorphopsia** without any evidence of a subjective scotoma .

The use of Snellen visual acuity chart alone to measure functional success may underestimate patient satisfaction. Other methods of **assessment** include:

- Biomicroscopic examination of the fundus.
- Scanning laser ophthalmoscope examination.
- Micro-perimetry.
- Optical coherence tomography.
- ERG.

Micro-perimetry performed preoperatively show an area of absolute scotoma that correspond to the size of the neuro-sensory defect surrounded by an area of relative scotoma. After surgery, areas with absolute scotoma disappear, and most eyes show partial or complete resolution of the surrounding relative scotoma.

Optical coherence tomography can be used in the postoperative evaluation of macular holes repair. Patients can be classified into one of three pattern: U type, associated with normal foveal contour and best visual acuity, V type, associated with steep foveal contour and intermediate visual acuity results, and W type, associated with foveal depression of the neuro-sensory retina and the worst visual acuity. Greater foveal thickness appears to be associated with better postoperative visual acuity.

Focal macular ERG significantly improves after surgery. The preoperative b-wave implicit time measured with 5 degree spot, correlates significantly with the postoperative improved visual acuity. A new method of differential perimetry that involves objective study of the retinal photoreceptors displacement and metamorphopsia has also been described. Patients with full thickness macular holes shoe evidence of centrifugal photoreceptors displacement.

complications

1. Nuclear **cataract** formation is common after pars plana vitrectomy. Phacoemulsification and posterior chamber IOL is a safe and effective technique of removing the cataract in these patients. A posterior capsule plaque is often present. It is sometimes difficult to remove the plaque safely. Postoperative thickening of posterior capsule is also common in these patients.

2. About 36% of patients with macular hole develop **increase in the IOP** after vitrectomy. There are several causes of IOP rise; these include; pupil block, migration of the oil to the anterior chamber, inflammation, and pre-existing glaucoma. The IOP rise may also be due to expansion of the gas bubble, reduction of the aqueous humour outflow, or due to reduction of the uveoscleral outflow caused by the scleral band. Anterior chamber angle closure may also be responsible in some eyes. Glaucoma often occur in the first postoperative week. IOP rise and treatment seem to occur only for a short period. The use of topical aqueous suppressant seems to be useful in preventing IOP

rise after pars plana vitrectomy with long acting gas tamponade. extended therapy may be needed in some patients. Aggressive treatment is often needed by oil removal, trabeculectomy, glaucoma shunts, or cyclodestructive procedures. All these methods may, however fail in controlling the IOP.

3. **Visual field abnormalities** may occur after vitrectomy and gas-fluid exchange. The most common visual field defect is a dense, wedge shaped temporal defect. The mechanism of visual field defects is not completely known. They may be caused by manipulation and trauma to the peripapillary blood vessels or the nerve fibre layer during elevation of the posterior vitreous face or aspiration during the gas-fluid exchange process. Occlusion of the peripapillary blood vessels by compression, and dehydration injury to the nerve fibre layer during fluid-air exchange may also play significant role in the mechanism of visual field loss. The field defects that occur after room air is used may result from desiccation of the retina by the room air. Some studies showed that **passing air, used for fluid–air exchange, through water** seems to prevent the development of visual field defects in these eyes. It has also been suggested that **confining peeling of the posterior hyaloid face to the macular area,** and avoiding membrane peeling in the peripapillary area may reduce the risk of inducing visual field defects.

4. **Retinal detachment** is a recognised complication after vitrectomy for macular hole (the rate of postoperative detachment varies from 1-14% in different reports). Prophylactic scleral buckling may reduce the rate of postoperative detachment.

5. **Ulnar nerve neuropathy** may occur with patient's positioning after macular hole surgery. Patients and surgeons should be caution in minimising the amount of time the elbow is bent, and also the pressure exerted on the bent elbow.

Paediatric Ophthalmology

Amblyopia and screening

Amblyopia may be due to strabismus, anisometropia or due to visual deprivation. Previous studies showed that abnormal level of hyperopia (more than 3.5D in one or more meridian) is frequent in children. Anisometropia, larger or equal to 3.00 D at one year of age persists till the age of ten years in 90% of cases and will be associated with significant risk of amblyopia.

It is not known if **pre-school screening** results in a better visual outcome than screening children at school. Recent studies indicate that pre-school orthoptic screening does not seem to have an influence on the age of detection of squint or squint amblyopia but may achieve a significant reduction in the age at which amblyopic eyes and refractive errors are diagnosed. The overall prevalence of amblyopia at age 7 seems to be similar in the children who were screened at 3 years old and controls. On the other hand, a significant number of children, without amblyopia, but with reduced vision due to uncorrected refractive error may be detected by pre-school screening.

The majority of amblyopic children detected by pre-school screening seem to achieve good visual outcome by hospital treatment. Poor compliance of patients follow up has been a problem in many studies. A family history of visual defect seems to have a protective effect on individual infants, most probably because more of these infants are brought in for a check-up at an early age on the parents initiative.

Amblyopic eyes, when compared with normal eye, have more widespread VEP abnormalities. The fellow eyes also show some abnormalities mainly in pattern reversal P100 amplitude, the pattern-offset P110 amplitude, and the pattern-offset n165 latency. These abnormalities may be due to occlusion therapy. Automated perimetry shows that all types of amblyopia are associated with a generalised depression of light sensitivity, which is correlated with visual acuity loss. Amblyopia is not associated with any area of focal loss of threshold light sensitivity. If a focal defect is present in the visual field of the amblyopic eye, organic causes of visual loss should be suspected.

refraction

Cycloplegic refraction is often needed in children, especially in children with esodeviation. Topical administration of cyclopentolate can be associated with CNS symptoms, e.g. confusion, psychosis, cerebellar dysfunction and seizures. Gastrointestinal disturbances in neonates and

generalised urticaria have also been reported. The use of proxymetacaine prior to cyclopentolate results in a less traumatic experience for the small children. Fundus examination may be helpful in assessing the refractive error in young children. In young children, the finding of abnormal disc shape should alert the physician, because abnormal disc shape may be associated with corneal astigmatism. The direction of the longest disc diameter seems to indicate the axis of the corneal astigmatism. Abnormal disc appearance in children warrant refraction to avoid the possibility of amblyopia.

auto-refraction

Refraction in children may be difficult due to poor co-operation. There is an increased acceptance of auto-refraction use in clinical practice by patients and physicians due to its speed, accuracy, and reproducibility. The use of advanced automatic refractors, in children and adult refraction seems to comparable or superior to subjective retinoscopy in accuracy and speed. Automatic cycloplegic refraction may safely be used to prescribe glasses in children. The instrument does not have to be used by doctors, but can safely be used by a technician. Hand held infrared auto-refractor (e.g. Retinomax auto-refractor), is a useful and quick method, that may be used to diagnose abnormal level of hyperopia without the use of cycloplegia.

photo-screening

A significant limitation of traditional screening techniques for young children is their reliance on subjective response. Photo-screening, a new and an acceptable technique for detecting the presence of absence of certain vision disorders from a photograph. The technique eliminates the subjective element and allows vision screening of preverbal children. Two types of photo-refraction systems have been used, they differ in the placement of the flash source:

- the on-axis system (coaxial flash)
- the off-axis system (eccentric flash).

The coaxial type is more accurate but it is more complicated to use because it needs several photos taken from different distances. The off-axis system is cheaper but it can not detect astigmatic errors and has less accuracy than the on-axis system.

Photo-refraction in infants 3 months of age or younger is particularly difficult. In black infants, photo-refraction is often improved after cycloplegic application. The technique is associated with a wide **variability** in the sensitivities and specificity which may be due to inconsistent photograph interpretation skills or deficient screening guidelines or both. Caution should be taken in relying on photo-screening in detecting strabismus and refractive errors in children. The technique

can also be used for screening for refractive errors in young patients with learning disabilities is effective.

Strabismus

infantile esotropia and exotropia

Infantile esotropia occurs before the age of 6 months. Prematurity, low birth weight, low Apgar scores, and a family history of strabismus are significant risk factors for congenital esotropia. While monocular visual acuity is relatively unaffected in these patients, the majority of patients fail to achieve normal stereopsis.

Children presenting with infantile exotropia and esotropia appear to be at risk for having **other ocular or systemic disease**. In a study of 70 patients diagnosed with exotropia in the first year of life, 67% of patients had a coexisting ocular or systemic abnormality. In the same study , about 49% of patients diagnosed with esotropia before 1 year of age also had coexisting abnormalities .

The association between Dissociated Vertical Deviation **DVD** and infantile esotropia ranges from 50% to 90%. It is possible that infantile esotropia may consist of two distinct subgroups: one consisting of esotropia with DVD, latent nystagmus and asymmetrical OKN and another group without these features. These two subgroups may have a different pathophysiology and prognosis.

Dissociated Vertical Deviation is thought to be due to lack of stability of fusion. Several factors are believed to be included in the pathogenesis of DVD. These factors include disorders in the optomotor transmission pathway, disorder in the optic chiasm or abnormal visual sensitivity.

There is no one single successful operation for the correction of the dissociated vertical deviation. The standard operations are:

1. Large superior rectus muscular recessions,
2. Conventional superior rectus recessions combined with posterior fixation suture (Faden procedure).
3. Recession of the ipsilateral inferior rectus muscle with or without superior rectus muscle recession. Large superior rectus recessions are currently the preferred surgical method of treating DVD, with a success rate of 72%.
4. Anterior transposition of the inferior oblique is an effective treatment for dissociated vertical deviation with an inferior oblique over action, but it may be less stable in the long-term when the pre-operative dissociated vertical deviation is more than 15 prism dioptres.
5. Inferior oblique resection and anterior transposition of both muscles may also be used in the treatment of asymmetric DVD and inferior oblique over-activity.

Surgical treatment of infantile esotropia may be followed by amblyopia. In some reports **amblyopia** was reported to be less common in untreated

patients compared to a similar group of surgically treated patients. This low incidence of amblyopia in untreated patients may be due to the presence of cross fixation and bilateral macular stimulation.

The risk of developing amblyopia is outweighed by the chance of developing a better binocular vision. Postoperative follow up to avoid amblyopia is, however, very important. When access to postoperative follow up is not possible, it is advisable that surgical treatment for infantile esotropia with alternating deviation, and no anisometropia should be postponed till later years. Psychological difficulties resulting from squint, may occur in school children, teenagers and adults. Correction of squint, even in adult age, may offer an improvement in the psychological functions of patients.

There is a potential for the development of some form of binocularity if appropriate ocular **alignment** is achieved early in life. It has been thought that amblyopia must be treated and reversed before surgical treatment of esodeviation. Recently it has been suggested that surgical alignment of the esotropia within the first 6 months of life may improve the development of binocularity. Surgical treatment for esotropia in children before full resolution of amblyopia is, now, thought to be safe and effective if the amblyopia therapy is continued after the operation.

In a study of 103 treated patients with infantile esotropia, the outcome of treatment was classified into the following groups:

1. Subnormal binocular vision.
2. Microtropia.
3. Small, cosmetically acceptable angle.
4. Large cosmetically unacceptable angle.

In this study, all eyes in group 1 remained aligned after a follow up period of 8 years. 20% of the eyes with microtropia and 26% of eyes with small angle squint lost the stability of ocular alignment during the follow up period. After surgery to infantile esotropia, the best result that can be expected is a mono-fixation syndrome with a residual small angle of esotropia and peripheral fusion.

Failure to align the eye and treat amblyopia in young age may result in poor vision for the rest of the patient life. **Surgery in adults** age not only eliminates ocular alignment deformity but can also improve fusion and increased field of binocular vision. Binocular field expansion occur in the great majority of adults with esotropia after squint surgery, even if the squint is long-standing. The expansion appears to be consistent with the degree of straightening the eye and not related to the type (infantile or acquired), duration of squint, visual acuity or history of squint surgery in childhood.

accommodative esotropia

Most children with refractive accommodative esotropia have an excellent outcome in terms of visual acuity and binocular single vision. In most patients the degree of hyperopia remains unchanged with poor prospects for discontinuing glasses wear. In accommodative esotropia, the classic teaching indicates that surgery should be used to correct only the part of esodeviation that is not corrected by full cycloplegic glasses. Some reports suggested that **correcting the whole angle** of squint (when measured without glasses) or an average angle (an average angle when measured with and without glasses) may lead to reduction of the hyperopia afterwards.

The prism adaptation test can be used to determine the potential for binocularity before surgical alignment of the squint. Patients with esodeviation are fitted with a base out prism to correct the angle of squint. Testing for binocularity is then carried out after sometimes of wearing the prism. Full surgical correction is then planned if there is evidence of binocularity. The test can also be used to determine the target angle that should be corrected. Prism responders show a better motor outcome as well as better fusion after surgery than eyes operated on before wearing prism.

exodeviation and Intermittent exotropia

Intermittent exotropia typically occurs late in childhood. This type of squint may be difficult to treat. High rates of recurrences may follow surgical treatment and repeated surgeries may be needed.

Patients ability to control intermittent exotropia deviation is often assessed by subjective means e.g. observation of eyes control in the clinic, questioning the patients or the family, and reports of mono-ocular eye closure in the bright light. Patients with intermittent exotropia demonstrate significantly worse distance stereo-acuity than the normal subjects. Diminished **distance stereo-acuity** seems to be an objective measure of poor control of the deviation. This test may provide important objective criteria for deciding when to perform surgery in patients with intermittent exotropia. Most of the patients with poor distance stereo-acuity preoperatively have dramatic improvement, after the operation, in their distance stereo-acuity.

In the treatment of intermittent exotropia, the conventional teaching is to correct refractive errors (e.g. anisometropia, astigmatism and myopia) to improve the retinal image and promote fusion and also to stimulate accommodative convergence. **Hyperopia** is not usually corrected on the assumption that, without correction, children are forced to accommodate and that the associated accommodative convergence might be beneficial. A trial of spectacle correction may be warranted in exotropic children (between 2-10 year old) with severe hyperopia (more than 5.D)

and also in those patients with moderate hyperopia and a low accommodative convergence / accommodation ratio.

The angle of squint in patients with intermittent exotropia undergoing surgery should be measured for an outdoor target and after one hour of monocular occlusion. Surgery should be carried out for the largest angle measured.

surgical treatment

- **recession-resection surgery**

Surgical alignment of congenital esotropia can be achieved with either bilateral medial rectus recession, or by medial rectus recession/lateral rectus resection surgery. At least one additional surgical procedure is required on average to maintain alignment in the first 10 years after initial successful surgery.

The degree of change of ocular alignment per millimetre of rectus muscle recession seems to correlate to the degree of preoperative esodeviation or exodeviation. The degree of changes also correlate significantly and inversely with axial length of the eye (larger eyes have smaller responses). This correlation does not appear to be clinically significant.

8 millimetres medial recti recession can correct up to 80-90 prism dioptres of esodeviation with no clinically significant limitation in adduction. However, muscle recession beyond the tangential point may result in mechanical restriction of ocular movements.

Most ophthalmologists prefer **augmented** medial rectus muscles recession than operating on three or four muscles for large angle esodeviation. It is easier and safer to perform large recessions by using (hang back) sutures whereby the muscle is re-attached to the sclera at the original muscle insertion and not at the new recession site. Mersilene and Teflon material have also been tried as muscle implants. In animal studies the Mersilene implants seem to induces a severe fibroblastic reaction, while the result of the Teflon implants appear to be more promising and, suggest that this material may be used as a spacer in squint surgery.

A and V patterns esotropia have often been treated by recession of the medial rectus muscle with vertical transposition of the new insertion. Slanting muscle insertion technique can also be used as an alternative in A or V esotropia without over-action of the vertical muscle. In A pattern the upper margin of the recessed medial rectus muscle is recessed more than the lower margin and vice versa in V pattern esotropia.

Squint surgery may be followed with the following **complications**:

- Endophthalmitis. Endophthalmitis after paediatric strabismus surgery is rare. Children may not show symptoms. Lethargy, asymmetric eye redness, eyelid swelling, or fever in the postoperative period, even if initial postoperative examination results are normal, should prompt urgent ocular examination.
- Postoperative pain.
- Permanent diplopia.
- Anterior segment ischaemia.
- Anisocoria.
- Lower eyelid retraction.
- Postoperative nausea and vomiting.

Postoperative pain after squint surgery can be managed by the administration of topical anaesthesia drops at the beginning and at the end of the operation or by sub-conjunctival bupivacaine (0.5%).

Intractable diplopia may occur after over-correction of exotropia. It may also occur if the inferior oblique muscle has accidentally been included into the lateral rectus muscle during surgery to the lateral rectus muscle. A vertical deviation or a deficiency of vertical rotation are significant indicators of the involvement of the inferior oblique muscle into the lateral rectus muscle insertion. Careful dissection during surgery is important as re-operation to free the inferior oblique muscle often fails.

Anisocoria May occur after routine squint surgery. A significant mydriasis May be observed in the operated eyes in some patients. It is thought that these changes in the pupillary diameter result from the release of neuro-transmitters from the tissue damage during the surgery. Other possible causes May be iris ischaemia. The pupillary changes seem to be independent of the number or the type of extra-ocular muscles surgery.

Lower eyelid retraction may occur after inferior rectus muscle recession because of the intimate anatomic correction between the inferior rectus muscle and the lower eyelid retractors. Wide dissection around the inferior rectus muscle or advancement of the Capsulo-palpebral head to counter the forces created by the recession of inferior rectus are new techniques to avoid this complication. Primary infra-tarsal eyelid retractors lysis is also an effective technique to prevent lid retraction. This procedure seems to be effective in large inferior rectus muscle recessions (up to 10 mm).

Postoperative nausea and vomiting is a major problem in paediatric patients undergoing strabismus surgery, and can prolong hospitalisation. It is thought that the oculo-cardiac reflex is a major cause for this complication. Orbital infiltration of anaesthetic solutions may reduce the incidence of postoperative vomiting by blocking the afferent limb of the reflex. It is possible that and sub-Tenon injection may also has the same effect. The prophylactic fentanyl-droperidol prolongs recovery time and provides no benefit over acetaminophen alone in children. Cost-

effectiveness analysis strongly favours the use of acetaminophen over fentanyl-droperidol prophylaxis in children undergoing primary strabismus surgery. Many authors also recommend routine intraoperative opiate analgesia and prophylactic anti-emetics

- **adjustable suture surgery**

The adjustable sutures technique has many advantages. This technique is thought to be more suitable in cases when traditional surgery has unpredictable results e.g. paralytic squint, previous surgery, dysthyroid eye disease, and squint surgery in eyes with scleral buckles. Adjustable sutures surgery is generally considered to carry no greater risks than standard squint surgery. The technique may also be successfully used in children with horizontal squint, especially in re-operation cases.

The adjustment is often carried out to the recessed muscle. Accurate adjustment may be difficult in eyes where performing a cover test might be difficult due to poor fixation. Suture adjustment is often carried out about **5 to 24 hours after surgery** when the patient has recovered completely from the anaesthesia, the results of suture adjustment at both times seem to be similar. The adjustment may be made difficult by the **vasovagal** effects of extraocular manipulations and the patient feeling of nausea. In adult patient, the use of intravenous anaesthesia using an infusion of propofol and mivacurium may enable the surgeon to carry out suture adjustment immediately after surgery in the operating room.

Ocular alignment may drift with time following adjustable sutures surgery. Delayed adjustment may be needed. Interseed is an absorbable cellulose material that is designed as a surgical adjunct to reduce postoperative adhesions. It may be useful in delaying the time of adjustment after adjustable suture surgery for up to one week. Interseed shows a promise as a method of delaying the formation of postoperative adhesions and delaying the time of adjusting the sutures for up to one week

- **botulinum toxin in squint surgery**

Botulinum toxin injection induces muscle palsy without causing damage to the rectus muscle or the peripheral nerve. The toxin has a long duration of action of 2 to 4 months. A localised injection to a specific extraocular muscle could achieve paralysis of the muscle without inducing unwanted side effects.

There is controversy concerning the efficacy of Botulinum treatment in establishing satisfactory motor alignment in patients with infantile esotropia. Botulinum toxin is believed, by most ophthalmologists, to be very helpful in treating small under-corrections and over-corrections following conventional strabismus surgery. It is also believed to be more effective when given within 3 months after surgery.

in intermittent and constant exodeviation, botulinum toxin injections to the lateral rectus muscles appears to be as effective as surgical treatment in children 2 to 4 years old. Toxin treatment is effective irrespective of the squint angle, it does not seems to be associated with complications or secondary abnormalities of the muscles.

Botulinum toxin injection may also be used in paralytic squint.. Toxin injection of the medial rectus muscle with full temporal tendon transposition of the ipsilateral superior and inferior rectus muscles seems to be the most effective treatment for chronic sixth nerve palsy.

Other promising indications for Botulinum toxin therapy include its use in adults exhibiting a small angle intermittent esotropia and exotropia with symptomatic diplopia. Temporary partial ptosis and unwanted vertical deviations may sometimes occur.

Miscellaneous

acute acquired concomitant esotropia

Acute acquired concomitant esotropia is a rare condition characterised by the sudden onset of a large angle concomitant esotropia and diplopia in association with good binocularity and no or minimal refractive errors, and no evidence of lateral rectus weakness. The condition has been previously classified into three subgroups:

1. Group 1 (swan type): characterised by acute onset of diplopia after occlusion
2. Group 2 (Franceschetti type): associated with minimal hyperopia with no accommodative element.
3. Group 3 (Bielschowsky): in which the esotropia is associated with myopia.

It has been thought that this condition is often benign and harmless. Recent reports however showed that this condition may be associated with CNS tumours and hydrocephalus. De-compensation of a pre-existing phoria or a mono-fixation syndrome are also commonly associated with this disease.

The management of this condition is controversial. It has been thought that the presence of abducting nystagmus, a V pattern of deviation, or failure to re-establish binocularity after alignment, should be considered as risk signs of a possible CNS disease. A recent report, on the other hand, showed that no clinical sign is reliable in the differentiation between benign and CNS related disease. Investigation of a possible CNS disease is essential in the absence of significant refractive error or in the presence of any CNS manifestations. Binocular function is also expected to be present in CNS related conditions.

Surgery has always been considered as the treatment of choice in these cases. Botulinum toxin therapy may also be used in the treatment of this condition. It may obviate the need for squint surgery.

microtropia

Microtropia or mono-fixation syndrome indicates the presence of a macular scotoma with binocular vision. Patients may or may not have a small angle of deviation. The condition may be classified into:

- primary, with no history of strabismus.
- secondary, following the treatment of a larger angle strabismus.

It has been believed that microtropia is always a static condition, with visual acuity of about 6/9 as the optimum results that can be achieved. It has been shown, recently, that treatment may result in improvement in

the visual acuity to levels of 6/5 with high grades of stereo-acuity. Elimination of the condition is also possible in some cases.

Treatment may include maximum refractive correction with occlusion therapy. It is thought that for patients who recover good visual acuity a period of normal development must have preceded the onset of the disease during which normal retinal correspondence was established.

strabismus with myopia

In adult patients with unilateral or bilateral high axial myopia, esotropia and hypotropia may develop. The cause of this restrictive type of strabismus is not understood. Numerous theories about the cause of acquired esotropia and hypotropia in high myopia have been published. Progressive neurogenic palsy, structural extra-ocular muscles changes and myositis have all been suggested. Another hypothesis assumes that the large globe compresses on the lateral rectus muscle leading to its atrophy (which also results in medial rectus muscle fibrosis in long standing cases). Atrophy of the orbital wall may also contribute in decreasing the protective effect to the lateral rectus muscle.

Surgical treatment of this restrictive motility is often problematic. Magnetic resonance imaging study in high myopia may give additional information on orbital anatomy and bio-mechanical mechanisms of strabismus, and may be useful before strabismus surgery in these patients. The path of the lateral rectus, in the anterior and mid-orbital regions, was shown, in some patients with typical esotropia and hypotropia, to be displaced downward an average of 3.4 mm. If this misalignment of the lateral rectus is detected by MRI, a common high dosage recess-resect procedure for esotropia may even aggravate the deviation. Fixing the lateral rectus in the physiological meridian at the equator with a silicone loop (guide pulley) or a non-absorbable suture seems to be successful. This results in a better alignment and improves abduction and elevation.

Retinopathy Of Prematurity (ROP)

introduction

There is a slight trend to improvement in the survival of premature neonates who are treated with prophylactic surfactant. The increased survival rate does not appear to be associated with any significant difference in the incidence of acute ROP in the long surviving treated patients. The increased survival of premature infants with and without retinopathy of prematurity causes a long term problem in terms of increased incidence of ocular complications. Many of these babies have other impairments and place considerable demands on health and educational services in the community. The onset of **involution** of acute retinopathy of prematurity correlates better with postmenstrual rather than with chronological age. Retinopathy begins to involute at a mean of 38.6 weeks postmenstrual age. Retinopathy of prematurity that is present only in zone III during a child's serial retinal examinations is never associated with the development of a partial or total retinal detachment.

basic science

A new hypothesis for the development of ROP has been described. In eyes with ROP. The vascular endothelium growth factor **(VEGF)** is produced in the part of the retina anterior to the developing blood vessels. Exposure of neonatal animals to hyperoxia is associated with a loss of VEGF production and this leads to cessation of the growth of developing blood vessels. The decrease in VEGF expression by hyperoxia is also associated with hyperoxia-induced vasoconstriction which can be inhibited by supplemental VEGF. As the retinal development proceeds, the metabolic demands of the avascular retina increases and the retina becomes more hypoxic. In response to hypoxia, VEGF production is increased and this stimulates abnormal neovascularisation from the retina. If VEGF production persists, the ROP progresses and if it decreases, regression of ROP can occur. It seems that VEGF does not only cause abnormal vascularisation, but it is also important for normal development of the blood vessels. Appropriate timing of intervention to increase or decrease VEGF production by the retina might prevent blinding complications in ROP.

Many **risk factors** have been associated with the development of ROP. The following risk factors have all been associated with a higher risk for the development of ROP:

- Lower birth weight (birth weight of less than or equal to 1500 grams).
- Younger gestation age (gestational age of 28 weeks or under).

- White race.
- Oxygen toxicity,
- Exchange blood transfusion during the neonatal period.
- Patent ductus arteriosus.

A relationship between **light** exposure and the development of ROP has been suggested. Some reports showed that a reduction in light intensity reduces the incidence of ROP in infants with birth weight less than 1000 grams by about 25%. Some reports, on the other hand, showed that patching of eyes from birth to 35 weeks of post-conception age does not seem to decrease the risk of ROP in pre-term infants when compared with controls. Advanced ROP has also been reported in patients with congenital cataract severe enough to greatly reduce the amount of light exposure of the retina. It seems that the role played by light exposure is probably not as important as prematurity, low birth weight and oxygen treatment.

The effect of **multiple** gestation pregnancy on the severity of ROP is not well defined. Recent report showed no difference between single and multiple gestation pregnancy on the severity of the disease. Antenatal **steroid** treatment has been shown to decrease the neonatal mortality and decrease the incidence of respiratory distress syndrome. It also appears to reduce the severity of intra-ventricular haemorrhage, and also the incidence of stage 2 or higher ROP.

clinical features

The disease can be divided into five stages:

Stage 1:	Flat retina with a white demarcation line separating vascular from non-vascular retina
Stage 2:	A ridge
Stage 3:	A ridge + extra-retinal fibro-vascular proliferation
Stage 4:	Exudative or traction retinal detachment with or without macular detachment
Stage 5:	Funnel shaped total retinal detachment

Each stage can also be either a **(+)** disease or not. A **(+)** disease indicate a more advanced disease and poorer prognosis. The features of a **(+)** disease are:

1. Vitreous haze
2. Marked vascular shunting
3. Dilated veins and arteries seen in the posterior pole
4. Iris vascular engorgement
5. Poor pupillary dilatation

The retinal changes can also be located into 3 zones. The more posterior the zone of ROP and the greater the extent of disease, the greater the unfavourable outcome will be. **The 3 zones are:**

Zone I :A circle centred at the optic disc with a radius twice the disc-macula distance (8 mm)
Zone II: From zone I to the nasal ora serrata nasally and to an equal distance temporally.
Zone III: Anterior to zone II temporally.

Premature birth is also associated with **abnormal refractive errors** (anisometropia, myopia and astigmatism). There is a linear growth in axial length during the neonatal period in premature infants. Premature infants with ROP have shorter axial length. Higher degrees of ROP seem to be associated with shorter axial length and higher risk of **myopia** and anisometropia. Myopia in these infants often occurs at a early age (as early as 3 months after birth). The occurrence and the degree of myopia appear to be related to the degree of retinal cicatrisation, depth of the anterior chamber, thickness of the lens, and axial length changes, rather than to the degree of cryotherapy treatment. Axial length alone does not appear to explain all the myopia found in ROP infants.

The distribution of refractive errors in preterm infants from age 3 months to 5.5 years varies with severity of acute-phase ROP and cicatricial disease. Changes in refractive error distribution occur primarily between 3 months and 1 years and involve a decrease in the proportion of eyes with hyperopia and an increase in the proportion with high degrees of myopia. Pre-term children should be followed up and screened for errors of refraction.

Premature children may develop **subtle visual impairment** irrespective of the presence of refractive errors, retinal changes, manifest squint or cerebral damages. These visual defects include decreased contrast sensitivity and colour vision even in the presence of normal visual acuity and stereopsis.

The diameter of the **foveal avascular zone** appears to be correlated with the gestation age of the child. It is thought that the FAZ is densely vascularised early in gestational period during the formation of the vasculature of the retina. The blood vessels in the FAZ undergoes regression by the process of apoptosis in all infants after the age of 36 weeks. Apoptosis does not occur in premature infants before the age of 30 weeks. A small or absent FAZ may be considered as a marker of prematurity.

screening and management

The timing of screening for ROP is controversial. The American academy of paediatrics and the American academy of Ophthalmology have

recommended that screening should be carried out **between 4 or 6 weeks of chronological age or between 31 and 33 weeks of post-conception age.** The royal college of British Ophthalmologists, on the other hand, recommend screening **between 6 and 7 weeks of chronological age**. Screening of children at risk at 7 weeks of chronological age or 34 weeks of post-conception age has shown that it can reliably detect the onset of threshold disease while reducing the number of unnecessary examinations. A recent paper suggested that screening can be carried out by non-ophthalmologists, by examining the retinal blood vessels, if there are no ophthalmologists available.

ROP screening is uncomfortable and painful for the infant. The distress caused by screening appears to be significantly reduced by good nursing care during the examination (infants may be placed on soft padded surface with boundaries that help to support them but still allow some body and arms movements). Follow up examinations depends on the findings:

- If the retinal vasculature is immature in Zone II but no disease is present, follow up examination should be planned at approximately 2 to 4 week intervals until vascularization proceeds into Zone III.
- Infants with ROP or immature vessels detected in Zone I should be seen at least every 1 to 2 weeks until normal vascularization proceeds to Zone III or the risk of attaining threshold conditions is passed.
- Infants with threshold disease (Stage III ROP, Zone I or II in 5 or more continuous clock hours or 8 cumulative clock hours with the presence of plus disease) should be considered candidates for ablative therapy of at least one eye within 72 hours of diagnosis.

Treatment of ROP may be carried out by:

Cryotherapy
Indirect argon (532 nm) laser
Indirect diode (810 nm) laser
Transscleral diode laser

Treatment of pre-threshold ROP by laser photocoagulation does not seem to lead to more favourable outcome than holding the treatment till the threshold stage develops. In threshold stage III ROP, Long term follow up (3, 5 years) shows that treatment with either cryotherapy, argon or diode laser photocoagulation is associated with the development of visual acuity of 6/12 or better. Treatment with either method does not seem to reduce vision. **Cryotherapy** may, however be associated with a higher incidence of myopia. In the ROP Cryotherapy study, cryotherapy of the peripheral avascular retinal reduced the incidence of unfavourable outcome by 49% in infants with threshold ROP. The eye that benefited the most were the eyes with Zone II disease, in Zone I disease the benefit appears to be marginal. It is thought that cryotherapy might not be

an appropriate method for treatment in zone I. Cryotherapy can be carried out under sedation with nasal ketamine and midazolam. A significant number of patients, however, progress to Stage IV and V (retinal detachment).

Argon and diode **laser** peripheral retinal oblation seem to be equally efficient and associated with fewer systemic complications than cryotherapy. Retinal lesions produced by the diode lasers are deeper than Argon laser lesions. Persistence of the tunica vasculosa lentis is often found in severe posterior ROP and the absorption of argon laser by haemoglobin may lead to a lens burn. The longer wave lengths of the diode makes this more unlikely.

The **diode** laser is more convenient, technically easier to administer and better tolerated by patients. One of the main advantages of the diode laser is that it can easily be transported to special babies units. Diode laser peripheral retinal photocoagulation is a safe and effective procedure for treating threshold retinopathy of prematurity. 85.4% of patients have bilateral favourable outcomes. A dense pattern of diode laser photocoagulation for threshold ROP significantly reduces the rate of progression of the disease in zone 2. The outcome appears to be similar between fellow eyes in 94.2% of patients.

Serious complications related to treatment are uncommon. Diode laser treatment for ROP is associated with significantly less myopia than cryotherapy up to three years after treatment. There is no trend of increasing **myopia** after diode laser treatment and refraction seems to stabilise after one year, unlike after cryotherapy where myopia significantly increases between 1-3 years after treatment. Diode laser photocoagulation treatment may also be complicated with the onset of **hyphaema**. Hyphaema is thought to be due iris clipping which is caused by the relatively large cone angle of some diode lasers. **A dense cataract** may occasionally develop after laser photoablation for threshold retinopathy of prematurity. The cataract may be due to anterior segment ischaemia. Dense cataract development after laser photocoagulation appears to be associated with a poor visual prognosis. Post-laser cataract may be prevented by light laser application at the 3 and 9 O'clock positions to prevent anterior segment ischaemia.

Transscleral diode laser coagulation appears to be as effective in the treatment of threshold ROP as trans-pupillary diode laser photocoagulation. Transscleral diode laser photocoagulation seems to be an advantageous treatment method if trans-pupillary treatment bears an increased risk of cataract formation. A recent study showed that 48% of eyes have 20/50 or better visual acuity three years after diode laser photocoagulation for threshold retinopathy of prematurity. Eyes with 4 or more D of myopia are less likely to achieve 20/50 or better visual acuity than eyes with less than 4 D of myopia.

Stage IV in ROP indicates the presence of retinal detachment. It is subdivided into IV-A (macula on), and IV-B (macula off) retinal detachment. Stage IV usually progresses very quickly and results in severe visual loss.

Localised retinal detachments may occur after the acute phase of ROP. The detachment may progress to total detachment, may involve the macula and cause macular fold, stay stable, or regress. Cryotherapy does not seem to affect the outcome but it is known to reduce the risk of developing complete retinal detachment. Scleral buckling repair of the retinal detachment in stage IV-A has been shown to be an effective way of preventing further progression of the detachment. The visual results after vitrectomy for stage V ROP are often disappointing. Vitrectomised eyes seem to function better than non-vitrectomised eyes. There is also evidence that visual function, however poor it might be, is still useful to these children and probably better than previously thought. Timely surgical intervention and appropriate postoperative care can result in useful vision in stages IV and V ROP.

Paediatric Cataract

Childhood cataract is a major cause of preventable blindness and severe visually impairment in many developing countries. The prevalence of paediatric cataract varies from one report to another. It is estimated that the prevalence of the disease is between 2.3 to 7.7 per 10000 of total births. The incidence of paediatric cataracts in developing countries is relatively high due to inter-family marriages.

Children with cataract should be evaluated by **ophthalmologists**, **paediatricians** and also possibly be **geneticists**. The role of ophthalmologists is to exclude any other ocular condition that may be associated with the cataract e.g. PHPV. All investigations should be arranged by the paediatricians depending on the systemic findings. Some investigations are however useful for routine screening e.g. urine amino acids, reducing substances, and organic acids and blood. Blood electrolytes, amino acids, lipids, and sugar and calcium and galactose enzymes.

The indications for surgery are mainly to improve vision, prevent complications (e.g. glaucoma and hypotony), and also for cosmetic reasons in disfiguring mature white cataract. It is suggested that in unilateral cases surgery should be carried out before 2 months of age, with early and aggressive occlusion and optical correction.

The currently available surgical technique for paediatric cataract include:

1. Lens aspiration
2. Extra-capsular cataract extraction with or without IOL implantation,
3. Extra-capsular cataract extraction with primary posterior capsulotomy, anterior vitrectomy and IOL implantation.
4. Lensectomy with anterior vitrectomy.

High incidence of **posterior capsule opacification** is a major concern in paediatrics cataract and IOL surgery. In extra-capsular cataract extraction technique about 44% to 100% of patients develop significant opacification of the posterior capsule which need laser treatment which might have to be repeated.

Lensectomy with anterior vitrectomy provides a long lasting clear visual axis but needs certain types of aphakic correction e.g. contact lenses wear which can have serious financial and clinical problems in children. Lensectomy with scleral approach is associated with a high incidence of retinal detachment. To avoid this complication, it is advised that the entry site for the lensectomy / vitrectomy instruments should be about 1.5 to 2.5 mm behind the limbus (not 4 mm behind as in adults). One of the advantages of lensectomy-vitrectomy operation is that a second procedure for the capsulotomy and a second general anaesthesia are avoided, however it has been reported that a membrane can form

posterior to the iris despite lensectomy-vitrectomy operation, and this membrane may require another intraocular operation for treatment.

The benefits of extracapsular cataract extraction without vitrectomy may outweigh the risks of a second general anaesthesia for non-invasive laser capsulotomy. The technique of extra-capsular cataract extraction with primary posterior capsulotomy, anterior vitrectomy and IOL implantation seems to be the most appropriate technique since it provides a long term clear visual axis and also enables IOL implantation as a good method of correcting aphakia.

Primary posterior capsulorhexis with IOL optic capture is a new technique to prevent posterior capsular opacification in paediatrics cataract and IOL implantation. This technique involves capturing of the IOL optics through a posterior capsulorhexis opening. This technique seems to be promising in preventing secondary membrane formation. It also ensures centration of the posterior chamber IOL while eliminating the need for an anterior vitrectomy. Apposition of the anterior and posterior capsule leaflet anterior to the optic would limit the migration of Elschning pearls, reducing the incidence of secondary membrane formation and the need for additional procedures.

IOLs have been used in paediatrics cataract surgery with increasing frequency. In a study of more than 300 children between 2 and 16 years of age, the use of IOL was reported to be favourable even in patients with traumatic cataract. Visual acuity better than 20/80 was reported in 71% of patients. Major complications were rare. Unilateral or bilateral IOL implantation can provide a good visual outcome in very small children. The foveal function, rather than the age of the child, appears to be the determining factor of the visual outcome. Surgery before the development of abnormal foveal function can therefore be beneficial. IOL implantation in children's **eyes with uveitis** may be beneficial. In children with JRA-associated uveitis, the final visual results remain guarded because of irreversible amblyopia and a more complicated postoperative course. Children with **JRA**-associated uveitis demonstrate an active intraocular inflammation for an extended period after surgery, and tended to have secondary membranes, necessitating a second surgical procedure. Implantation of a **heparin** surface modified PMMA IOL may be used to correct aphakia in children with uveitis.

Axial length increases in children, rapidly till the age of 2 to 3 years old, and then slows down till the age of 8 to 10 years old. Pseudophakia in children is predicted to lead to myopic shift after surgery specially in very young children. The myopic shift appears to be greatest in younger age groups and seems to persist till the age of 8 years old. Postoperative refraction may be predicted by using SRK II formula with intraoperative corneal curvature and axial length measurement. Planned postoperative hyperopia is recommended to lessen the quantity of the postoperative myopic shift. Myopic shift in pseudophakic eyes seem to be more than in

normal phakic eyes. The mean refraction shift is estimated to be - 0.99 +/- 0.22 D with a range between - 3.25 and +0.38 D. It is advised that children should be under-corrected by about 1 D when IOL power is considered. A rule of thumb is to use a lens 3 D. under-corrected for a two years old baby rising to a lens to achieve emmetropia in an eight years old baby.

Prediction of postoperative refraction course is difficult. It is thought that removing the crystalline lens in infancy may retard the axial growth in human and monkeys eyes. This finding may have implication on the postoperative refraction in children. The retardation in axial growth in monkeys appears to be age related being of small degree after the age of 7.5 months old.

postoperative complications

Stimulus deprivation **amblyopia** commonly occurs after unilateral congenital cataract extraction and is a major cause of visual impairment in these patients. Visual rehabilitation following cataract surgery in infants is important to prevent amblyopia. The most widely used method is contact lenses. Improvement in contact lens materials have made it possible to successfully rehabilitate many children with monocular aphakia. Contact lens intolerance is still a significant problem in young children at an age when immediate aphakic correction is imperative to prevent deprivation amblyopia.

Most surgeons are reluctant to place an intraocular lens in an eye of a child with a monocular cataract who is younger than 1 year. Secondary placement of an intraocular lens in the posterior chamber appears to be a safe, effective alternative for correction of aphakia in the contact lens or spectacles intolerant child or young adult. The risk of secondary implantation does not seem to be greater than primary implantation. Epikeratophakia has also been used but it may be associated with a significant complication rate. It is not widely practised.

Glaucoma is another well recognised complications after congenital cataract surgery. It is not possible to recognise in which eye glaucoma will develop. It is not also known how soon glaucoma will develop after the cataract surgery. Careful and prolonged follow up is required. Closed angle glaucoma usually occurs early and open angle glaucoma usually occurs late (up to 65 years) after congenital cataract surgery. All aphakic children should have glaucoma assessment at least every year. Other complications include endophthalmitis, vitreous strands in the wound, hyphaema, and endothelial cell loss.

Paediatric glaucoma

Glaucoma in children may be:

- Primary
- Secondary to other ocular disease (e.g. Aniridia, Axenfield's anomaly, Rieger's anomaly or syndrome or persistent hyperplastic primary vitreous).
- Associated with systemic diseases (e.g. Lowe's syndrome, rubella, phakomatosis, homocystinuria).

Important advances in the field of genetics and glaucoma have been made. The following genes have been identified is these types of glaucoma, TIGR gene (trabecular meshwork inducible glucocorticoids response) gene in adult and juvenile glaucoma, the CYP1B1 gene (GLC34 locus) in congenital glaucoma, and the RIEG homebox gene (R1 locus) in developmental glaucoma. it is thought that genetics studies might lead, in the near future, to a better understanding of the mechanism and classification of glaucoma.

Glaucoma in children may be associated with **Aniridia**. Aniridia is a rare sporadic or familiar disease that affect the iris, cornea, angle structures, lens and macula. Goblet cell density is also increase in the conjunctiva and the peripheral cornea of these eyes. It has been thought that there are two chromosomes associated with aniridia, chromosome number 11 (band 13) for the sporadic type and possibly chromosome number 2 for the inherited type. The Wilms' tumour gene has also been located on chromosome.

The disease should be **differentiated** from congenital megalocornea, high myopia, corneal endothelial dystrophy, and birth trauma (birth trauma is often associated with vertical or oblique Descemet's tears, while congenital glaucoma is often associated with horizontal or concentric). Measuring the IOP often needs general anaesthesia. General anaesthesia may lower the IOP except when ketamine hydrochloride is used.

Surgical treatment is the main line of treatment, it can stabilise the IOP in primary and secondary types. Many procedures are often needed to achieve satisfactory results. The first line of treatment is often with **goniotomy**, followed by trabeculotomy, or trabeculectomy.

The success rate of **trabeculectomy** in children glaucoma is low. Trabeculectomy with Mitomycin C is effective in children with resistant glaucoma, especially phakic children over one year old. Filtering surgery with or without Mitomycin C seems to be the most effective surgical treatment. Late onset bleb related complication is still a major problem as in adult population. Some patients may continue to lose vision despite all efforts. Primary combined **trabeculotomy-trabeculectomy** is safe,

effective and sufficiently predictable to be considered as the first choice of surgical treatment in primary congenital glaucoma with corneal oedema.

Cyclocryotherapy is also an effective option in the treatment of resistant paediatric glaucoma. Eyes with aniridia have a high rate of phthysis, and may be poor candidates for this procedure. Molteno type glaucoma **implants** are often reserved for resistant cases. The use of these implants may achieve a good IOP control and preservation of sight. Some eyes may need further surgery due to implants-related complications.

Non-Accidental Injury
(Shaken Baby Syndrome)

It is not often easy to diagnose non-accidental injury in infants. Extensive **retinal haemorrhage** in an infants is suggestive of child abuse and non-accidental injury (shaken baby syndrome). The earliest intraocular lesions to be found in accidental or non-accidental head injuries are peripheral sub-hyaloid haemorrhages with or without localised retinal detachments. The haemorrhages are typically of different duration, some may be fresh, while others are old haemorrhage. Unilateral retinal or pre-retinal haemorrhage may also occur.

Retinal haemorrhage can result from severe angular positive or negative acceleration forces alone, without impact or direct ocular trauma. The **mechanism** of the haemorrhages may be due to the vitreous traction forces with or without the additional rise in the intracranial and central venous pressure. Extensive retinal haemorrhage are more likely to be due non-accidental rather than accidental injury. The haemorrhage is often bilateral, but it may also be unilateral. Mild flame shaped haemorrhage may resolve in 24 hours, severe retinal and vitreous haemorrhage may take months before it disappear.

In shaken baby syndrome retinal haemorrhages are extremely common, but vision loss is most often the result of brain injury. The patient's visual reaction and pupillary response on presentation shows a high correlation with **survival**. Good initial visual reaction is highly correlated with good final vision and neurologic outcome.

There are many conditions that may be associated with retinal haemorrhage. Neonatal retinal haemorrhage is common. The majority of these haemorrhages disappear in about 8 days. Some sub-hyaloid haemorrhage may, however, persists for up to 3 months. Leukaemia, ROP, sickle cell disease, extra-corporal membrane oxygenation, and haemorrhagic disease on the new born, are among these conditions that cause retinal haemorrhage. Most of these diseases can be identified by clinical examinations. An extensive investigations approach does not seem to be appropriate.

In children under the age of 2 years, convulsions alone are unlikely to cause retinal haemorrhage. The finding of retinal haemorrhage in a child admitted for convulsion should raise suspicion about the possibility of non-accidental injury. The association between retinal haemorrhage and intracranial damage and sub-dural haemorrhage is not invariable. Cardiopulmonary resuscitation is very unlikely to cause retinal haemorrhage. Causes of Valsalva's manoeuvre have not been reported with retinal haemorrhage in children. Pertussis may be an exception.

In shaken baby syndrome the visual outcome appears to be related to the baby's need to assisted ventilation more than to the initial visual

acuity. Non-reactive pupil and midline shift of the brain structures, in these babies, correlate with mortality, neuro-surgical examination is recommended in these situations as the baby's life is likely to be in danger.

Neuro-ophthalmology

Congenital anomalies

optic nerve hypoplasia and dysplasia

Optic nerve hypoplasia is, now, considered to be the most common congenital optic nerve head anomaly. Most of the reported severe cases have been associated with major central nervous system anomalies and other congenital malformation resulting in death shortly after birth. Bilateral aplasia of the optic nerves, chiasm and optic tracts may also occur in an otherwise healthy infant.

Optic nerve hypoplasia may be caused by intracranial **tumours** or congenital suprasellar **teratoma**. It is thought that nerve hypoplasia, in these cases, may be due to compression. Superior segmental optic disc hypoplasia is a special type of optic disc hypoplasia known as **Topless Disc**. This condition is characterised by superior disc pallor, scleral halo, and superior nerve fibre layer loss associated with inferior visual field defects. Female sex, low birth weight, short gestation period, maternal diabetes are known predisposing risk factors.

MRI may be used to demonstrate associated central nervous system abnormalities in these patients and provide specific prognostic information regarding the development of the nervous system and pituitary gland problems. Based on the MRI findings, patients can be classified into the following groups:

1. Isolated optic nerve hypoplasia
2. Absence of the septum pellucidum
3. Posterior pituitary ectopia
4. Hemispheric migration anomalies
5. Intra uterine/pre-natal hemispheric injury

Groups (3), (4) and (5) are highly predictive of pituitary gland hormones deficiency and neuro-developmental anomalies. Thinning or agenesis of the corpus callosum is also predictive of neuro-development anomalies. In contrast to previous reports, endocrine abnormalities are seen in only one quarter of patients, and the full-blown **deMorsier syndrome** (septo-optic dysplasia with pan-hypopituitarism) is seen in only 11.5% of patients with Bilateral optic nerve hypoplasia. The clinical association of septo-optic dysplasia (optic nerve hypoplasia with an absent septum pellucidum and a thin corpus callosum) with pituitary hormone deficiency is known. Children with septo-optic dysplasia and hypo-cortisolism are at risk for sudden death during febrile illness. Thermo-regulatory disturbances and dehydration from diabetes insidious may also occur.

Prevention of sudden death in septo-optic dysplasia requires early recognition and treatment of these major risk factors.

Although the **visual prognosis** of children with Bilateral optic nerve hypoplasia is generally poor, 10% of patients have excellent visual acuity. Optic nerve size could predict the visual outcome in patients with optic nerve hypoplasia. Visual acuity is related to the **ratio of the horizontal optic disc diameter to the disc-macula distance**, pupillary reaction, nystagmus and also to VER. All eyes with ratio more than 0.3 have a good visual acuity and all eyes with ratio less than 0.3 have poor visual acuity. No eyes with ratio less than 0.15 has a visual acuity better than light perception. These findings should help to assess visual acuity in young children and infants with optic nerve hypoplasia and may lead to diagnostic criteria for the severity of the disease.

morning glory disc

Morning glory disc anomaly is a rare unilateral congenital anomaly characterised by a congenital excavation of the peripapillary fundus, enlargement of the optic disc, abnormal peripapillary glial tissue and a complex pattern of retinal vascular anomalies including arteriovenous communication on the optic disc head or on the retina. This condition may also be associated with difficult cases of **non-rhegmatogenous retinal detachment.**

Visual acuity is often poor even in uncomplicated cases. Morning glory syndrome is generally an isolated ocular abnormality. However some **systemic abnormalities** have been associated with this condition e.g.:

1. Mid line cranial facial defects.
2. Hypertelorism.
3. Cleft lip and cleft palate.
4. Basal encephalocele.
5. Renal anomalies, occasionally.
6. CHARGE syndrome.

It may also be associated with pituitary dwarfism possibly due to pituitary compression by an encephalocele. Children with morning glory syndrome should have a complete general examination and growth evaluation. V-shaped or tongue-shaped infra-papillary retinochoroidal de-pigmentation has been reported in association with this condition. In patients with optic disc dysplasia (e.g. morning glory disc anomaly), the finding of this retinochoroidal pigmentary anomaly should prompt neuro-imaging to look for **trans-sphenoid encephalocele**.

Ischaemic Optic neuropathies and Giant cell arteritis

risk factors

Risk factors which have been associated with non-arteritic anterior optic neuropathy include: **vasculitis, migraine, blood loss, diabetes, smoking, glaucoma and cataract surgery**. There is also a significant association between non-arteritic anterior ischaemic optic neuropathy and elevated **serum cholesterol and fibrinogen levels** as well as with smoking. Appropriate medical treatment of these risk factors may prevent recurrence in the fellow eyes. Anterior ischaemic optic neuropathy has been reported in children with sickle cell trait (AS haemoglobinaopathy) and migraine. It has also been hypothesised that carotid artery **micro-emboli** may play a role in the pathogenesis of non-arteritic anterior ischaemic optic neuropathy. Recent trans-cranial Doppler studies found no evidence that emboli from the carotid arteries are common in patients with the disease.

The **anatomical features** of the optic nerve head may be related to the development of some diseases of the optic nerve. Non-arteritic anterior ischaemic optic neuropathy, papillopathy in young diabetic patients and optic discs in Leber's hereditary optic neuropathy are often associated with small optic disc, small or absent physiological disc cup, abnormal branching of the blood vessels and heaping of the nerve fibre layer at the edges of the optic disc. Eyes that have anterior ischaemic optic neuropathy also tend to be less myopic than controls.

clinical features and diagnosis

In a study of 170 patients with giant cell arteritis, **50%** of the patients presented with ocular involvement. Visual loss occurred in 97.7%, amaurosis fugax in 30%, diplopia in 5.9% and ocular pain in about 8.2% of patients. Anterior ischaemic optic neuropathy occurred in 81.2%, central retinal artery occlusion in 14.%, celioretinal artery occlusion in 21.8%, posterior ischaemic optic neuropathy in 7.1%, and ocular ischaemia in about 1.2%.

The visual loss in giant cell arteritis is unilateral in 46%, sequential in 37% and simultaneous in 17% of patients. Bilateral non-arteritic anterior ischaemic optic neuropathy is a well recognised clinical condition. The time interval between the first and the second eye involvement is very variable. Amaurosis fugax is usually caused by ocular ischaemia related to atheromatous disease of the carotid artery and is almost always unilateral. **Alternating amaurosis fugax** in an elderly patient suggests arteritis rather than atheromatous disease and temporal artery biopsy should be considered.

Anterior ischaemic optic neuropathy is the commonest cause of visual loss in patients with giant cell arteritis. Giant cell arteritis should also be considered in the differential diagnosis of non-embolic branch retinal artery occlusions in old patients. It is thought that involvement of the ophthalmic or the central retinal artery may reduce the blood flow in branches of the retinal artery predisposing them to the development of occlusion. Cotton wool spots may precede visual loss in patients with giant cell arteritis. Old patients with visual symptoms and at least one cotton wool spot, even in the absence of other clinical signs, should be suspected of having giant cell arteritis.

The detection of RAPD is an important sign in the diagnosis of anterior ischaemic optic neuropathy. The **Marcus Gun phenomenon** (pupillary re-dilation under sustained illumination), and the **alternating light tests** (a flash-light passing back and forth from one eye to the other) are often used to elicit RAPD. The alternating light test is believed to be superior to the Marcus Gunn test for detecting relative afferent pupillary defects.

Isolated **choroidal ischaemia** may be a potential cause of reversible visual loss in giant cell arteritis. Ophthalmic examination may show scattered yellow white lesions at the level of the retinal pigment epithelium. There may be no ophthalmic or angiographic evidence of anterior ischaemic optic neuropathy or central retinal artery occlusion. Fluorescein angiography shows **marked delay in choroidal filling** in the macula in the affected eye. After intravenous steroid treatment patient's visual acuity may improves and repeat fluorescein angiography may show normal choroidal circulation. Choroidal non-perfusion often accompanies central retinal artery occlusion and anterior ischaemic optic neuropathy and might also be the only manifestation of giant cell arteritis. Fluorescein angiography may help in making the diagnosis of this condition

Cutaneous involvement in giant cell arteritis is common. **Scalp necrosis**, on the other hand is an unusual sign of the disease. It is characterised by oedema, urticaria, erythema, vesicles, and crusting in the area of distribution of the temporal artery. Misdiagnosis in these cases should be avoided as this sign may represent a sever case of vasculitis, resulting in visual loss, and possibly death.

occult GCA

Occult GCA denotes an ocular involvement without systemic features. Almost **21%** of patients with visual loss do not have systemic manifestations. In people 55 years of age or older, with amaurosis fugax, anterior ischaemic optic neuropathy, and abnormal C-reactive protein with or without elevated ESR should raise a high rate of suspicion. Anterior ischaemic optic neuropathy with cilio-retinal artery occlusion, and chalky white optic disc head are very helpful indicators of the disease.

management

The clinical and laboratory features most strongly suggestive of giant cell arteritis include the following findings in the following order:

1. Jaw claudication.
2. C-reactive protein above 2.45 mg/dl. C-reactive protein appears to be more sensitive (100%) than erythrocyte sedimentation rate (92%) for detection of giant cell arteritis. Erythrocyte sedimentation rate combined with C-reactive protein have the best specificity (97%).
3. Neck pain.
4. An erythrocyte sedimentation (ESR) rate of 47 mm/hour or more.

The ESR has traditionally been measured by the Westergren method which dates back to 1921. This methods seems to be well correlated with the Seditainer which is currently been used in many eye departments. Newer **automated methods** of measuring the ESR, within 25 minutes, have been introduced. A new report compared the results of measuring the ESR with the Seditainer and with the new automated methods in patients with GCA. It was found that there is a wide scatter in the results of ESR measuring with the new methods, which lead the authors to advise continuing using the Seditainer method.

Bilateral simultaneous or sequential **temporal artery biopsy** improves the diagnostic yield in some cases of giant cell arteritis. There is a high probability of obtaining the correct diagnosis in patients in whom only one artery can be biopsied. Although the improvement in diagnostic yield of bilateral temporal artery biopsies is low, the consequences of both delayed diagnosis and treatment of giant cell arteritis as well as the use of systemic corticosteroid in patients who do not have giant cell arteritis are of such potential severity that consideration should always be given to performing bilateral temporal artery biopsies in patients suspected of having the disease.

Patient with anterior ischaemic optic neuropathy are at increased risk of developing **macro-vascular diseases** (e.g. myocardial infarction and cerebrovascular accidents). In high risk patients it has been shown that anti-platelets therapy (aspirin 75-325 mg daily) reduces the risk of vascular death, myocardial infarction and stroke. In view of the increased mortality noticed in patient with central retinal vein or artery occlusion it seems appropriate to treat patients with anti-platelets drugs.

Systemic steroid treatment has proved effective in preventing the ocular and systemic complications of giant cell arteritis. Temporal artery biopsy may be indicated to confirm the clinical diagnosis and may show granulomatous inflammation even after several month of systemic corticosteroid therapy. Arteritic ischaemic optic neuropathy can still develop despite using systemic steroids treatment even when the systemic symptoms and signs of the disease have responded to the

treatment. The results of IV methyl-Prednisolone treatment of patients with visual loss from GCA are similar to the results of treatment with oral corticosteroid, with IV methyl-Prednisolone treatment being more costly and having a small risk of sudden death.

Osteoporosis is recognised as an important problem in patients on high-dose corticosteroid therapy. The steroid effect on bone mass may occur early during treatment and once established the osteoporosis may be hard to reverse. Alternate days steroids treatment does not seem to protect against the development of the disease. The Department of Health Advisory Group Report on Osteoporosis states that patients on more than **5 mg of prednisolone daily for more than 3 months** should be screened. Calcium supplementation, should be given routinely to steroid patients. There is also evidence to suggest that HRT should be given to postmenopausal women or women who have had a hysterectomy when put on corticosteroid treatment for a long time.

Newly published British guidelines suggest that the following are indications for a diagnostic work-up and further investigations with bone mass densitometry measurement:

1. Patients on more than 15 mg/day for six months
2. Previous osteoporosis fracture
3. Patients older than 65 years of age
4. Menopause before the age of 45
5. Body mass index less than 20
6. Family history of low trauma fracture
7. Smoking

Bone mass **densitometry** of the spine or the hip is indicated for patients taking a dose more than 7.5 mg/day but less than 15 mg/day. Patients with a score of less than -1.5 should have a diagnostic work up followed by intervention, while patients with a score of 0-1.5 should have a repeated densitometry measurement in one year.

The role of **aspirin** in the treatment of this condition id still controversial. A recent study showed that aspirin (325 mg/day) may be effective in reducing second eye involvement in patients with non-arteritic anterior ischaemic optic neuropathy. It has also been reported that **Levodopa and carbidopa** can significantly improve the visual acuity and decrease visual loss in some patients, especially when given within the first 45 days of onset. Visual improvement in long standing cases (more than 6 months) has also been documented. The mechanism of action may be related to the presence of dopamine receptors and mediators in the retina.

In a 24 months follow-up study for patient with non-arteritic anterior ischaemic optic neuropathy, optic nerve decompression surgery did not lead to any visual benefits when compared with observation. The value of

optic nerve sheath decompression in the treatment of non-arteritic anterior ischaemic optic neuropathy has been evaluated in a single masked multicentre randomised controlled trial. This procedure does not appear to offer any benefit on visual outcome in patients with ischaemic optic neuropathy and should not to be recommended to patients with non arteritic ischaemic optic neuropathy.

Demyelinating Optic neuritis

clinical features

Visual recovery in patients with an initial episode of optic neuritis is typically rapid, begins within 2 weeks and may continue in some patients for up to 12 months. Most patients retain good to excellent vision in the 5 years following an attack of optic neuritis, even if the optic neuritis recurred. Recurrences are more frequent in patients with multiple sclerosis and in those treated with oral prednisolone alone. In patients with acute unilateral optic neuritis, abnormalities in the visual acuity, contrast sensitivity, colour vision and visual field are often found in the fellow eye. The presence of abnormal visual tests in the **fellow eyes** without, prior clinical attacks, does not necessarily mean a second demyelinating process. Ophthalmologist should be cautious in making the diagnosis of multiple sclerosis, in patients with optic neuritis, only on the basis of finding abnormal visual functions in the fellow eyes.

Visual field defects are common in optic neuritis. The disease does not seem to have any predilection for any particular visual field defect. Central visual field is affected more than peripheral visual field in most patients. The majority of patients with visual field defects from acute optic neuritis return to normal after the first year. Recovery of visual field function seems to be greater around fixation than in the periphery. Many fields show variation in the pattern and the location of the field loss. Patients with resolved optic neuritis may also have different visual field results on different days and different times of the same day. The variations may affect both pattern and severity of visual field test results. Care should be taken in interpreting visual field results in patients with previous optic neuritis.

Brain MRI at presentation of isolated optic neuritis is predictive of subsequent risk of developing multiple sclerosis. A normal MRI does not, however, preclude the development of multiple sclerosis. Eyes with optic neuritis with MRI lesions less than **17.5 mm** on the optic nerve seem to have good visual prognosis. Lesions greater than 17.5 mm on the optic nerve or lesions involving the intra-canalicular part of the optic nerve lead to incomplete or partial visual recovery. The presence of three or more MS-like MRI lesions with **CSF** oligo-clonal bands appears to be strongly associated with the development of multiple sclerosis. CSF oligo-clonal bands has been reported to have a sensitivity of 96% and a specificity of 42%. MRI has s sensitivity of 85%, and specificity of 65%. The number of MRI lesions seem to be associated with the extent of subsequent disability. **Optic neuritis in children** has a low risk of recurrence and progression to multiple sclerosis. The history of a bilateral sequential, or recurrent episodes is, on the other hand, associated with increased risk

Diseases of the sphenoid sinuses should be considered in patients presenting with optic nerve disease that do not look typical of

demyelinating disease. CAT scan may to the paranasal sinuses be needed.

treatment

The Optic Neuritis Treatment Trial's major conclusions regarding treatment include the following:

1. Treatment with high-dose **intravenous** followed by oral corticosteroid accelerated visual recovery but provided no long-term benefit to vision. The recommended dose of treatment is IV methyl Prednisolone 250 mg 6 hourly for 3 days followed by 1 mg / Kg body weight for 11 days of oral Prednisolone.
2. Treatment with 'standard-dose' **oral** Prednisolone alone does not improve the visual outcome and is associated with an increased rate of new attacks of optic neuritis; and treatment with intravenous followed by oral corticosteroid regimen reduces the rate of development of clinically definite MS during the first two years. Oral steroids alone should not be used as it is associated with a higher rate of recurrent optic neuritis
3. Brain **MRI** should be considered to assess the risk of future neurologic events of MS.
4. Treatment with intravenous methylprednisolone should be considered, particularly if the brain MRI demonstrates multiple signal abnormalities consistent with MS, or if a patient has a need to recover vision rapidly.

However, a recent study showed that high dose of oral steroids (500 mg of methyl prednisolone/day for 5 days) may be beneficial in improving recovery at 1 and 3 weeks after the onset of the condition. The same study also showed no effect of the oral treatment at 8 weeks, and no effect on the number of subsequent attacks.

gene therapy

Gene transfer is a new method for treating some diseases. The process relies on transferring a specific gene to human tissue. This is often achieved by using a vector which may be a viral (e.g. adenovirus) or a non-viral (e.g. DNA injection) vector. Gene transfer may used to achieve gene replacement, addition or control. Gene therapy may be useful in the treatment of demyelinating optic neuritis.

Reactive oxygen species e.g. nitric oxide and super-oxide are chemical mediators in the demyelinating process. Catalase is considered as a super-oxide scavenger. The endogenous levels of catalase are not enough to prevent to protect the optic nerve from these mediators. The administration of the gene coding for catalase by adenoviral increases catalase levels in the optic nerve cells and may suppress the demyelination process and the blood-brain barriers disruption. The

increased cellular levels of catalase decreases demyelination by about 30%.

Disorders of the pupil

horner's syndrome

Horner's syndrome is caused by a lesion in the sympathetic pathway to the eye. The syndrome is characterised by the following features:

Mild ptosis. Miosis. Occasionally anhidrosis. Heterochromia, in congenital cases.

Horner's syndrome is often classified into three types depending on the level of the lesion:

type of lesion	important causes	diagnostic features
First order neurone lesion.	• stroke • tumours • osteo-arthritis of the neck	affected pupil dilates less well than normal pupil with the cocaine test.
Second order neurone lesion.	• lung carcinoma • thyroid tumours • neuroblastoma • metastases	same as first neurone lesion.
Third order neurone lesion.	• internal carotid artery dissection • cluster headache • herpes zoster virus infection	can be differentiated from the other two lesions by the Hydroxy-amphetamine test, the pupil does not dilate as much as the other pupil.

Apraclonidine may be a useful medication for the diagnosis of Horner syndrome. The drug is an adrenergic receptor agonist. Its major site of pharmacological action (for reduction of aqueous production) is on post-junctional alpha 2 receptors in the ciliary body. Instillation of apraclonidine into eyes with Horner syndrome produces mydriasis of 1.0 to 4.5 mm. There is no significant change in the PD of normal eyes after ipsilateral instillation of apraclonidine.

Heterochromia does not always indicate a congenital origin, the syndrome can still be caused by a progressive acquired condition even in the presence of heterochromia. **Corneal endothelial de-compensation** has recently been reported with acute onset traumatic Horner's syndrome (after right jugular vein catheterization during cardiac valve surgery). It is thought that the corneal de-compensation may be due to traumatic injury to the sympathetic nerve supply to the cornea, which is known to have a neurotrophic role in the cornea.

In 70% of **infants** with Horner's syndrome, presenting in the first year, no cause is identified. Routine diagnostic imaging in isolated Horner's

syndrome in children is not necessary. Infants should be examined for cervical or abdominal masses and involvement of the other cranial nerves. **Urinary vanillymandelic acid** is levels is indicated to rule out cases associated with neuroblastoma. More investigations are needed if the Horner's syndrome is acquired or if other signs are present.

Surgery may be needed to repair the mild ptosis if the patient is interested. In mild cases of Horner syndrome, sympathomimetic drugs (e.g. phenylephrine) may be used for treatment of mild ptosis if the patient is not interested in surgical treatment.

adie's tonic pupil

Adie's tonic pupil is characterised by poor constriction to light sometimes with light-near dissociation. It is often seen in patient between the ages of 20 and 40 years of age and rarely in children. Patients typically present with anisocoria more obvious in the light than in dark.

The progression and pattern of iris denervation and re-enervation in patients with Adie's pupil may be observed by the technique of videographic infrared transillumination. A miotic tonic pupil is thought to result from rich re-enervation of the iris sphincter by accommodation fibres. Segments that become richly enervated seem to lose their cholinergic sensitivity.

Pseudotumour cerebri

Pseudotumour cerebri (idiopathic intracranial hypertension) is a condition characterised by **raised intracranial pressure** (greater than 250 mm of water), in the absence of intracranial focal lesion, with normal CSF composition and normal or small ventricular system. Conditions that may be associated with idiopathic intracranial hypertension include:

- infections (otitis media, viral infections, febrile illness).
- drugs (steroid withdrawal, vitamin A intoxication, nalidixic acid, antibiotics and Cyclosporin, and minocycline).
- endocrine disorders.

Pseudotumour cerebri may be asymptomatic in some patients. **Visual field loss** is the main complication of this condition, and field defects may take different pattern. Visual field examination is the most sensitive test to measure visual function in these patients. Humphrey's visual field analyser or Goldmann perimetry may be used. The final visual outcome is often good in the majority of patients. **Macular oedema** is often associated with disc oedema in patients with benign intracranial hypertension. In the majority of cases, the macular oedema resolves and do not cause a significant visual loss. Patients with marked and persistent macular oedema may develop permanent visual loss. These patients should be considered for optic nerve sheath fenestration surgery. **Choroidal folds** may be the only ocular manifestation of increased intracranial pressure. Papilloedema may not present in some cases depending on the timing of ocular examination. Patients with choroidal folds should have a complete work-up to exclude raise intracranial pressure.

management

MRI is often ordered in this disease in order to exclude any other focal intracranial lesions. The disease may, however, be associated with **characteristic MRI abnormalities**, and it can be used in making the diagnosis of this condition. Characteristic MRI findings include:

Flattening of the posterior sclera (80%),
Empty pituitary sella (70%),
Distension of the peri-optic subarachnoid space (45%),
Enhancement of the pre-laminar optic nerve (5%),
Vertical tortuosity of the orbital optic nerve (40%),
Intraocular protrusion of the pre-laminar optic nerve (30%).

The presence of two or more of these signs should indicate to raised intracranial pressure.

Treatment of pseudotumour cerebri is indicated if there is an intractable headache, or if there is a progressive visual field loss. Weight loss and carbonic anhydrase inhibitors may be associated with the resolution of papilloedema. **Weight loss** appears to be a main factor in reducing the severity of papilloedema. Systemic **steroid** may also be used, but many patients rebounds after stopping the steroids. If medical treatment fails two surgical procedure,

Optic nerve sheath decompression, and lumboperitoneal shunts may also be indicated. The relative advantages and disadvantages of both Optic nerve sheath decompression and lumboperitoneal shunts operations are not yet defined . The choice of either operation seems to be determined by the surgeon's choice and experience.

The mechanism by which optic nerve sheath decompression works is unknown. It may be due to filtration of the CSF surrounding the intraorbital optic nerve or reversal of the ischaemic process. The procedure may be associated with many **complications**, most of these complications are minor (e.g. temporary motility disorder or pupillary dysfunction). Other significant complications include central retina or branch retinal artery occlusions with outer retinal ischaemia with significant visual loss may also occur. Patient should realise that there is a higher risk of visual loss, stroke and death. Complete loss of vision may occur after optic nerve decompression surgery. The mechanism of visual loss after this surgery may be due to traction or ischaemic injury to the nerve or due to vasospasm of the central retinal artery or due to orbital oedema. Visual recovery may still occur even after a protracted blindness. Patients with no identifiable cause for vision loss and who do not respond to intravenous steroids should be evaluated for an urgent lumboperitoneal shunt operation.

Optic nerve decompression may be carried out through a medial approach with disinsertion of the medial rectus muscle, through a lateral approach with removal of the lateral orbital rim to gain access to the retrobulbar optic nerve, or through a lateral canthotomy incision without the removal of bone or disinsertion of any extra-ocular muscles.

30% of optic nerve sheath decompression operations eventually fail. Treatment options in failed cases include repeated decompression, Diamox therapy, lumboperitoneal shunts, repeated lumbar punctures or steroids treatment. **Adjunctive Mitomycin and Molteno type tubes** offer additional options in failed cases and also in cases of refractory pseudotumour cerebri, the application of Mitomycin C to the optic nerve has a dose dependent toxic effect in the short term post-surgical follow up period.

Miscellaneous conditions

essential blepharospasm

Essential Blepharospasm is a rare condition characterised by bilateral spasm of the upper facial muscles. The usual cause of the facial muscles spasm is vascular compression of the facial nerve root by a loop of the posterior-inferior cerebellar artery. Bony compression in the facial canal caused by ostitis deformans is an uncommon cause. The disease may also have a psychological as well an underlying physical origin. The disease affects women more commonly than men. It often starts in the fourth to the sixth decades of life.

Patients often complain of increased frequency of blinking, this often progresses to prolonged spasmodic eye lid closure, not related to any external provocative factor. The disease may become severe enough to render patients functionally blind. **Meige syndrome** is a similar condition characterised by bilateral blepharospasm associated with involuntary movement of the lower face and mouth muscles (oro-facial dystonia). Symptoms of both conditions may disappear spontaneously especially during the first five years after the onset of symptoms.

Botulinum toxin is the most effective treatment for benign essential blepharospasm and Meige Syndrome. 55% of patients are expected to benefit from the treatment. The mean duration of action of the toxin is about 14.9 weeks for blepharospasm and 11 weeks for Meige Syndrome. The duration of relieve following Botulinum toxin injection for essential blepharospasm has been reported to increase, decrease, or not change for repeated injections. In the long term the mean duration of relief changes little over a period of repeated injections. Adjunct medical treatment with minor tranquillisers and eyelid surgery (**orbicularis myectomy**) may increase the effect of Botulinum toxins.

ocular neuromyotonia

Ocular neuromyotonia is a condition characterised by spontaneous **spasms** of extraocular muscle contractions resulting from spontaneous neural discharge of ocular motor nerves. **Surgery** and **irradiation,** to the pituitary fossa, are the common causes. Prior radiation therapy is the most common reported cause of ocular neuromyotonia. Neuromyotonia may present with episodic diplopia many years after radiation therapy. The length of time from radiation to neuromyotonia in these patients ranged from 2 months to 9 years (mean 3.5 years). Dysthyroid orbitopathy has also been described in some patients. Ocular neuromyotonia may also occur secondary to infectious cavernous sinus thrombosis. This condition may also occur with other intracranial space occupying lesions e.g. tumours or aneurysms or in the absence of any associated conditions. A careful examination, including the effect of

prolonged voluntary muscle action, to initiate the episode, is needed. Neuro-imaging is also needed to exclude any intracranial lesions. A trial of anti-convulsant treatment (e.g. Carbamazepine) should be given.

ocular side effects of vigabatrin

Vigabatrin is an anti-epileptic drug that is used in the treatment of seizures and infantile spasms. The drug acts by **inhibiting GABA trasminase enzymes** resulting in an increases in the brain GABA. The incidence of visual field constriction and asymptomatic visual field loss, in patients taking vigabatrin, may be higher and more common than previously reported. A recent report postulated that **Muller cell** dysfunction, in the peripheral retina, may occur in some patients. Patients taking the drug may also show abnormal ERG, EOG, and VEP. Epileptic patients taking the drug are at much higher risk of developing visual field defects than similar patients not taking the drug.

The total dose of vigabatrin seems to be correlated with the severity of the visual field defects. In a recent controlled study, in a recent study a total dose of **1500 g** of the drug was associated with risk of developing significant visual field defect. When vigabatrin treatment is considered the risks of developing visual field loss should weighed against any potential improvement in the patient's quality of life. Visual field loss may be severe enough, in some patients, to limit patient's ability to perform some routine daily activities. The visual field loss **may not recover** after the cessation of treatment. Patient receiving the drug should have a base line visual field examination and also regular follow-up with peripheral **visual field examinations**.

Vigabatrin (and also carbamazepine) causes **acquired colour vision defects**. The abnormal colour perception seems to be associated with constricted visual fields in the vigabatrin monotherapy patients. The best method for detecting dyschromatopsia in patients treated with vigabatrin or carbamazepine was the Farnsworth-Munsell 100 hue test. Vigabatrin also seems to impair **contrast sensitivity** in patients who have constricted visual fields. The drug does not seem to affect glare sensitivity.

Tumours Of The Eye And Ocular Adnexa

Conjunctival melanomas

Pigmented conjunctival lesion may be benign, malignant, or intermediate types of melanotic tumours. Malignant melanoma of the conjunctiva is rare. The disease often affects middle age white individual. It is extremely rare in black people. There is also a subset of melanocytic lesions that cannot be reproducibly classified by pathologists as benign, malignant, or indeterminate.

Conjunctival malignant melanoma arises from naevi in 26%, in primary acquired melanosis in 56%, and de novo in 18% of cases. Primary acquired melanosis lesions may show some enlargement in adolescent age without any malignant transformation. Malignant melanoma associated with primary acquired melanosis has a worse prognosis than those arising de novo or from a naevus. Clinical features suggestive of **malignant transformation** in primary acquired melanosis include:

- increased thickness
- change in the pigmentation
- loss of conjunctival mobility on the lesion
- the appearance of a prominent blood vessel feeding a tumour

The tumour may arise from the bulbar conjunctiva, the palpebral conjunctiva, or from the plica. The disease may present in a superficial spreading pattern, or in a nodular pattern. It may also be **pigmented or non-pigmented**. Amelanotic conjunctival malignant melanoma my rarely arise in association with primary acquired melanosis sine pigmento. This rare type of conjunctival melanoma is aggressive and has a poor prognosis and high risk of metastases. The lack of pigmentation makes the clinical diagnosis very difficult and diagnosis is often made by histological examination.

In conjunctival malignant melanoma, risk factors of **systemic metastases** include:

1. large size.
2. fornix or caruncle involvement.
3. multicentre tumours, mixed spindle and epithelioid cell type, or epithelioid cell type and high mitotic index.

Conjunctival melanomas may be **treated** with surgical excision (with or without cryotherapy), radiotherapy, or exenteration, depending on the size and the location of the tumour. The role of orbital exenteration in the treatment of conjunctival malignant melanoma is controversial. A combination of de-bulking surgery and adjunct cryotherapy or beta irradiation seems to be more appropriate than exenteration, which is often a very disfiguring procedure. In malignant melanomas of the eyelid and palpebral conjunctiva **Iodine^{125} brachytherapy** can also be used as an alternative to wide excision or exenteration with good local control, reasonable maintenance of vision, and good cosmetic results..

Orbital exenteration should be reserved to advanced cases as a palliative measure. It may be followed by recurrence of the tumour in the orbit and paranasal sinuses. Eyes with **recurrent conjunctival malignant melanoma** should be carefully monitored for intraocular extension of the disease. deep excision of the tumour with sclero-keratectomy may reduce the natural barriers against tumour extension.

Topical **Mitomycin C** may also be considered for the treatment of conjunctival melanoma and PAM with atypia in patients who can not or are not willing to have surgical or cryotherapy treatment. Topical mitomycin chemotherapy seems to be most effective for superficial tumours. Nodular tumours may be resistant to the treatment. The treatment may also be complicated with the development of keratoconjunctivitis in some patients and secondary changes in the superficial layers of the conjunctival epithelium. These changes should be differentiated from recurrent tumour.

carcinoma of the external eye surface

Corneal intra-epithelial neoplasia (CIN) is a slowly progressive unilateral lesion, that has a low malignant potential. The condition is known to lead to **squamous cell carcinoma**. It may be difficult to differentiate between advanced CIN and early invasive disease. Pre-invasive (CIN) and invasive carcinomas of the conjunctiva and the cornea are more common in people in the hot tropical areas, especially fair-complexion middle age individuals. The disease may also affect younger immunosuppressed patients (due to drugs, AIDS, or lymphomas) with no significant history of solar exposure. It is thought that the **papilloma virus** plays an important role in the pathogenesis of this tumour in these patients. When the tumour is diagnosed in patients younger than 50 years of age, HIV infection should be considered.

The treatment of choice, of this tumour is by surgical excision. Single excision is followed by recurrence in about 25-35% of cases. The slow growth of the recurrent lesions combined with the ever present malignant potential suggest that all patients with a history of CIN warrant annual follow-up for the remainder of their lives. The recurrence rate falls when single excision is followed by cryotherapy, beta irradiation therapy and also after topical application of **Mitomycin C**. Excimer photo-therapeutic keratectomy and Sub-conjunctival injection of Interferon alpha-2b may also be used in selected cases.

choroidal melanoma

The **incidences** of intraocular melanoma varies between 0.49 to 0.75 cases per 100,000 population per year. Uveal melanoma is rare in children and teenagers. Oculo-dermal melanocytosis is estimated to be 9 times more common in young patients with uveal melanoma than in the general population with uveal melanoma. Young patients with uveal melanoma have short-term (5-year) survival better than that of adults.

The risk of uveal melanoma in black individuals is low. The reason for the lower risk of uveal melanoma in this group of patients is not known. It could be related to the protective effects associated with dark skin pigmentation or may be due to cultural, environmental or socio-economic factors. About 40% of uveal melanomas metastasise within 10 years of diagnosis. The commonest site for metastases is to the **liver** via the blood stream. Blood levels of gamma-glutamyl transpeptidase, and alkaline phosphatase enzymes, as well as chest X ray and liver ultrasound scan can be used for screening purposes for tumour metastases.

Progress has been made in elucidating the genetic basis of cutaneous melanoma with three well-defined loci (chromosomes 1, 6 and recently chromosomes 9). A few reports have also shown abnormalities on **chromosomes 3, 6 and 8** in uveal melanomas. The p53 gene plays a major role in inhibiting DNA synthesis after DNA damage. Mutation in the p53 gene have been found in more than 50% of human cancers. Some mutations have been associated with more aggressive tumours and metastases. Mutation in the p53 gene does not seem to be common in uveal melanomas. The exact role of mutation in the p53 gene in the pathogenesis of uveal melanomas in not understood. It does not, however, seem to be common.

Immunological factors may also play a role in the pathogenesis of ocular malignant melanoma. Choroidal malignant melanoma may be associated with ipsilateral ocular inflammation and sympathetic ophthalmia. Choroidal melanoma may also be associated with bilateral retinal vasculitis. The inflammatory signs may improve in the fellow eyes in some patients after enucleation of the eye with the tumour.

Ocular ultrasound, MRI and CAT scan can be used in making the diagnosis of ocular tumours, and their extraocular spread. Controversy exists about the **best imaging tool** to detect the extension. Some reports showed that MRI is superior to others while other reports showed that ultrasonography is more superior to MRI.

Choroidal melanomas should be **differentiated** from secondary choroidal metastases. The shape and the height of the tumour / its base ratio in B scan ultrasound can be used in the differentiation of choroidal metastases from choroidal melanoma. Metastases demonstrate a

significantly lower height / base ratio than melanoma. Choroidal excavation also seems to be present only in melanomas. The reflectivity is also significantly higher in metastases than in melanomas. Ultrasound biomicroscopy can be useful in the management of some iris melanomas. It is an accurate imaging technique for the assessment of anterior tumour margins of peripheral choroidal melanomas.

Malignant melanomas exhibit different patterns on **MRI** testing. It has been thought that variable melanin content and the presence of iron (as methaemoglobin or haemosiderin) may be responsible. Contrast-enhanced MRI (by Godopentetate dimeglumine) is useful in evaluating intraocular tumours and in differentiating between uveal melanomas and other similar tumours.

Bilateral primary uveal melanoma, familial uveal melanoma, diffuse choroidal malignant melanoma, and retina-invasive melanomas are rare **types** of the disease. Bilateral primary uveal melanoma is rare. The occurrence of bilateral primary uveal melanoma may be associated with ocular melanocytosis. There does not seem to be any clinical evidence of inherited genetic predisposition for these tumours. There is no relation to familial atypical mole and melanoma syndrome, cutaneous melanoma, neurofibromatosis, or familial uveal melanoma. Unidentified germ-line mutation may be involved in the pathogenesis of these tumours.

Although **familial** occurrences of uveal melanoma are rare, there may be a hereditary basis for this tumour in certain families. Diffuse choroidal malignant melanoma occurs in about 4% of all choroidal melanomas. These melanomas carry a metastatic potential of 24% at five year periods in spite of its flat appearance.

Retina-invasive melanoma is a rare but distinct type of uveal melanoma. Retina-invasive tumours tend to arise from a ring melanoma, they grow slowly. Frequent secondary angle closure glaucoma may promote invasion of the tumour cells into the optic nerve.

Cutaneous malignant melanoma may, rarely metastasise to the eye. Ocular metastases often present by pigmented or non-pigmented vitreous cells. Metastatic malignant melanoma may also present with heavy pigmentation of the anterior segment and trabecular meshwork and pigmentary dispersion in the aqueous and the vitreous with visual loss with no echographic or pathological evidence of discrete tumour masses. The prognosis for life in these cases is often poor.

Extraocular extension of choroidal malignant melanoma may be associated with proptosis, restriction of EOM movements and manifestations of orbital inflammation. Uveal malignant melanomas may also present with symptoms and signs of orbital inflammation due to tumour necrosis and intraocular inflammation, even in the absence of orbital extension. The possibility of intraocular tumours in patients

presenting with acute orbital inflammation should be excluded. Orbital extension of choroidal melanoma may be treated with local excision of the orbital lesion as well as proton beam irradiation of the ocular tumour.

prognosis

Although the diagnostic accuracy for tumours that are more than 4 mm thick is greater than 98%, the sensitivity and specificity of clinical examination, ultrasound and fluorescein angiography are uncertain for pigmented tumours less than 3 mm in height. In choroidal and ciliary body melanomas, measurement of the largest tumour dimension in contact with the sclera (a measurement known as **The Largest Tumour Dimension**) has been shown to be of great prognostic significance. Fine needle aspiration biopsy results may also achieve a correct diagnosis and management in 9% of cases presumed to be small uveal melanoma by non-invasive methods. The problem of insufficient material for cytological examination can be minimised by the use of a 22 gauge needle.

Cytomorphometric analysis of uveal malignant melanoma may help in predicting the prognosis in patients with malignant melanoma. The standard deviation of nuclear area seems to be a very significant variable correlated with the malignancy of the tumour within each Callender group classification. The **PC-10 count** also appears to have a prognostic value in uveal melanomas when adjusting for the effect of the mean of the largest nucleoli and diverse vascular patterns.

The presence of **vascular loops** (defined as periodic acid-Schiff-positive fibrovascular septa that completely surround lobules of tumour cells), and micro-vessels density are indications of poor tumour outcome. Quantifying cross-sectional tumour area and the percentage area occupied by networks and parallel vessels with cross-linking micro-circulatory patterns in ciliary body and choroidal melanomas provides significant prognostic information. The micro-circulatory pattern of primary choroidal melanoma also appears in the metastases regardless of its site.

Indocyanine green angiography with confocal scanning laser ophthalmoscopy can be used in imaging the micro-vascular structure of choroidal melanoma. A prognostic index combining two or more indicators may have a better prognostic value. In posterior uveal malignant melanoma, specific chromosomal abnormalities have been shown to correlate with the prognosis. Fine needle aspiration biopsy may provide an opportunity for cytological analysis, and may provide an accurate assessment of uveal tumours.

treatment

Small choroidal melanocytic tumours are often treated by **observation**. Periodic follow up with photography and ultrasonography may be all is needed in these cases to check for tumour growth. In small choroidal melanocytic tumours, these risk actors may be predictive of tumour growth; the presence of several factors seems to increase the risk:

1. Tumour thickness greater than 2 mm.
2. Posterior tumour margin touching the disc.
3. Visual symptoms.
4. Orange pigmentation of the tumour.
5. The presence of subretinal fluid.

Currently the efficacy of treatment in uveal malignant melanoma, in preventing metastatic death, is uncertain. It is predicted that, within the next 25 years, obtaining and analysing tumour samples will be possible by using small-needle aspiration and DNA probes technology. Genetic defects will also be determined, and treatment based on drugs designed to inhibit molecules related to the genetic defect in the tumour may be possible.

Recognised **methods** of treatment of uveal melanomas include:

Enucleation
Radiotherapy (plaque and charged particles)
Radiotherapy with Hyperthermia
Trans-pupillary Thermotherapy
Transscleral resection
Photo-dynamic therapy
The radio-surgical Leskell Gamma knife
Interferon alpha and gamma
Vaccination

Plaque and charged particles radiotherapy are the main lines of treatment. In **plaque radiotherapy** treatment several isotopes have been used e.g.:

- Iodine-125.
- Ruthenium-106.
- Iridium-192.
- Palladium-103.

Charged particles treatment has also been carried out by using:

- Proton.
- Helium ions

Both methods seem to be effective in the treatment of choroidal melanomas. Data suggest that there is no difference in patients survival between treatment by irradiation, by enucleation or by brachytherapy

using radioactive scleral plaques. It is not known if physical manipulation during surgery increases the risk of developing micro-metastases.

When the tumour is judged to be too large to be treated by any conservative method **enucleation** is often carried out. Mildly curved scissors should be used for enucleation when a long optic nerve specimen is desired. Strongly curved scissors should be avoided. Previous studies indicated that **pre-enucleation irradiation** is associated with a worse prognosis for survival when compared with no irradiation before the enucleation, but it has been shown, recently, that pre-enucleation irradiation does not have an effect on the survival of patients with uveal malignant melanoma. In the absence of tumour viability, enucleation, after primary irradiation, does not appear to affect patient's survival. If there is an evidence that the tumour re-grows after irradiation, enucleation may then be associated with a higher mortality rate. More than 40% of post-radiation mortality after choroidal melanoma is due to causes not related to the tumour or to the metastases.

Plaque radiotherapy is, currently, the most popular form of conservative treatment for choroidal and ciliary body melanomas. Initially, cobalt plaques were widely used but the high incidence of radiation complications has led to the adoption of less energetic isotopes (such as ruthenium, iodine and recently palladium). Ruthenium plaques appear to be associated with higher rates of local recurrences of the tumour than proton beam irradiation or Iodine plaque treatment. The frequency of radiation related complications after ruthenium radiotherapy for uveal malignant melanomas are acceptable especially in small to medium sized tumours. Localisation of the scleral plaque may be better carried out by a three dimension ultrasound than with the conventional two dimensional one.

Custom designed plaque radiotherapy can be used, and seems to be effective and safe in controlling iris malignant melanoma that can not be excised and also in localised iris metastases. Possible complications of this technique include iris vasculopathy, posterior synechiae and cataract.

Radiation **vasculopathy** and **retinopathy** are common finding after plaque radiotherapy for choroidal melanoma (they occur in 42% of patients after 5 years). Radiation vasculopathy is a leading cause to visual acuity loss. The earliest changes observed after radiotherapy are peri-tumour atrophy of the retinal pigment epithelium and choriocapillaris. The susceptibility of the retinal vascular endothelium to radiation is the main biological factor leading to vascular occlusion and retinopathy. The main **predictors** of radiation retinopathy are posterior tumour location with margin near the foveola and high radiation dose rate to the tumour base. Patient factors, such as diabetes, may also play a determining role. Radiation therapy may also be associated with the development of idiopathic peri-foveal telangiectasis.

Charged particle radiotherapy of uveal melanomas is currently possible in few centres world-wide. **Proton beam** irradiation for uveal malignant melanoma is associated with excellent local control and retention of useful vision. Proton beam irradiation administer radiation to a circumscribed area and is thought to minimise the damaging effect on the neighbouring tissues. External beam irradiation may, however, be associated with ocular complications e.g. dry eye syndrome, cataract and macular oedema. Progressive visual field loss is also common after proton beam irradiation for peripapillary choroidal malignant melanoma and seems to be related to the area of the retina treated. Radiation papillopathy does not seem to associated with progressive field loss in most patients. Dry eyes is also a main complication after treatment. The radiation dose to the cornea appears to be a more important factor in causing dry eye than the radiation dose to the lacrimal gland. Large radiation dose to the cornea may be associated with severe complications even if the lacrimal gland is well protected.

Radiation-induced **macular oedema** may also occur. The oedema may be treated with focal laser photocoagulation. Short-term results are encouraging but the long-term results are often poor. Posterior sub-capsular **cataract** develops in about 41% of patients 3 years after treatment. The incidence increases significantly with increasing the treatment dose and tumour light. Cataract development is related to the amount of lens in the pathway of radiation, patient age, pre-existing cortical opacities and also tumour height.

Neovascularisation glaucoma develops mainly in the first few years after radiation but cataract may continue to develop for much longer period. The strongest risk indicator for radiation cataract and vitreous haemorrhage is thought to be the height of the tumour, for neovascular glaucoma the TNM class of the tumour, for radiation maculopathy the posterior tumour margin within 2 mm from the fovea, and for radiation optic neuropathy the location of the tumour margin within 1 disc diameter from the optic disc. Recent studies indicate that fractionated radiotherapy doses may spare the normal tissue while delivering the right dose to the tumour tissue.

Helium ion can be used for the treatment of tumours less than 6 mm in thickness and more than 3 mm away from the disc. This method is associated with good local control and reasonable retention of the treated eyes. In a 10 years follow up after helium ion therapy for uveal melanoma the melanoma mortality rate was estimated to be 21%.

Trans-pupillary thermotherapy is a new technique that uses an infra-red radiation at 700 to 900 nm to produce a temperature above 45 degrees but below the retinal photoreceptor damage level. Trans-pupillary thermotherapy appears to be an effective treatment for selected

small malignant melanoma, specially those near to the fovea or the optic disc. Some tumours may fail to respond to thermotherapy.

Hyperthermia seems to have a synergistic action with radiation. The effect of thermotherapy is maximum at the top of the tumour while the effect of brachytherapy is maximum at the base of the tumour (sandwich treatment). Trans-pupillary thermotherapy may be used as a treatment alternative for both pigmented and amelanotic small choroidal melanoma. Treatment may be associated with nerve fibre layer defect and dense scotomas. Juxta-papillary tumours may be at higher risk for recurrence. Planned combined treatment of radiotherapy, thermotherapy, photocoagulation and resection may have a significant role in the treatment.

Transscleral resection of choroidal malignant melanoma is becoming more popular in some centres. Tumours extending to one disc diameter to the optic disc or the fovea is at risk of having a residual tumour, and of recurrence after transscleral resection. Recurrence often occurs within 7 years of resection. A histological report of complete excision is not a guarantee against recurrence. Recurrent tumours should be treated very aggressively by plaque radiotherapy, unless they are small and flat in which case photocoagulation may be sufficient. Survival after transscleral resection of malignant melanoma, at 15 years, diminishes from 92% (if there are less than two risk factors), to less than 30% in 3.5 years (if there are more than 3 risk factors). These risk factors include:

60 years of age or older.
Mixed or Epithelioid cell type.
Superior location of mixed or Epithelioid cell type.
Basal tumour diameter of 16 mm or more.
Lack of adjunct therapy.
Secondary enucleation for bulky residual tumours.
Recurrent small tumour or extraocular extension.

Surgical resection of choroidal malignant melanomas may be used in tumours close to the optic nerve or the fovea. Surgical resection may help to preserve central vision and field of vision when radiotherapy is thought to be risky in causing ischaemic optic neuropathy. The most common complications of this method of treatment are vitreous haemorrhage, cataract, and retinal detachment.

Photo-dynamic therapy may have an important role in the treatment of pigmented choroidal malignant melanoma. Animals with pigmented choroidal malignant melanoma show complete tumour regression when treated with Benzoporphyrin derivative and light. Tumour regression is probably due to vascular occlusion, tumour necrosis and inflammatory cell infiltration.

The **radio-surgical Leskell Gamma knife** therapy is an alternative, relatively new method to microsurgery and conventional radiation therapy in the treatment of many skull-base lesions. In this treatment, a single-session delivery of a high dose of ionising radiation to a localised volume of tissue is applied. Treatment with the Leksell gamma knife may lead to significant reduction of the blood flow in the central retinal and the short posterior ciliary arteries. Optic neuropathy may also follow radio-surgery to lesions near the visual pathways. Careful dose planning guided by MRI with restriction of the maximal dose to the visual pathways to less than 8 G y will likely reduce the incidence of this complication. The pattern of echographic reflectivity and decrease in tumour size is similar to after treatment with brachytherapy. An increase in reflectivity and a decrease in tumour size in the first 6-8 months can be considered as a success.

The anti-tumour activity of **interferon-alpha** and gamma have been studied in some human tumour (e.g. haematological and cutaneous malignancies). The exact mechanism of interferon alpha and gamma is not exactly understood but it is thought that it may modulate some cell surface molecules. The effects of interferon alpha and gamma, on human uveal malignant melanoma in vitro, suggest that these drugs may have a potential role in the treatment of malignant melanoma. Interferon alpha and gamma treatment might stimulate an important anti tumour immunological effect in vivo.

Vaccination of melanoma patients with tumour lysate-pulsed dendritic cells may lead to partial or complete tumour regression in some patients. Dendritic cells are antigen presenting cells involved in the induction of T cell response. These cells have been shown to attack melanoma cells in an HLA restricted manner. Large scale clinical trial are needed before reaching any definite conclusions.

Retinoblastoma

Retinoblastoma typically presents with **leukocoria** in children between 12 and 18 months of age. The tumour may also be associated with **retinal detachment**. Advanced retinoblastoma, with massive necrosis and anterior chamber reaction, may rarely present with preseptal **orbital cellulitis** which may be due an immunological mechanism. The presence of cellulitis does not necessarily indicate extra-ocular extension. The cellulitis may be treated by systemic steroid treatment. The tumour may also masquerade as **uveitis**. In children presenting with uveitis, the absence of pain, conjunctival redness, posterior synechiae and cataract should raise suspicion to the possibility of a retinoblastoma masquerading as uveitis.

The prognosis of retinoblastoma depends on whether the **optic nerve** is involved or not. CAT scan is very useful in the evaluation of eyes with retinoblastoma, because of the presence of calcium in most tumours. High resolution scan with 1.5 mm or thinner sections is useful in assessing optic nerve involvement. Non-visualisation of the central retinal vein is another reliable indicator of optic nerve involvement.

Orbital involvement with the tumour has a poor prognosis for life. Aggressive management approach with treatment with radical surgery, chemotherapy and external beam radiotherapy may achieve longer life survival for the patients.

treatment

In the past several years there has been a trend towards **conservative** treatment of retinoblastoma. Enucleation remains the standard treatment for advanced unilateral and for the worst eye in most bilateral cases. Many eyes, however, can be saved by conservative treatment which includes:

- External beam radiotherapy.
- Radiation brachytherapy (using episcleral radioactive plaques).
- Cryotherapy.
- Chemotherapy.
- Argon laser photocoagulation (for small tumours).
- Contact transscleral diode laser photocoagulation may also be a good alternative method for treatment.

Second tumours may occur in long term survivors after radiotherapy. Most of the tumours occurs outside the field of irradiation. Some investigators also showed that second tumours are relatively more common in hereditary disease even without prior radiation therapy. The incidence of second tumours varies significantly in the literature. The variable incidence of non-ocular tumours recorded in various reports may

be due to difference in the technique and in the dosage of irradiation. The risk of second tumours decreases with increased patient age at the time of treatment. The incidence of second tumours is very small if the treatment is administered after 12 months of age. In a study of 180 children with hereditary retinoblastoma, the incidence of second non-ocular tumours after radiotherapy was 12% after 10 years and 30% after 40 years. Radiotherapy may also result in the development of cataract. Cataract extraction with posterior chamber IOL, in eyes with regressed tumours, is safe and beneficial.

Chemoreduction is a treatment method designed to reduce the tumour size to allow for more focused and less damaging other methods of treatment. This method enhances the effect of other therapeutic modalities (e.g. cryotherapy, laser photocoagulation, thermotherapy or plaque radiotherapy). Chemoreduction may also be used as a primary treatment , but different methods of treatment should also be used if there is no tumour regression after the chemoreduction.

Chemoreduction, when used with other adjunct therapy (e.g. laser photocoagulation, thermotherapy, and plaque radiotherapy) is particularly useful in massive tumours involving more than half the retina with and without vitreous seeding. This method of treatment, in these advanced cases, may help to avoid external beam irradiation and enucleation. Chemoreduction may be carried out by:

Vincristine.
Etoposide.
Carboplatin.

Carboplatin is often administered intravenously. **Sub-conjunctival** and **episcleral** (by a balloon) administration of carboplatin is associated with higher levels in the aqueous and the vitreous than after intravenous administration. This method of administration was reported to be effective and safe for the treatment of intraocular retinoblastoma and may prove to be useful in young children. Vitreous disease seems to respond well but subretinal tumour may not respond very well to this method of treatment. In a recent report, the authors used this protocol for the treatment: 1.4–2.0 ml of a 10-mg/ml solution, 1–7 injections per eye, at a median interval of 21 days between injections. This method of treatment may be associated with transient peri-orbital oedema and optic atrophy. It does not, however, appear to be associated with systemic toxicity. **Adverse effects** e.g. myelosuppression and infection are likely to complicate the systemic treatment. These adverse effects are often treatable and do not often lead to cessation of the treatment.

Cryotherapy, 24 hours before the administration of chemotherapy, significantly increases the intravitreal penetration of carboplatin. The increased vitreous level of the drug after cryotherapy may be due to the induced retinal oedema and sub-retinal fluid. High doses of **Cyclosporin**,

before chemotherapy, can also result in higher vitreous levels of the carboplatin. A combination of Etoposide-carboplatin may also be in the treatment of extraocular and intraocular retinoblastoma. The use of **hyperthermia** (by diode laser), may enhance the effect of chemotherapy, avoid the need for enucleation or external beam radiotherapy, and thus save many eyes. Thermotherapy, alone, may also be used for relatively small tumours without associated vitreous or subretinal seeds.

- **Retinocytoma**

Retinocytoma is considered as a benign type of retinoblastoma. These tumours are composed of well differentiated retinal cells with no mitosis or necrosis. The mean age of diagnosis of these tumours is 15 years of age. The tumour may be unilateral or bilateral and family history of retinoblastoma may be present. The characteristic features of these tumours include:

- translucent retinal mass
- calcification
- changes in retinal pigment epithelium
- chorioretinal atrophy

It is important to recognise these tumours because they often need only observation and no active treatment. The tumour also belong to the same gene of retinoblastoma chromosome 13q14. Members of the same family may develop either retinoblastoma or retinocytoma. Malignant transformation to retinoblastoma may very rarely occurs.

Choroidal haemangiomas

The diagnosis of choroidal haemangiomas may be difficult. Several ancillary tests (fluorescein angiography, ultrasound, and MRI) are often needed to help with making the diagnosis. **Indocyanine green** angiography may show specific characteristic patterns that do not show with fluorescein angiography. Haemangiomas, if left untreated, may evolve to exudative retinal detachment and marked loss in the visual acuity. Close follow-up is recommended.

Various methods of **treatment** have been used for the treatment of choroidal haemangioma. These methods include laser photocoagulation, xenon arc photocoagulation, diathermy, cryotherapy, external irradiation, trans-pupillary thermotherapy and brachytherapy.

The treatment of macular and juxta-papillary choroidal haemangioma is often difficult. **Cobalt-60 radiotherapy** is a valuable method of treatment especially when the tumour involves the maculae or when it is associated with bullous retinal detachment. The role of **Proton beam** radiotherapy in the treatment of choroidal haemangiomas is new and not completely known. Diffuse haemangiomas may be treated with lens sparing irradiation, while circumscribed choroidal haemangiomas, with symptomatic serous retinal detachment, appear to respond well to proton irradiation therapy. Some reports, however, showed disappointing results of proton irradiation in preventing radiation optic neuropathy, and maculopathy.

Ocular Lymphoma

Primary intraocular-CNS lymphoma is a non-Hodgkin type lymphoma. It has previously been called **reticulum cell carcinoma**. The disease often **masquerade** as idiopathic vitritis in elderly patients. It may also presents either as a subretinal pigment epithelium infiltrates or as vitreous opacities. The tumour should be considered in old patients with vitreous cells, floaters and also in patients with painless visual loss without inflammatory signs. Central nervous system involvement is frequent and associated with a high mortality rate. Early diagnosis and treatment may improve the prognosis. A **high index of suspicion** in elderly patients with uveitis is important so that a diagnostic vitrectomy can be arranged. Vitreous cytology is a sensitive, reliable, and reproducible method of making the diagnosing. Malignant cells (**B lymphocytes**) are often present in the CSF at the time of ocular lymphoma is diagnosed, but their finding is often difficult. Multiple vitrectomy operations and lumbar punctures may be necessary before finding the malignant cells and making the correct diagnosis.

Interleukin-10 is a growth and differentiating factor for B cell lymphocytes. Concentration of Interleukin-10 in the vitreous is raised in most patients with intraocular lymphomas and may be helpful in making the diagnosis. An interleukin-10 / interleukin-6 ratio greater than 1.0 in ocular fluids is a useful adjuncts in the diagnosis. The levels of the Interleukin-10 in the vitreous also seem to correlated with the clinical activities of the tumour. Histologically proven cases, however, have been reported in which interleukin-10 to interleukin-6 ratio was less than 1.0. Elevated Vitreous Interleukin-10 Level is not diagnostic of the disease, and chorioretinal biopsy may be needed in these cases to establish the diagnosis.

Abnormal lymphocytes may be sequestered between the retinal pigment epithelium and the Bruch's membrane with minimal vitreous spill over which might lead to a false negative biopsy. A subretinal pigment epithelium **biopsy** may be used in cases when deep retinal infiltration is seen with minimal vitreous cells. Transscleral or trans-retinal approach may be used. **PCR** technique is a useful method that can be used in making the diagnosis of suspected intraocular lymphoma. It can be used to detect B- and T-cell gene re-arrangements in the vitreous washing specimens in patient with Intraocular Lymphoma. It is important that the specimens are handed with care to prevent degradation of the DNA. Appropriate handling of specimens and examination by experienced pathologists are critical in the diagnosis. Diagnostic yields may be improved if the specimens are obtained from patients not receiving systemic steroids because steroids are cytotoxic for the non-Hodgkin lymphoma cells.

Re-arrangement of the **Ig H gene** may also be helpful as a marker for primary CNS lymphomas. When the suspicion of intraocular lymphoma

remains high despite previous negative vitreous biopsies, retinal biopsy and aspiration biopsy of subretinal lesions may enhance the diagnostic yield.

Irradiation alone or a combination of **irradiation and chemotherapy** have been shown to be effective in inducing remission of the disease.

The most frequent type of ocular lymphoma has been linked to lymphoma of mucosa-associated lymphoid tissue arising in the gastrointestinal tract. The term mucosa-associated lymphoid tissue **(MALT)** has been introduced to describe the characteristic arrangement of lymphoid tissues found in certain mucosal tissues (e.g. the gastrointestinal tract). MALT lymphoma is now recognised as a specific form of tumour that is distinguished from primary, non-Hodgkin, extra-nodal lymphoma. It has been suggested that primary conjunctival lymphomas originates from this MALT tissue. The conjunctival MALT lymphoma may be bilateral or unilateral, the typical **histological features** include:

sub-mucosal B -cells follicles,
a surrounding mantle zone of small lymphocytes,
a region of B-cells extending from the mantle zone to the overlying epithelium,
extension of these B-cells to the overlying epithelium.

Patients with MALT may be **treated** with radiation, chemotherapy, surgical excision, cryotherapy or by intra-lesion injection of interferon alpha-2b. Conjunctival lymphoma may recur in other mucosal associated lymphoid tissue.

Basal cell carcinoma

Basal cell carcinoma is the most common malignant **skin** tumour in humans. It accounts for approximately 75% of all malignant skin lesions. Ultraviolet radiation exposure plays a part in the aetiology of this disease. Most basal cell carcinomas of the **conjunctiva** are cutaneous in origin. Conjunctival involvement is often secondary to skin involvement. Conjunctival tumours may result from seeding during the excision of an adjacent lid tumour.

The basal cell carcinomas are stroma-dependent tumours and a break in the conjunctiva epithelium seems to be necessary for such seeding to occur, the conjunctiva surface should be maintained and protected during lid tumour surgery. Primary basal cell carcinoma arising from the caruncle has also been described.

Surgery, radiation therapy and cryotherapy are the currently accepted methods for the **treatment** of basal cell carcinoma. Complete tumour excision is the treatment of choice. Recurrence in margin positive excised tumour is high. An aggressive treatment of margin positive tumours is necessary. **Moh's technique** for excision of peri-orbital tumours provides horizontal as well vertical tissue sections, which allows examination of 100% of the tumour margins. Excision of lids and orbital tumours by the Moh's technique may reveal extensive sub-clinical extension of the tumour. The technique may also be useful in providing an evidence for less extensive excision of tissue, and less reconstructive surgery than otherwise would have been predicted. The technique provides the best cure rate as well as a maximal preservation of tissue for good reconstruction. Laser microsurgery with microscope-mounted CO_2 laser may also be used for the treatment of primary superficial tumours without conjunctival extension.

Diseases of The Ocular Adnexa

Oculoplastic

ptosis and ptosis surgery

Ptosis is generally classified into two types congenital or acquired. Congenital ptosis is thought to be due to **dystrophic changes** in the levator muscle. Some investigators believe that it is more likely to be due levator muscle dysgenesis. In a recent report, levator muscle fibres from patients with congenital ptosis and normal individuals were examined and compared microscopically. The authors of the report found no significant difference in the muscle fibres diameters or its distribution between the two groups. The results of this report does not, therefore, support the assumption that this condition is due a dystrophic changes.

Patients with congenital ptosis have an increased incidence of **refractive errors** and corneal astigmatism. Amblyopia in these patients may be due to either visual deprivation, if the pupil is completely covered by the upper lid, or due to the refractive error. Congenital ptosis may also be associated with **strabismus** in about 32% of patients. The association of congenital ptosis with weakness, or over-action of the ipsilateral superior rectus muscle, or with double elevator palsy has been previously reported.

In acquired ptosis the **degree** of ptosis is typically the same on primary position and on down gaze. Patients with congenital ptosis, on the other hand, demonstrate a widening of the palpebral fissure on down gaze due to lack of elasticity of the levator muscle. This sign may be helpful in the differentiation between congenital and acquired ptosis. Some patients with acquired ptosis, however, may have worsening of the ptosis in down gaze position. The increased ptosis in down gaze noted in some patients with acquired ptosis may be a normal physiological processes. Older patients with no ptosis tend to have a greater decrease in their upper eyelid margin-corneal light reflex distance on down gaze.

The increase in ptosis on down gaze may interfere with some activities e.g. reading. Many patients with acquired ptosis complain of **fatigue**, headache and brow ache after prolonged periods of reading or working in down gaze position. The continuous action of the frontalis muscle to raise the upper lid, may explain the symptoms of fatigue and headache in this subgroup of patients. Ptosis repair is associated with significant widening of the palpebral fissure height in down gaze and a significant decrease in the use of the frontalis muscle and return of the patients ability to sustain down gaze work more comfortably.

Acquired ptosis may be caused by old age, cataract surgery, contact lens wear and myasthenia gravis. **Contact lens wear** is reported to be the commonest cause of ptosis in young healthy adults. Imbedding of the contact lens in the upper lid conjunctiva may lead to inflammatory changes causing the ptosis. Rubbing of the contact lens against the upper lid may also cause inflammatory changes causing the lid to droop down. The mechanism of removing the contact lens by pulling on the upper lid and forcibly blink may be another mechanism for causing the ptosis.

Myasthenia gravis is an important cause of acquired ptosis. Exclusion of the disease is important as this condition is often treated medically. Diagnosis of the disease is often established by invasive tests e.g. the edrophonium test. **The ICE test** is a fairly new, safe, quick and easy test to help with the diagnosis of the disease. The test is performed as follows:

1. Apply an ice pack to the ptotic eye lid for two minutes.
2. Two or more millimetres of elevation of the lid after ice application is considered positive and highly suggestive of the disease.

The test is based on the fact that increased temperature has a detrimental effect and cooling has a beneficial effect on muscle force generation in myasthenia gravis, presumably by inhibiting anticholinesterases function. The specificity of the test is estimated to be 100%, while The sensitivity ranges between 80% and 100%. The results are not affected if the patients are taking anticholinesterases at the time of the test. It may be positive in cases with negative edrophonium test or anti-ACh R antibodies.

management and surgical techniques

Patient's quality of life is reduced by ptosis. Surgical repair often results in measurable increase in patient's health-related quality of life. In the preoperative evaluation of ptosis there are two methods of evaluating the levator muscle complex function: either by measuring the lid excursion, or by measuring the **levator force** (as measured by a new instrument). Diagnosing the cause of ptosis (*neurogenic, myogenic, aponeurotic or mechanical*) based on the levator force measurement is significantly more accurate than when based on the lid excursion specially when combined with clinical examination. It is suggested that levator force measurement should be an important component and a constant part in the assessment of cases of ptosis.

- **brow suspension**

Children with severe unilateral congenital ptosis are at risk of developing deprivation **amblyopia** if the lid covers the visual axis. In this situation

urgent repair of the ptosis is indicated. Frontalis suspension is often the treatment of choice because it is difficult to evaluate the levator function properly in children. Frontalis suspension is also indicated in ptosis patients with poor or no levator function (e.g. congenital ptosis and ptosis associated with progressive external ophthalmoplegia, third nerve palsy or myasthenia gravis). Using **autogenous fascia lata** is the preferred method of suspension. Harvesting fascia lata is reported to cause minimal or no postoperative morbidity though complications can arise when a large area of fascia lata is removed. The traditional method of harvesting fascia lata has been through an incision above the lateral knee. Problems with this method include a conspicuous scar, herniation of the muscle belly and haematoma formation. Fascia lata can also be harvested safely from the region of the **iliac crest** with an inconspicuous scar and with fewer complications than with the more traditional site slightly above the lateral knee.

In young children there is insufficient autogenous fascia lata to use. **Different materials** have also been used to suspend the upper lid from the eye brow including. These methods include; non-absorbable Prolene Mono-filaments sutures, sclera, or preserved fascia lata, supramid and temporalis fascia. Supramid sling is often associated with only temporary correction of the ptosis. Recurrence may be noticed any time within the first 18 months. Mersilene mesh can also be used in patients not suitable for autogenous fascia lata. Mersilene mesh acts as a scaffold which support fibrovascular in-growth. Complications of this technique include extrusion of the mesh, infection and granuloma formation. Complications can be reduced by meticulous closure of the wound. Silicon rods are also effective and can be used in both children and adults. Silicon rods have the advantages of being elastic and easy to adjust. Long term recurrence of ptosis is possible and follow up is recommended. **The palmaris longus tendon** can also be used as a sling material for frontalis muscle suspension in adults and children. The loss of this tendon is not associated with any functional deficits. The tendon often lies in a superficial location and can be identified and isolated easily. It is also strong, long and thin enough to be easily placed in the eyelid.

- **levator surgery**

Levator aponeurosis ptosis surgery is often carried out via an anterior approach through the skin or by a posterior approach through the conjunctiva. Controlling the height of skin crease is easier to achieve via the anterior approach. The anterior approach may be carried out through a small **8 mm eyelid crease incision**, in some selected patients.

The technique of **levator transposition** may be used in unilateral cases of ptosis and aberrant eyelid movement. Further levator resection may be needed to achieve better elevation of the lid. Maximum function of the muscle may not be achieved for 12 months after surgery (time for motor enervation to establish). It is recommended that this procedure should be

reserved for patients with unilateral disease, and that patients should also be warned that they might need more than one operation and the final outcome might take about one year to establish.

The most common **complication** after levator muscle surgery for ptosis are under-correction, over-correction or abnormalities of eyelid contour. In a study of 164 cases, 40% of cases reached their final level at one week after surgery, and 52% continued to rise by a mean of 1.1 mm. Most lids seem to achieve their maximum height by 6 weeks. **MRI** may be used in the evaluation of the upper lid contour in patients with ptosis or lid retraction.

Revision and further adjustment of the lid height and contour can be performed three to four days after the operation as an out-patient procedure. Postoperative oedema or haemorrhage, which distorts the eyelid, are contraindications to early revision as they make revision more difficult technically and also harder to predict.

- **adjustable sutures technique**

Adjustable sutures surgery for ptosis, and lid retraction is a useful technique when surgery is performed under general anaesthesia (e.g. in children). The technique is also useful in the following conditions:

1. Traumatic ptosis.
2. Thyroid eye disease.
3. Ptosis correction after excessive upper lid lowering.

Adjustable sutures allow the lid height to be adjusted for over- and under-correction to achieve the optimal surgical results. Suture adjustment is a simple procedure and is recommended to be carried out within 24 hours after the operation. Marked postoperative lid oedema may make suture adjustment more difficult. In the anterior approach technique the sutures pass from the levator muscle through the anterior surface of the tarsal plate exiting through the upper and lower skin edges. The position of the skin crease can also be adjusted. In the posterior approach the sutures pass from the levator through the cut upper edge of the tarsal plate and then tied and positioned at the position of the desired skin crease.

- **the single stage aponeurotic tuck technique**

The single stage aponeurotic tuck technique is a simple and effective method of treating ptosis for involutional, post-cataract, traumatic and also congenital types of ptosis (under general anaesthesia). This procedure may be used for degrees of ptosis ranging from 1-5 mm with levator function greater than 8 mm. The procedure involves dissection of the aponeurosis in the usual way. A 6/0 nylon suture is then inserted 2 mm medial to the pupil in the anterior surface of the superior tarsal border and then re-inserted at the healthy substance of the levator aponeurosis

higher up. Asking the patient to look down will ensure that the second suture bite will be taken as high as possible in the levator aponeurosis. A slip knot is then tied first to judge the crease level and the height of the lid and then is readjusted accordingly. An over-correction of 1.0 to 1.5 mm is aimed at the end of the operation to ensure a good postoperative level.

- **upper blepharoplasty**

The traditional treatment in Progressive myopathic ptosis is by levator muscle resection or by frontalis sling. Either of these procedures may result in lagophthalmos and exposure keratopathy. Upper blepharoplasty (removing all excess skin and orbicularis between the eye brow and the eyelid margin) may be used as an alternative method for ptosis correction in these patients. The procedure leads to an improvement in the degree of ptosis with no corneal exposure with fewer postoperative complications and clinics visits.

hydroxyapatite orbital implants

Hydroxyapatite orbital implants have gained popularity in recent years because of the excellent **cosmetic results** that can be achieved with the technique. The implants are made of calcium phosphate that is derived from coral. They become integrated into the orbit by a fibrovascular growth. **Fibrovascular growth** may occur in the pores of hydroxyapatite orbital implants as early as 4 weeks after implantation. Bone may form within the implant if it is implanted in a direct contact with bone. Bone may also be produced by transformation of the circulating monocytes cells or by osseous metaplasia of the fibrocytes which migrate inside the implant. Ossification of the implant may occur in some patients after up to 18 months. **MRI** can identify the progression of fibrovascular in-growth into hydroxyapatite implants and guide surgical planning of a successful prosthesis attachment. It may also identify implants that failed to develop good vascularisation and hence avoid possible complications of drilling into avascular implants.

The presence of complete vascularisation of hydroxyapatite implants at the time of drilling is crucial for the epithelialisation of the wall of the hole. The **technetium bone scan** is sensitive to the vascularisation of the hydroxyapatite implant and indicates when complete vascularisation is approached. At least a 4-week interval between the time the bone scan showing complete vascularisation and peg drilling is recommended.

Pegging of the implant is often carried out as a secondary procedure. it may also be, reliably and safely, fitted during the primary procedure. The main **advantages** of these implants are good motility results. The postoperative results after Hydroxyapatite implants, without pegging, are similar to those obtained after other types of orbital implants. Motility of the of the artificial eye is, however, enhanced by pegging the prosthesis to the implants by means of drilling a hole in the implants and then fixing the prosthesis to the peg. **Pegging** the implant seems to increases the motility and stability of the prosthesis. Inserting a begging system in the Hydroxyapatite results in a better motility of the prosthesis. Some authorities believe that non-pegged implants are not superior to other spherical orbital implants at all.

Hydroxyapatite implants can be used after enucleation as a primary or secondary procedure for many different reasons (e.g. malignant melanoma, retinoblastoma and blind painful eyes). Prior radiotherapy treatment does not seem to increase the complication rate. Hydroxyapatite orbital implants are also well tolerated, and provide good cosmetic results in the **paediatric** age group. In this age group it is critical to fit the implant comfortably to avoid conjunctival erosions and thinning. Drilling and peg placement may be delayed until the child is old enough.

complications

Problems encountered with this Hydroxyapatite implants include orbital injection, conjunctival thinning and erosions. Evaluation of the fibrovascular state of the implant is important before considering any secondary procedure (e.g. drilling a peg hole) as this may also induce exposure.

The reported incidence of implant **exposure** varies between 0% to 11%. Implant exposure occurs more frequently after evisceration than after enucleation. It is also more frequent in unwrapped implants or with implants wrapped in preserved fascia rather than in sclera. Spontaneous healing rarely occur, and conservative treatment is only limited to exposures less than 4 mm^2. Several techniques have been described for the repair of implant exposure e.g. scleral or conjunctival flaps, or by using free autogenous tissues (e.g. hard palate mucosa or dermis grafts). A tarsoconjunctival pedicle flap may also be fashioned from the upper lid to cover the exposed area. Division of the pedicle can be carried out later on as a second stage procedure. Choosing the right size implant with meticulous coverage with good vascular tissue and with minimal tension helps to avoid the problem of exposure.

Dexon mesh wrapping is thought to be similar to scleral wrapping with respect to complications, although more posterior implant placement may be necessary to avoid exposure in the Dexon-wrapped implants. Autogenous posterior auricular muscle may also be considered as wrapping material in primary and secondary orbital implants after enucleation.

Most of the complications associated with the pegging system are minor. Severe **infection** may, however, occur and may lead to the removal of the implants. Persistent orbital discomfort, discharge or the development of pyogenic granuloma after implantation should warn the surgeon of potential implant infection and abscess formation. Infection associated with hydroxyapatite implants is rare, yet it is difficult to treat and implant removal is often required.

Extrusion of the pegs is another problem which can be minimised by employing a sleeved peg rather than a non-sleeved peg system. Medial or lateral implant deviation is a rare postoperative complication. In patients with pre-existing risk factors (e.g. strabismus, or severe trauma to the extraocular muscles), it is recommended that, the anterior face the implant is modified to avoid this complication. Some authorities advocated flattening the anterior surface of the implants which may help in the pigging procedure afterwards. Rotation of the flattened implants may occur after surgery especially in patients with strabismus.

Some patients may experience **severe pain** after implantation of Hydroxyapatite implants. Patients with primary implant may suffer more pain than patients with secondary implantation. Patients should be counselled, and precautions should be taken to deal with complication.

Superior sulcus orbital defects is a major complication after orbital implants surgery. A new design of a conical-shaped enucleation implant to help minimise the occurrence of superior sulcus defects and maximise motility of the prosthesis has been described.

miscellaneous

- **floppy eyelids**

Floppy eyelid syndrome is typically associated with easily evertable upper lid with papillary conjunctivitis of the upper palpebral conjunctiva. **Eye lashes ptosis** and loss of eye lashes **parallelism** have also been reported. This condition usually occurs in middle aged obese women. Floppy eyelid syndrome may also manifest in **childhood** without other contributing conditions and should be considered in the differential diagnosis of chronic papillary conjunctivitis in patients at any age.

The syndrome has been described in association with various **other syndromes** (e.g. keratoconus, sleep apnoea, meibomian gland dysfunction and blepharochalasis). Lax eyelid may also occur due to involutional changes in the medial or lateral canthal tendon or in the orbital fat. Most elderly patients with lax eyelids are asymptomatic. The term (**Lax eyelid syndrome**) is suggested for use with these various conditions. The clinical features of the syndrome may be due to decreased tarsal elastin.

- **entropion and ectropion**

Involutional entropion is often associated with increased lid laxity. The definite treatment of entropion of the lower lid is by surgery. Surgical treatment of this condition has traditionally been with lid splitting procedures (e.g. the Weiss procedure) or by lid shortening ones (e.g. Quickert operation). A recent report indicates that surgical success is much higher, in involutional entropion with lid laxity, if the lid is **shortened**. Reinsertion of the lower eyelid retractor aponeurosis to the tarsal plate, without horizontal shortening or resection of the skin or orbicularis muscle is an effective procedure for the surgical repair of involutional entropion. The procedure has a low recurrence rate. In the **absence of horizontal laxity** of the lower eyelid, a retrospective case series comparative study showed that a successful outcome is more likely after Jones retractor plication than after the Wies procedure.

Recurrence of the entropion may also be due to laxity of the lower lid retractors. Shortening and tightening of the lid retractors may be needed. A **trans-conjunctival** approach to advance or strengthen the lower eyelid retractor in entropion surgery has been described. This technique can also be associated with a lateral canthal suspension procedure to shorten the eyelid or with trans-conjunctival blepharoplasty. In this technique a lateral canthotomy is carried out, the inferior crus of the lateral canthal ligament is incised. An incision is then made below the tarsal plate through the conjunctiva and the lid retractors and a strip of the orbicularis muscle is excised. The retractors are then separated from the conjunctiva and then re-inserted in the inferior and anterior tarsal palate.

When surgery is not possible botulinum toxin may be used. The use of **botulinum** toxin is highly effective. It is also associated with few complications and does not seem to have any adverse effects on the results of future surgical entropion repair. The mean duration of action of the toxin is about 12.5 weeks. The use of the drug does nor appear to be associated with consistent changes in orbicularis oculi morphology after injection.

- **centurion syndrome**

Centurion syndrome is a recently described syndrome characterised by anterior displacement of the anterior part of the medial canthal tendon and a prominent nasal bridge, with lid malposition away from the globe and the lacrimal punctum outside the tear lake. Patients typically have epiphora dating from birth which gets worse at puberty. Syringing of the nasolacrimal duct is often patent. Treatment may be achieved by surgical correction of the anterior limb of the medial canthus with / or without DCR operation.

- **capillary haemangioma**

Capillary haemangioma of the eye lids can be treated by intra-lesion injection of **steroids**. Central retinal artery occlusion (due to embolization) leading to visual loss has been reported after this method of treatment. Care should be taken when injecting long acting steroids. The solution should not be mixed with local anaesthesia or epinephrine or allowed to rest for any length of time before use as these two conditions may cause a significant increase in the steroid particle size. If mixing the steroid with local anaesthesia or epinephrine is necessary, it is recommended that injection takes place immediately after mixing the solutions. Most steroid injections show an increase in their particles size within one hour of mixing with anaesthetic solutions. Mixing different types of steroids does not seem to cause an increase in the solution particles size.

Lacrimal Diseases

dacryocystitis

Lacrimal drainage dysfunction may be due to an anatomical obstruction, or due to a physiological dysfunction. Anatomical block is often caused by a post-inflammatory fibrosis, stenosis or due to the presence of a lacrimal stone or tumour. Primary acquired nasolacrimal duct obstruction is more prevalent in women than in men because women have significantly smaller dimensions in the lower nasolacrimal fossa and the middle nasolacrimal duct than men. Chronic intra-nasal **cocaine abuse** may result in bony destruction of the orbit, orbital cellulitis and also nasolacrimal duct obstruction. Dacryocystitis may also be caused by diseases of the lateral nasal wall.

Systemic 5 FU is commonly used in the treatment of some tumours. A high concentration of the drug is secreted in the tears. The systemic use of 5 FU may be associated with ocular side effects e.g. lacrimal canalicular fibrosis and epiphora, and ectropion. The canalicular fibrosis in these cases may be localised or diffuse. Treatment is often difficult. If the drug can not be stopped, prophylactic silicon intubation should be used.

The most frequently cultured bacterial species from cases of dacryocystitis is Staphylococcus epidermidis. Chronic dacryocystitis in adults is also associated with an increased proportion of **Gram negative** bacteria which may be a reservoir for postoperative intraocular infection. It is recommended that specimen should always be sent for culture and sensitivity in cases of dacryocystitis since infection may be caused by aerobic as well as anaerobic organisms.

Herpetic canaliculitis has been recognised as a distinct entity recently. Primary herpes simplex virus infection may result in canalicular obstruction or stenosis. Lester Jones tube has been the traditional method of treatment in the absence of enough patent canaliculus. DCR operation with retrograde or antegrade intubation may also be used in the treatment of these cases. It is also suggested that all patients with ocular primary herpes simplex infection should be prophylactically intubated with silicone lacrimal stents in order to prevent herpetic cicatricial canalicular stenosis.

investigative procedures

Jones test I and II, syringing, probing, the micro-Reflux test and dacryocystography may all be used in the evaluation of patency of the nasolacrimal system.

Jones tests can be carried out and interpreted as follows:

	Jones I test	Jones II test
How is it done?	A drop of fluorescein is instilled in the conjunctival sac.	• If, 5 minuets after the primary test, no fluorescein is seen in the inferior meatus, Jones II test is carried out. • Flush all the fluorescein remaining in the conjunctival sac. • Irrigate the lacrimal system with clear saline solution.
Positive test	If fluorescein spontaneously appears in the inferior meatus of the nose within 1-5 minutes (can be demonstrated by using a cotton bud) the test is considered positive.	• If fluorescein-stained saline is retrieved from the nose the test is considered positive. • This can be checked by tilting the patient's head forward to retrieve the saline coming out of the nose.
Negative test	No fluorescein appears in the nose	If clear saline, or partially stained saline comes out of the nose, the test is considered negative
Interpretation	Positive Jones I indicates normal drainage system.	A positive Jones II test establishes that the upper part of the drainage system is patent, since some saline must have entered and stayed in the lacrimal sac.

Fluorescein dye disappearance test is another useful test that can be used. in this test, a drop of fluorescein is instilled in the conjunctival sac. The amount of fluorescein in the conjunctival sac is then observed 5 minutes after instilling the drops. The intensity of discoloration of the tear meniscus can be used as an indication of the amount of fluorescein remaining in the sac.

When Jones I and II tests are carried out in association with the fluorescein disappearance test, the results can be interpreted according to the following table:

Test				
Fluorescein dye disappearance	No residual dye	Residual dye	Residual dye	Residual dye
Jones I	Positive	Negative	Negative	Negative
Jones II	Not done	Positive	Negative	Negative
Diagnosis	Normal system	Functional block	Upper system block	Upper and lower system block

The Micro-Reflux test is a new test that can be reliably used for the diagnosis of complete nasolacrimal duct obstruction. A recent study demonstrated that the test has a specificity of 95% and sensitivity of 97%. The test can be carried out and interpreted as follows:

Two drops of fluorescein are instilled in the lower fornix.
The patient is then asked to blink 5 times to activate the lacrimal pump.
The inferior punctum is examined under the slit lamp.
The lacrimal sac in then massaged in a counter clockwise direction to empty the inferior canaliculus.

The test is considered positive if there was a continued reflux of the dye-stained tears from the lower punctum after the massage.

Dacryocystography is useful in demonstrating areas of obstruction around the common canaliculus and the nasolacrimal duct. The test successfully shows the area of obstruction in about 98% of common canaliculus obstruction, and in 100% of cases of nasolacrimal obstruction. The procedure can also predict multiple, congenital and, physiological blocks. Syringing and probing alone does not seem to be enough for the diagnosis and localisation of these cases.

Syringing and dacryocystography may show normal drainage system in functional lacrimal obstruction. Lacrimal scintigraphy and dacryocystography can be used to diagnose this condition even in the presence of normal tear duct syringing. **Lacrimal scintigraphy** appears to be slightly more sensitive than dacryocystography in showing the drainage system abnormalities in this condition. The test might be useful in patients with epiphora in whom dacryocystography is normal.

Lacrimal **endoscopy** is a new technique that may be used to visualise the lacrimal drainage system. Small calibre endoscope can be especially designed to be coupled to a lacrimal probe and a camera. The technique may be useful in localisation of lacrimal obstruction and in aiding decision making regarding choosing the right surgical procedure.

surgical techniques

- **dacryocystorhinostomy**

External DCR operations are highly successful for treating nasolacrimal duct obstruction. DCR operations can safely be carried out on a day-case surgery basis, with local or general anaesthesia. Careful selection of patients is important. Narrowing of the **osteotomy** size is the most common cause of failure of DCR and recurrence of the symptoms. Narrowing of the rhinostomy occurs mainly due to fibrosis. New bone formation may also occur. Large size osteotomy is, therefore, an important part for the success of this operation. The size and patency of the osteotomy may be assessed by the Jones test, dacryocystography, and also be nasal endoscopy. B mode **ultrasound** examination may also be used for evaluating the size of the osteotomy. Intraoperative **Mitomycin C** may be used during the surgery to maintain a larger osteotomy size. It has also been suggested that laser-DCR surgery may be a useful approach for the revision of failed DCR cases.

Establishing a lacrimal pathway in DCR operation can be achieved by several techniques. The use of large **anterior** nasal mucosa and lacrimal sac flaps, with no posterior flaps anastomosis may be used to simplify the operation. The large anterior flaps are easier to suture, but they need to be elevated and anchored anteriorly, to the subcutaneous tissues in order to prevent blockage of the lacrimal pathway by the large flaps.

Postoperative soft tissue **infection** may predispose to failure of DCR surgery. Antibiotic therapy for established postoperative infection is less effective than preventative therapy in improving the success rate of surgery. It is recommended that all patients undergoing open lacrimal surgery should receive prophylactic antibiotics (e.g. Cephalexin or erythromycin).

- **external or endonasal laser-assisted approach?**

Endonasal laser **DCR** is a rapidly developing surgical procedure for the treatment of nasolacrimal duct obstruction. **C-DCR with Jones** tube may also be performed by an endoscopic technique The use of modern endolacrimal endoscopic instruments has improved the results after endonasal lacrimal surgery. Endonasal DCR has many potential **advantages** over conventional external DCR:

1. Less disruption of the inner canthus region.
2. Enhanced haemostasis.
3. Avoidance of scar.

External-DCR, when compared with endonasal laser-DCR, seems to provide **superior results**, in primary acquired nasolacrimal duct obstruction. The success rate of endonasal laser-DCR is thought to be

less than the external conventional approach mainly due to the closure of the ostium. In one study, the success rate at 1 year after surgery was 91% for external-DCR and 63% for endonasal laser-DCR after primary surgery. Intraoperative use of **Mitomycin C** has been tried to increase the success rate but, in some studies it failed to do so. Endonasal laser-DCR seems to need some adjunctive treatment (e.g. lacrimal intubation) to improve maintenance of the nasal mucosal opening.

Endonasal laser treatment has also been thought to be unsuitable for **canalicular** obstruction disease. A recent study, however, showed that an erbium YAG laser, attached to a flexible endoscope may be used for treating obstructive lesion at the level of the upper and lower canaliculi, when inserted into the canaliculi. Silicon intubation is required in these cases.

- **probing of the nasolacrimal system**

When DCR surgery is contraindicated or considered inappropriate for elderly patients, **probing** of the nasolacrimal duct, may be used instead. Probing is effective, easy and does not appear to affect future surgical treatment if required. This procedure is reported to be successful in about 82% of eyes. Silicon intubation of the nasolacrimal duct may also be used. The treatment leads to complete or partial resolution in a high percentage of patients. Recurrence may also occur in some patients. Failure of the procedure does not seem to affect later DCR surgery.

- **balloon dacryocystoplasty**

Dacryocystoplasty is a new method for treatment of nasolacrimal duct obstruction. The procedure can be carried out under topical anaesthesia to the conjunctiva, infiltration anaesthesia to the infra-trochlear area and to the nose. A 0.018 inch guide wire is then passed through the lacrimal canaliculus to the nose, and a French balloon angioplasty catheter is then passed through the nasolacrimal duct in a retrograde manner till it reaches the nasolacrimal sac. The balloon is then inflated and left in situ for 3-4 minutes after which it is deflated and removed.

The advantages of this procedure is that it is easy to perform under local anaesthesia as a day case, can be repeated and does not change the anatomy of the lacrimal passages. A conventional DCR operation can be carried out later if this procedure fails. In children with congenital nasolacrimal duct obstruction balloon catheter dilatation of the lacrimal drainage system offers an alternative to silicon tube intubation. This technique is generally effective in the treatment of **congenital** nasolacrimal duct obstruction as a primary procedure and also after failure of probing or silicon intubation. Balloon Dacryocystoplasty may also be suitable for the treatment of **partial** obstruction below the level of the lacrimal sac, but it is not effective for treatment of complete obstruction of the lacrimal drainage system.

congenital nasolacrimal duct obstruction

Epiphora is a common symptom in young children, it is often due to delayed canalisation of the nasolacrimal duct. Congenital nasolacrimal duct obstruction affects about 20% of all infants. The majority of cases resolve spontaneously, and 60% of eyes resolve spontaneously, without treatment, before the age of 18 months. There is also a 50% chance of spontaneous resolution during the period between 12 and 18 months of age.

The traditional teaching is that, probing of the duct should be tried within the **first year** of life if this procedure was to succeed. Both early (at 6 months) and late (at 12 months) probing have been shown to have a similar high success rate (99%). Success rate seems to be slightly higher in the younger age group. Increasing frequency of epiphora seems to be associated with lower success rate.

Probing **beyond the first year** of age is also reported to be highly successful, and the cure rate does not seem to vary significantly at intervals of increasing age. Delaying nasolacrimal duct probing beyond the first year does not appear to lead to more lacrimal dysfunction in later years. Epiphora in later childhood may be due to other atopic conditions rather than due to persistent stenosis of the nasolacrimal duct.

When probing fails to open the nasolacrimal duct obstruction, **closed** silicon tube intubation (e.g. Crawford system) may be used. This procedure may be difficult to carry out due to the compact anatomy of the nose in children, and the need to retrieve the metal tube from the nose. The **Ritleng lacrimal intubation** system is a new easy technique that provides bicanalicular intubation of the nasolacrimal duct without the need to retrieve any metal probes from the inferior meatus. The technique involves the introduction of a Prolene guide thread, into a tubular Ritleng probe, into the inferior meatus. A silicon tube, firmly attached to the Prolene thread, is then drawn into the nasolacrimal duct as the Prolene thread is pulled out of the nose.

Another new type of silastic tube that can be used for mono-canalicular intubation in congenital nasolacrimal duct obstruction is the **Monoka** tubes. The tube is inserted into the nasolacrimal duct through the upper punctum, it is then anchored to the upper punctum by a special wide flange. The overall success rate reported in some reports is 79% (which is lower than the reported success rate with the bicanalicular technique). One of the main complications of this tube is that it can easily pulled out by the child. The upper punctum flange may also rub against the cornea causing corneal abrasion. This tube has also been used in the treatment of traumatic lacerations of the lower canaliculus.

canalicular trauma

Lacrimal canalicular damage may occur due to trauma, animal bites or following excision of lid tumours. Various methods have been used to repair the canalicular damage. These methods include direct reconstruction and anastomosis of the canaliculi, pig tail probe and also mono-canalicular intubation. Data from the literature do not conclusively favour any of this methods over the others. It is very important that, during repair of a mono-canalicular laceration, that great care should be taken that the **other canaliculus** is not damaged. Simple repair of lid injuries without any canalicular repair is probably better than any repair which might prejudice the patency of the other canaliculus.

Diseases of the Orbit

idiopathic orbital myositis

Orbital myositis is a localised non-specific orbital inflammatory condition that can affect any of the extraocular muscles. It is often an isolated disorder but it has also been reported in association with upper respiratory tract infections, myocarditis, Lyme disease and Herpes Zoster infection. Bilateral orbital myositis has also been described in patients with high grade non-Hodgkin **lymphomas**. It is believed that these features constitute a paraneoplastic syndrome to the lymphoma.

Patients with unexplained enlargement of the extraocular muscles should have a full medical examination with or without muscle biopsy to exclude any underlying malignancy. The mechanism of orbital inflammation is not known. Human orbital fibroblasts produce chemokines, interleukin 8 and monocytes chemotactic protein.

Patients often present with orbital pain (which increases on eye movements), redness, diplopia and headache. This condition should be differentiated from dysthyroid eye disease, orbital pseudotumour, orbital cellulitis, other conditions associated with ocular muscle enlargement and other causes of globe retraction (Duane's, generalised fibrosis syndrome, blow out fracture). CAT, MRI and ultrasound scan show swelling of the muscle insertion and reduced reflectivity of the muscle belly. The condition often responds dramatically to systemic steroids in the acute stages.

Dexamethasone is found to be a potent inhibitor to interleukin 8 and monocytes chemotactic protein, in contrast to cyclosporin which seems to enhance interleukin 8 production and suppress monocytes chemotactic protein. This observation may explain the lack of response to cyclosporin in orbital inflammatory disease that respond to steroids. In the more chronic stages, a second line anti-inflammatory drugs may be needed (e.g. methotrexate and orbital irradiation). Treatment for squint should be delayed for at least three months to allow spontaneous recovery or full recovery after steroid treatment or the full development of any restrictive motility disorder.

preseptal and orbital cellulitis

Orbital cellulitis can affect any age. The disease is, however more common in the **paediatrics** age group. The disease may be classified according to severity to several **stages**:

1. Lid oedema due to preseptal infection.
2. Post-septal orbital cellulitis with proptosis, restricted eye movements.
3. Sub-periosteal abscess.

4. Orbital abscess.
5. Complication due to posterior extension (e.g. cavernous sinus thrombosis endophthalmitis, and meningitis).

Patients in stage 1 can be treated conservatively or with oral antibiotics on an out-patient basis. Stages 2 or above should be admitted to hospital for daily examination and intravenous antibiotics.

The ophthalmic and orbital **venous plexus** is in direct contact with other facial and intracranial plexuses with a valve-less system making direct spread from the ear, sinuses or facial injuries, and also spread from the orbit backward, easy.

It has always been thought that orbital cellulitis, in children should be treated aggressively as it is often caused by Haemophilus sp. infection and can be sight threatening. In a retrospective study of 70 cases with preseptal and orbital cellulitis, the incidence of Haemophilus associated bacteraemia, in children, was very low. **Streptococcal** infection was the main infecting organism. The incidence of severe preseptal cellulitis caused by group A streptococcal infection is increasing, especially after post-traumatic preseptal cellulitis. Streptococcal toxic **shock syndrome** secondary to group A beta haemolytic streptococcal preseptal cellulitis has been described. In sexually active patients with peri-orbital infection, **Neisseria** gonorrhoeae should also be considered as a possible causal organism, especially if there is a previous history of sexually transmitted diseases. The infection in these cases represents auto-inoculation from an asymptomatic episode of genital gonorrhoea. Nasal **cocaine abuse** may be associated with cartilaginous and bony orbital destruction due to ischaemia which may be complicated with pre-septal orbital cellulitis.

Some clinician recommend blood culture as routine. The yield of this test seems to be very low. Blood culture, CSF analysis, and urine tests seems to be very important mainly in children younger than **three years** of age. Culturing specimens from the throat is also fruitless as most children will have positive results of organism considered normal to the throat flora.

Plain X ray as routine are also thought to be of no value as most children will have some degree of opacification in the maxillary or the ethmoid sinuses. **CAT scan** is recommended, however, in cases where surgery is considered, or when there is no progress with medical treatment to rule out orbital or sub-periosteal abscess.

thyroid eye disease

pathogenesis

Grave's ophthalmopathy tends to follow hyperactive thyroid conditions, but it can also precedes the thyroid dysfunction. Most ophthalmologists believe that dysthyroid eye disease is most probably due to an **auto-immune disease**. The primary target cell is believed to be the orbital fibroblasts. Proliferation of fibroblasts and glycosaminoglycan has been shown in this disease. Glycosaminoglycan is a hydrophilic molecule that absorbs extra-cellular fluid and causes increase in the orbital volume. A recent study, on biopsies taken from extraocular muscles, demonstrated that **T-cells are much more involved in the early stages** of the disease and that early activation of fibroblasts occurs. Early intervention by aggressive immunosuppression therapy may, thus, prevent later fibrosis of extraocular muscles.

Viral causes have also been suggested. In a study of 93 patients, a strong correlation was found between Graves disease and Human T-Cell lymphotropic virus type 1 (HTLV-type 1) uveitis. Human T-Cell lymphotropic virus type 1 is a retrovirus that is highly endemic in the Caribbean islands, parts of central Africa and south west Japan. It is not known if these 2 auto-immune diseases (uveitis and Graves disease) occur independently as a part of infection by this virus, or if there might be a link between the two disease.

The cause of the variation between the course of ocular manifestations and systemic manifestation in Grave's disease is not known. The ocular manifestations in Grave's disease may depend on the presence or absence eof certain HLA antigens HLA-DR 14 and DQ 1 Antigens have been found in higher levels in patients with severe ophthalmopathy. They may be genetic markers of ocular predisposition to severe ophthalmopathy.

dysthyroid eye disease and glaucoma

There has been some evidence that primary open angle glaucoma is associated with hypothyroidism. 23.4% of primary **open angle glaucoma** patients are believed to also have **hypothyroidism**, and about 10.9% of glaucoma patient have undiagnosed hypothyroidism. Poor glaucoma control may be reversed after the diagnosis and the treatment of associated hypothyroidism. Patients with hypothyroidism seem to have poor aqueous humour outflow facilities when measured using tonometry and tonography techniques, this poor outflow facilities improve after the treatment of hypothyroidism. A recent study showed that the prevalence of normal-tension glaucoma as well as open-angle glaucoma and ocular hypertension was significantly higher among patients with **Graves disease** than in the general population. A study in the UK, on the other hand, examined 100 consecutive patients with primary open angle

glaucoma and found that there is **no association** of hypothyroidism with glaucoma.

Another study, in Holland, found that the prevalence of primary open angle glaucoma was similar in the general population as in patients with Grave's ophthalmopathy. It seems that only a prolonged duration of active thyroid associated orbitopathy in association with ocular hypertension is correlated with progression to glaucomatous damage. Patients with chronic thyroid associated orbitopathy need special attention and close follow-up to prevent optic nerve damage caused by raised IOP. In dysthyroid patients with elevated IOP and visual field defects, orbital decompression and ocular muscle surgery may lower the IOP.

management

Most patients with dysthyroid eye disease needs only conservative treatment. More invasive treatment is indicated in progressive disease. Disease activity, In dysthyroid eye disease, can be assessed by:

1. The STIR sequence on the MRI.
2. Ocular movements restriction (as measured by the Hess chart or by the field of binocular single vision).
3. The extraocular muscle size on CAT scan.
4. Changes in the uniocular field of fixation also appear to reflect changes in the disease activities and can be used to select and monitor patients for immunosuppression treatment. Uniocular field of fixation can be measured by fixing on a size 3, 4E target on the Goldmann machine.

- **medical treatment**

Systemic **steroids** and orbital **radiotherapy** have been used in the treatment of active dysthyroid eye disease. Approximately 65% of patients with Graves disease respond successfully to steroids treatment or to retrobulbar radiotherapy treatment. The determinant of the response are generally unknown. **Combined** orbital radiotherapy and medical immunosuppression, by low dose steroids and azathioprine, seems to be more effective than either method on its own. The combined treatment may also lead to a fewer side affects of steroid and a reduction in the need for surgical intervention. **Antioxidant agents** *(e.g. allopurinol and nicotinamide)* are also thought to be associated with encouraging results in the treatment of mild and moderately severe Graves' ophthalmopathy. The two drugs have previously been shown to prevent in vitro fibroblast proliferation.

The effect of systemic treatment for the **hyperthyroidism** on the eye disease is not known. Radio-active iodine treatment for Grave's disease may be followed by the appearance or worsening of ophthalmopathy more often than after medical treatment (methimazole). The worsening

effect is often transient and may be prevented by systemic steroid treatment.

- **orbital surgical decompression**

Orbital decompression is indicated in dysthyroid eye diseases in the presence of exposure keratitis, optic neuropathy, and also in the presence of disfiguring proptosis. Various approaches have been used previously (lateral, trans-ethmoidal, three wall, four wall, or coronal decompression). The most commonly used technique is the **trans-ethmoidal** approach. The operation may be complicated with several and potentially serious complications.

Postoperative **diplopia** is seen after all types of decompression with any approach (about 19% in all cases). Many factors contribute to its incidence. The most important factor is probably the state of the extraocular muscles preoperatively. Complete **loss of vision** may occur after optic nerve decompression surgery. Visual recovery may still occur even after a protracted blindness. The mechanism of visual loss after surgery may be due to traction or ischaemic injury to the nerve or due to vasospasm of the central retinal artery or due to orbital oedema.

Trans-conjunctival orbital decompression, through a lateral wall approach ab interno, has recently been described for one, two, or three wall orbital decompression in patients with Graves' ophthalmopathy. The technique has the advantages of low incidence of induced diplopia and peri-orbital hypaesthesia, hidden and small incision, minimal surgical trauma to the temporalis muscle, and fast patient recovery. The main disadvantage is the limited exposure of the posterior medial and lateral wall.

Trans-nasal endoscopic approach can offer both medial and inferior wall decompression without the disfiguring external facial scars. The endoscopic approach achieves good enough decompression with regard to saving visual acuity and optic nerve protection, but not for proptosis relieve. Motility disorders may occur as with the other methods of decompression. The procedure can be performed under local anaesthesia. Infection within the frontal sinus can cause **secondary orbital cellulitis** or abscess after endoscopic orbital decompression when the frontal sinus ostium is obstructed by orbital fat or scar tissue. Early signs and symptoms of a frontal sinus infection can be easily misdiagnosed as progression of the patient's thyroid eye disease. Awareness of this possible complication followed by appropriate early intervention will prevent a potentially blinding condition.

Orbital fat decompression may also be used as a surgical alternative to bony decompression in patients with an enlarged orbital fat compartment and in whom extraocular muscle enlargement is not the main cause of optic neuropathy,

- **extraocular muscle surgery**

Patients with tight inferior rectus muscle, may present with the symptoms of **flashing lights** in up gaze, which may be due to "the phosphene phenomena" as a result of compression of the inferior rectus muscle or due to the traction of its insertion.

In dysthyroid eye disease, euthyroid state should be maintained, and a stable orthoptic measures should be established for six months before any squint surgery is considered. Tight muscles may be recessed by an **adjustable suture technique** aiming to under-correct the vertical deviation at the time of surgery. **Late over-correction** after inferior rectus recessions is a known complication in thyroid and non-thyroid eye disease patients which may be due to scar contracture near the Lockwood ligament that may pull the inferior rectus muscle anteriorly, thus slackening the anterior aspect of the muscle. Patients should be intentionally under-corrected by about 4-6 prism D. Under-correction after Inferior rectus recession surgery may also occur in some patients.

- **lid surgery**

Upper lid retraction is one of the main disfiguring problems in patients with dysthyroid eye disease. In Graves disease, the peak of the upper eyelid contour is often displaced laterally and **persistent lateral under-correction** is a main problem after upper lids retraction surgery in patients with dysthyroid eye disease. Lower eye lid retraction is also a problem in patients with dysthyroid eye disease. Dysthyroid eye disease patients with lid retraction often develop over-action of the Glabellar muscles resulting in the typical thyroid face with frown lines. **Botulinum** toxins A denervation is effective in relieving these muscle over-activity. The need for Glabellar muscles denervation is often reduced when the lid retraction is treated.

Surgical treatment is often carried out by a donor scleral graft. Virus transmission is however a definite risk in these cases. Partial tenotomy and anti-metabolite is another alternative treatment. Donor scleral grafts seem to lead to longer lasting results.

Uveitis

general considerations

Uveitis is estimated to account for 10% of severe visual loss in the Western world. Uveitis patients often do not suffer from ocular disease alone; approximately 25% to 50% have an underlying systemic disease. HLA-B27 associated uveitis, CMV retinopathy and toxoplasmosis uveitis are among the most common causes.

About 4% of uveitis patients develop bilateral legal **blindness**. The major reasons for loss of vision in patient with posterior uveitis are macular oedema due to breakdown of the blood-retina barrier, direct inflammatory damage to the retina, or retinal vessels closure with consequent ischaemic changes.

aetiology

In about 33% of patients with intraocular inflammation **no specific cause** can be found. Investigations of serum antibodies titres give little information about the cause of uveitis. Paracentesis and aqueous analysis is recommended in the investigation of uveitis conditions with unknown cause. Cytological and immunological studies may be performed with the ocular fluids. Analysis of ocular fluids by the polymerase chain reaction tests seems to be a promising diagnostic technique. Aqueous and serum levels of **interferon** and **interleukin-2** are elevated in patients with uveitis. Elevated serum interferon may predispose the patient to more serious loss of vision.

Ultrasound biomicroscopy of the anterior segment is a useful tool in monitoring cases of anterior uveitis. In difficult cases, in which diagnosis can not be made by less invasive methods. Intraocular biopsy of choroido-retinal tissues may help in making the diagnosis. The technique of intraocular biopsy would also help in differentiating intraocular inflammatory lesions from neoplastic lesion presenting as intraocular inflammation. The risk of such a procedure should be weighed against its possible benefits.

Uveitis typically present for the first time in the 3rd or 4th decades. Uveitis presenting for the first time in the **elderly** in not rare. Idiopathic causes accounts for most cases. It may also be associated with systemic diseases (diabetes, sarcoidosis, hypothyroidism) and herpes zoster infection.

Masquerade syndrome refers to uveitis secondary to systemic disease. The commonest causes are intraocular lymphoma (Hodgkin and non-Hodgkin types) and melanoma. Diagnosis of CNS lymphoma is often difficult as all the signs and symptoms associated with disease is non-specific. Vitritis seems to be the only universal sign in CNS lymphoma. Lymphoma associated uveitis may be steroid responsive. Vitreous biopsy is recommended only in patients with abnormal looking vitreous cells, poor response to steroids or classical chorioretinal lesions in the presence of vitritis when progressive anterior segment inflammation disease threatens vision.

Uveitis in **children** is uncommon. Juvenile rheumatoid arthritis-associated uveitis is the main cause of children uveitis (41.5%), followed by idiopathic uveitis (21.5%), and pars planitis (15.3%). Patients with Juvenile rheumatoid arthritis-associated uveitis have the highest rate of complications which include cataract (71%), glaucoma (30%), band keratopathy (66%), and hypotony (19%).

treatment

The appropriate treatment and choice of **immunosuppressive** therapy for uveitis depends on cause as well as the extent and severity of the inflammatory process. Treatment should be commenced when sight threatening inflammation is present. Before considering and commencing immunosuppressive therapy for uveitis, infectious causes must be excluded. Poor visual prognosis in patients with posterior uveitis may be predicted by fluorescein angiography (macular ischaemia). Systemic immunosuppression in these patients should be used with caution.

Several other immunosuppressive agents have been used to treat uveitis. These agents include: steroids cyclosporin A, azathioprine which may be used either as an alternative to Cyclosporin A in combination with steroids or in addition to Cyclosporin A and steroid therapy. Treatment with systemic immunosuppression (with or without steroids) for chronic ocular inflammations does not appear to be associated with a higher risk of developing systemic side effects than treatment with systemic steroids only.

Immunosuppression can be achieved by **steroids** as primary therapy in acute / active stages of disease. Steroids may be administered by several routes. Topical steroids is often the main line of treatment of simple anterior uveitis. Care should be taken in prolonged topical steroids treatment as corneal stromal calcification may develop after topical steroid-phosphate medication, in spite of normal serum levels of calcium and phosphorus.

Uniocular, mild intraocular inflammation is often treated with **orbital floor** steroids to avoid systemically induced side effects. 48% of patients have a positive response to the orbital floor injections with a mean duration of

action of nine weeks. After a peribulbar injection of 5 mg of dexamethasone, an average intravitreal dexamethasone concentration is reached with a 75 times greater anti-inflammatory potency than physiological levels. Dexamethasone concentration in serum is also increased several folds. Peribulbar injection should not be considered as a local treatment as it results in serum levels comparable to those achieved by a high oral dose.

Long term control is then maintained with low dose **Cyclosporin A** as primary therapy, with or without low doses of steroids. Additional immuno-suppressants may be required when inflammation is present despite the low dose therapy with Cyclosporin A and steroids. Patients should be reassessed two weeks after induction of immunosuppression and thereafter at four week intervals until stability is achieved.

50% of patients, with posterior pole chronic uveitis, unresponsive to steroids alone are controlled on Cyclosporin A or a combination of Cyclosporin A and steroids. Cyclosporin A, in contrast to steroids, specifically inhibits the helper T-cells function mainly through the reversible inhibition of the interleukin-2 production. Low doses of Cyclosporin A (2.5-5.0 mg/kg daily) when used alone or in combination with other immune-suppressive agents seem to be effective in achieving inflammatory control with a favourable visual outcome and reduced renal complications.

The Cyclosporin A associated nephrotoxicity may also be further reduced if the drug treatment is initiated with a very low dose and incremental increase in the dose as required. Cyclosporin monitoring according to **T6** (6 hours after the morning dose) levels is associated with optimal immunosuppression and stable renal function. The Cyclosporin dose may be adjusted to achieve a Cyclosporin T6 level of 150 to 250 ng /ml.

A **sustained release device** for intra-vitreous cyclosporin treatment is proved to be effective in the treatment of posterior uveitis in animal models. Therapeutic levels of the drug remain in the vitreous for up to 6 months while blood levels remain very low. This method of treatment may be used in resistant cases in humans. Topical Cyclosporin A may be used in external eye inflammatory diseases. It seems to induce a marked reduction in the number of immunocompetent cells in the conjunctival epithelium and substantia propria

FK 506 is a new immune-suppressive agent isolated from Streptomyces tsukubaensis. It ha been shown that this agent has a similar immune-suppressive action similar to that of Cyclosporin. A multi-centre study has shown that treatment with FK 506 produced therapeutic effects in a dose dependent manner. The recommended dose of FK 506 for cases with refractory uveitis is 0.1-0.15 mg/Kg body weight /day. It is also recommended to maintain the trough of blood level between 15-25 ng / ml. Treatment may be associated with some side effects e.g. renal

impairment, neurological and gastrointestinal symptoms and also hyperglycaemia.

Monoclonal antibody (mab-Campath-1H) therapy is a new treatment that has recently been used successfully in the treatment of resistant cases of chronic inflammation. Campath-1 therapy may provide a long-lasting remission in patients with resistant intraocular inflammatory diseases. The mechanism of action of this new method is not clearly understood.

Some types of uveitis may be resistant to all methods of immunosuppression. **Intravenous immunoglobulin** can benefit some of these refractory cases. The use of Intravenous immunoglobulin for uveitis should be limited because of its cost, toxicity, the requirement for repeated administration.

Cystoid macular oedema is a common complication after uveitis. Optical coherence tomography appears to be, at least, as goof as fluorescein angiography in detecting cystoid macular oedema. The oedema may be treated with steroids, **Diamox**, vitrectomy, and grid laser photocoagulation. Acetazolamide appear to improve visual acuity in patients with chronic iridocyclitis with CMO, especially in patients younger than 55 years of age. The dose of acetazolamide should be adjusted according to the visual acuity and the amount of the cystoid macular oedema.

Pars plana vitrectomy with or without lensectomy may improve vision in patients with chronic uveitis. Pars plana vitrectomy also results in marked reduction in activity of the inflammation and also in the frequency or recurrences. Grid laser photocoagulation may be beneficial if performed at an early stage. A temporary increase in the oedema and in the patients central scotoma may occur in the early posterior operative period.

Specific types of uveitis

Toxoplasmosis

Ocular involvement in toxoplasmosis is often **congenital**. Recurrent toxoplasmosis has traditionally been considered to be due to a reactivation of congenital infection. Postnatal acquired infection may also occur.

Congenital toxoplasmosis may have long term ocular, endocrinological and neurological complications (e.g. pan-hypopituitarism, gonads failure with dwarfism, precocious puberty, thyroid deficiency, diabetes mellitus and obstructive hydrocephalus with dilated third ventricle and optic atrophy). Many children with congenital toxoplasmosis have severe retinal changes at birth. Chorioretinal and macular scars are the most common eye finding. The central, bilateral lesions, especially the macular ones, are more common in the congenital form, while the acquired form tends to be unilateral, discrete and solitary. Severe intraocular inflammation may also be associated with a higher incidence of retinal detachment and retinal breaks.

Acquired ocular toxoplasmosis should be considered in all patients with acquired disease, of any age group, that present with unilateral focal retinochoroiditis, even without associated old retinal scars in the posterior segment. Ocular involvement may complicate both the acute and the chronic phase of the disease. Treatment of these patients with anti-toxoplasmosis medications may help in preventing late choroido-retinal scars.

Acquired toxoplasmosis infection is often asymptomatic. The disease may also present with fever, malaise and lymphadenopathy. Acquired infection is often associated with **Ig M, A, and high levels of Ig G.** In patients with unilateral focal retinochoroiditis anti-toxoplasmosis Ig G and Ig M antibodies should be determined to help with the diagnosis. In acute acquired toxoplasmosis, the antibody titres are usually very high and therefore serology could be very useful in making the diagnosis.

The absence of circulating antibodies does not exclude ocular involvement. Clinical diagnosis can be confirmed by analysing the intraocular antibody response by the immunofluorescent technique. The intraocular response in these patients may be different from the serum response. Verification of toxoplasmosis infection can also be carried out by using the **polymerase chain reaction** test on small ocular samples from the aqueous or the vitreous.

Immunocompromised patients may develop **lethal** disseminated toxoplasmosis and / or toxoplasmic encephalitis. Ocular disease is not common in such cases. Ocular involvement may, however, be atypical with such features as bilateral multifocal lesions

Necrotising retinochoroiditis is the hallmark of ocular involvement. Retinal vasculitis with inflammatory signs in the anterior or the posterior segment may also be the only ocular manifestation in the early stages of the acquired disease. The **pathogenesis** of the disease is not completely understood. tissue destruction may be due to parasite -induced damage, damage from parasite-secreted toxins, immune mediated mechanism, or due to an anti-retinal autoimmune mechanism. The last mechanism of anti-retinal autoimmune mechanism has been suggested after some reports showed that there is an increased activity of anti-retina antibodies in the sera of toxoplasmosis patients.

Initial ocular involvement may be caused by the presence of the proliferating parasite in the eye. Administration of systemic steroids in the acute phase may be associated with more tissue damage. **Anti-Toxoplasma drugs** are often needed. The usual **indications** for treatment of ocular toxoplasmosis include:

1. Lesions in the papillo-macular area which threaten visual acuity.
2. Large retinal lesions (>2 disc diameters) with marked vitritis.
3. All lesions in immunocompromised patients.
4. It is also recommended that any active lesion in children should be treated, regardless of its location, as peripheral lesions in children could cause retinal detachment or macular dragging.

Despite prompt response to anti-parasitic drug therapy, prolonged treatment is usually required and patients may have retinitis reactivation after discontinuing treatment. Sulphadiazine, Pyrimethamine, Clindamycin, and Trimethoprim have traditionally been used in the treatment of toxoplasmosis. **Azithromycin** may also be used for patients who can not tolerated other methods of treatment. The drug, however does not appear to prevent recurrent disease. **Atovaquone** is a new drug that selectively inhibits mitochondrial electron transport chain in protozoa organisms. The drug has been used successfully in the treatment of pneumocystitis carinii Infections in AIDS patients. The drug also seems to be well tolerated as an alternative treatment for toxoplasmosis, when given 750 mg four times a day for 3 months. Mild side effects may occur in some patients.

The resistance to treatment in T. gondii is primarily due to macrophages activated by T-cell lymphokines, oxygen radicals and also cytotoxic T-cells. **Nitric oxide** also appears to play an important role in the protection against T. gondii. The inhibition of nitric oxide production in mice results in a marked increase in the symptoms of ocular inflammation. The expression of nitric oxide synthetase gene is inhibited by steroid. The use of anti-inflammatory drugs that have no negative effect on nitric oxide production should, therefore, be considered

Presumed ocular histoplasmosis Syndrome (POH Syndrome)

Ocular infection with the fungus Histoplasma capsulatum may present with the classical features of presumed ocular histoplasmosis syndrome in healthy patients, or with an acute onset of granulomatous uveitis or panophthalmitis in immunocompromised patients. Presumed ocular histoplasmosis syndrome is **characterised** by the following:

- Multiple choroidal spots (Histo spots).
- Peripapillary atrophic changes.
- Disciform macular scar.
- No vitritis.
- HLA-B7 sero-positivity.
- Residence in an endemic area (Midwest of the USA).

presumed ocular histoplasmosis -like retinopathy have also been reported in several conditions e.g. Fuchs' heterochromic cyclitis, punctate inner choroiditis and myopia. The characteristic features of the syndrome may be due to several different aetiological factors.

81% of patients retain a visual acuity of 20/20 in one eye for a period of 5 years, while 20% of patients retain this visual acuity in both eyes. The risk of choroidal neovascular membrane development and visual deterioration appears to be higher in patients with ocular histoplasmosis and Histo spots in the macular area. Estimates of an annual increase of the choroidal neovascular membrane in the second eye in patients with ocular histoplasmosis ranges from 2% to 12%.

Medical treatment with anti-fungal drugs does not seem to have any role in the treatment of the disease. systemic steroids may be given for the acute stages of the disease when there is macular lesion.

Choroidal neovascular membrane associated with ocular histoplasmosis can be treated with laser photocoagulation or by surgical excision. The visual results of eyes with presumed ocular histoplasmosis syndrome and extra- or juxta-foveal choroidal neovascular membrane that have been treated with laser photocoagulation show continued long term benefit from the treatment. Recurrences of the choroidal neovascular membrane occur in 23% of the treated eyes during a mean follow up period of 9.6 years, continued follow up is indicated.

Surgical excision of subfoveal choroidal neovascular membrane may be an effective therapeutic modality. Factors possibly associated with a favourable visual prognosis include younger patient age and the absence of previous laser photocoagulation.

Juvenile rheumatoid arthritis-associated uveitis

Juvenile rheumatoid arthritis-associated uveitis is a serious disease that is often associated with a guarded visual prognosis. The mean age of onset of uveitis is 13 years, with females having on average 4 years earlier onset of disease compared to males. 93% of patients have chronic, 5% have recurrent, and 2% have an acute monophasic disease course.

Male sex, shorter duration of uveitis, older age at disease onset and a shorter delay in presentation to a sub-specialist are good prognostic factors regarding the visual outcome. Cataract, glaucoma, and corneal changes are known complications. Disc neovascularisation may also occur in some children. The disc new vessels may respond to oral steroids. Secondary glaucoma occurs in about 14% to 27% of patients. Although some cases of uveitic glaucoma can be controlled with medical therapy, the long-standing effects are disappointing. The Molteno implant appears to be useful and well tolerated in controlling IOP in patients with glaucoma secondary to juvenile rheumatoid arthritis.

Systemic steroids may be needed in severe inflammation. Medium and long term treatment with systemic steroids is often associated with significant side effects. Cyclosporin A is effective in the treatment of refractory non-infectious uveitis in children. It is also safe for the short and medium term use. Continuos monitoring of kidney function, and blood pressure is important.

Pars planitis, and Intermediate Uveitis

The aetiology of intermediate uveitis is unknown in the majority of cases. The disease is probably caused by an **immune mediated disease**. HLA-DR2 is found in 50%-70% of white pars planitis patients compared to 20%-25% of control. 72% of patient are positive for HLA-DR I5. The disease is thought to belong to a group of HLA-DR I5-related disorders, which includes multiple sclerosis, optic neuritis, and narcolepsy. Raised serum levels of interleukin-8 are also found in patients with active intermediate uveitis of unknown cause. Raised level also seem to predispose patients to future systemic diseases.

Long term complications of pars planitis include cystoid macular oedema, epiretinal membrane formation, vitreous haemorrhage, cataract, glaucoma and peripheral neovascularisation at the vitreous base and also possibly multiple sclerosis.

Multiple Sclerosis has been reported to precede or follow pars planitis. The presence of peri-phlebitis increases the risk of developing optic neuritis or multiple sclerosis. Patients who are HLA-DR 15 positive and have intermediate uveitis may have systemic findings of other HLA DR 15 related disorders.

Cataract occurs in 36%-42% of patients with pars planitis due to both the chronic inflammation and the steroid treatment. Limited visual results is often due to CMO, epiretinal membrane or optic atrophy. Patients with significant cataract appear to be at a higher risk of developing retinal detachment. Firm vitreo-macular adhesions traction as well as the presence of inflammatory cells in the vitreous is believed to be the main cause of CMO.

A step-ladder approach, in treating pars planitis cases, by topical and regional steroids, NSAIDs, oral steroids, retinal cryotherapy and immunosuppressive therapy, has been recommended. Posterior sub-Tenon injection of Triamcinolone is effective in decreasing cystoid macular oedema and also improving visual acuity especially in young patients. This technique ensure a more direct contact between the medication and the globe and may lead to higher intraocular concentration. It may also reduce the need for systemic steroids and its complications. Sub-Tenon injection of steroids may be associated with increased IOP which might last for up to 3 to 14 weeks. Deep sub-Tenon injection of steroids does not appear to be associated with increased IOP.

Cryotherapy of the peripheral exudate can also be effective in steroids resistant patients. Peripheral cryotherapy appears to be effective in the treatment of peripheral neo-vascularisation, but may be associated with the development of rhegmatogenous retinal detachment. Peripheral scatter laser photocoagulation (with or without pars plana vitrectomy) is

also as effective as cryotherapy in causing regression of the peripheral neovascularisation, regression of the inflammatory process and the cystoid macula oedema, with less incidence of retinal detachment.

Behcet's disease

Behcet's disease, is the leading cause of endogenous uveitis in Japan. The disease is responsible for 10-15% of the acquired blindness in Japan. The most common ocular feature of Behcet's disease is recurrent attacks of anterior uveitis. Posterior ocular segment involvement may also occur and may cause blindness. Sudden onset of bilateral vision loss may be associated with bilateral retinal vascular disease and macular ischaemia. The conjunctiva is not often clinically involved in patients with Behcet's disease. However immuno-histochemical studies have shown some conjunctival abnormalities in active and inactive cases.

There are several sets of clinical criteria that has been established for the diagnosis of the Behcet disease. Most of these sets are based on finding some major and minor features of the disease. The disease can also be classified into complete or incomplete forms depending on the number of major or minor features present.

major features	minor features
• recurrent oral ulcers of the mouth	• arthritis • intestinal ulcers • vascular occlusion, obliteration or aneurysms • neuro-psychiatric symptoms.

The first two years after diagnosis is the most critical period for eye involvement. It is difficult to predict, in which patient the eyes will be involved and what the outcome will be. Young age is the most significant factor for eye involvement. Vascular thrombosis, central nervous system involvement and male gender are other risk factors.

The disease is known to be associated with HLA B51 in Japanese and in the Irish people. Auto-immunity to retinal specific antigens may play a role in the ocular inflammation. In the active stages of the disease, the ratio of D arabinatol (which is a major metabolite of candida species) / creatinine show higher values than in the controls. It is suggested that D arabinatol (or other metabolite of the candida species) may be related in part to the active phase of Behcet's disease.

Behcet disease is often treated with immunosuppressive drugs (e.g. steroids, azathioprine, or cyclosporin), or with cytotoxic drugs (e.g. chlorambucil, colchicine, or cyclophosphamide). Side effects from systemic use of the Cyclosporin may limit it's use. Intravitreal devices that provide sustained delivery of Cyclosporin are promising new treatment for chronic cases of uveitis in humans. Therapeutic levels of the drug remain in the vitreous for up to 6 months while blood levels remain very low. Treatment with Interferon alpha-2 with or without a small dose of

steroids may also be used with good results, and may also prevent retinal and optic nerve damage.

Birdshot Chorioretinopathy

Birdshot chorioretinopathy is characterised by bilateral, multiple white creamy patches at the level of pigment epithelium and choroid, vitritis, vasculopathy with leakage, cystoid macular oedema and optic disc oedema. The disease is more common in white, female patients in their 40s to 50s. It is presumed to be an auto-immune disease (**HLA-A29** is positive in 94% of patients). **Ocular Lyme disease** may also play a role in the pathogenesis of Birdshot chorioretinopathy. Abnormalities in the small choroidal vessels within the birdshot lesions have been demonstrated by Indocyanine green angiography. Th disease may be treated with systemic steroids or cyclosporin.

Treatment with systemic and periocular steroids has inconsistent results and may be associated with side effects. Vision can be preserved by the use of low dose (2.5-5 mg/Kg daily) of Cyclosporin A. This low dose of Cyclosporin A does not seem to be associated with significant nephrotoxicity or increased blood pressure. The dose of systemic cyclosporin may be considerably reduced if ketoconazole is added to the treatment, ketoconazole delays the metabolism of cyclosporin. This combination of treatment seems to be safe and effective.

Vogt-Koyanagi-Harada (VKH) syndrome

VKH Syndrome is a bilateral chronic panuveitis associated with systemic manifestation. The disease may present with ocular or extraocular manifestations, the following table demonstrate some of the common ocular and extraocular features:

Ocular manifestations	Extraocular manifestations
• Granulomatous uveitis. • Non-rhegmatogenous retinal detachment. • Optic nerve head swelling. • Choroidal neovascular membrane. • De-pigmentation of the posterior pole.	• Headache, and orbital pain. • Stiff neck. • Vertigo. • Hearing difficulties and tinnitus. • Sensitivity to touch to both hair and skin. • Vitiligo, alopecia and poliosis.

The aetiology of VKH is unknown but it is thought to be an auto-immune disease. It has been suggested that the cell mediated immune process involving melanocytes plays an important role in the pathogenesis of the disease. In clinical practice, detecting melanin laden macrophages in CSF provides useful information on the activity of the patient's systemic immunological reactions. HLA-DR 4 is significantly related to VKH Syndrome in Caucasian European patients.

In VKH syndrome 66% of patients retain visual acuity of 20/30 or better, the 3 main vision threatening complications are:

Cataract.
Glaucoma.
Choroidal neovascular membrane.

Risk factor for the development of cataract include long standing recurrence anterior uveitis and systemic steroids treatment for 6 months or more. If intraocular inflammation is controlled, cataract extraction operation can be safely and effectively performed with significant increase in the visual acuity.

Glaucoma occur in about 38% of patients with Vogt-Koyanagi-Harada syndrome, it may be an open angle or angle closure glaucoma due to pupillary block. Angle closure glaucoma may be the first manifestation of the disease. Shallowing of the anterior chamber may be caused by swelling of the ciliary body and cilio-choroidal detachment secondary to the uveitis. Many patients require surgical treatment e.g. laser or surgical peripheral iridectomy, broad iridectomy or filtration operations with or without anti-metabolites.

Eyes with choroidal neovascular membrane have a tendency for recurrent or chronic anterior or posterior inflammation. The choroidal neovascular membrane are often located in the peripapillary subfoveal or extra-foveal regions. Systemic pulse or posterior sub-Tenon steroids or occasionally laser photocoagulation may be required for the choroidal neovascular membrane.

Eye movement may be abnormal in patients with Vogt-Koyanagi-Harada, 53% of patients show horizontal jerky nystagmus that is completely inhibited with visual fixation and some patients have defective smooth pursuit movements with reduced gain on the side of nystagmus. Impaired eye movement in these patients may be due to asymmetry of vestibular function secondary to the labyrinthine inflammation.

The main line of treatment is systemic steroids. The dose needed to control the disease may be very high. Cyclosporin has also been successfully used.

Uveitis Associated with HLA-B27

HLA B27 is positive only in 10% of normal controls. About 50% of patients with acute anterior uveitis are associated with HLA B27. Acute anterior uveitis is the most common form of uveitis in HLA B27 positive patients. Most patients have associated systemic illnesses e.g. sero-negative spondylitis, inflammatory bowel disease and Reiter's syndrome. The systemic diseases are frequently undiagnosed before the onset of the uveitis.

Acute non-granulomatous anterior uveitis is the most common form of uveitis. HLA B27 associated uveitis may be associated with severe sight threatening posterior segment manifestations, as well as anterior segment manifestations in some patients.

The most common findings in the posterior segment include severe and diffuse vitritis, papillitis, retinal vasculitis and pars plana exudates. Cystoid macular oedema and epiretinal membrane are common causes of visual impairment in posterior segment disease. These patients may need to be treated by aggressive systemic immune-suppressive therapy. A subgroup of patients may have a severe and bilateral disease which may be associated with severe complications.

Sarcoidosis

Sarcoidosis is a **multi-systemic** disease of unknown aetiology. The cause of the disease is not completely known. Infections and environmental factors may play a role in the pathogenesis of the disease. Other aetiological factors e.g. Epstein Barr virus, atypical mycobacterium and fungi have been suggested. The immuno-pathogenesis of the disease is thought to be mediated via antigenic activation of alveolar macrophages and T lymphocytes.

Ophthalmic involvement in the disease is reported to be between 25% to 50%. The onset of ocular involvement in sarcoidosis is often bilateral, it may precede or follow the systemic disease. Ocular sarcoidosis may also be isolated. The ocular prognosis of sarcoid uveitis does not appear to be related to the extent of the disease. The presence of extraocular manifestations of the disease does affect the visual outcome. The presence of uveitis seems to increase the risk of having CNS involvement.

Most patients have **anterior or intermediate uveitis** alone. 91% have chronic disease, 7% have recurrent flares and only a minority of patients have a monophasic acute course of the disease. **Choroiditis** is frequently found in patients with posterior segment inflammation associated with the disease. The most frequent pattern is well circumscribed pre-equatorial choroidal de-pigmentation that becomes associated with retinal pigment epithelial hyper- or hypo-pigmentation with time. Extensive confluent choroiditis with retinal pigment epithelial changes resembling serpiginous choroiditis may also occur. Patients with sarcoidosis may also present with multiple placoid choroidal lesions resembling acute posterior multifocal pigment epitheliopathy.

Retinal vasculitis may also occur. It may be ischaemic or non-ischaemic. The ischaemic type is often due to localised thrombosis. The disease should be considered in the differential diagnosis of ischaemic retinal vasculitis. Uhthoff phenomena is typically associated with demyelinating optic neuritis. The phenomena has also been described with sarcoidosis.

Orbital sarcoidosis is rare and almost always unilateral when it is not involving the lacrimal gland. Orbital sarcoidosis may be associated with painful or painless extra-ocular muscles involvement with diplopia. Sarcoidosis of the anterior visual pathway may also present with Uhthoff phenomena.

diagnosis

There is no pathognomonic feature of ocular sarcoidosis. The definitive diagnosis of the disease can only be made by a positive **biopsy** showing a non-caseating granulomatous, non-infectious inflammatory process.

Chest x-ray often show hilar lymph nodes enlargement, with nodular shadowing or fibrosis of the lung. **Serum angiotensin converting enzyme** levels also reflect the activity of the disease (it is elevated in 30-80% of clinically active disease). Normal levels, however, do not exclude the disease especially in isolated organ involvement as in ocular disease. false positive results may also occur in some other conditions e.g. tuberculosis, histoplasmosis, and Hodgkin disease). **Gallium scans** have been shown to be useful in the diagnosis of this condition, the scan typically show increased uptake in the lungs, mediastinum, parotid and salivary glands. The combination of raised serum angiotensin converting enzyme and whole body gallium scan is considered sensitive and specific enough for the diagnosis of the disease even if the chest X-ray is normal. In suspicious cases, **trans-bronchial lung biopsy** can establish the diagnosis of sarcoidosis by showing a non-caseating epithelioid granuloma. **Pulmonary function tests** may also show restrictive features. The **Kveim test** is now rarely used because of the risk of HIV transmission.

treatment

The main treatment in sarcoidosis is by systemic, topical, or orbital floor injection **steroids**. Treatment is often indicated for several months as premature cessation of the treatment may result in flare up of the disease. **Methotrexate** also seems to be effective as a steroid sparing drug.

Human T-cell lymphotropic virus type 1-associated uveitis

Human T-Cell lymphotropic virus type 1 is a retrovirus that is highly endemic in the Caribbean islands, parts of central Africa and south west Japan. The virus is a well known cause of:

1. Adult T-Cell leukaemia and lymphoma.
2. Certain types of (idiopathic) uveitis.
3. Non-neoplastic inflammatory disorder (e.g. myelopathy and tropical spastic paraparesis).

The uveitis associated with this virus often affects one or both eyes in middle-aged adults, it may be an isolated ocular condition or may be associated with other conditions (e.g. myelopathy).

Uveitis seen in seropositive patients have significantly higher incidence of floaters, vitreous opacities, retinal vasculitis and intermediate uveitis than in sero-negative patients. It is often mild to moderate and resolves in a few weeks with steroid treatment. About 14.5% of patients develop vascular lesions in the retina (grey white granular deposits scattered on the retinal veins or arteries in the posterior pole). These lesions often resolve either spontaneously or with steroid treatment. Human T-Cell lymphotropic virus infection can also present by ocular inflammation similar to acute retinal necrosis.

Onchocerciasis

Onchocerciasis is a major global public health problem. It is estimated that about 18,000,000 individuals affected with the disease with a further 68,000,000 at risk of the infection. Blindness prevalence exceeding 10% have been reported in heavily affected populations. It is thought that the presence of micro-filaria is important for the induction of the disease but the progression of the disease may be related to the micro-filaria or to other immunological factors. The main **drugs** used in the treatment of the disease are:

- DEC
- Suramin sodium
- Ivermectin
- Amocarzine

DEC has been the most frequently used drug in onchocerciasis. It is a micro-filaricidal that regularly produces a marked eosinophilic reaction. The side effects of the drug are dermatitis, headache and vertigo. It has also been suggested that DEC might also result in impairment of vision, in particular through the precipitation of optic neuropathy. Suramin sodium treatment may be associated with photophopsia, uveitis, optic atrophy, vortex keratopathy, and also hyperopic refractive shift. These ophthalmic side effects seem to be common but they are not considered a dose limiting toxic reactions. Administration of suramin requires hospital admission and monitoring since it is given intravenously. The drug may also cause reversible nephrotoxicity and idiosyncratic reactions in some people. Ivermectin improves the anterior segment lesions and also reduces the incidence of optic atrophy. The drug can be given in four 6 monthly doses followed by annual doses. The response of posterior segment lesions are variable and there is a highly significant rate of deterioration and emergence of new lesions. Ivermectin does not appear to precipitate or exacerbate optic neuritis unlike the drug DEC. Amocarzine is a new macro- and micro-filaricidal drug.

Trauma Of The Eye And The Orbit

Traumatic hyphaema

Trauma is the commonest cause of hyphaema in children. Child abuse, and tumours e.g. retinoblastoma and xanthogranuloma are other cause of hyphaema in children. In adults the disease can also be caused by iris neovascularisation and by abnormal vascular tuft on the pupils. Raised IOP and corneal staining are major complication of hyphaema. The IOP may initially be raised in large hyphaema. Some eyes may also show varying degrees of hypotony after the initial IOP rise. Corneal staining occurs in about 5.6% of all cases of hyphaema. The incidence of the disease is increased in more than 50% hyphaema and also in hyphaema of longer than 6 days of duration.

Secondary hyphaema is a major complication in traumatic hyphaema. It occurs in about 22% of cases. Secondary haemorrhage seems to be significantly more frequent in:

- African patients
- Eyes with initial visual acuity of 20/200 or less.
- Initial hyphaema more than one third of anterior chamber.
- Delayed attention for more than one day after injury.
- Elevated intraocular pressure at the time of first examination.
- Sickle cell trait disease .
- Patients receiving anticoagulants.

Secondary haemorrhage seems to be very rare in white children (who do not take aspirin). The release of melanin into the anterior chamber during ocular trauma may be partly responsible for the susceptibility of darker-pigmented individuals to more serious complications following a traumatic hyphaema, which may be due to occlusion of the trabecular meshwork with melanin-laden macrophages.

Most ophthalmologists admit patient with traumatic hyphaema for observation. Close Outpatient follow-up of traumatic hyphaema appears to be safe and effective. **Hospitalisation** for hyphaema does not appear to decrease the rate of re-bleeding. Decreased vision with traumatic hyphaema generally results from other causes not affected by Inpatient management. Outpatient treatment needs daily examination and measuring of IOP. Outpatient observation is not recommended in uncooperative patients. Hospitalisation is recommended in cases with sickle cell disease, secondary bleeding, more than 50% hyphaema, and when there is a suspicion of penetrating injury.

The use of systemic **anti-fibrinolytic drugs** in the treatment of traumatic hyphaema is controversial. Aminocaproic acid, is an anti-fibrinolytic agent which reduces the incidence of re-bleeding when given orally or topically. The drug is believed to stop clot lysis. It is not recommended in cases with more than 75% of hyphaema.

Surgical evacuation of the hyphaema and blood clot is indicated in resistant cases, cases with more than 75% of hyphaema, cases with increased IOP resistant to medical treatment. Evacuation may be carried out by a paracentesis or by a two ports vitrectomy approach. Surgical evacuation is better delayed for 4 days after the onset of the disease.

Bungee jumping

Bungee jumping may be associated with several complications. Scattered superficial retinal and pre-retinal haemorrhages and cotton wool spots in the macular areas of each eye have been reported in patient who noticed blurred vision after jumping head first. Sub-conjunctival haemorrhage may also develop. The retinopathy may be typical of Purtscher's traumatic retinopathy which is thought to be due to an abrupt rise of intravascular pressure in the upper part of the body. Ocular morbidity in bungee jumping may also be due to the cord itself. Corneal lacerations, hyphaema, angle recession, irido-dialysis, lens subluxation and retinal detachment have been reported

Air bag injuries

The frequency of air bag eye injuries is increasing, even after a low impact collision, e.g. during parking. Corneal endothelial cell loss, complete angle recession, multiple iris sphincter ruptures, loss of accommodation, corneo-scleral laceration, and cataract have all been reported in patients following an air bag eye injury. Posterior segment injuries may also occur. Commotio retinae, choroidal rupture, intraretinal, subretinal and vitreous haemorrhage, retinal tears, and retinal dialysis with retinal detachment have all been reported before. Patients sustaining air bag injuries should undergo complete ocular examination. Most of ocular injuries are due to the mechanical force. Corneal injury may also result from the release of the powder used in cars air bag. Corneo-scleral laceration due to passenger-side airbag inflation has also been described.

Traumatic optic neuropathy

In traumatic optic neuropathy, mega-dose of steroids and optic nerve canal decompression have been advocated for the treatment. Visual results seem to be better in patients younger than 4o years of age than in older patients. Interval between the injury and surgery, preoperative visual acuity, and the optic canal fracture does not seem to affect the outcome. A recent comparative non-randomised study found no clear benefit for either corticosteroid therapy or optic canal decompression surgery. It was concluded, in this study, that it would be reasonable to decide to treat or not treat on an individual patient basis.

Recurrent corneal abrasions

Recurrent corneal erosions may be due to corneal **trauma** or basement membrane **dystrophy**. Patients with epithelial basement membrane dystrophy are more likely to present with chronic recurrent symptoms than trauma related cases. Epithelial basement membrane dystrophy is also a risk factor for failure of treatment. Chronic recurrent corneal ulceration may also be associated with smoking amphetamine (known as ice) abuse in healthy people. Corneal vascularization and oedema may also be associated with the ulceration. Complications of recurrent corneal epithelial erosion are infrequent, they include anterior uveitis, stromal scarring, and stromal infiltrates.

- **surgical treatment**

The commonest method of treatment of traumatic corneal abrasion is by topical antibiotics, cycloplegic, and **padding** of the eye. Many patients report loss of vision, blurring of vision or intermittent fuzziness of vision in the uncovered eye while wearing an eye patch. This seems to be more common if the dominant eye is covered. These visual symptoms may be due to binocular rivalry suppression by the patched eye. Patients should be informed about this possibility as these visual symptoms may occur while driving.

Although many patients with recurrent corneal abrasions respond well to conservative treatment, resistant cases may require further intervention. Many methods have been tried for the treatment of resistant recurrence cornea abrasions including anterior keratectomy, micro-diathermy, needle anterior stromal puncture, excimer laser photo-keratectomy and YAG laser anterior stromal puncture.

Anterior stromal puncture may be used in recurrent corneal abrasions, and also in bullous keratopathy. Anterior stromal puncture can be carried out on the slit lamp in the following way:

- A 20 gauge ½ inch needle is used to create two to three punctures per a square millimetre in the corneal epithelium.
- The penetration depth of the needle is often about ¼ of the corneal stromal thickness.
- The needle is held at 60 degree angle to the corneal surface.
- About 200 punctures are carried out depending on the surface area of the epithelial bullae.
- Systemic analgesics and topical antibiotics are used after the treatment .

A new technique, YAG **laser** , or excimer laser photo-induced corneal adhesions, has been described. A number of 0.4 to 0.5 m J. pulses of laser is applied to the Bowman's layer through an intact epithelium. Electron microscopy studies show minute foci of disruption in the

Bowman's layer with new collagen formation and fine fibrils connecting the basal epithelial cells to the new collagen. The minimal discomfort associated with the YAG laser photo-induced adhesions treatment may be advantageous compared with the severe pain reported by patients during the re-epithelialisation period after excimer laser treatment.

Photo-therapeutic keratectomy, in selected patients may also be used. The creation of a smooth new bed for migrating epithelium may result in new hemidesinosomal adhesion complexes. A combination of PRK and Photo-therapeutic keratectomy is effective in the alleviation of symptoms and prevention of recurrences of corneal erosion. Extensive excimer laser ablation is required to prevent recurrence and to alleviate symptoms completely.

Amniotic membrane transplantation may be considered an alternative method for treating persistent epithelial defects and sterile ulceration that are refractory to conventional treatment and before considering treatment by conjunctival flaps or tarsorrhaphy.

Blow out fracture

Orbital floor fracture is typically associated with:

- restricted eye movements, mainly upwards and laterally.
- subcutaneous emphysema.
- decreased sensation in the distribution of the infra-orbital nerve.
- enophthalmos.

When **hypertropia** and vertical diplopia are noted after orbital trauma a posterior orbital floor fracture should be suspected. Characteristic features on CAT scan may include depressed fracture of the orbital floor, extending posteriorly to the maxillary sinus. The inferior rectus muscle may also appear to loop down in the depressed fracture and then upward to insert in the globe at a very steep angle. Infra-duction may be diminished due to changes in the effective origin and insertion of the inferior rectus muscle.

Trapdoor-type fractures, usually involving the orbital floor, are common in **the paediatric age group**. These features may be small with minimal soft-tissue incarceration, making the findings on computed tomography scans quite subtle at times. Marked motility restriction and nausea/vomiting should alert the physician to the possibility of a trapdoor-type fracture and the need for prompt surgical intervention. Missed orbital wall fracture may cause a **post-enucleation syndrome**. All patients presenting with this syndrome with a suggestive trauma history should have a CAT scan for the orbit to exclude this treatable condition.

Orbital volume measurements by CAT Scan is important in predicting whether surgical treatment would be needed. Orbital volume measurements may show discrepancy, between the two eyes, in patients who have orbital floor fracture. Large discrepancy between the two orbits indicates that surgical treatment may be needed.

Orbital floor exploration and repair should be undertaken if the motility disorder persists for 10 to 15 days. Orbital floor fracture with entrapment of the inferior rectus muscle may be associated with **oculo-cardiac reflex**. Patients may present with bradycardia, nausea, and syncope associated with upward gaze. The finding of oculo-cardiac reflex in patient with orbital floor fracture should be considered as an indication for urgent surgical repair.

Orbital floor implants may be used in the treatment of orbital floor fracture. Complications of orbital floor implants include: implant extrusion, motility restriction, haemorrhage about the implant causing proptosis and diplopia, Infection, and Mydriasis (mainly due to manipulations of the inferior oblique muscle, and the ciliary ganglion). Medopar is a high density porous polyethylene material that has been used successfully in the treatment of orbital and facial fractures repair. The materiel has the

following advantage: low cost, well tolerated, non antigenic, good resistance to infections, it can also promotes tissue in-growth, and has the ability to pass sutures through it.

Post-traumatic endophthalmitis

Post-traumatic endophthalmitis, generally, has poor results partly because it includes poly-microbial infections among other causes. Endophthalmitis caused by coagulase negative seems to be associated with the best visual outcome. Intraocular foreign bodies, rural areas settings and delayed primary repair, and disruption of the crystalline lens are associated with increased risk of endophthalmitis. Streptococcal organisms are the most common infecting organism in children (unlike adults where the commonest organism is Staphylococcus epidermidis and Bacillus). Bacillus cereus is often associated with very poor visual and anatomical outcome because the organism produces a number of exotoxins that often result in cell death and tissue necrosis.

A favourable outcome may be achieved by prompt pars plana vitrectomy and intravitreal antibiotics. Intravitreal broad spectrum antibiotics remain the treatment of choice for this condition. Oral Ciprofloxacin also achieves intravitreal levels exceeding minimal inhibitory concentration for common ocular pathogens suggesting that this drug could be a good prophylactic measure in post-traumatic endophthalmitis. Ciprofloxacin has a good activity against staphylococcus, bacillus and most gram negative organisms including Pseudomonas species.