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Drug-Induced Glaucomas
Mechanism and Management

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Abstract

Glaucoma comprises a heterogeneous group of diseases that have in common a characteristic optic neuropathy and visual field defects, for which elevated intraocular pressure is the major risk factor. The level of intraocular pressure within the eye depends on the steady state of formation and drainage of the clear watery fluid, called the aqueous humour, in the anterior chamber of the eye. An obstruction in the circulatory pathway of aqueous humour causes an elevation in intraocular pressure. Because intraocular pressure is the most modifiable parameter, therapeutic measures (medical and surgical) are aimed at reducing the pressure to protect against optic nerve damage. Glaucomatous optic neuropathy results from degeneration of the axonal nerve fibres in the optic nerve and death of their cell bodies, the retinal ganglion cells. Clinical examination of the optic nerve head or disc and the peripapillary nerve fibre layer of the retina reveals specific changes, and the resulting visual field defects can be documented by perimetry.

Glaucoma can be classified into four main groups: primary open-angle glaucoma; angle-closure glaucoma; secondary glaucoma; and developmental glaucoma. Drug-induced glaucoma should be considered as a form of secondary glaucoma because it is brought about by specific systemic or topical medications. Although there is a high prevalence of glaucoma worldwide, the incidence of drug-induced glaucoma is uncertain.

Drugs that cause or exacerbate open-angle glaucoma are mostly glucocorticoids. Several classes of drugs, including adrenergic agonists, cholinergics, anticholinergics, sulpha-based drugs, selective serotonin reuptake inhibitors, tricyclic and tetracyclic antidepressants, anticoagulants and histamine H_1 and H_2 receptor antagonists, have been reported to induce or precipitate acute angle-closure glaucoma, especially in individuals predisposed with narrow angles of the anterior chamber. In some instances, bilateral involvement and even blindness have occurred. In this article, the mechanism and management of drug-induced glaucomatous disease of the eye are emphasised. Although the product package insert may mention glaucoma as a contraindication or as an adverse effect, the type of glaucoma is usually not specified. Clinicians should be mindful of the possibility of drug-induced glaucoma, whether or not it is listed as a contraindication and, if in doubt, consult an ophthalmologist.

This review focuses on drugs used currently in medical practice that are known to alter one or more of the cardinal features of glaucomatous disease of the eye and/or can induce or exacerbate the pre-existing process of glaucoma, diagnosed or undetected. We review the current concepts and perspectives of this blinding disease, and describe the different types and mechanisms of glaucoma so that clinicians can relate these to the mechanism by which a particular drug can induce glaucoma or augment the pathogenesis of the disease and can thus institute appropriate management.

This review is based in part on papers published in peer-reviewed, ophthalmic and non-ophthalmic scientific journals indexed by the Medline database, drug product inserts, and the 56th edition of the Physicians Desk Reference.[1] Searches included va-

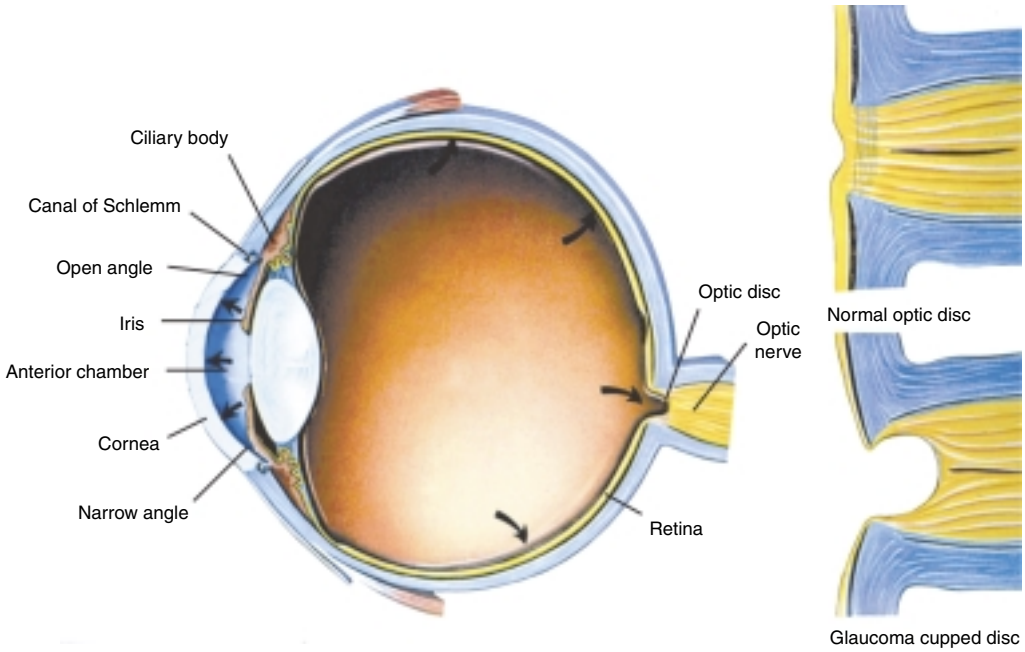

Fig. 1. Diagrammatic representation of human eye depicting structural alterations in glaucomatous disease. The anterior chamber contains aqueous humour that originates from the ciliary body. Obstruction in the drainage pathway of the aqueous humour results in an increase in intraocular pressure (shown by arrows) and leads to excavation or cupping of the optic disc (diagrammatic representation comparing a normal optic cup and a glaucomatous cupped disc on the right side). The cupping or atrophy of the disc is characteristic of glaucomatous optic neuropathy. The diagram also illustrates the difference between open and narrow angle of the anterior chamber; hence the terminology open-angle and closed-angle glaucoma (modified from a poster from Alcon Laboratories Inc., Fort Worth, Texas, USA, with permission).

rious combinations of terms such as glaucoma, primary open-angle glaucoma, angle-closure glaucoma, drug-induced glaucoma, glucocorticoid, epidemiology, toxicity, chemically induced, pathology, physiopathology and human. Selected articles cited in *Drug-Induced Ocular Side Effects*[2] were also searched. Citations were included at the authors' discretion.

1. Glaucomatous Disease of the Eye

1.1 Historical Background

The term glaucoma originates from the Greek word glaukos, meaning bluish-grey. This term was used originally by Hippocrates (460–377 BC), probably because of the appearance of the cornea that occurred with an acute rise of intraocular pressure (IOP). In the 1820s, the term glaucoma became synonymous with hardness of the eye (i.e. high IOP) and resulting loss of visual function. Definitive signs of glaucoma were not established until the 1850s, when the ophthalmoscope became available as a clinical tool. Since then, glaucoma has been defined classically as a state of IOP that is inconsistent with the normal structures and function of the eye,[3] but recently this definition has changed.

1.2 What is Glaucoma?

Glaucoma is currently defined as a heterogeneous group of diseases that have in common a characteristic optic neuropathy and visual field defects, for which elevated IOP is the primary risk factor (figure 1). These cardinal features of glaucoma, and their severity, vary in relation to each other.

1.3 Epidemiology, Prevalence and Risk Factors for Glaucoma

Some 67 million persons worldwide have glaucomatous disease of the eye;[4-9] of these, 7 million are blind in both eyes.[10,11] In the US, some 3 million have the disease (one report states that more than 15 million Americans may have glaucoma[12]), half do not even know they have glaucoma, 50 million are at risk according to National Eye Institute estimates,[5] and approximately 120 000 are blind as a result of the disease. These figures probably do not include drug-induced glaucoma because precise information on the incidence of glaucoma as a result of local or systemic therapies is uncertain. Among Caucasians aged 40 years or older, a prevalence of 2.1% has been reported in population-based studies. Primary open-angle glaucoma (POAG) is most prevalent in older individuals (3–8 times higher in those aged ≥70 years versus 40 years) and is much higher in the Black population (4–6 times more than Caucasians and probably even higher in the Caribbean[12]), which is reflected by a 10% incidence in Blacks over the age of 70 years. The risk factors for glaucoma (mainly open-angle glaucoma) are summarised in table I. Recent evidence suggests that although the relationship between POAG and systemic blood pressure is complex, low perfusion pressure (i.e. blood pressure minus IOP) in the optic nerve and ganglion cell layer of the retina is strongly associated with increased prevalence of the disease.[13,14]

Table I. Risk factors for open-angle glaucoma

Increased intraocular pressure
Altered optic cup-to-disc ratio
Peripapillary atrophy
Optic disc haemorrhages
Age >40 years
Ethnicity (Blacks 4–6 times greater risk vs Whites)
Family history (5 times increase)
Myopia (80% vs 30% in normal eyes)
Pseudoexfoliation syndrome
Pigment dispersion syndrome
Systemic diseases: diabetes mellitus, hypertension, autoimmune disease, thyroid defect
Low vascular perfusion pressure
Low cerebrospinal fluid pressure
Exotoxins (e.g. sanguinarine)
Low pituitary hormone level
Ocular trauma

Table II. Risk factors for acute closed-angle glaucoma

Ethnicity (Eskimo, Asian and Hispanic at increased risk)
Narrow angle of anterior chamber
Shallow anterior chamber depth
Hyperopia
Nanophthalmos (small eye)
History of attack in fellow eye
Positive family history of angle closure
Elderly
Female sex
Use of drugs that cause pupillary dilation and excitatory situations

Angle-closure glaucoma is a disease with acute onset that occurs in 1 of 1000 Caucasians, about 1 in 100 Asians (especially Mongoloids) and Hispanics, and 2–4 of 100 Inuits (Eskimos).[4,15] However, the incidence of angle-closure glaucoma in Blacks is low.[16] Additional risk factors for angle-closure glaucoma are provided in table II.

1.4 General Mechanisms of Glaucoma

1.4.1 Intraocular Pressure (IOP)

The average normal IOP in the human eye is 14.5mm Hg (range 9–21mm Hg). The level of IOP can vary slightly depending on age, corneal thickness (thinner in myopic eyes and after laser *in situ* keratomileusis surgery; thicker in hyperopic eyes and in eyes with corneal decompensation), method of measurement and interobserver variation. Certain drugs and the lifestyle of an individual can induce variations in normal IOP (table III). The steady state of IOP is maintained by the continuous formation and drainage of aqueous humour, the clear watery fluid contained in the anterior segment of the eye. Aqueous humour is formed by the ciliary epithelium, and the rate of formation (approximately 2 μL/min) is largely dependent on the process of active secretion. The major drainage pathway of aqueous humour consists of structures located in the angular region of the anterior chamber of the eye – the trabecular meshwork and Schlemm's canal system – that is responsible for some 90% of outflow of

aqueous humour from the eye.[17] Accessory drainage pathways include the uveoscleral system, which accounts for approximately 10% of the outflow in normal eyes, with a negligible contribution by transcorneal and transvitreal flux (figure 2). Obstruction in the circulatory pathway of aqueous humour causes elevation of IOP.

Elevation in IOP is the major risk factor for glaucoma. IOP is the most modifiable parameter in the treatment of the disease, and its modification is aimed at protecting the optic nerve from damage. Currently, treatment options are medical therapy and surgical regimens (e.g. incisional surgery to facilitate aqueous humour drainage, lasers and ciliary body ablation). Pharmacologically, many drugs are available that either reduce production of aqueous humour by the ciliary body or increase drainage of this fluid; e.g. β-adrenergic antagonists reduce aqueous production; cholinergic (miotics) and adrenergic agonists increase outflow; hyperosmotic drugs increase fluid reabsorption at the ciliary body; and carbonic anhydrase inhibitors decrease aqueous production. α-Adrenergic agonists decrease formation of aqueous humour and increase its outflow. The newest class of drugs, prostaglandin analogues, increase outflow of aqueous humour mainly through the uveoscleral pathway.[4,18]

Table III. Dose-dependent variations in normal intraocular pressure (IOP) due to food, drugs and endogenous hormonal production

Substance	Effect
Alcohol (dilution dependent)	Transient decrease in IOP, more in glaucoma
Marijuana, heroin	Short-term decrease in IOP
Tobacco	Transient increase in IOP, more in glaucoma
Caffeine	Transient rise in IOP then levels off
Lysergide and calcium channel blockers	Increase IOP
Corticosteroids	Increase IOP and can induce glaucoma
Topical cyclopentolate	Transient increase in IOP
Endogenous catecholamine	Transient decrease in IOP, but may induce glaucoma in eyes with narrow angles
Diuretics	Decrease IOP
Dietary/herbal supplements	Not known

1.4.2 Human Optic Nerve

The hallmark of glaucomatous damage to the eye is atrophy of the optic nerve, which is attributed mainly to the major risk factor, raised IOP. The normal human optic nerve consists of approximately 1.2 million axons, the cell bodies of which are the ganglion cells located in the retina. The optic nerve axons are separated into fascicles lined by astrocytes. The nerve head (also known as optic disc or papilla) is slightly oval, approximately 1.5mm in diameter, and has a physiological depression or optic cup (figure 3, figure 4). The neuroretinal rim is the tissue region between the optic cup and the disc margin. For descriptive purposes, the optic nerve is divisible into four regions: from anterior to posterior these are the nerve fibre layer, the prelaminar layer, the laminar layer and the retrolaminar portion.[19]

Glaucomatous optic neuropathy is a progressive disorder that results from death of ganglion cells in the retina and the associated loss of their axons within the optic nerve. As the nerve fibres degenerate, the neuroretinal rim of the optic nerve head thins, which results in enlargement of the optic cup and a larger cup-to-disc ratio (figure 5). In glaucoma, the cup-to-disc ratio usually increases above 0.5. The optic cup gradually becomes deeply excavated as a result of degeneration of the axons and backward bowing of the connective tissue plates of the lamina cribrosa, through which the optic nerve fibres pass to reach the lateral geniculate body in the brain (figure 6).

Clinical examination of the optic disc by direct ophthalmoscopy, indirect ophthalmoscopy, slit-lamp biomicroscopy using a fundus lens or other modalities is crucial to detect glaucomatous changes.[4] Particular attention should be given to size, shape, colour (pallor) and margin of the disc, excavation in the optic nerve head, peripapillary atrophy, disc splinter haemorrhages, and asymmetry of cup-to-disc ratio between the two eyes of the patient; the characteristic changes are appended in table IV. In normal eyes, the neuroretinal rim is usually widest in the region of the inferior disc, followed by the superior, nasal and temporal regions (the ISNT rule). Because the sequence of damage to specific regions of the disc correlates with the devel-

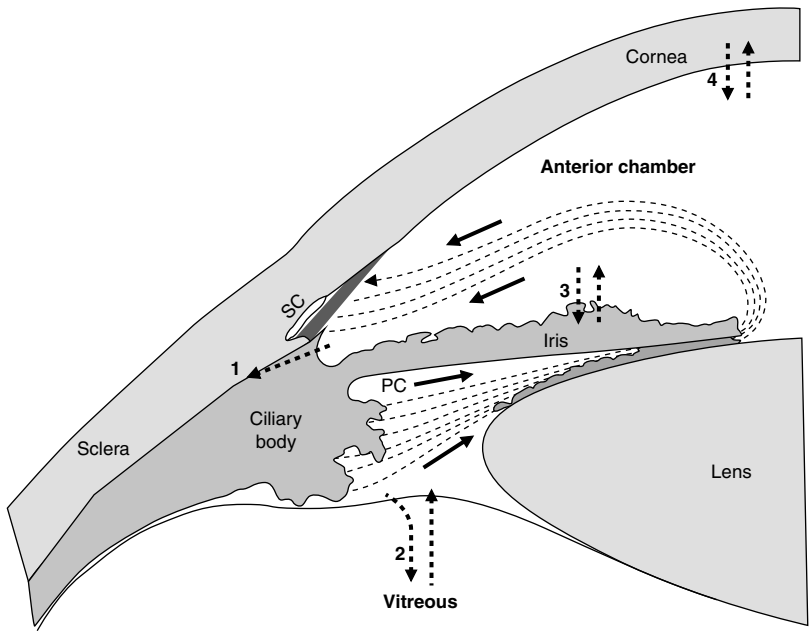

Fig. 2. Diagrammatic representation of the drainage pathways of aqueous humour. The aqueous humour is secreted into the posterior chamber (PC) by the ciliary processes and flows into the anterior chamber through the pupil. In normal eyes, the main drainage route for the bulk outflow consists of the trabecular meshwork/Schlemm's canal (SC) system. Subsidiary drainage routes include: (1) the uveoslceral pathway, i.e. through the anterior face of the ciliary body into the suprachoroidal space; (2) exchange of fluid across the anterior vitreous face; (3) exchange of fluid across the iris vessels; and (4) exchange of fluid across the corneal endothelium. Because net loss is approximately equivalent to net gain in the two-way exchange process, the role of routes 2, 3 and 4 in the drainage of aqueous humour is regarded as insignificant (reproduced from Tripathi and Tripathi,[17] with permission).

opment of visual field defects, the changes in thickness of the inferior and superior temporal regions of the neuroretinal rim are most significant in the diagnosis of early glaucomatous damage.[20] Clinicians must realise that disc appearances do change with time and age of the patient, and a chronological photographic or computerised record visual, as well as changes in the field (see section 1.4.4) is regarded as most useful in follow-up of the progression of the optic nerve changes.

1.4.3 Clinical Evaluation of Retinal Nerve Fibre Layer

Examination of the peripapillary nerve fibre layer of the retina, especially by using a red-free filter, stereoscopic biomicroscope with a wide slit-beam and posterior pole (fundus) lens, can provide detailed information. Retinal nerve fibre layer defects can be categorised as focal and diffuse. Focal abnormalities manifest as slit-like grooves or wedge de-

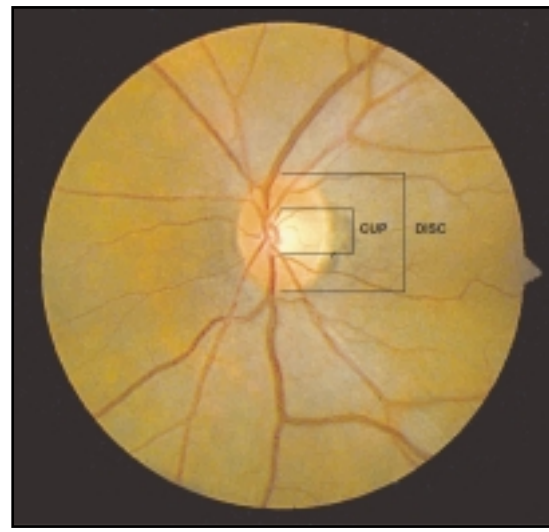

Fig. 3. Fundus photograph of optic disc in a normal human eye. The physiological cup and the optic disc are denoted. Retinal vessels radiating from the optic nerve are also visible.

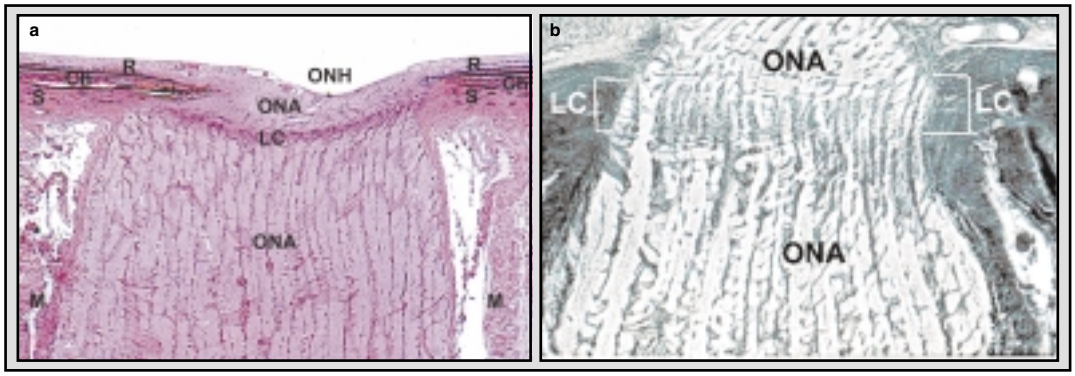

Fig. 4. (**a**) Longitudinal section of the normal optic nerve and its connection with the retina. The axons originate from the retina (R) and pass through the cribiform plate of the sclera (S), which consists of a stack of approximately ten fenestrated connective tissue sheets, known collectively as the lamina cribrosa (LC). At this location, the nerve fibres become ensheathed by myelin produced by oligodendrocytes. Meningeal sheaths (M), that extend from the brain, cover the optic nerve and merge with the sclera. The optic nerve, which comprises axons, glial cells and connective tissue components, receives a rich vascular supply from the central retinal artery, short posterior ciliary arteries and, posteriorly, from branches of the meningeal arteries. (**b**) Silver-stained preparation of optic nerve showing axons passing through the stacks of the collagen and elastic connective tissue of the lamina cribrosa, not readily apparent in (**a**). **Ch** = choroid; **ONA** = optic nerve axons; **ONH** = optic nerve head.

fects. Although diffuse nerve fibre loss is more common than focal loss in early stages of glaucoma, it is more difficult to observe by ophthalmoscopy and can be recorded by fundus photography.[4]

Specialised technology is available to evaluate optic nerve and retinal nerve fibre layer damage.[4] Because assessment of the optic nerve and the retinal nerve fibre layer can be subjective and open to inter- and intra-observer variation, image analysis systems have been developed to provide quantitative assessment of various anatomic parameters.

Confocal scanning laser ophthalmoscopy can create a three-dimensional image of the optic nerve head. The acquired images are stored as computer files and used for data analyses on parameters such as cup area and volume, cup-to-disc ratio and thickness of the peripapillary nerve fibre layer.

Optical coherence tomography utilises interferometry and low coherence light to render a high-resolution, cross section of tissues. In the eye, the resolution obtained is 1–10μm and this method has the potential for providing a clinical measurement of the nerve fibre layer thickness *in vivo*.

1.4.4 Visual Field

Changes in visual fields are subjective findings dependent on the level of IOP and state of optic nerve as well as the patient's performance but, in chronic conditions such as POAG, the alterations that occur are important and characteristic diagnostic signs. Most commonly, the ability of the individual to distinguish a stimulus light from background illumination is used as a clinical measure of visual function and is known as perimetry.[4] The hallmark of glaucomatous damage is the nerve fibre bundle defect that results from damage to the axons in the optic nerve or to the ganglion cell bodies in the

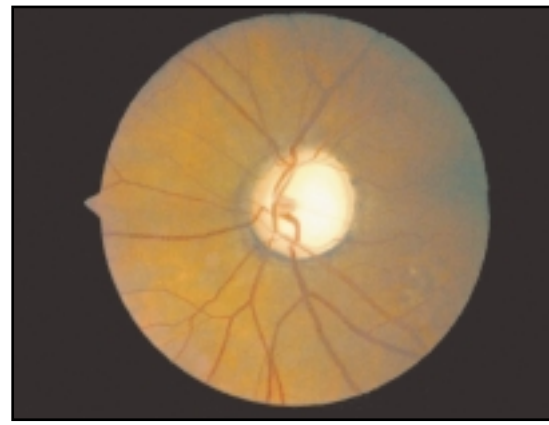

Fig. 5. Clinical photograph of optic disc and retina of a patient with advanced glaucoma. The optic nerve cup has widened to almost the entire perimeter of the optic nerve head. The retinal vessels at the optic nerve have also shifted nasally.

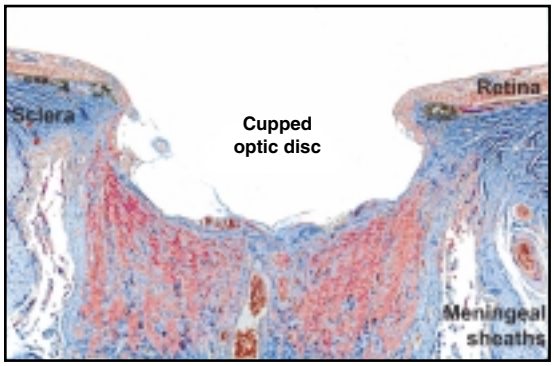

Fig. 6. Longitudinal section of optic nerve of a patient with advanced glaucoma. Note the deep excavation of the optic nerve head (cupping) resulting from loss of optic nerve axons and posterior bowing of the lamina cribrosa. Histological section stained with Masson trichrome.

retina, or both occurring concurrently. The characteristic manifestations of glaucomatous visual field defects are shown in figure 7.

Several other methods are used to test visual function in the glaucoma patient:

- Blue/yellow perimetry: studies suggest that a blue stimulus on a yellow background is a more sensitive method than a white background for detecting defects in early stages of glaucomatous disease.
- High-pass resolution perimetry: because the stimulus is a ring-shaped target that is variable in size, this method determines spatial resolution thresholds.
- Frequency doubling perimetry: presentation of a low spatial frequency sinusoidal grating appears to have twice as many alternating light and dark bands; thus the name frequency doubling. The stimuli are thought to activate M ganglion cells, which are the cells believed to be selectively damaged early in glaucomatous disease.
- Visually evoked responses: electrical responses to a stimulus in the retina (as in electroretinography [ERG]) or in the brain cortex are recorded, thus excluding subjective variations. The multifocal ERG may be a useful method for assessing function of the retinal ganglion cells.

1.5 Classification of Glaucoma

Glaucomas can be categorised into four main groups: primary open-angle, angle-closure, secondary and developmental.[4,21,22]

1.5.1 Primary Open-Angle Glaucoma

POAG is a chronic painless disease that accounts for about 90% of all glaucomas and is often designated as the 'sneak thief of sight'. It is believed that the elevated IOP is attributable to increased resistance to aqueous outflow in the trabecular meshwork/Schlemm's canal system, most likely because of cellular changes and a build-up of extracellular materials. However, approximately 25–30% of patients with POAG have an IOP within normal range and are characterised as a subset with the term 'normal' or 'low' tension glaucoma. POAG has no definitively known aetiology with respect to either increased IOP or optic neuropathy. Although mutations in a gene (trabecular meshwork-induced glucocorticoid response/myocilin [TIGR/MYOC]) have been identified in 3–5% of patients with glaucoma,[23] recently its value in the evaluation of POAG patients has been questioned.[24] Mutations in the optineurin gene (OPTN) are reported in 16.7% of 54 families with autosomal dominantly inherited, adult-onset POAG, including some individuals with

Table IV. Changes in optic nerve head in glaucoma

Generalised	Focal	Other associated findings
Increased cup-to-disc ratio	Narrowing and notching of rim	Exposed lamina cribrosa (advanced stage)
Asymmetry of cups between two eyes	Vertical elongation of cup	Nasal displacement of vessels
Progressive enlargement of cups	Cupping to rim margin (advanced stage)	Peripapillary atrophy and crescent
	Regional pallor	
	Splinter haemorrhage	
	Loss of nerve fibre layer	

normal IOP.[25] This is one of the many genes that may be linked to the pathogenesis of POAG.

The usual management of POAG is to reduce the production of aqueous humour by the ciliary body or enhance drainage of this fluid or both (see section 1.4.1).[4,21,22]

1.5.2 Angle-Closure Glaucoma

Angle-closure glaucoma is a disease with acute onset and can cause a sudden and high increase in IOP. It is one of the most painful conditions of the body and results from narrowing or closure of the angle of the anterior chamber due to the forward bowing of the iris, thus obstructing outflow of aqueous humour through the trabecular meshwork/Schlemm's canal system (figure 8). Two main processes account for acute angle-closure glaucoma: mechanisms that push the iris-lens diaphragm forward from behind; and mechanisms that pull the iris forward into contact with the trabecular meshwork.

Several drugs can precipitate angle-closure glaucoma by narrowing the angle of the anterior chamber, by pupillary dilation and/or forward movement of the iris/lens diaphragm (pupillary block glaucoma), and by swelling of the ciliary body/epithelium, lens or vitreous body. The exact mechanism of drug-induced angle-closure glaucoma is not specified in the product literature and most inserts simply mention the generalised term 'glaucoma' as a contraindication, or can cause 'glaucoma' without specifying the type. Such statements are often confusing to both clinicians and patients.

An acute angle-closure glaucomatous episode can be treated medically using miotics, osmotic agents (e.g. mannitol, isosorbide, urea), drugs that suppress aqueous formation (e.g. carbonic anhydras inhibitors, α- and β-receptor antagonists) and surgically (peripheral iridotomy or iridectomy).[4,21,22]

1.5.3 Secondary Glaucoma

Secondary glaucoma is a condition of raised IOP secondary to a variety of ocular and systemic disorders, such as uveitis, trauma, lens anomalies, rubeosis iridis (iris neovascularisation), intraocular tumours, developmental defects, orbital congestion, retinopathy of prematurity, pigmentary or pseudoexfoliation syndrome. In these conditions, physi-

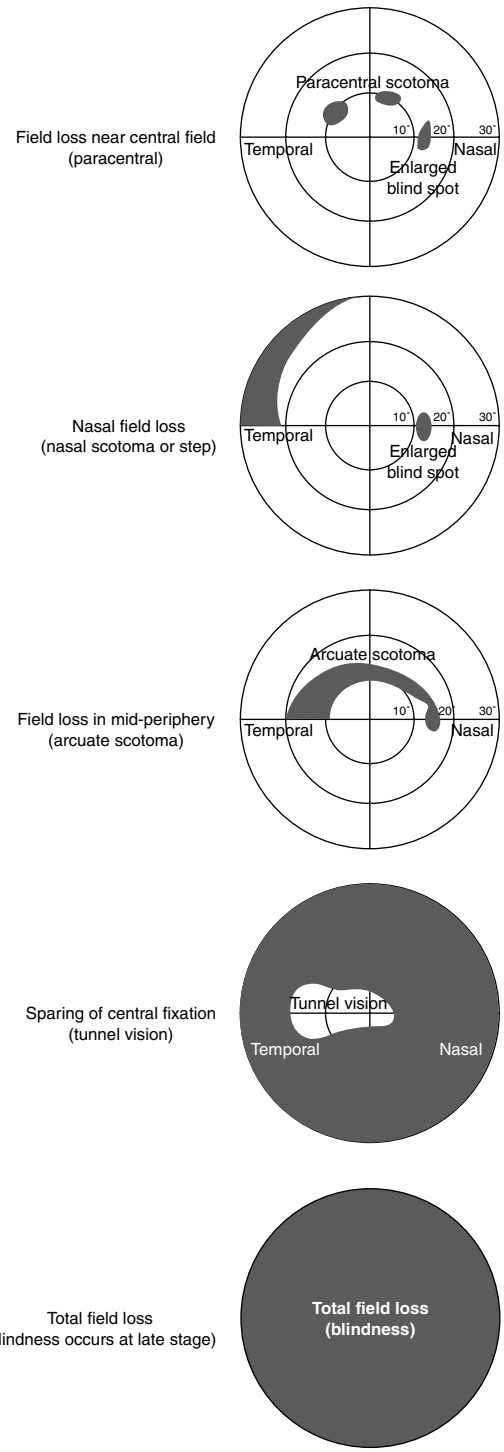

Fig. 7. Visual field defects characteristic of glaucomatous disease.

cal blockage to aqueous outflow through the trabecular meshwork/Schlemm's canal system occurs because of clogging of the drainage pathway, e.g. pigment released from the iris or ciliary body as in pigmentary glaucoma, lens capsule-like material as in pseudo-exfoliation glaucoma, lens protein material as in phacolytic glaucoma, blood components as a result of trauma, and leucocytes in inflammatory disorders of the eye.

Drug-induced glaucoma should be considered as a secondary glaucoma because it is brought about by the use of specific systemic or topical medications.

The management of secondary glaucomas includes anti-inflammatory agents, antiglaucoma drugs and surgical modalities, similar to angle-closure and open-angle glaucomas.[4,21,22]

1.5.4 Developmental Glaucoma

Developmental glaucoma includes diseases that are present at birth (congenital glaucoma) and/or manifest early in life (childhood or juvenile onset glaucoma). Some forms of developmental glaucoma are associated with other congenital anomalies, such as aniridia, or are secondary to other causes, such as fetal rubella, and may also be precipitated by maternal use of drugs or consumable substances (e.g. fetal alcohol syndrome).

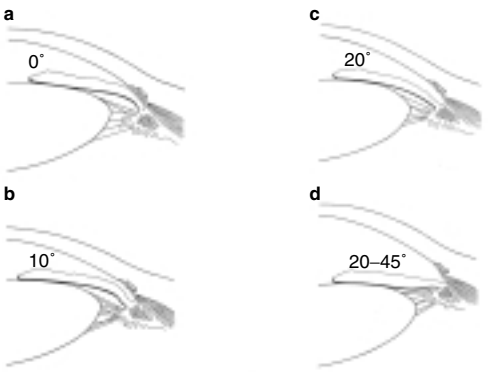

Fig. 8. Different grades of anterior chamber angle width. (**a**) Grade 0, closure imminent or present; (**b**) grade 1, approximately 10° open, narrow angle susceptible to closure; (**c**) grade 2, approximately 20° open, moderately narrow angle, less occludable although closure possible; (**d**) grades 3–4, wide open angle (20–45°). Such angles are usually associated with a deep anterior chamber and relatively flat iris profile. Angle closure is not usually possible (reproduced from Tripathi and Tripathi,[17] with permission).

The management of developmental glaucoma includes use of anti-glaucoma drugs and various surgical modalities to facilitate aqueous outflow or reduce aqueous production.[4,21,22]

1.5.5 Drug-Induced Glaucomatous Disease

Drugs may cause temporary or prolonged damage to the optic nerve and visual fields, without significant rise of IOP, thus simulating normal-tension glaucoma. Visual field changes can be verified by using sensitive tests (see section 1.4.4) to evaluate the status of the retina, especially the nerve fibre layer and ganglion cells, and morpho-pathophysiological changes in the optic nerve head. A number of drugs have been reported to the National Registry of Drug-Induced Ocular Side Effects (Casey Eye Institute, Oregon Health Sciences University, Portland, Oregon, USA) that cause visual field defects or optic neuropathy, but these patients were not diagnosed as having glaucoma.[2]

2. Drugs that Cause or Exacerbate Primary Open-Angle Glaucoma

2.1 Ophthalmic and Systemic Glucocorticoids (Corticosteroids)

The term steroids refers to naturally occurring and synthetic compounds such as corticosteroids, sterols, bile acids, cardiac glycosides, sex hormones and precursors of vitamin D. Corticosteroids refer to both mineralocorticoids and glucocorticoids. Many practitioners use the term corticosteroids mainly to refer to glucocorticoids. As early as 1930, it was known that glucocorticoids were produced by the adrenal gland. In 1949, the use of corticotropin and cortisone was first reported in the treatment of rheumatoid arthritis, and shortly thereafter, their use was extended to include ocular inflammatory diseases. By the 1950s glucocorticoids were used for many ophthalmic disorders. New formulations of steroids were produced as researchers attempted to find the optimal delivery system and minimal adverse effects. Understanding of the anti-inflammatory and immunosuppressive properties of glucocorticoids progressed rapidly, although the exact mechanisms

remained unelucidated despite the adverse effects of corticosteroids.

Glucocorticoids are used both systemically and locally for their anti-inflammatory properties. Exogenous glucocorticoids, administered topically to the eye and the periocular tissues, intravenously, and in pill form or as inhalants, are well known to cause increased IOP.[26] Excess production of endogenous glucocorticoids as in Cushing's syndrome can also cause increased IOP. Inhaled glucocorticoids are becoming a mainstay of treatment for respiratory disorders.

Examples of common indications for topically applied glucocorticoids to the eye are uveitis, iritis/iridocyclitis, episcleritis, scleritis, interstitial keratitis, allergic conjunctivitis, prevention of corneal graft rejection, herpes zoster keratitis, and at surgery and postoperatively to minimise inflammatory reaction. Periocular injections, which provide a repository of a high concentration of corticosteroid, result in less reduction of inflammation than topically applied corticosteroids, but their combination is synergistic and has a higher reduction of inflammation than topical glucocorticoids alone. Retrobulbar injections can provide a high concentration of corticosteroids to the posterior segment for several days and are useful for treating conditions such as posterior uveitis, endophthalmitis, chorioretinitis and cystoid macular oedema. Systemic corticosteroids are the treatment of choice for severe posterior segment inflammatory diseases such as optic neuritis, temporal arteritis, posterior uveitis, choroiditis and sarcoidosis.

2.1.1 Epidemiology

Eighteen to thirty-six percent of the general population and 46–92% of patients with POAG respond to topical ocular administration of corticosteroids with an elevation of IOP, usually within 2–4 weeks after therapy has been instituted.[26] Although not everyone responds to glucocorticoid therapy with an increase in IOP, some of the risk factors for steroid responders are diabetes mellitus, age over 40 years, high myopia and family history of POAG.

2.1.2 Glucocorticoids and Children

Children do manifest increased IOP with topical or systemic administration of glucocorticoids. Our own studies have shown that 31.5% of children treated with prednisone for inflammatory bowel disease had a significant increase in mean IOP but after decreasing prednisone to ≤10 mg/day for 30 days, 20.7% of these children had a decrease in IOP to within 2 standard deviations of controls.[27,28] In addition, children had the same risk as adults in developing posterior subcapsular cataracts secondary to corticosteroid therapy. Dexamethasone administered topically to children after bilateral strabismus surgery induced a significant increase in IOP, usually within 8 days of institution of therapy, in a dose-dependent manner.[29,30]

2.1.3 Mechanism of Increased IOP

Glucocorticoids can impair aqueous drainage through the trabecular meshwork/Schlemm's canal system by mechanisms other than angle closure, mostly by inducing structural and functional changes in the trabecular meshwork system similar to that in POAG. Anterior segments of human eyes perfused *in vitro* with dexamethasone for 12 days showed elevated ocular pressure and increased amounts of amorphogranular material in the extracellular spaces beneath the endothelial lining of the canal of Schlemm, in the juxtacanalicular region and in the trabecular beams, as well as decreased inter- and intratrabecular spaces.[31] Although the exact mechanism is not known, considerable research is under way to identify the cause(s). Some of the proposed mechanisms include:

- Glucocorticoids stabilise lysosomal membranes, leading to decreased release of catabolic enzymes and hence an increase in indigestible polymerised glycosaminoglycans (GAGs) that become hydrated and cause physical obstruction to the flow of aqueous humour through the trabecular meshwork system.[32]
- As dexamethasone regulates the expression and function of the sodium-potassium-chloride cotransport system in trabecular cells, it is conceivable that alterations in this cotransport system

lead to cell swelling and blockage of drainage through the trabecular meshwork system.[33]

- Trabecular cells exposed to glucocorticoids increase production of elastin, fibronectin and laminin and decrease production of tissue plasminogen activator, collagenase IV and stromelysin, which causes an accumulation of extracellular matrix (ECM) and increases resistance to aqueous outflow.[34-38]
- Cross-linked actin networks form within the trabecular cells treated with glucocorticoids, which inhibit their proliferation, migration and phagocytic activity and cause accumulation of cellular debris and clogging of the aqueous outflow channels.[39-41]
- Trabecular cells overproduce a sialoglycoprotein, which is transcribed from the GLC1A gene.[42-44] This glycoprotein interacts with GAGs and other components of the ECM and results in the formation of complexes that block aqueous humour drainage channels.
- Cultured trabecular meshwork cells exposed to hydrocortisone showed an enlargement of the cell cytoplasm and nucleus with a 36% increase in the amount of DNA and an increase in the fraction of polyploid DNA.[45] This study implicates a definite role for glucocorticoids at the level of DNA in trabecular cells, possibly at the TIGR/MYOC gene.

2.1.4 Clinical Signs

Corticosteroid-induced glaucoma presents in infants similarly to primary infantile glaucoma with decreased vision, increased IOP, enlarged oedematous and cloudy corneas, photophobia, tearing, blepharospasm and damage to the optic disc. In older children, adults and elderly, the clinical presentation is similar to POAG, with elevated IOP, open angles and, eventually, cupped discs and visual field loss.[21,22]

2.1.5 Management/Prevention of Increased IOP

The time frame when ocular hypertension begins and the degree of IOP elevation depends on the specific drug, the dose, the frequency of administration, and the individual patient.[26] In addition to the systemic adverse effects of corticosteroid administration and possibility of glaucoma, other ocular adverse effects may occur including posterior subcapsular cataracts, mydriasis, atrophy of the eyelid skin, ocular infection, delayed wound healing, and corneal ulceration. These risks are especially high with topical corticosteroids applied to the eyes and require special attention by non-ophthalmologists. Physicians should be cognisant of the ocular adverse effects of corticosteroids and arrange for ophthalmic referral of patients at risk or when in doubt. If IOP increases, corticosteroids should be tapered as soon as possible. A correlation exists between the length corticosteroid treatment and the time it takes to lower the IOP. Usually, the IOP returns to normal within 2–4 weeks after cessation of treatment, but corticosteroids can exacerbate or lead to long-term elevation of IOP similar to POAG.[26] In patients where IOP is increased after repository corticosteroid injection, the residual material should be removed from beneath the conjunctiva or Tenons' capsule. As an alternative, corticosteroids such as fluorometholone or rimexolone that have a lower potential for raising the IOP can be used. Nonsteroidal anti-inflammatory agents such as flurbiprofen, ketorolac and diclofenac,[46] which do not seem to raise IOP, can be used in some instances. If the corticosteroid therapy cannot be discontinued, or the IOP does not lower after cessation of the corticosteroid, increased IOP should be treated medically and surgically, as for POAG.

2.1.6 Comparison of Ophthalmic Glucocorticoids

Dexamethasone is the most potent ophthalmic glucocorticoid, and thus has a high incidence of adverse effects (glaucoma, cataract, etc.). The alcohol suspension has been shown to have a slightly more effective anti-inflammatory action than the sodium phosphate solution.[47]

Prednisolone is a synthetic analogue of hydrocortisone and is considered the standard for anti-inflammatory therapy. The acetate suspension has a higher tissue penetration than the sodium phosphate solution, although the clinical significance of this difference is uncertain. Because of its high potency, prednisolone also is associated with a high incidence of raised IOP and cataract.[47]

Fluorometholone is an analogue of progesterone. The alcohol suspension of fluorometholone is a less effective anti-inflammatory agent than prednisolone and has less potential to raise IOP.[47] The acetate suspension has higher anti-inflammatory activity, reported to equal that of prednisolone in some studies.[47]

Medrysone is also a derivative of progesterone but has low potency as an anti-inflammatory agent and a low potential for increasing IOP.[47]

Loteprednol is a relatively new 'soft drug' that is rapidly transformed to an inactive metabolite in the anterior chamber, thus minimising adverse effects while still being therapeutically effective for external inflammation.[48,49]

Rimexolone is a synthetic corticosteroid that has effective anti-inflammatory activity and a low potential for raising IOP.[49] Its anti-inflammatory action is comparable to that of prednisolone, while the potential for raising IOP is equivalent to that of fluorometholone, making rimexolone a relatively safe choice for anti-inflammatory therapy.[49]

2.2 Docetaxel and Paclitaxel

Docetaxel and paclitaxel are a new generation of anticancer agents with a novel mechanism of action. The mechanism by which these agents cause or exacerbate glaucomatous disease is unknown. One patient developed open-angle glaucoma with high IOPs, optic disc cupping and visual field scotomas in both eyes after receiving docetaxel, which recurred on follow-up treatment of the metastases with paclitaxel.[50] Another patient developed bilateral visual field loss and, 6 months later, increased IOPs.[51] Although docetaxel is known to induce fluid retention and paclitaxel is neurotoxic, it is not clear whether either of these agents induces open-angle glaucoma with or without raised IOP.[52] It is likely that the glaucomatous changes were precipitated by the repetitive low or high doses of corticosteroids that patients receive as an adjunct to chemotherapy.

3. Drugs that Cause Angle-Closure Glaucoma

3.1 Adrenergic Agonists

Phenylephrine is used to induce pupillary dilation for ophthalmic examination of the fundus. Epinephrine (adrenaline) is used in the treatment of ventricular fibrillation, allergic reactions and anaphylactic shock and ephedrine is used for the treatment of nasal decongestion and for anaesthesia-related hypotension.

Adrenergic agonists induce pupillary dilation, which can precipitate an attack of acute angle-closure glaucoma in susceptible patients.[4,53] They are discussed separately from salbutamol (albuterol) [see section 3.2] to emphasise that medications used to dilate pupils or used in emergency code situations can induce narrow-angle glaucoma. Increased IOP should be managed/prevented by discontinuing the medication and managing as for acute angle-closure glaucoma (see section 1.5.2).

Cases have been reported in which acute angle-closure glaucoma has occurred after systemic administration of ephedrine for surgical anaesthesia. Succinylcholine (which causes contraction of extraocular muscles and increases IOP) as well as psychological stress as a result of endogenous production of catecholamines and other hormones can contribute to pupillary dilation and precipitate angle-closure glaucoma (see also atropine, section 3.6.)

3.2 Salbutamol (Albuterol)

Salbutamol is a β_2-specific adrenergic agonist used as an inhalant for bronchodilation in patients with asthma or chronic obstructive pulmonary disease.

Because the salbutamol is absorbed through the cornea and conjunctiva, partial dilation of the pupil occurs and induces pupillary block in the circulatory pathway of the aqueous humour from the posterior chamber to the anterior chamber of the eye.[54] Consequently, the periphery of the iris is pushed forward and against the trabecular meshwork, which ob-

structs the drainage pathway of the aqueous humour. This form of angle-closure glaucoma is likely to occur more frequently in patients with pre-existing narrow/shallow anterior chamber angles; whether salbutamol increases production of aqueous humour to raise IOP is not known.

Increased IOP can be prevented/managed by use of properly fitted masks and hand-held nebulisers that could decrease absorption of salbutamol through the cornea and conjunctiva. Protective eyewear may offer an additional benefit. If raised IOP and acute angle-closure glaucoma are detected, salbutamol should be discontinued. Medications (e.g. miotics) can be used as adjunctive therapy to constrict the pupil before peripheral laser iridotomy. Other anti-inflammatory medications may be administered topically or orally to lower IOP and decrease inflammation.

3.3 Noncatecholamine Adrenergic Agonists

The noncatecholamine adrenergic agonists amphetamine, dextroamphetamine, methamphetamine and phendimetrazine are all still available for use in the management of obesity, hence they are commonly referred to as anorexiants. Amphetamine, dextroamphetamine and methamphetamine are also used in conditions such as narcolepsy and minimal brain dysfunction in children. In toxic doses, these agents can cause mydriasis and induce narrow-angle glaucoma in susceptible individuals.[2] To manage/prevent increased IOP the medication should be discontinued and the increased IOP managed as per acute angle-closure glaucoma (see section 1.5.2).

3.4 Pilocarpine

The cholinergic agent pilocarpine is used in some forms of glaucoma to constrict the pupil and increase aqueous outflow through the major aqueous outflow pathways. Although this drug is often used to treat narrow-angle glaucoma, it can induce an acute attack of angle-closure glaucoma due to anterior movement of the lens-iris diaphragm, thus completely occluding the angle of the anterior chamber.[4,53] It may also decrease aqueous outflow through the uveoscleral route, which can be problematic for patients with pre-existing decreased outflow through the trabecular meshwork.[4,53] To manage/prevent increased IOP the pilocarpine should be discontinued and the increased IOP managed as per acute angle-closure glaucoma (see section 1.5.2). A cell-culture assay demonstrated that high concentrations of pilocarpine are toxic to rat retinal ganglion cells in a dose-dependent manner and this toxicity is potentiated by lithium.[55] Whether this finding is applicable to human patients treated with pilocarpine, and thereby may simulate an open-angle glaucoma, remains unknown.

3.5 Cholinergic Agents

Various cholinergic agents are available such as acetylcholine and carbachol. These fast-acting topical medications are used to constrict the pupil during intraocular surgery especially cataract removal. These drugs can induce pupillary block in susceptible patients (who do not have a peripheral iridotomy), leading to an acute rise of IOP as in angle-closure glaucoma.[53] To manage/prevent increased IOP the pilocarpine should be discontinued and the increased IOP managed as per acute angle-closure glaucoma (see section 1.5.2).

3.6 Anticholinergics

Tropicamide, a short-acting anticholinergic, is commonly used in combination with phenylephrine to dilate pupils for ophthalmic examination of the posterior segment of the eye (the fundus). Other longer-acting topical anticholinergics such as atropine, homatropine and cyclopentolate are used to relax the ciliary muscle and dilate the pupil in conditions such as iritis and uveitis. Atropine is also used systemically for life threatening bradycardia as well as for induction of anaesthesia. Disopyramide is an anticholinergic agent used for the suppression and prevention of cardiac arrhythmias.[4,53]

Anticholinergics induce pupillary dilation that can induce an attack of acute angle-closure glaucoma in susceptible patients.[56,57] Bilateral simultaneous angle closure has been reported in patients after general anaesthesia for non-ocular surgery.[58]

To manage/prevent increased IOP the anticholinergic should be discontinued and the symptoms managed as for acute angle-closure glaucoma (see section 1.5.2). Use of the simple oblique penlight illumination test to estimate the depth of the anterior chambers preoperatively enables identification of patients who have narrow angles before administration of general anaesthesia. Ophthalmologists use the slit-lamp and gonioscopy for definitive evaluation of the depth of the anterior chamber angle.

3.6.1 Ipratropium Bromide

Ipratropium bromide is used in combination with salbutamol as a bronchodilator in patients with COPD. It induces pupillary dilation and, thus, angle-closure glaucoma, as described for salbutamol (section 3.2).[59,60] The management and prevention is also similar to that for salbutamol. Patients with chronic bronchitis and pre-existing narrow angles who received a nebulised salbutamol/ipratropium combination showed increased IOP; 50% of them manifested transient angle-closure glaucoma.[59]

3.7 Sulpha-Based Drugs

Sulpha-based drugs known to be associated with drug-induced angle-closure glaucoma are acetazolamide, used in ophthalmology to reduce IOP, hydrochlorothiazide, a diuretic and hypotensive agent, and cotrimoxazole (trimethoprim-sulfamethoxazole), an antibiotic commonly used to treat urinary tract infections.

An allergic reaction to the sulpha component of these drugs induces ciliary body oedema and relaxation of lens zonules that results in an increase in the anterior-posterior diameter of the lens and myopia.[61-64] The ciliary body, lens and iris are displaced anteriorly that causes the anterior chamber to shallow and increase the susceptibility for angle-closure glaucoma. Choroidal detachment and supraciliary choroidal effusion are possible contributing factors. To manage/prevent increased IOP the sulpha-containing drug should be discontinued and the elevated IOP treated medically. Because the angle-closure glaucoma occurs without pupillary block, peripheral iridotomy may be ineffective.

3.7.1 Topiramate

Topiramate is a sulfamate-substituted monosaccharide antiepileptic agent also used in management of migraine, depression and neuropathic pain.

As with other sulfa-based drugs, swelling of the ciliary body and forward displacement of the lens-iris diaphragm cause shallowing of the anterior chamber angle and acute angle-closure glaucoma.[65-68] Although there is controversy as to the precise mechanism of angle-closure glaucoma and acute myopia precipitated by sulfa-containing drugs, ciliary body swelling and the associated forward migration of the lens has been documented by sequential ultrasound examinations and slit-lamp photographs.[66] An acute hypersensitivity reaction has been questioned and it has been suggested that drug-induced elevated prostaglandin levels contribute to the oedema in the ciliary body.[69]

To manage/prevent increased IOP the sulpha-containing drug should be discontinued and treat raised IOP medically. Because the mechanism of angle closure does not involve pupillary block, peripheral iridectomy and topical miotics are not effective in the treatment.

One hundred and fourteen cases, of which 82 were bilateral and 3 unilateral, are reported in the literature in which acute secondary closed-angle glaucoma has been documented. Acute elevation of IOP usually occurred within the first 2 weeks of starting topiramate therapy. The presenting symptom in most cases was blurred vision and seven patients sustained permanent visual loss. However, if the drug is stopped and medical management is instituted, IOP may return to normal in a period of hours to days.[68]

3.8 Antidepressants

Fluoxetine, paroxetine, fluvoxamine (all selective serotonin reuptake inhibitors [SSRIs]) and venlafaxine (a serotonin and noradrenaline reuptake inhibitor) have been associated with angle-closure glaucoma.[70-76] Although the exact mechanism is not known, acute angle-closure glaucoma is believed to be induced by either the anticholinergic adverse effects or the increased levels of serotonin

that cause mydriasis (partial pupillary dilation). The anticholinergic adverse effects of SSRIs are less than those of the tricyclic antidepressants. Serotonin may also cause mydriasis. To manage/prevent increased IOP the agents should be discontinued and the symptoms managed as for acute angle-closure glaucoma (as in section 1.5.2).

Episodes of acute angle-closure glaucoma have been reported to occur both within a short time of starting these drugs and also after several days. This has led clinicians to suspect that both the anticholinergic adverse effects and the direct effect of serotonin can induce mydriasis and subsequent angle-closure glaucoma in susceptible patients. One study reports a transient rise in IOP in patients treated with fluoxetine.[70]

Imipramine is a tricyclic antidepressant and maprotiline is a tetracyclic antidepressant. The anticholinergic adverse effect of these drugs can induce mydriasis and precipitate acute angle-closure glaucoma in patients with pre-existing narrow angles.[77,78] To manage/prevent increased IOP the agents should be discontinued and the symptoms managed as for acute angle-closure glaucoma (as in section 1.5.2). One report documents visual acuity decreasing to no light perception bilaterally despite appropriate treatment.[78]

3.9 Warfarin

Warfarin is an anticoagulant. An episode of bilateral haemorrhagic retinal detachment, which led to anterior movement of the lens-iris diaphragm from a posterior pushing mechanism, caused an attack of acute narrow-angle glaucoma in a patient with nanophthalmic eyes who was taking warfarin.[79] The small size of the eye probably increased this outcome. Uveal effusion associated with nanophthalmos can cause acute angle-closure glaucoma from a mechanism of anterior pushing of the iris-lens.

To manage/prevent increased IOP warfarin should be discontinued and the symptoms managed as for acute angle-closure glaucoma (as in section 1.5.2). Because the aetiology can be a nonpupillary block mechanism, peripheral iridotomy is not effective in the management. In addition to the usual treatment for angle closure, surgery may be needed to drain choroidal effusion/haemorrhages. The risk of angle-closure glaucoma is applicable to all anticoagulants.

3.10 Histamine H_1 Receptor Antagonists (Antihistamines)

Brompheniramine, chlorpheniramine, dexbrompheniramine, dexchlorpheniramine, dimethindene, pheniramine, triprolidine are antihistamines that are used to treat allergic conjunctivitis, rhinitis and skin manifestations of allergic disease. These antihistamines have a weak anticholinergic adverse effect, which can induce mydriasis and narrow-angle glaucoma in susceptible individuals (see section 3.6) as described above for other agents that cause pupillary dilation.[2] To manage/prevent increased IOP the antihistamine should be discontinued and the symptoms managed as for acute angle-closure glaucoma (as in section 1.5.2).

3.11 Histamine H_2 Receptor Antagonists

Cimetidine and ranitidine are histamine H_2 receptor antagonists used to treat gastroesophageal reflux disease and duodenal ulcers. These agents may have a weak anticholinergic adverse effect, which can cause mydriasis and induce narrow-angle glaucoma in susceptible individuals as described above for other agents.[80] To manage/prevent increased IOP the cimetidine and ranitidine should be discontinued and the symptoms managed as for acute angle-closure glaucoma (as in section 1.5.2). It is uncertain whether this class of drugs increases IOP.[2]

3.12 ACE Inhibitors

ACE inhibitors are used widely for the treatment of high blood pressure. Although it is recognised that up to 0.7% of patients treated with ACE inhibitors and angiotensin II receptor antagonists develop angioedema,[81] a recent report documents candesartan cilexetil-induced angioedema in the choroid of the eye that led to a choroidal effusion syndrome with shallow anterior chamber and pre-

cipitated malignant glaucoma.[82] Management of this condition is similar to acute angle-closure glaucoma (section 1.5.2) and may require surgical drainage of the choroidal effusion.

4. Concluding Remarks

The term glaucoma is often used to designate a condition with raised IOP as a causative factor for optic nerve degeneration. The recognition of 'normal'-tension glaucoma and several drugs that cause optic neuropathy, which on clinical examination can mimic glaucomatous atrophy of the optic nerve, has raised the question as to the definition and pathogenesis of glaucoma. The recent definition, as provided in section 1.2, places emphasis on the characteristic optic neuropathy for which raised IOP is the major risk factor. Drugs used in medical practice and included in this review cause raised IOP and/or optic neuropathy, which simulate a 'glaucomatous' condition of the eye. The drugs that cause an acute rise of IOP are especially emphasised. Although product package inserts may mention glaucoma as a contraindication, they do not specify the type of glaucoma. Children are as susceptible to drug-induced glaucoma as adults. For general enquiry, readers are referred to the National Registry of Drug-Induced Ocular Side Effects, Casey Eye Institute, Oregon Health Sciences University, USA. It is still uncertain what effect drugs have on ganglion cells in the retina, from where the optic nerve axons originate. What is certain from current knowledge is that the major structural changes manifest in the optic nerve fibres and their retinal ganglion cell bodies. The various functional and ophthalmoscopic changes are designed to detect manifestations of glaucomatous optic neuropathy with or without raised IOP. These parameters are useful for clinicians to evaluate adverse effects of drugs and treatment/prevention of apparent or occult manifestations of glaucoma. General practitioners should be cognisant of the risk factors for glaucoma before prescribing a drug that has the potential to cause, precipitate or exacerbate glaucomatous disease of the eye. When in doubt, a doctor should seek consultation with an ophthalmologist.

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