OCULAR PHARMACOLOGY*

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The medical management of a number of ocular diseases, or of ocular lesions associated with systemic disease, has undergone profound changes in recent years. Major advances in pharmacology and therapeutics have provided the ophthalmologist with new methods for the management of his patients.

It is impossible to give full details of all the many and varied drugs currently in vogue for ophthalmological purposes. Therefore consideration will be given to only 3 important groups of drugs, i.e. the antibiotics, the steroids, and the agents used in the treatment of glaucoma.

CHEMOTHERAPY OF OCULAR INFECTIONS

A. The Use of Antibiotics

The great advantage of chemotherapy in ophthalmology is that much use may be made of the topical application of drugs, and relatively high concentrations may be used in this way. It is unfortunate that chemotherapeutic agents pass from the circulation into the eye with some difficulty, and relatively high systemic concentrations of drugs are necessary for penetration into the eyeball.

The selection of the most appropriate antimicrobial agent presents a difficulty. The necessity for sensitivity tests is a matter of judgment. Treatment may need to be instituted immediately on the basis of clinical experience and the laboratory report may support the empirical chemotherapy. Certainly there is need for culture and sensitivity tests when there is inadequate response to initial chemotherapy. Unfortunately the microbiological studies are not always helpful.

Certain organisms are resistant to chemotherapeutic agents. This may be inherent in the microorganism, e.g. the hospital staphylococcus, which by producing the enzyme penicillinase, destroys penicillin rapidly. Gram-negative organisms also have inherent resistance. There is also the problem of acquired resistance. As the organisms multiply, they produce mutants which have decreased resistance to drugs, but particularly important are those which have increased resistance to drugs. It is fortunate that newer antibiotics have been developed to deal with resistant organisms especially as regards Gram-positive organisms; however, we are lagging behind in the treatment of infections caused by Gram-negative organisms. There are newer penicillins which can deal with penicillinase-producing staphylococci. These, e.g. methicillin sodium and cloxacillin, should be reserved for such special use. Ampicillin which is used especially against Gram-negative organisms is not effective against penicillinase-producing staphylococci (Table I).

TABLE I. PENICILLINS

Drug	*Dosage*
Benzylpenicillin Injection	by IM inj., 150 - 600 mg. (250,000 - 1,000,000 units) 2 - 12 times daily
Procaine Penicillin	by IM inj., 300 - 900 mg. (500,000 - 1,000,000 units) daily
Fortified Procaine Penicillin Injection	e.g. 300 mg. Procaine Penicillin with 60 mg. Benzyl Penicillin
Phenoxymethylpenicillin (Penicillin V)	orally 125 - 500 mg. every 4 hrs.
Potassium Phenethicillin (Bendralan; Broxil)	orally 125 - 250 mg. 3 times daily, before meals
Methicillin Sodium (Staphcillin; Celbenin)	by IM inj., 1 G every 4 - 6 hrs., for 3 days
Oxacillin (Prostaphlin)	orally 0·25 - 1 G, or by IM inj., every 4 - 6 hrs.
Cloxacillin (Orbenin)	orally 500 mg., or by IM inj., every 6 hrs.
Ampicillin (Penbritin; Pentrex)	orally 0·25 G, every 6 - 8 hrs., for 5 - 7 days

To combat certain organisms it may be necessary to use a combination of drugs (antimicrobial synergism), especially

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those that are bactericidal in action. Care is required with certain combinations of drugs, since they may show antagonism to each other[1] (Table II). Fortunately this is rarely of clinical importance.

TABLE II. ANTIBACTERIAL ACTION OF ANTIBIOTICS

Group I *Bactericidal*	*Group II* *Bacteriostatic*
Penicillin	Tetracyclines
Streptomycin	Chloramphenicol
Neomycin	Erythromycin
Bacitracin	Sulphonamides
Polymyxin	

I + I Additive or synergistic II + II Additive or indifferent
I + II May be synergistic, if the organism is relatively insensitive to I.
I + II May be antagonistic, if the organism is relatively sensitive to I.

1. *For Local Instillation in the Eye*

Bacitracin, neomycin, polymyxin, and gramicidin have been used because they have little sensitizing potential and are not likely to be used systemically. Penicillin is likely to cause sensitization which may prevent its use for a more serious infection at a later date.

If there is no satisfactory response within 48, or at most 72 hours, a change to other medication is indicated. Failure of antibiotic therapy may allow considerable destruction of normal tissue to take place and visual loss may continue. Corneal abscesses may become sterile under treatment but because of the tissue destruction from the infectious process the cornea may perforate.

2. *For Systemic Use in Intraocular Infections*

In the potentially infected wound, e.g. from a penetrating foreign body, it is advisable to treat the eye as though it were infected. A broad-spectrum antibiotic, e.g. chloramphenicol or tetracycline which penetrates into the ocular tissues, or a combination of antibiotics, e.g. penicillin with streptomycin, should be used. Novobiocin ('albamycin') penetrates poorly into the intraocular tissues when given by mouth, but it will penetrate when injected subconjunctivally. Because of the frequent resistance of *Staph. aureus* to penicillin, erythromycin with sulphafurazole ('sulfisoxazole') ('gantrisin') have been recommended for use against ocular infections.

The use of antibiotics in traumatic open wounds of the eye should begin at once and continue through the operative period and for 72 hours afterwards. Further medication will be determined according to the ocular appearance.

Intraocular infections due to fungi may improve after administration of amphotericin B given by intravenous, subconjunctival or intracameral injection.

The prophylactic use of anti-infective drugs in intraocular surgery is not favoured by some ophthalmologists.

3. *For Subconjunctival Injection*

The following antibiotics have been used:
In Gram-positive and Gram-negative infections—neomycin, penicillin with streptomycin, bacitracin with polymyxin. In Gram-positive infections, especially against penicillin-resistant staphylococci—erythromycin succinate. In fungus infections—amphotericin B.

B. Antiviral Agents

Idoxuridine (IDU) ('kerecid') has a specific action against DNA-containing viruses. It interferes with the synthesis of DNA by acting as an antimetabolite for thymidine. It has been found by many workers to be effective in the treatment of superficial herpes simplex keratitis (the so-called dendritic ulcer). It is used by instillation in the conjunctival sac, e.g. in 0·1% solution every hour during the day and every 2 hours during the night for 5 - 10 days.

This antiviral agent should not be used where there is deep ulceration of the cornea since perforation may occur. Steroids should be avoided since they accelerate the spread of viral infection.

Continued administration of idoxuridine may damage the cornea. Pain, photophobia, oedema, and punctate deposits, not going on to ulceration, may occur. The drug is too toxic for systemic use; stomatitis, vomiting, depression of the bone marrow, and alopecia can be produced.

C. Other Antimicrobial Drugs

Among the drugs not considered here are those used, e.g., in the treatment of syphilis or tuberculosis; the same agents are used as in treatment for these diseases in other parts of the body. In toxoplasmosis pyrimethamine ('daraprim') (25 mg. daily) is used with sulphadiazine (500 mg. thrice daily, for 14 days). Both these drugs interfere with folic acid metabolism.

STEROID THERAPY

Actions

The pharmacological actions of the glucocorticoid steroids have been widely publicized. Not only can they produce much relief of symptoms but the effect on mood may be so intense as to simulate the action of morphine. However, it has to be emphasized that they cure nothing. They relieve symptoms by suppressing adaptive processes. They suppress many of the responses to injury, desirable as well as undesirable, the reparative as well as the destructive. They therefore tend to mask the course of the basic disease and conceal the development of complications. The development of secondary infections seems to be enhanced.

However, therapy with steroids has definite value in a wide variety of ocular conditions.[1] They control inflammation and exudation produced by allergy, trauma, and bacteria, until other forces overcome the inflammation. They are used by topical as well as systemic administration. Most ocular conditions can be treated locally and do not require prolonged systemic use of these drugs. Topical therapy tends to produce high local concentrations without causing systemic effects. The steroid absorbed into the anterior segment is of benefit in iritis, aphakic toxic reactions, and other conditions of the anterior uveal tract.

There is no evidence that the local application of steroids has any influence on the deeper structures of the eye.

1. *Local Application*

The following table indicates conditions for which steroids are applied to the eye.[2]

TABLE III. CONDITIONS FOR WHICH STEROIDS ARE APPLIED TO THE EYE

(1) *Lids.* Squamous (seborrhoeic) blepharitis; allergic reactions from drugs, pollens, cosmetics
(2) *Conjunctiva.* Non-infective conjunctivitis (phlyctenular disease; spring catarrh; follicular conjunctivitis; episcleritis
(3) *Cornea.* Marginal keratitis; interstitial keratitis; herpes zoster keratitis (sometimes); acne rosacea
(4) *Iris.* Iritis and iridocyclitis

Conditions where local steroids are valueless or contraindicated include the following:
(i) Lids: stye; chalazion; ulcerative blepharitis
(ii) Conjunctiva: infective conjunctivitis
(iii) Cornea: septic corneal ulcer; dendritic (herpetic) corneal ulcer; punctate keratitis
(iv) Acute glaucoma
(v) All retinal and choroidal conditions

2. *Subconjunctival Injection*

Subconjunctival injection of certain steroids produces benefit in certain ocular conditions, especially in acute diseases of the anterior segment, e.g. in scleritis, episcleritis, keratitis.[3] They are contraindicated in herpes simplex keratitis. Once the steroid is injected its effect cannot be reversed for 3 - 4 weeks and topically applied steroids are probably safer. Chronic anterior uveitis associated with ankylosing spondylitis, rheumatoid arthritis, and Reiter's disease are regarded as not suitable for this therapy, but in sarcoidosis subconjunctival injection is especially useful in acute exacerbations of the disease when systemic steroids could not be used.

3. *Oral Medication*

Oral medication with steroids for posterior ocular diseases should be intensive when there is severe diffuse inflammation, severe localized inflammations which produce heavy vitreous exudation, and inflammations near the macula and disc. If oral therapy fails, the type of corticosteroids should be changed or corticotrophin used. Relatively quiet single lesions, chronic diffuse disease, and those at the equator and periphery, which do not produce heavy vitreous exudate, should be treated with steroids unless they become suddenly active. Other drugs may need to be used in addition, e.g. antituberculosis drugs when there are suspected tuberculous lesions.

In some types of conjunctival, corneal, and anterior segment inflammation all routes of steroid therapy need to be used—topical, subconjunctival, and systemic. Systemic and local steroid therapy is used in nonspecific posterior uveitis, e.g. sympathetic ophthalmia, sarcoidosis, blood dyscrasias (leukaemia) and Hodgkin's disease. Better results are claimed by some workers in specific posterior uveitis, e.g. in toxoplasmic chorioretinitis, when steroids are given concurrently with pyrimethamine and sulphonamide chemotherapy.

The choice of the best steroid for systemic use is complicated by the large number of new compounds. Cortisone itself is now little used. Prednisone and prednisolone are in favour, since they promote salt and water retention to a lesser degree than their parent compounds cortisone and hydrocortisone; nevertheless they too can produce undesirable effects, e.g. features of Cushing's syndrome, especially if administration is prolonged for more than 3 weeks. Dexamethasone ('decadron', 'deronil') is potent for systemic anti-inflammatory action, but it can produce the undesirable features of hypercortisonism; it offers no advantage over prednisolone and appears to be less desirable. Similar remarks apply to methylprednisolone ('medrol') and triamcinolone ('aristocort', 'kenacort'), which have undesirable effects on the electrolytes. There is evidence that the anti-inflammatory action of these steroids cannot be separated from their ulcerogenic potential.

Failure of an inflammatory process to respond to one type of steroid should be followed by a change to another preparation which may be more successful.

The following table indicates preparations recommended for use.[1]

TABLE IV. STEROID PREPARATIONS RECOMMENDED FOR USE

(a) *Topical*

Prednisone (solution) 0·25% and 0·5%
Prednisone (ointment) 0·1% and 0·25%
Dexamethasone (solution) 0·1%
Dexamethasone (ointment) 0·1%

Solutions: 1 drop every ½ - 1 hour during the day

Ointments: Place in conjunctival sac 4 times/day and at night

(b) *Subconjunctival*

Prednisone (solution) 0·25%; 0·5 ml. every 2 - 4 days
Dexamethasone (solution) 0·1%; 0·5 ml. every 2 - 4 days
Methylprednisolone (Depot-Medrol); 0·5 ml. every 4 weeks

(c) *Systemic*

Prednisone 20 - 80 mg./day
Dexamethasone 2 - 4 mg./day

Failure of steroid to control the inflammation within a week should lead to consideration of a change in therapy, unless the disease is acute and severe. *Care is required to reduce steroid dosage gradually when treatment is to be stopped.*

The Undesirable Effects of Steroids

These occur with all the steroids.

1. *The General Dangers of Hypercortisonism*

The features of overdosage produced by corticosteroids, and the clinical observations required in their use, are familiar to physicians. The untoward reactions include inhibition of fibroblastic and normal mesenchymal tissue replacement, with retardation of wound healing and development of peptic ulcer; decrease in the rate of replacement of desquamated cells; increased protein catabolism, disturbances in electrolyte balance, osteoporosis and fractures, diabetes, and diminished antibody response. Many, if not all, the features of Cushing's syndrome may be produced.

Such effects may occur after ordinary therapeutic doses, which is in contrast to the usual effect of drugs in which the therapeutic and toxic actions tend to be distinct and separable, the therapeutic and toxic actions being usually produced by different orders of dosage.

The systematic undesirable effects of cortisone-like steroids are usually temporary and are likely to subside promptly after withdrawal of the drug. Occasionally, however, more serious effects may persist after long-continued administration; one of these is a state of adrenocortical insufficiency resulting from the depression or even atrophy of the adrenal cortex. Some patients cannot be weaned from corticosteroids for many months despite repeated attempts.

There is a long list of conditions in which there are absolute or relative contraindications to systemic use of the steroids, e.g. they should not be used in patients with unstable personalities; tuberculosis is generally to be considered a contraindication although with the concomitant use of tuberculostatic drugs they may be helpful; peptic ulcer, severe hypertension, diabetes, cardiac disease, and acute infectious processes are other contraindications.

2. *Untoward Effects on the Eye*

These are caused by local application of steroids:

(*a*) Absorption of blood from the anterior chamber, and also of cortical material after extracapsular extraction of the lens or traumatic injury of the lens, may possibly be delayed.

(*b*) Since the normal defence inflammation is suppressed, the rapid spread of infection is encouraged; regeneration of the vital epithelium may be arrested or retarded.

(*c*) The prolonged use of a combination of steroids with antibiotics may contribute to an increase in the incidence of fungus infections of the cornea.

(*d*) Herpes keratitis may be promoted by the use of steroids. The presence of this infection should first be excluded, and the patient observed closely during treatment with steroids It is advisable to consider any ocular infection (virus, fungal, tuberculous, or purulent) as well as thinning of the cornea, as contraindications to the topical use of steroids.

(*e*) Prolonged topical application (or systemic use) may produce a serious decrease in aqueous outflow and reversible increase in intraocular pressure in certain individuals, even in normal eyes.[4] It occurs especially in patients with primary open-angle glaucoma, and appears to be genetically determined. Intraocular pressure should be checked frequently during such treatment.

(*f*) Superficial punctate staining similar to that caused by other local applications (antibiotics, local anaesthetics) has been described following local instillation of corticosteroid suspensions and ointments.

Untoward effects resulting from prolonged systemic therapy with corticosteroids:

(*g*) Posterior subcapsular cataract may be produced. The lens opacity may be seen easily with the ophthalmoscope but severe visual impairment has not been observed and subjective complaints have been minimal.

(*h*) Papilloedema has been attributed to therapy with triamcinolone.

DRUGS USED IN GLAUCOMA

Certain drugs are applied locally to the eye and others are administered systemically to lower the intraocular pressure.[5]

A. Topical Treatment of Chronic Simple Glaucoma

Miotics

A number of cholinergic drugs may be applied to the eye in glaucoma. They constrict the pupil and make the ciliary muscle contract. Some act, like acetylcholine, directly on the smooth muscle, e.g. pilocarpine, carbachol, methacholine. Some inhibit cholinesterase and so allow acetylcholine to act; such

anticholinesterases include physostigmine, neostigmine, and the longer-acting drugs dyflos (DFP), echothiophate ('phospholine iodide'), and demecarium bromide ('humorsol', 'tosmilen').

Pilocarpine hydrochloride is usually used as a 2% solution and acts for up to 6 hours. Its main disadvantage is its brief action, but this may be prolonged by adding methylcellulose to the preparation. Side-effects, which may be transient, include ciliary spasm, myopia, pain in the eye, and poor vision in dim light.

Physostigmine is irritating to many eyes and decomposition further increases the irritating potential; preparations in an oily medium are less irritating. This drug may be used at night if pilocarpine fails to maintain control.

Neostigmine (3%) is sometimes used when pilocarpine and physostigmine have failed.

Echothiophate (0·06 - 0·25%) and demecarium bromide (0·12 - 0·25%) are water-soluble, potent, long-acting anticholinesterases which are administered once every 12 - 48 hours. They may improve outflow and control pressure in many patients refractory to other eye-drops. Dyflos is useful in comparatively few patients. These anticholinesterases are effective in the control of chronic wide-angle glaucoma, but should not be used in eyes with narrow angles, since they may cause a rise in intraocular pressure. Because they are long-acting they require less frequent administration than pilocarpine and give round-the-clock control.

Side-effects. These anticholinesterases can produce the side-effects of pilocarpine, especially ciliary pain and dim vision, but these occur more frequently with the more potent drugs, and are more severe. With higher concentrations, watering of the eye, fixed miosis, cysts of the iris, posterior synechiae, fibrinous iritis, vitreous haemorrhage, and rarely retinal detachment may occur. Acute glaucoma may be precipitated in patients with narrow angles. Systemic side-effects including nausea, vomiting, colic, diarrhoea, bradycardia, flushing and sweating may occur. Most of the side-effects are rapidly reversed by stopping the drug or by giving atropine, or pralidoxime (pyridine 2-aldoxime methiodide; PAM) which is a cholinesterase reactivator.

The long-acting anticholinesterases should not be given to patients with narrow-angle glaucoma, nor to patients with asthma or peptic ulcer, and anaesthetists should be told they are being used if a skeletal muscle relaxant is to be administered. Drug resistance is common with all the drugs mentioned, but control may be regained by alternating from pilocarpine to physostigmine. The long-acting anticholinesterases should only be used when these older-established drugs fail.

Mydriatics

Certain adrenergic agents, although mydriatic, reduce the production of aqueous humour and may also increase the outflow. Caution should always be exercised in the instillation of any mydriatic into the eye, especially when the intraocular pressure is unknown. They should not be used when the angles of the anterior chamber are narrow. They are mostly used together with pilocarpine, and can usefully improve nocturnal control by counteracting excessive miosis. This may be particularly important in patients with central lens opacities.

Phenylephrine ('neosynephrine') in 10% solution has frequently been used in the treatment of wide-angle glaucoma, and in glaucoma secondary to uveitis the dilatation of the pupil helps to put the eye at rest, prevents synechiae, and also tends to lower the intraocular pressure.

Adrenaline ('epinephrine') in a stable solution (pH 4) has been used for chronic simple wide-angle glaucoma, but not for narrow-angle glaucoma, e.g. 'eppy' (1%), 'epitrate' (2%), 'glaucon' (2%), or 'lyophrin' (2%). Care is required in patients with hypertension. The prolonged use of adrenaline eye-drops may produce black deposits in the conjunctiva.

Oral Drugs

In chronic simple glaucoma which is not controlled by topical applications, a carbonic anhydrase inhibitor such as acetazolamide, or glycerin may be used, in addition, or by itself (see below).

B. Drugs used in Acute Glaucoma

Miotics

In acute glaucoma (congestive, narrow-angle, or closed-angle glaucoma) physostigmine (1%) is used and possibly pilocarpine as well. These drugs have been considered above.

Carbonic Anhydrase Inhibitors

The drugs in this group include acetazolamide ('diamox'), dichlorphenamide ('daranide'), ethoxzolamide ('cardrase'), and methazolamide ('neptazane'). No significant difference in the efficacy of these drugs appears to have been established, except for the time of onset and the duration of action. The differences in absolute potency can be made up by adjustment in dosage so that for practical purposes they are equally useful. With acetazolamide the initial dose is 500 mg.; subsequent doses of 250 mg. may be given every 6 hours. Dichlorphenamide is given in doses of 25 - 50 mg. 1 - 4 times a day. These are official (BP) drugs. The dose of methazolamide is 50 mg. 2 or 3 times a day. These drugs may act by reducing the bicarbonate content of the aqueous humour and thereby the gradient of osmotic pressure and the amount of aqueous humour formed.

These agents have proved of definite value in the therapy of all types of glaucoma. Dramatic effects may be produced in acute glaucoma, but in chronic glaucoma the self-limiting action renders them less helpful. They have been used in some patients for years, together with miotics.

Side-effects. Prolonged use in angle-closure glaucoma may allow peripheral synechiae to develop so that more serious intraocular surgery will be required when the pressure is no longer controlled. With long-continued administration the carbonic anhydrase inhibitors are liable to produce undesirable systemic effects such as weakness, central nervous disturbances, drowsiness, paraesthesiae in the face, fingers and toes, renal calculi and colic, skin eruptions, and blood dyscrasias. Daily administration of 2 G of potassium chloride causes certain of these general side-effects to subside, and the efficacy of the drugs in controlling intraocular pressure can be maintained in this way for a long time.

Note: *Unlike the carbonic anhydrase inhibitors the thiazide diuretics do not lower intraocular pressure.*

Osmotic Agents

Rapid alterations in the osmolarity of the plasma may result in considerable changes in intraocular pressure.

Hypertonic urea solution (30% in 10% invert sugar solution), freshly prepared, may be administered intravenously in a dose of 1 - 1·5 G/kg. body weight at a rate of approximately 60 drops per minute. This solution has proved especially useful in angle-closure glaucoma that has not responded to other drugs. The disadvantages of the preparation are slowness of the procedure, pain in the arm during the infusion, and extravasation into the tissues causing necrosis.

Mannitol has tended to replace the use of urea, since it produces fewer side-effects. It is used as a 20% solution which is inert and non-toxic, given intravenously in a dose of 0·5 G/kg. body weight; a larger amount may be given according to the needs of the patient. The high molecular weight of mannitol allows little, if any, penetration into the ocular fluids. The effect is not due to re-opening of the channels for aqueous outflow, because the ocular tension is lowered despite obvious continued closure of the anterior-chamber angle. The action is prompt, a definite effect being observed within 30 minutes and lasting about 5 - 7 hours. Rapid administration of large doses in patients with cardiac failure or low cardiac reserve may be dangerous because of rapid overloading of the cardiovascular system.[6]

Both urea and mannitol may cause nausea, headache, and dizziness.

Glycerin administered by mouth is recommended for acute closed-angle glaucoma and also for chronic glaucoma.[7,8] It raises the osmotic pressure of the plasma and so reduces intraocular tension, presumably by dehydration of the vitreous. Its action lasts about 5 hours, thus allowing miotics and acetazolamide to take control. The dose is 1·5 G/kg. body weight (75 ml. for an average person, 140 lb. in weight); it is given

in fruit juice and soda. Most patients experience some headache after administration.

Glycerin is readily absorbed, and provides calories. The ingestion of very large doses may produce haemolysis, convulsions, and paralysis.

Other Drugs that Lower Intraocular Pressure

Certain adrenergic blocking agents have been used to induce mild miosis by causing relaxation of the dilator of the pupil. Dibenamine given intravenously is effective in acute glaucoma, but should not be used in patients with cardiovascular disorders. Tolazoline ('priscoline'), given parenterally, has no significant influence on intraocular pressure.

Guanethidine ('ismelin'), given intravenously, produces effects especially in chronic wide-angle glaucoma, and a 10% solution applied locally produces some fall in intraocular pressure. A number of other drugs lower the intraocular pressure, e.g. autonomic blocking agents like hexamethonium, chlorpromazine, reserpine, thiopentone ('pentothal') and some other central nervous depressants, digitalis, curariform agents, progesterone, and local anaesthetics injected retrobulbarly. There is no practical value derived from most of these. Some may be useful, e.g. in the pre- and postoperative care of patients, or in temporarily lowering intraocular pressure so that miotics can become effective.

DRUGS THAT MAY EXAGGERATE GLAUCOMA

These include anticholinesterases, mentioned above, from their topical use, or less commonly from their systemic administration, in patients with narrow-angle glaucoma. Systemic vasodilator drugs such as glyceryl trinitrate ('nitroglycerin') have been regarded as occasionally producing a transient unimportant increase in pressure; however there is no evidence that elevation of intraocular pressure occurs when nitrates and nitrites are used as vasodilators, e.g. in angina pectoris.[9] Caffeine beverages may occasionally induce a brief rise in intraocular pressure in narrow-angle glaucoma, probably as a result of central nervous stimulation. The antidepressant drug imipramine ('tofranil') should be used with caution in glaucoma; this is not surprising since it has actions like atropine, which is a classical drug known to be dangerous in glaucoma.

PROVOCATIVE TESTS FOR GLAUCOMA

Certain drugs have been used for this purpose, but only after a dark-room dilatation test has failed.

Hydroxyamphetamine ('paredine'), phenylephrine ('neosynephrine'), naphazoline ('privine'), and eucatropine ('euphthalmine') have been used; a rise of 8 mm.Hg, or more, may be considered a positive test for angle-closure glaucoma. However, a negative provocative test is no guarantee of the absence of angle-closure glaucoma. Only one eye should be tested, and after completion of the test pilocarpine nitrate 2% solution, or a stronger miotic, should be instilled to constrict the pupils.

Tolazoline ('priscoline') and butylsympatol ('vasculat') cause a slight rise in intraocular pressure when injected subconjunctivally. They have been used as a provocative test for early glaucoma.

The ingestion of a litre of water after fasting for 4 or more hours will produce a rise in intraocular pressure of 8 mm.Hg, or more, in many patients with open-angle glaucoma. The normal eye rarely reacts in this fashion.

REFERENCES

1. Kimura, S. J. and Goodner, E. K. (1963): *Ocular Pharmacology and Therapeutics*. Oxford: Blackwell Scientific Publications.
2. Jackson, C. R. S. (1964): Practitioner, **191**, 754.
3. Coles, R. S. *et al.* (1962): Amer. J. Ophthal., **54**, 407.
4. Becker, B. and Hahn, K. A. (1964): *Ibid.*, **57**, 543.
5. Modell, W. (1964-1965): *Drugs of Choice*. St. Louis: Mosby.
6. Hill, K. (1964): Amer. J. Ophthal., **58**, 79.
7. Casey, T. A. and Trevor-Roper, P. D. (1963): Brit. Med. J., **2**, 851.
8. Trevor-Roper, P. D. (1964): Proc. Roy. Soc. Med., **57**, 37.
9. Whitworth, C. and Grant, W. (1964): Arch. Ophthal., **71**, 492.