call these cases of malignant glaucoma, using the old term in a new broader sense, or whether we devise a new terminology to describe such phenomena should perhaps await further experimentation.

Conclusion

Many questions still remain in regard to malignant glaucoma, and it is to be hoped that future observations will gradually elucidate them. Today, however, medical therapy consisting of the concurrent use of mydriatic-cycloplegic drops, carbonic anhydrase inhibitors, and hyperosmotic agents is available, and is proving to be effective in half the cases when continued for 5 days. In addition, the vitreous surgery described above is in our opinion a safe and reliable surgical procedure in cases of malignant glaucoma which are not relieved by medical therapy.

COMMENTARY

MALIGNANT GLAUCOMA

Chandler's anterior chamber deepening procedure with gonioscopy used for diagnosis of the extent of synechial closure of the angle does not seem to predispose to malignant glaucoma.

Even though it is known that there is a predisposition to malignant glaucoma in the fellow eye, this eye should always be treated with a peripheral iridectomy as early as possible after the onset of malignant glaucoma in the opposite eye. No medical treatment of any sort should be given before the peripheral iridectomy, since both miotics and mydriatics may be dangerous before surgery is performed. If the fellow eye has been operated upon when the angle has been completely open, then malignant glaucoma has not occurred. However, if angle-closure is present in the fellow eye at the time of surgery, then malignant glaucoma becomes very common. Malignant glaucoma sometimes follows routine cataract extraction.

Medical control of the glaucomas

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The principles of medical therapy in chronic glaucoma are straightforward once the physician has determined the pressure level required for adequate control. This pressure level must, of course, relate to the particular patient and must not be simply some average pressure arrived at by manipulating random population statistics. It is impossible to set rigid guidelines for achieving adequate pressure control but, in general, these should relate to the "functional status" of the patient, since the need for more consistent and lower pressure control increases as his functional status deteriorates. Guidelines for pressure control may thus be roughly related to functional status (Figure, opposite).

Functional Status I (ocular hypertension)	Fields — Normal (I_2 or $1/1000$)	
	Discs — Normal	
	Cup { < 0.3 C/D No asymmetry
	Rim { Width uniform Colour rosy	
Functional Status II (chronic glaucoma)	Fields — Incomplete Bjerrum defect Nasal depression (step)	
	Discs — Cup { > 0.3 C/D --- (vertical diameter greater than horizontal) Asymmetry
	Rim { Width variable Colour rosy Haemorrhage	
Functional Status III (chronic glaucoma)	Fields — Complete Bjerrum (arcuate)	
	Discs — Cup > 0.6 C/D
	Rim { Width variably narrow Colour pale	
Functional Status IV (chronic glaucoma)	Fields — Central and/or temporal island	
	Discs — Cup End-stage
	Rim { Width narrow Colour pale	

FUNCTIONAL STATUS I (ocular hypertension)

These patients may be followed without medical therapy with pressures in the mid to high 20s if this proves necessary. All patients with consistent pressures greater than 24 mm.Hg should have a therapeutic trial with pilocarpine (as described later) and if the pressure reduction is great and their symptoms minimal, the pilocarpine may reasonably be continued. If the pressure reduction is insignificant or the symptoms resulting from its use are debilitating, patients in this category may be followed without therapy, so long as frequent careful visual field and optic disc examinations are carried out.

FUNCTIONAL STATUS II (chronic glaucoma)

Patients who have definite early signs of glaucoma damage should have the pressure controlled below 20 mm.Hg consistently if further deterioration of the functional status is to be avoided. They should be encouraged to tolerate the visual side-effects of miotic therapy. The physician must be certain that the patient understands the serious nature of his disease and the necessity for "round the clock" medical control.

FUNCTIONAL STATUS III

When such an advanced state of functional deterioration is present, every effort must be made to reduce the intraocular pressure to the lowest possible level and further deterioration should be anticipated if intraocular pressures are above 16 or 17 mm.Hg. In this group of patients, all medications, including those known to be potentially cataractogenic, and surgery, must be considered justifiable in gaining adequate control. The patient is obliged to tolerate the side-effects of his medical regimen or to submit to surgery if these are intolerable.

FUNCTIONAL STATUS IV

Intraocular pressures above the 16 or 17 mm.Hg will very likely cause this group of patients ultimately to become blind. Even pressures reduced to very low levels may be insufficient to halt the downhill slide. Many of these patients will require surgery at least in one eye in an attempt to achieve the lowest possible intraocular pressure.

A variety of medications are available to the ophthalmologist for lowering intraocular pressure. Parasympathomimetics and sympathomimetics (particularly those capable of beta stimulation) have so far proved to be the most useful agents. Carbonic anhydrase inhibitors are equally valuable in those patients who can tolerate the systemic side-effects. Osmotic agents have been used infrequently in chronic glaucomas, although their usefulness in reducing intraocular pressure transiently is great.

Parasympathomimetics (Richardson, 1970a)

Acetylcholine is the physiological mediator for neuron-to-neuron transmission throughout the nervous system and for neuron-to-effector cell transmission within the parasympathetic system. It is both manufactured and stored within the neuron and probably achieves its stimulating effect on the postsynaptic membrane by altering its permeability to sodium, thus allowing an inrush of sodium with the consequent depolarization of the postsynaptic membrane. This bolus of positive charges then skips from one node of Ranvier to the next until it reaches the axon terminal (presynaptic membrane) where the depolarization of the presynaptic membrane allows the release of a quanta of acetylcholine molecules into the synaptic cleft. These engage with the specific receptor site, causing an inrush of sodium into the next neuron in the chain, and thus sequentially the nervous impulse spreads distally, ultimately to reach the effector cell. Acetylcholine is very rapidly destroyed at the postsynaptic membrane by the membrane-bound cholinesterase.

Both carbachol and pilocarpine can simulate the effect of acetylcholine, presumably by becoming engaged with the acetylcholine receptor site on the postsynaptic membrane or effector cell. In addition to its direct effect, carbachol binds a small amount of cholinesterase and acts as a weak anticholinesterase. There is some evidence suggesting that carbachol may also increase the amount of acetylcholine released per given stimulus. Carbachol has a molecular structure which differs from acetylcholine only in the presence of one CH_3 and one NH_2 radical. The addition of these radicals to the basic acetylcholine molecule increases its resistance to cholinesterase remarkably. Unfortunately (for therapeutic usefulness), it continues to have the same lack of lipid solubility as acetylcholine. Because of this, it is unable to pass through the corneal epithelium unless this epithelium is disturbed by "wetting agents" such as benzalkonium or methylcellulose.

It is surprising that pilocarpine effectively engages with the acetylcholine receptor site, since its molecular structure in no way resembles that of acetylcholine. The physiological or pharmacological mediator and its receptor site should be structurally complementary.

Pilocarpine is an alkaloid (weak organic base) and exists in an equilibrium between its undissociated (lipid soluble) state and its ionized (water soluble) state. The lipid soluble, undissociated pilocarpine passes easily through the epithelium of the cornea and ultimately into the anterior chamber. Pilocarpine thus does not require a "wetting agent" to aid its corneal penetration and maintains a therapeutic advantage over carbachol in this regard.

Pilocarpine 1 to 4 per cent. and carbachol 0.75 to 1.5 per cent. can be expected to achieve a similar therapeutic response both in magnitude of pressure reduction and in duration of effectiveness. Pilocarpine 8 per cent. has an 8-hour duration of action (Drance and Nash, 1971) compared with 6 hours for the weaker strengths of pilocarpine and carbachol, but does not seem to achieve any greater reduction of intraocular pressure. Carbachol 3 per cent. likewise has an extended duration of action (8 hours) (Flindall and Drance, 1966), and may achieve a greater pressure reduction than the weaker strengths of pilocarpine and carbachol.

Anticholinesterases bind cholinesterase at the postsynaptic membrane and effector cell,

thereby maintaining physiological acetylcholine in its active biostate, effectively prolonging its action. These cholinesterases have been categorized as reversible (physo-stigmine) and irreversible (DFP, echothiophate, decamerium). The reversible anticholinesterases release the bound cholinesterase after a period of time so that it once again becomes active in hydrolysing acetylcholine. The irreversible anticholinesterases in contrast do not release cholinesterase spontaneously or release it in a degraded, ineffective form. However, these irreversible anticholinesterases can be pharmacologically separated from cholinesterase by oximes. If this is accomplished promptly after the anticholinesterase binding, the released cholinesterase is still active. As the duration of anticholinesterase-cholinesterase binding increases, the cholinesterase becomes gradually degraded so that if it has been bound for longer than a few hours, it is ineffective when finally released (Nishimura, Tamura, and Uchida, 1967).

Asymmetrical therapeutic trials with parasympathomimetic agents are clinically useful in determining the effectiveness of pilocarpine or the relative effectiveness of pilocarpine as compared to anticholinesterases. In evaluating the therapeutic response to pilocarpine in a case of bilateral chronic open-angle glaucoma, the drug may be used every 6 hours in one eye and the difference in pressure between the treated and untreated eyes compared. Such asymmetrical therapy helps to reduce the possibility that diurnal variation may interfere with the physician's judgment regarding therapeutic response. This approach is also useful in determining the effectiveness of anticholinesterase agents compared to pilocarpine. If the patient has been treated with pilocarpine in both eyes and the physician chooses to consider the use of an anticholinesterase, the latter should be started in one eye while the pilocarpine is continued in the fellow eye. The difference between the intraocular pressures represents the true value of the anticholinesterase agent and, if the patient is phakic, can be considered to be the value of the cataractogenic potential of the anticholinesterase. When such an asymmetrical therapeutic trial is attempted with anticholinesterases, it must be kept in mind that the initial response to these drugs is frequently not maintained after the first few months of therapy. Thus it is important to continue asymmetrical therapy when evaluating anticholinesterases for a few months before arriving at a judgment as to its value.

Sympathomimetics (Richardson, 1970b; Acheson, 1966)

Noradrenaline (L-norepinephrine), the physiological mediator between the sympathetic axon and sympathetic effector cell, is manufactured and stored within the neuron. It is released from the sympathetic axon in response to a stimulus and becomes engaged at the specific receptor site of the sympathetic effector cell. In contrast to the single mode of destruction of acetylcholine, three possible fates await the released noradrenaline. Under physiological conditions, 90 per cent. of the noradrenaline re-enters the axon from whence it came. Of the remaining 10 per cent. of noradrenaline, a portion is destroyed by catechol-o-methyl transferase (COMT), and the remainder diffuses away from the site of release into the surrounding tissue. Because of these three possible fates of noradrenaline, the pharmacology of the indirect-acting sympathomimetics is somewhat more complex than that of their parasympathetic counterparts. Sympathetic pharmacology is still further complicated, since sympathetic effector cells have both alpha and beta receptor sites. Stimulation of either of these sites reduces intraocular pressure—alpha stimulation by increasing outflow through the trabecular meshwork, and beta stimulation by decreasing aqueous production at the ciliary body. Stimulation of the beta receptors (decreased aqueous production) in general has a greater intraocular pressure-reducing effect than

alpha stimulation. Those pharmacological agents which are capable of stimulating the beta receptors (isoprenaline (isoproterenol); adrenaline (epinephrine)) have a greater pressure-lowering potential than those sympathomimetic agents which possess only alpha-stimulating capabilities (noradrenaline; phenylephrine). Pupil dilation is achieved solely by alpha stimulation. Thus in general, sympathomimetics which have the greatest ability to dilate the pupil (alpha stimulators) are the least likely substantially to reduce intraocular pressure.

Three direct-acting sympathomimetic agents need to be considered. Noradrenaline, the physiological mediator, is solely an alpha stimulator (dilates pupil, increases outflow, decreases intraocular pressure slightly). Isoprenaline is solely a beta stimulator (decreases aqueous production, decreases intraocular pressure). Adrenaline stimulates both the alpha and beta receptors.

Adrenaline continues to be the only direct-acting sympathomimetic agent of clinical usefulness in the glaucomas. Isoprenaline achieves a significant intraocular pressure reduction because of its beta-stimulating capability, but unfortunately the fact that it induces a significant tachycardia in most individuals precludes its clinical usage.

The indirect-acting sympathomimetic agents can be grouped into three categories: those which increase the amount of noradrenaline released per given stimulus (amphetamines), those which block the re-entry of noradrenaline into the axon terminal (cocaine, protriptyline), and those which interfere with its enzymatic destruction (catechol-O-methyltransferase inhibitors and possibly monamine oxidase inhibitors). Since all of these agents achieve their pharmacological effects by exaggerating the alpha-stimulating effect of noradrenaline per given stimulus, they cannot be expected to reduce intraocular pressure as effectively as those agents which are capable of beta stimulation. Similarly, all of these indirect-acting sympathomimetic agents are able to dilate the pupil.

Osmotic agents

When considering the relative effectiveness of the variety of osmotic agents now available, both the direct osmotic effect of the agent and the indirect secondary osmotic effect resulting from induced hypotonic diuresis need to be considered. The direct effect of the osmotic agent relates to the number of molecules introduced and their molecular size. Semipermeable membranes (*i.e.* the blood-aqueous barrier) permit the passage of water-soluble, non-charged molecules with molecular weights less than 100 (*e.g.* urea, mol. wt. 60; ethyl alcohol, mol. wt. 46; glycerol, mol. wt. 92). As molecular weights exceed 100, water-soluble molecules have progressively increasing difficulty in passing through semi-permeable membranes (*e.g.* mannitol, mol. wt. 180; penicillin, mol. wt. 256), while those with a molecular weight greater than 500 usually are unable to filter through cellular membranes. Certain charged molecules do not pass easily through semi-permeable membranes in spite of their low molecular weights unless they are actively transported. Thus sodium, with a molecular weight of 23 and potassium, mol. wt. 39, are passively transferred with difficulty and require an energy-dependent, active transport system to ensure adequate membrane transfer. The ascorbate ion also requires an active transport system to ensure its rapid transfer across a membrane. In view of this, the best direct-acting osmotic agents are likely to be compounds of large molecular weight, such as mannitol, or ionic substances, such as sodium and ascorbate, which rely on active transport (which can easily become overloaded). Glycerol (mol. wt. 92) and urea (mol. wt. 60) would be decreasingly effective as *direct* osmotic agents, and ethyl alcohol (mol. wt. 46) only transiently and weakly effective.

Plasma hyperosmolality stimulates the neurosecretory neurons in the supraoptic and paraventricular nuclei of the hypothalamus to release antidiuretic hormone *via* the posterior pituitary which stimulates reabsorption of pure water from the distal tubules of the kidney. At first glance, it would seem reasonable that the patient receiving osmotic agents would have a decreased urinary production. Clinical experience indicates that this is not the case and that patients so treated experience a sizeable hypotonic diuresis. This apparent paradox is readily understood if one recognizes the dual control exercised over diuresis. Increased intrathoracic, intravascular volume is a strong stimulus inducing rapid hypotonic diuresis. This control system overrides that mediated by way of the osmo-receptors of the hypothalamus so that the patient receiving a large volume of mannitol experiences diuresis in spite of the primary increased serum hyperosmolality. The induced hypotonic diuresis increases the concentration of all molecular and ions within the plasma (the most significant of which is sodium) and creates a secondary hyperosmolar state in the plasma which adds to and prolongs the primary direct effect of the intravenously administered osmotic agent. This secondary hypotonic diuresis is exaggerated as the volume administered is increased or in direct proportion to the molecular size of the osmotic agent. The latter is a factor since agents such as mannitol (mol. wt. 180) remain in the blood vessels and induce the movement of extravascular fluid into the vascular compartments, thereby increasing the blood volume substantially above that caused by the actual infusion of mannitol. Agents such as urea, which easily escape from the blood vessels, do not cause as much increase in the blood volume and thus induce less hypotonic diuresis and secondary osmotic effect.

Mannitol achieves its osmotic effect by both a primary initial effect and a secondary hyperosmolar state; urea also has a dual effect but can be expected to be less effective than mannitol in both the primary and secondary modes of action.

Ethyl alcohol is relatively ineffective as a primary osmotic agent and exerts most of its effect through secondary hyperosmolality induced by hypotonic diuresis. It has a specific depressant effect on the neurosecretory neurons of the supraoptic and paraventricular nucleus and reduces the output of antidiuretic hormone from the posterior pituitary, thereby inducing a serum hyperosmolality relating to hypotonic diuresis.

Medical *versus* surgical therapy in glaucoma simplex

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Miller (1955) stated that as far as he knew the literature contained no description of a prospective trial of medical versus surgical therapy in glaucoma simplex.

A trial has therefore been proceeding at Moorfields since 1964. The preliminary results were described by Smith (1968).