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Papers

Role of Adrenergic Mechanisms in Development and Therapy of Open-angled Glaucoma

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I would like to begin by citing what is one of the earliest characteristics of the eye with primary open-angle glaucoma. This characteristic is not, as you may expect me to say, the simple increase of intraocular pressure, but an increase in fluctuation of the intraocular pressure. A definition of glaucoma in these terms is not new and I could not find words which express this viewpoint more clearly than those of Duke-Elder when he said in his Proctor Lecture (1952) that simple glaucoma was 'characterized initially by an instability of the ocular tension which shows a diurnal phasic variation of more than 5 mmHg, a state which usually – but not invariably – results in a permanent increase'.

This pressure fluctuation cannot adequately be explained as a result of the failure of the aqueous humour to drain from the eye due to an increased resistance, i.e. organic blockage in the trabecular meshwork. It can, however, be fully explained by the following concept concerning the nature of glaucoma. Glaucoma is a vascular disease which develops from a failure of adrenergic mechanisms to regulate pressure in the normal eye.

Glaucoma: Loss of Regulatory Capacity

Keeping in mind the concept of glaucoma as a functional disease of neurovascular systems within the eye, let us look at intraocular pressure and the capacity of the body to regulate pressure more closely. The intraocular pressures of normal eyes of both animals and man are similar in magnitude and show extremely little variation from day to day (Table 1). This similarity between species exists in spite of marked anatomical differences in the tissues through which aqueous humour enters and leaves the eye.

In order to determine the regulatory capacity, pressure must be disturbed and a measurement made of the mechanism in action. Manometric procedures have been developed and used for this purpose in both animals and man (Langham 1959, Langham & Eisenlohr 1963, Langham 1967) but these are not adaptable for studies on conscious subjects. It was therefore necessary to develop an alternative approach which would simulate the manometric technique and this was achieved in the pressure cup procedure (Langham 1962, 1963). An accumulation of aqueous humour is effected by a temporary occlusion of the outflow vessels. An occlusion induced by the application of the pressure cup for ten minutes gives an average pressure increment of 8 mmHg which is sufficient in clinical studies to allow an accurate analysis of the rate of recovery of the intraocular pressure; in normal eyes this pressure increment corresponds to a total accumulation of 14 µl of aqueous humour. Following release of the occlusion, the excess pressure decreases to its initial value, i.e. its normal value, as a simple exponential function of time. For a normal adult eye the excess pressure declines at approximately 12% per minute (i.e. the decay constant is 0·12). It is the value of this decay constant which defines for an individual eye its regulatory capacity

Table 1
Reproducibility of measurements on pairs of eyes of 2 individual subjects

	Pupil diameter (mm)				*Intraocular pressure (mmHg)*				*Tonographic outflow facility (µl min⁻¹ mmHg⁻¹)*			
Time	*Subject 1*		*Subject 2*		*Subject 1*		*Subject 2*		*Subject 1*		*Subject 2*	
(hour)	*Left*	*Right*	*Left*	*Right*	*Left*	*Right*	*Left*	*Right*	*Left*	*Right*	*Left*	*Right*
0	4	4	5	5	13	13	12·5	12·5	0·25	0·25	0·26	0·28
6	4	4	5	5	12	12	12·5	12·5	0·25	0·21	—	—
24	4	4	5	5	12·5	12·5	12·5	12·5	—	—	—	—
28	4	4	5	5	12	12	13	13	—	—	0·24	0·27
120	4	4	5	5	12	12	12·5	12·5	0·25	0·20	—	—
123	4	4	5	5	12	12	13	13	—	—	0·27	0·27
126	4	4	5	5	12	12	13	13	—	—	—	—
144	4	4	5	5	12·5	12·5	13	13	0·22	0·20	—	—
147	4	4	5	5	12	12	13	13	—	—	—	—
150	4	4	5	5	12	12	13	13	0·25	0·24	0·28	0·28

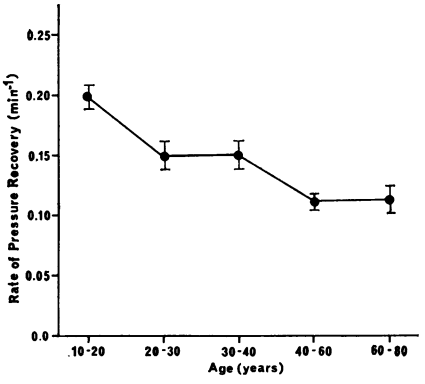

Fig 1 *Influence of age on mean regulatory capacity of eyes of normal subjects. The vertical bars represent the standard error of the mean*

(Langham 1963, Langham & Maumenee 1964, Langham 1967). Since initiating studies with this procedure in 1958 at the Institute of Ophthalmology in London we have made detailed analyses on more than 1,000 normal subjects, glaucoma patients and glaucoma suspects.

A dramatic change in the capacity of normal human eyes to regulate intraocular pressure was found to occur early in life and by the age of 40 to 60 years the mean value had decreased by more than 50% (Fig 1). It is of fundamental importance that this is not reflected in a corresponding increase in intraocular pressure.

In patients with open-angle glaucoma, the regulatory capacity is always severely impaired, and appears absent in approximately 50% (Langham & Maumenee 1964, Rosenthal 1969). Thus the increased pressure resulting from the accumulation of aqueous humour during occlusion of the drainage channels either fails to fall to the initial pressure or decreases at a very slow rate towards it.

Medical treatment of glaucoma patients may improve the regulatory capacity but will not generally bring the capacity within a normal range of values (Langham 1967). Similarly, the regulatory capacity has been found to be absent or seriously impaired in those glaucoma patients who subsequently developed ocular hypotension with onset of retinal detachment (Langham & Regan 1968).

On the other hand, it is not without significance that the ocular hypertension induced by the topical administration of glucocorticoids to normal subjects leaves the regulatory capacity intact although decreased in value (Langham 1967).

Hereditary Aspect of Pressure Regulation

It is well known that the incidence of open-angle glaucoma in the offspring of families with glaucoma is at least ten times in excess of the glaucoma incidence in the general population. If then we assume that the loss of pressure regulation leads to glaucoma it is important to know whether the glaucoma subject starts life with this abnormality. To find the answer, a comparative study was made of 50 young adolescents of families with no history of glaucoma and 50 adolescents who had at least one parent or grandparent with established open-angle glaucoma. The results summarized in a histogram are shown in Fig 2. The offspring of the glaucoma families showed a distribution of pressure regulatory capacity significantly lower than that of the offspring from normal families. Thus, there exists a strong possibility that glaucoma subjects may be identified many years before impairment of vision. This possibility is increased by my observations of glaucoma suspects who over a period of years developed field loss and who had shown loss of regulatory capacity several years previously.

From our studies on normal subjects, on patients with open-angle glaucoma and on the offspring of glaucoma patients, we have seen that regulatory capacity as measured by the pressure cup technique is a definitive indication of the eye's health. If, however, we have only an indication that the eye is not functioning properly, our battle is half won. We must find a way to treat the eye which is not functioning properly and, ideally, we must find a way to treat the eye before severe damage to the visual field has occurred. For this treatment we must return to the regulatory capacity itself.

Adrenergic Mechanisms and Intraocular Pressure

A good deal of experimental evidence has been compiled which indicates that the adrenergic

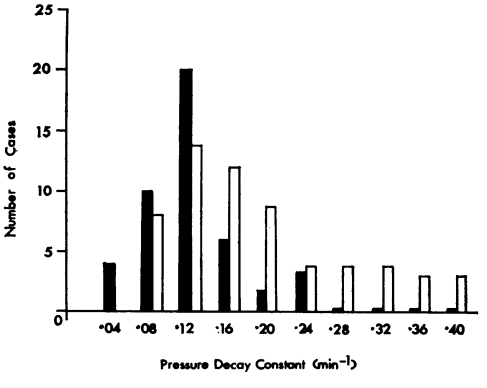

Fig 2 *Comparison of pressure regulatory capacity in adolescent children from families without a history of open-angle glaucoma (white columns) and from families in which at least one parent or grandparent had confirmed open-angle glaucoma (black columns)*

Table 2
Response of adult subjects to l-norepinephrine

Concentration (mol/l)	*Pupil*		*Intraocular pressure*		*Outflow facility*	
	Control	*Experimental*	*Control*	*Experimental*	*Control*	*Experimental*
0·06	3·7±0·2 (5)	3·7±0·2 (5)	14·5±0·5 (5)	14·5±0·5 (5)	0·30±0·02 (5)	0·29±0·02 (5)
0·12	3·7±0·2 (5)	5·5±0·4 (5)	12·1±0·3 (5)	12·1±0·4 (5)	0·25±0·02 (5)	0·25±0·03 (5)
0·25	3·8±0·2 (5)	7·3±0·4 (5)	—	—	—	—
0·50	3·9±0·7 (5)	8·7±0·5 (5)	17·4±1·0 (5)	15·9±0·8 (5)	0·23±0·02 (5)	0·28±0·03 (5)
1·0	3·9±0·2 (5)	8·9±0·3 (6)	16·2±0·8	14·0±1·1	0·27±0·01	0·35±0·02

50 µl of l-norepinephrine bitartrate was applied to one eye of individual subjects. The mean pupil diameters of the experimental eyes is the mean of the maximal dilatation. The intraocular pressure and outflow facilities are the mean value recorded at 6 hours after administration of the drug. Number of subjects shown in parentheses

nervous system is the key to the regulatory capacity of the eye. Adrenergic amines produced by the sympathetic innervation in the eye have been found to modify the following three ocular processes: aqueous humour formation, uveal blood flow, and aqueous humour outflow. These three processes are fundamental to the eye's mechanism of regulation. Our pharmacological therapy must, therefore, be based on these very mechanisms.

I would like to consider in detail the role of these adrenergic mechanisms. I will confine my discussion to the role of the adrenergic mechanism in the human eye, and in particular to the response of the ocular tissues to norepinephrine, the transmitter substance of the sympathetic nervous system, which is an α-adrenergic agonist; isoproterenol, a β-adrenergic agonist; and epinephrine, a catecholamine which shows both α- and β-adrenergic agonistic activity.

The ability of α-adrenergic mechanisms to decrease intraocular pressure and increase the outflow facility is seen in the response of normal eyes to norepinephrine applied topically (Table 2). In addition to showing vasomotor activity norepinephrine also acts on the myoepithelial cells of the iris to cause pupillary dilatation. This response is easy to quantitate and provides a good indication of the sensitivity of the α-adrenergic receptors. The dose-response curve of pupillary dilatation to l-norepinephrine is summarized in Fig 3. Each point corresponds to the mean maximal dilatation. Maximal dilatation occurs within one to three hours, complete recovery occurring within twenty-four hours.

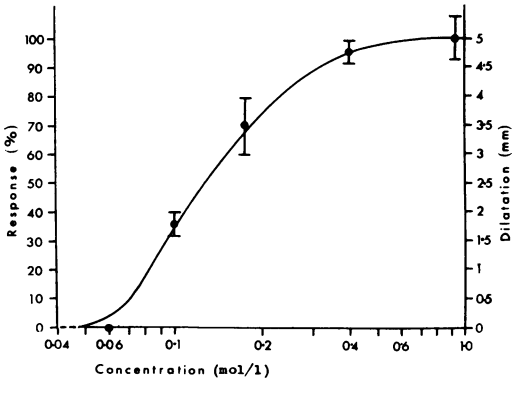

Fig 3 *Dose response curve of the pupils of normal adult subjects to solutions of norepinephrine, 50 µl applied topically*

The responses of the human eye to norepinephrine are similar to those observed in conscious rabbits and lightly anæsthetized monkeys. In these species confirmation of the α-adrenergic mechanisms has been derived from observations that the responses to norepinephrine may be blocked by prior administration of the α-adrenergic antagonist, phenoxybenzamine (Langham 1965, Kitazawa & Langham 1968).

The presence of β-adrenergic mechanisms in the human eye capable of effecting reduced intraocular pressure in a qualitatively different manner from norepinephrine has been demonstrated by isoproterenol applied topically. This catecholamine reduces intraocular pressure without either pupil dilatation or increased outflow facility (Table 3). These responses are also identical to those observed in rabbits and monkeys and may be blocked by the β-adrenergic receptor antagonist propranolol (Langham 1965, Kitazawa & Langham 1968).

Epinephrine, a catecholamine which has been widely used in the treatment of glaucoma is more complex in its action on animal and human eyes in that it is an agonist for both α- and β-adrenergic receptors. Its ocular effect differs quantitatively from norepinephrine in that mydriasis is more difficult to elicit, and that it may induce pressure decrease without either pupil dilatation or increased outflow facility (Langham *et al.* 1971). In this respect epinephrine in the concentrations available for therapy of glaucoma closely resembles the action of isoproterenol (Langham *et al.* 1971).

The ability of both α- and β-adrenergic mechanisms to decrease intraocular pressure both in normal animal and in human eyes raises a distinct possibility that the anatomical functional interrelationship is qualitatively similar in the different species. This viewpoint finds support in fluorescent histochemical and electron microscopic studies of the adrenergic innervation of

Table 3
Influence of 0·05 mol/l solution of dl-isoproterenol on eyes of 16 subjects

Time (hour)	*Control (C)*	*Experimental (E)*	*C − E*▲
	Pupil size (mm)		
0	4·3±0·1	4·3±0·1	0
3	4·3±0·2	4·1±0·2	−0·2±0·3
6	4·2±0·2	4·0±0·3	−0·2±0·3
24	4·3±0·1	4·3±0·2	0 ±0·1
	Intraocular pressure (mmHg)●		
0	16·8±0·9	16·7±0·9	−0·1±0·1
1	17·6±1·0	16·1±1·2	−1·5±0·4
4	16·0±0·9	12·8±0·9	−3·2±0·8
24	16·3±0·8	14·9±0·9	−1·4±0·6
	Tonographic outflow facility(μl min^{-1} $mmHg^{-1}$)■		
0	0·28±0·02	0·28±0·02	0·0±0·02
4	0·25±0·02	0·29±0·03	0·04±0·02
24	0·28±0·02	0·26±0·03	−0·02±0·01

50 μl of 0·05 mol/l dl-isoproterenol was applied topically to the experimental eye at T = 0 hour.
●measured by Goldmann applanation tonometer
■measured by the Schiøtz indentation tonographic procedure
▲difference in pairs of eyes of the 16 individual subjects

the eye. In man and all animal species a dense adrenergic innervation of the iris, ciliary body and a less dense network to the intrascleral vessels has been found (Staflova 1969*a*, *b*, Ehinger 1966).

It would seem, therefore, that the role of adrenergic mechanisms in regulating intraocular pressure in animals is a good indication of a similar mechanism in normal man. Unfortunately, confirmation of this hypothesis has not yet been possible, for the necessary manometric and electrophysiological experiments can only be performed in animals. Nevertheless, let us accept the assumption that adrenergic control of intraocular pressure in man is similar to that demonstrable in animals and see how well this may help unravel the problem of glaucoma therapy.

The important question facing us several years ago was whether we could use our new understanding of the role of the sympathetic nervous system, the adrenergic receptors and catecholamines in regulating pressure in animal eyes to influence favourably the intraocular pressure and fluid circulation in the glaucomatous eye in ways better than are presently available to us. Several theoretical possibilities were considered, including the use of denervation supersensitivity induced either surgically or pharmacologically or, alternatively, potentiation of the effect of normal sympathetic nervous activity and exogenously administered catecholamines on the ocular tissues. I would like to consider our choice of adrenergic potentiation as this has become the principal basis of our new therapeutic approach to glaucoma.

The ability of certain antidepressants to potentiate the peripheral action of norepinephrine has been related to their ability to inhibit the uptake of norepinephrine into the adrenergic neurone (*see* Langham & Carmel 1968). In this connexion it has become increasingly clear that neuronal uptake of the adrenergic transmitter norepinephrine is the principal mechanism for terminating the adrenergic response. To elucidate the potential application of this concept to influence favourably intraocular pressure, I chose the compound protriptyline (Fig 4) because it was known to be an active adrenergic potentiator and a powerful inhibitor of norepinephrine uptake into the adrenergic neurone (Malmfors 1965). In addition, its chemical stability and aqueous solubility made it suitable for topical administration on the eye. Recently, we have extended our studies to include an oxygen bridged analogue of protriptyline (Fig 4) which appears to be less irritating than protriptyline to the cornea and to have more specific adrenergic properties (Langham & Diggs 1971).

The ability of protriptyline to potentiate the ocular response both to norepinephrine released endogenously or norepinephrine applied topically in animals and man has been documented (Langham & Carmel 1968, Kitazawa & Langham 1968, 1971*a*, *b*, Langham *et al.* 1971). Typical results on normal subjects are shown in Figs 5 and 6. The adrenergic potentiation of norepinephrine applied topically has been found to correspond to a shift of the dose-response curve by approximately 15 times, which indicates a greater than 90% inhibition of norepinephrine uptake (Langham & Diggs 1971). It is of particular significance that the duration of the pressure response to norepinephrine may be increased to more than twenty-four hours (Fig 6).

In an extension of the studies on norepinephrine and protriptyline, Kitazawa & Langham (1968) compared the potentiating activity of protriptyline on the ocular response to the α- and β-adrenergic agonists – norepinephrine, epinephrine and isoproterenol in rhesus monkeys. They found the potentiation of the epinephrine response to be much less than for norepinephrine and absent for isoproterenol. Similar conclusions were later found in analogous studies on normal subjects (Kitazawa & Langham 1971*a*, *b*, Langham *et al.* 1971).

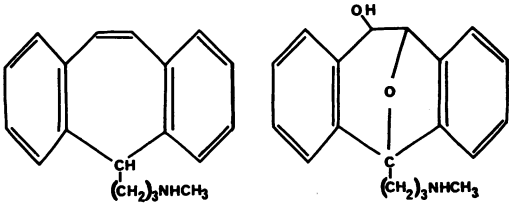

Fig 4 *Chemical structures of adrenergic potentiators. Left, protriptyline 5-(3-methylaminopropyl)-5H-dibenzo [a,d] cycloheptene. Right, oxygen bridged analogue of protriptyline trans 10,11 dihydro-5-(3-methylaminopropyl)-5,10 epoxy-11-hydroxy 5H-dibenzo [a,d] cycloheptene*

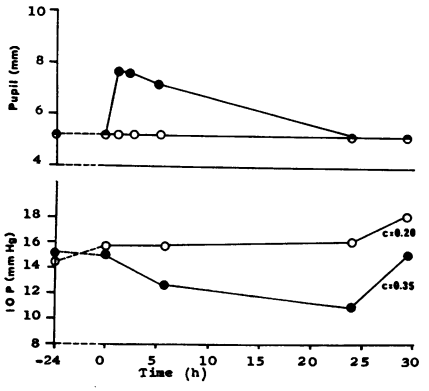

Fig 5 *Pupillary and intraocular pressure responses of eyes of a normal adult subject to either norepinephrine alone or to a combination of norepinephrine and protriptyline. At T=O, 50 µl of 0·1 M norepinephrine was applied topically to one eye (o———o), and 50 µl of 0·1 M norepinephrine with 0·05% protriptyline to the contralateral eye (●———●). c=outflow facilities 30 hours after administration of the drugs. Seven days after completion of the study outflow facilities in the two eyes were 0·20 and 0·22 µl min^{-1} mmHg^{-1} respectively*

Glaucoma Therapy: New Possibilities

We therefore arrive at the concept that open-angle glaucoma is a neurovascular disease in which there is a failure of the adrenergic mechanisms to regulate and stabilize the intraocular pressure. Two questions, one theoretical and one clinical, remain to be answered: (1) Do α- and β-adrenergic mechanisms act to reduce intraocular pressure in the glaucomatous eye and does neuronal uptake of norepinephrine limit the response in the glaucomatous eye? (2) What qualitative and quantitative differences are we to expect in the responses of glaucomatous eyes to the catecholamines and adrenergic potentiators?

Before presenting experimental observations relating to these questions, it is important to emphasize that the marked instability of intraocular pressure in the glaucomatous subject means that strictly controlled experimental procedures must be adhered to in order to interpret correctly whether an ocular response is due either to the drug or to a spontaneous variability of intraocular pressure. The spontaneous variation in intraocular pressure is minimized when the glaucoma patient is kept in bed and it is under these conditions that the most definitive results may be obtained. This problem of drug evaluation in glaucoma is compounded by the fact that whereas no contralateral effects are seen in the adrenergic treatment of normal eyes, it has been found that reduction of an elevated intraocular pressure in glaucomatous eyes can induce a consensual pressure decrement (Kitazawa & Langham, unpublished). Fortunately, the consensual response is normally small compared with the direct effect of the drug on the treated eye, and consequently, the untreated eye may be used as a reference.

The effectiveness of α-adrenergic agonists, e.g. norepinephrine, to decrease intraocular pressure in the glaucomatous patient has been established (Kitazawa & Langham 1971*b*). Significant reduction in intraocular pressure associated with increased outflow facility was sustained over the seven-day period of treatment. Withdrawal of the norepinephrine led to a reversal of the response.

It is of clinical interest that the pressure and outflow facility responses to norepinephrine closely simulate, qualitatively and quantitatively, those observed by Linner (1958) in his well-controlled study of the response of the glaucomatous eye to pilocarpine.

In similar studies isoproterenol, the β-adrenergic agonist, was found to decrease intraocular pressure without either pupil dilatation or increased outflow facility in glaucomatous eyes (Kitazawa & Langham 1971*b*). These results agree with those recently reported by Ross & Drance (personal communication).

The old and well-established observations that epinephrine with its α- and β-adrenergic activity may reduce intraocular pressure, increase outflow facility and decrease aqueous humour formation in early and advanced cases of open-angle glaucoma add further weight to the conclusion that in the glaucomatous eye the responses to α- and β-adrenergic agonists are qualitatively similar to those of normal eyes.

We now turn to the action of neuronal uptake in limiting the pressure response in the glaucomatous eye to α-adrenergic agonists and in particular to norepinephrine. This has been investigated by comparing the response of eyes of individual glaucomatous patients to norepinephrine alone or to a combination of norepinephrine and an adrenergic potentiator. The results showed significant potentiation both in terms of pupil dilatation and in increased time of pressure response (Kitazawa & Langham 1971*b*).

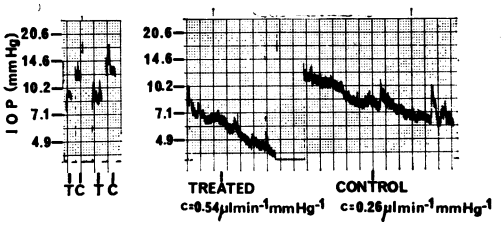

Fig 6 *Records of intraocular pressure and tonograms of eyes of a normal subject 24 hours after application of 50 µl of 0·1 M norepinephrine to one eye* (C) *and 50 µl of 0·1 M norepinephrine containing 0·05% protriptyline to the contralateral eye* (T). *Prior to the initiation of this study, pressures and outflow facilities in the two eyes were equal*

It is on the basis of these results confirming the qualitative similarity of the adrenergic response in normal and glaucomatous eyes that we may clarify the clinical approach to the individual patient. The important question will arise each time a patient is seen whether the quantitative responses to drug therapy will reduce the pressure sufficiently to slow or stop progression of the disease. In keeping with all forms of medical and surgical treatment of glaucoma, it must be anticipated that the success of adrenergic therapy will be greatest when the glaucoma is diagnosed early. In this respect adrenergic therapy would appear to have significant theoretical and practical advantages over miotic therapy.

Pilocarpine therapy has to contend with two unfortunate side-effects. First, the spasm of accommodation which may impair vision for one to two hours following topical administration of the drug; second, the induction of extreme miosis and an immobile pupil which curtails night vision. The adrenergic potentiator alone or in combination with norepinephrine has neither of these disadvantages. The effect on accommodation is generally negligible and the pupil remains mobile and, of course, is not constricted.

A further potential of the adrenergic therapy over pilocarpine is seen in its ability to influence intraocular pressure and the regulatory capacity in normal eyes (Langham & Carmel 1968). These positive responses are in marked contrast to the inability of pilocarpine to induce a sustained decrease of pressure in normal eyes even though it causes marked miosis (Willetts 1968).

In a patient with advanced glaucoma the prospects of halting progressive loss of vision may best be evaluated by assessing the patient's regulatory capacity (Langham & Maumenee 1964). If the regulatory capacity is unresponsive to therapy, even though the intraocular pressure appears to be in the normal range, glaucoma surgery is probably the only recourse. I have said the pressure 'appears to be low' because I feel that if the regulatory capacity is not functioning the pressures will inevitably fluctuate and rise. If, however, the regulatory capacity is responsive to adrenergic therapy and the pressure remains normal, the prognosis is good. Of course, nothing can be done to reverse structural damage to retinal tissue if it has already occurred.

In conclusion, I will refer to the anatomical aspects of the vascular control of intraocular pressure which we are hoping to elucidate.

Norepinephrine, the α-adrenergic agonist, generally acts by constricting blood vessels, whereas isoproterenol is a vasodilator. Thus, it is necessary to explain why vasoconstriction increases outflow facility and vasodilatation decreases aqueous humour formation. The problem appears paradoxical at first sight, but I would like to suggest that the explanation will be found on the basis that the rate of bloodflow to the ciliary processes determines the rate of aqueous humour formation and that aqueous humour and blood compete for the same channels. Experimental evidence that aqueous humour formation is proportionate to bloodflow to the ciliary processes has been found by Langham & Rosenthal (1966) in studies in which decreased bloodflow was induced by electrical stimulation of the preganglionic cervical sympathetic nerve. In human subjects a similar correlation most probably explains the significant reduction of aqueous humour formation that occurs over the age of 60 years (Langham 1967). In the outflow system the competition of blood and aqueous humour for the same exit veins finds support in the many studies on aqueous veins and in the detailed studies of Ashton (1951, 1952).

Under these conditions it may be hypothesized that vasoconstriction in the blood vessels leading to the intrascleral venous plexus would decrease the vascular filling of the system and result in increased facility of outflow of the aqueous humour. Similarly, the action of isoproterenol in decreasing the rate of aqueous humour formation would be visualized in terms of drawing off blood from the ciliary processes by vasodilatation. Evidence consistent with a shunting of blood from the ciliary processes has been put forward recently by Cole & Rumble (1970). The anatomical observations of Kiss (1943) on the anterior ciliary plexus are of special interest in this connexion. Kiss showed by perfusion techniques the presence of relatively large veins connecting directly with the episcleral venous system. Adrenergic innervation of vessels in this area have been described (Ehinger 1966) and it is this system which appears to provide the means of modifying bloodflow both to the ciliary processes and to the intra- and epi-scleral plexuses. The general nature of this neurovascular concept of regulation of intraocular pressure and aqueous humour dynamics has recently found strong support in the exciting and extensive theoretical analysis of Hart (1970).

Concepts are the essential stepping stones leading to new knowledge. The value of the concept rapidly wanes when it is no longer able to explain and unify experimental observations. It was the inadequacy of current concepts of aqueous humour dynamics to explain regulation of intraocular pressure (*see* Langham 1958) that led me to seek alternative experimental approaches to the problem. The resulting concept which has been presented in this paper will doubtless undergo modification, but it has already served well in providing the scientific rationale for the development of a new drug therapy for glaucoma and its prevention. Now is the opportunity for

wider consideration and application of this knowledge.

Finally, I would like to pay tribute to the enthusiastic research collaborators working in the specialties of physiology, electron microscopy, pharmacology, biophysics and the clinical sciences who have made this research endeavour possible.

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Pharmacogenetics in Ophthalmology

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The clinical experience of variable drug reaction is both frustrating and a stimulus to reappraisal of the action of the particular compound. The improved quality of the pharmaceutical preparations and the greater knowledge of genetic influences aided by statistical analysis have led to the development of a branch of pharmacology which is called pharmacogenetics.

In ophthalmology a pharmacogenetic concept has existed for more than a century, since the first observations in 1862 of an unusual response in certain rabbits to atropine. Fleischman in 1910 isolated atropine esterase. Attempts to implicate such an enzyme in human blood have been negative, but the concept exists that there is both a racial and an individual difference in response to mydriatics, in particular that blue irises are more responsive to mydriatics than brown.

This was tested in Caucasians, the subjects being further subdivided on the basis of the eye colour scale of Professor R Martin. Paredrine hydrobromide was the mydriatic employed, and measurements were made before application and after thirty minutes. While a bimodal trend existed, there was not statistical significance at the 95% level. It is undoubtedly true that a racial difference occurs and this has been shown in the response of Negroes to atropine. A similar difference is not clearly shown in the response to sympathomimetics, which would indicate that this parasympatholytic variability is related to a difference in acetylcholine metabolism and perhaps unrelated to the melanin content.

An important occurrence is the sensitivity to suxamethonium bromide occasionally seen during anæsthesia (about 1/2,000–1/3,000) and possibly potentiated, in those susceptible children undergoing strabismus surgery, by pre-operative long-acting miotics. The percentage inhibition of the enzyme by a local anæsthetic dibucaine not only gives a method for calculation of enzyme activity but also serves to trace genetically the family sibs likely to be affected. It has been shown that a triphasic distribution occurs in pseudocholinesterase levels.

It can be postulated that some of the reactions seen after relatively large amounts of local anæsthetics, particularly lignocaine, are related to the inability of serum cholinesterol to inhibit systemically absorbed local anæsthetic agents. This is of particular significance in ophthalmology, where the retrobulbar anæsthetic is given into an area rich in large veins; and in glaucoma surgery the patients are often potentially sensitized by their miotic regime.

[A list of references is available on request.]

The following papers were also read:

Richardson Cross Lecture:
Ocular Reactions Due to Drugs
Dr Irving Henry Leopold
(Mount Sinai Hospital, New York)

Ophthalmic Medicaments – Pharmaceutical Considerations and Criteria
Professor D A Norton
(Bath University of Technology)