COMMUNICATIONS

VASO-MOTOR FACTOR IN GLAUCOMA*†

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The history of glaucoma may be summarized by referring to its recognition by an Arabian, Sams-ad-din, writing about the middle of the 14th century, who described it as "headache of the pupil", and by recalling the statement of Mackenzie (1830) that raised ocular tension was a fundamental feature of the disease, his logical remedy of surgical decompression, and the 20th-century interest in its "medical" basis.

The finding that the aqueous fluid has an osmotic pressure higher than that of plasma (Kinsey, 1950) implies that any freely filtering scar may interfere with this special internal environment, and stresses—if such emphasis were necessary—the general tendency of surgery to involve drawbacks in spite of its undoubted immediate value.

Aetiology

The "vascular" theory of the aetiology of glaucoma has been gaining ground for the past 50 years. Sulzer and Ayrignac (1914) first drew attention to what we now know as the diurnal variations.

To identify the cause of the phasic rise of pressure in the eye and venous outflow system, Duke-Elder (1955) cites the following facts:

(i) The phasic variation is abolished by orbital (retrobulbar) anaesthesia affecting the ciliary ganglion (sympathetic and parasympathetic supplies both abolished).

(ii) Simultaneously the phasic variations in the contralateral eye are reduced or abolished (interocular effects by axon reflexes).

(iii) The phasic variation is abolished by blocking the stellate ganglion—proof of a predominant sympathetic agency.

(iv) Similar effects are obtained with hexamethonium or dibenamine (pharmacological sympathetic block).

Eserine and pilocarpine have, of course, both vasodilator and miotic effects, and their defensive efficacy in the presence of aniridia or iridectomy shows that it is the former (vasomotor) action that is at work.

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E. Gordon Mackie

The well-known effect of excitement or emotion in precipitating attacks further supports the notion of vasomotor (sympathicotonic) influences on the disease—alleged to occur by vasoconstriction and high pressure in the relatively direct arteriolar-venous communications in the uvea.

For the views of present-day leaders of international ophthalmological thought on the matter the student must consult the symposium on glaucoma edited by Duke-Elder (1955).

Espildora-Luque (1948) regarded such localized vasomotor disturbances as exclusively due to cephalic hypertension and presumed the existence of a similar local ocular state. His observations—endorsed by other workers—accord with the findings of Franklin (1951), and gain support from the effect of amyl nitrite, caffeine, and antipyrine (by mouth) in lessening systemic blood pressure but causing dilatation of cerebral vessels and increasing ocular tension.

It would be wise at this stage to mention—if only to by-pass—the theories that depend on resistance to outflow. These fall into two groups:

(i) The resistance is regarded as structural—arising possibly in the trabecular tissue (influenced by hyaluronidase, ascorbic acid, and probably other agents—e.g. steroid; diminished by perfusion with saline; preserved or "protected" by some characteristic factor in the aqueous). Or it may arise in the intra-scleral channels; Samoiloff (1948) argues for oedema of the scleral tissues as an impediment—the oedema simultaneously affecting the retina and producing the scotomata found in glaucoma.

(ii) The resistance is said to arise by vascular turgescence closing an "angle" (of the anterior chamber) formerly quite open, and so obstructing outflow. In this case a disorder of physiology causes a complete block, leading to the sudden acute (congestive) glaucoma of tradition.

None of these theories of obstruction needs to be denied. On the contrary, a varying and especially a raised outflow resistance would cause (spasmodically or steadily) an enhanced effect from vascular variations, the two processes proving complementary.

If we then return to the known facts of the phasic variations and their probable sympathicotonic basis, it may help us if we review the available sites of therapeutic action and note past successes and new possibilities. We may try to prevent the initiation of the impulses (implying central sedation), to impede the propagation by ganglion block, or to impede the effector action by adrenergic blocking agents acting at the end organ (Mullen and Leopold, 1951).

Ganglion Block.—This has been made possible by the methonium compounds, but these are too comprehensive in action, and the side-effects (e.g. on bowel action and on accommodation) and the need for an injection technique preclude their use.
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Adrenergic Block to impede Effector Action.—Christensen, Swann, and Gould (1948) used Dibenamine effectively in chronic glaucoma, and this drug is listed by Mullen and Leopold (1951), together with Benzodioxans, Imidazolines (Priscol, etc.), Yohimbins, and Ergot alkaloids, as a possible agent. The clinical results have been generally disappointing, Dibenamine alone appearing to have real value. It may be relevant that this is the only drug that has a full effect, not only in reversing the pressor action of Adrenalin, but also in abolishing that of Nor-Adrenalin (e.g. Priscoline and Rogitine fail in the latter). The Dibenamine successes accrued in hypertensive patients, so stressing the vascular factor. Dibenamine must be given under hospital conditions in dilute intravenous drip, and therefore remains an experimental tool. However, Stoll and Hoffman (1943) showed that, while ergot alkaloids are themselves very inactive in the desired way, their hydrogenated products are both less toxic and pharmacologically more potent; the mixture called Hydergine (Sandoz) was used by Posner (1950) with good effect in congestive cases and with much relief of pain, but the results were disappointing in chronic cases. Rintelen and Smolik (1950) are quoted as confirming this, and Agarwal (1954) published results in 27 cases somewhat resembling those of Posner, in which all the patients experienced relief of pain. Tension, pain, and congestion were significantly improved in six chronic congestive patients, who also relapsed less on discontinuance. The most marked ocular responses occurred in patients whose blood pressure responded by a useful reduction, and a moderate rise or none was seen on ceasing treatment. Agarwal remarks that, if glaucoma is primarily due to sympathetic overactivity, then the effect of this drug, Hydergine, should have been greater and more prolonged: “It may be that sympathetic overactivity is only one of the many aetiological factors involved in glaucoma.”

So we may sum up as follows:

(1) The concept that glaucoma is largely due to vascular disturbance is valid.
(2) The influence of sympathicotonia cannot be denied, but it may be only one of the factors involved (Agarwal, 1954).
(3) Repeated but ill-defined observations of renal and hepatic dysfunction have been made in glaucoma patients.
(4) The responses to treatment are associated with the power to block both Adrenalin and Nor-Adrenalin (Dibenamine).
(5) Either the disease is associated with an excess output of adrenergic materials, or the presence of some factor causes excess sensitivity of the vasomotor system to normal adrenergic stimulation.
(6) Since the factor postulated under (5) must be one that is compatible with the known age incidence of the disease, the latter hypothesis seems the more tenable.

We might reasonably hope to derive some help from the provocative tests, but these are neither very reliable nor very informative, tending to be positive most frequently in cases already diagnosed.

Systemic Considerations

In considering the instability of the vasomotor system, systemic hypertension and its mechanism should repay study; on this subject a masterly assembly of fact is presented by Smith (1951). A discussion of the role of
the sympathetic nervous system in vascular hypertension was given by Adler (1951), who quoted work showing a normal peripheral blood flow everywhere, except possibly for a very slight reduction in the kidneys, implying a narrowing and sclerosis of the arterioles. (This special state of the renal vessels may have a particular significance.) Discussing the possible agency of experimental renal hypertension, Adler showed that the evidence inculcated a humoral agent, the sympathetic system being secondary. Starting with the raised basic pressure level of hypertension (both experimental and essential human types), vaso-constrictor impulses could produce disproportionate effects and sympathectomy had a value in eliminating such pressure peaks. (It may be recalled in this connexion that an efficient sympathetic block abolishes the phasic variations in the eye.)

Hypertension can be produced by experimental neurogenic mechanisms, but is then of a different character from the essential type.

In brief, in hypertension, we have an essential state caused by a presumed humoral agent, and another state of neurogenic origin, which can be superimposed upon the former or can arise independently. Let that statement be recast as if it referred to glaucoma, and it reads: "In the one case we have both an essential state (increased phasic variations or chronic glaucoma) caused by a presumed humoral agent, and another state of neurogenic origin (acute or congestive glaucoma) which can be superimposed on the former or can arise independently." This superficial parallelism may be accidental but is nevertheless startling, and it appears to justify, or even encourage, further study to test the point.

Franklin (1951) discussed regional control and the selective direction of blood flow to serve the needs of the organism in emergencies, e.g. haemorrhage or obstetric shock, and also as a physiological adjustment for special needs, e.g. the cerebral blood supply in diving mammals. As part of this mechanism, he described the phenomenon of by-passing capillaries through direct connexions between contractile arterial branches and venous networks, e.g. in the lungs. (Cristini (1951) demonstrated these shunts in the choroid of glaucoma patients.) Franklin (1951) quoted the demonstration of Trueta, Barclay, Daniel, Franklin, and Prichard (1947) that in a variety of conditions a diversion of part or all of the renal cortical blood flow could cause the relative anoxia of cells in the ischaemic tissue. (The kidney is normally kept under a high oxygen tension; renal venous blood in the dog is over 85 per cent. oxygenated.)

Under the condition of relative anoxia the renal cortex produces an enzyme, renin, and a vasotropie factor, “vaso-exciton material” (V.E.M.).

(i) Renin (known since 1898) is an agent which acts on the arterioles and is concerned with the inception of hypertensive states. Wilson (1953) says: “It may operate in acute hypertension but does not in chronic, and another agent must be there.”
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(ii) V.E.M. is a vasotropic factor which has been physiologically detected and studied for 12 years. It is inactivated by the renal cortex when that part of the kidney is once again adequately supplied with oxygen.

Another vasotropic factor (vaso-depressor material—"V.D.M.") which has been chemically identified by Mazur and Shorr (1948) as Ferritin or Apoferritin, is produced pre-eminently by the liver under anoxic conditions.

In the compensatory phase of shock, the renal cortex is rendered anoxic before the liver; so V.E.M. is produced but not yet V.D.M. In the decompensatory phase, V.E.M. is still produced, but the renal cortical blood flow has become too scanty to carry it away into the general circulation. Meanwhile, reduction in the oxygen supply to the liver results in the anoxic production of V.D.M. So V.E.M. predominates in the first phase of shock and V.D.M. in the second phase.

The part of the vascular system upon which these particular vasotropic factors exert their influence lies between the arterioles and the venules (already mentioned as the probable site of disturbance in the eye in glaucoma).

V.E.M. enhances the frequency and amplitude of the rhythmic constrictor activity (vasomotion) of the metarterioles and precapillary sphincters, and very greatly enhances their reactivity to the topical application of Adrenalin (Rosenheim, 1954).

V.D.M. has the reverse effect, diverting blood to the true capillaries and causing venular stagnation and inadequate venous return, which, if sufficiently widespread in the body, may lead to death.

The initial shock reaction, able to provide the anoxic conditions necessary for the production of V.E.M., may be a nervously intermediated one, such as Trueta and others (1947) found in their tourniquet experiments, i.e. in a relatively acute and severe emergency. But these pressor substances have been identified in the blood in less transient conditions, such as essential hypertension (V.E.M.) and cardiac failure (Smith, 1951, p. 778).

Apart from such intercurrent factors, another process of general incidence is capable of actuating the production of V.E.M. Franklin (1951) noted in animals that loss of blood or other forms of severe circulatory handicap were followed by a selective order of reduction of blood flow, the skin and non-vital skeletal muscles being the first to be starved, then the spleen and renal cortex, and much later the brain and spinal cord. This "order of sacrifice" corresponds roughly to the reverse order of development of functional activity in intra-uterine and immediate post-natal life:

"The heart is busy from very early stages in the foetus. In the central nervous system the demonstrable onset of activity occurs about a fifth or more on the way towards full term. The renal cortex in many species is still not fully formed at birth and, until birth, excretory functions are subserved mainly by the placenta. Skeletal muscle, after its long period of intra-uterine nervously-induced quiescence, becomes visibly active at
birth, and spikes appear for the first time in the electrical records. Finally, within a few days after birth, the skin has settled down to its new duties of temperature regulation, etc."

This sequence of development of functional activity is reversed in the "order of sacrifice", with reduction of blood flow first to skin, then to non-vital skeletal muscles, then to spleen and renal cortex, and lastly to brain and spinal cord. The "order of circulatory sacrifice" that occurs almost instantaneously in conditions of shock and acute stress is the same sequence that occurs slowly in senile involution. There are ample experimental data showing the reduction in renal plasma flow with age. Smith (1951, p. 552) quotes Goldring, Chasis, Ranges, and Smith (1940) as finding a decline in renal plasma flow of 53 per cent. between the ages of 22 and 90 years. More relevantly, the mean value for age 50 to 59 is significantly less than that for age 20 to 29.

We may here have an inkling of the neuro-vascular basis of glaucoma. This disease is one that occurs in the late phases of life and conditions of senescence must be accounted for in any theory of its causation.

If Franklin's ideas are correct, it is not necessary to make the difficult assumption that the quiet elderly person produces excess adrenaline or suffers from sympathicotonia—the probability now is that an ordinary endocrine output is given an excessive effect on fine blood vessels by involutionary conditions, causing the kidney cortex to produce V.E.M. and so creating this pathological sensitivity (Rosenheim, 1954).

Given that suggestion, the immediate obligation is to seek methods of reducing the production of V.E.M. or else of blocking its action, and to note if, by these methods, excessive diurnal variations can be normalized and therapeutic effects in actual glaucoma can be obtained. As the excessive diurnal variations occur in both simple and congestive glaucoma, any therapeutic effects of this method should accrue in both conditions.

Vascular reactivity to Adrenalin and Nor-adrenalin in normal and glaucoma cases was tested as follows:

The finest available conjunctival vessel was observed by the slit lamp to ascertain the weakest dilution (in normal saline at blood heat) that would cause vessel narrowing to the point of identifiable corpuscular streaming. Adrenalin was tested in the right eye and Nor-adrenalin in the left.

Throughout the series, the readings showed a general downward trend, attributed to increasing facility on the part of the observers in selecting progressively finer vessels for test. Thus the absolute values are uninformative, but the comparison of virtually simultaneous readings for Adrenalin and Nor-adrenalin remains valid, and the sensitivity ranges were as follows:

\[
\text{In Glaucoma:} \quad \frac{\text{Nor-adrenalin}}{\text{Adrenalin}} \text{ concentrations range 1 to 0.5 (Average 0.736).}
\]

\[
\text{In Controls:} \quad \frac{\text{Nor-adrenalin}}{\text{Adrenalin}} \text{ concentrations range 1 to 0.6 (Average 0.864).}
\]
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In no case was a ratio found over 1, i.e. no case was more sensitive to Adrenalin than to Nor-adrenalin. The ratios are set out in Table I. The controls were comparable in age but were deficient in male subjects. As males show less sensitivity than females in both glaucoma and control cases, the extra glaucomatous males in the material strengthen the conclusion of enhanced sensitivity to Nor-adrenalin in glaucoma patients.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Glaucoma</th>
<th>Controls</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Ratio</td>
</tr>
<tr>
<td>Male</td>
<td>10</td>
<td>0.763</td>
</tr>
<tr>
<td>Female</td>
<td>15</td>
<td>0.715</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>0.736</td>
</tr>
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</table>

This overall excess of sensitivity to Nor-adrenalin may be illustrated (though not to imply any exact measurement) by the ratio Controls : Glaucoma = 864 : 736.

It has already been noted that the therapeutic efficacy of Dibenamine in glaucoma might be derived from its special power to block Nor-adrenalin. These features appear to suggest some special importance of Nor-adrenalin in our problem but attempts at interpretation might be premature. While these findings afford no proof of the V.E.M. concept, they are quite compatible with it.

The picture is, of course, incomplete. It ignores other “pressor” materials—Cerebrotonin, Angiotonin, Serotonin, etc.—which may complicate the reactions. Further, it is advisable to recall the two factors—stress and involution—that can operate the mechanism described; both involve reversed recapitulation of the developmental sequence. Involution appears causally compatible with the elderly low-grade glaucoma patient with visual loss often disproportionate to the degree of ocular tension. The association of the acute case with stress, is not unacceptable. But one large group remains unaccounted for. Many patients aged 45 to 60 (and so not involutionary by age) and having no special emotional crisis or stress, yet have glaucoma of chronic type. This association is not incompatible with the relationships so far suggested. Thorn, Jenkins, and Laidlaw (1953) showed that mild stresses could cause as marked glucocorticoid manifestations as severe trauma. This is the result of a conditioning which enables certain stressors to enhance the effect of small quantities of corticoids (Selye, 1954). Selye calls this the “anti-inflammatory corticoid conditioning effect” (“A.C.C.”), and finds that chronic malnutrition, emotional stimuli, and most mild stressors act chiefly by this mechanism in man. The results are those characteristic of the corticoids in full quantity; they cannot be elicited by the conditioning agent.
in the absence of corticoids, but can be produced by high doses of cortisone even after adrenalectomy.

It is known that the pressor effect of Nor-adrenalin and Adrenalin in man may be intensified by the previous administration of DOCA, ACTH, or cortisone. Here in the A.C.C. effect is that administration by physiological processes.

Selye also mentions the special position of the kidney in the stress response, in that the mutual antagonism between the pro- and anti-phlogistic hormones (mineralo- and gluco-corticoids) does not operate as far as renal effects are concerned. Far from being antagonistic and mutually exclusive, the renal effects of the two corticoid groups are summated and enhanced and rapidly kill the animal.

We have here a mechanism whereby emotional stimuli characteristic of the perfectionist or anxious personality can create “shock” reactions of disproportionate severity.

It is relevant to recall here that the diurnal variations of ocular tension are associated with inverse variations of the blood eosinophil count. Remembering the associations of eosinophil drop with the ACTH effect (Thorn reaction), the implication of a possible shock (steroid) effect acquires further support.

To check this, the level of excretion of 17-ketogenic steroids in glaucoma patients was tested. Four of the first fifteen showed an abnormally high level, but the extension of the series to fifty cases disproved the first impression. Unfortunately, all the patients tested were under treatment (including sedatives where indicated) and being of average age 69 would tend to show more involuntary than stress characteristics.

In ACTH therapy, the mineralo-corticoids cause retention of water, and in predisposed cases this can precipitate a glaucoma. It seems unlikely that the corticoid production of Selye’s A.C.C. reaction could cause water retention of more than contributory degree, but nevertheless it cannot be dismissed (Schmerl and Steinberg, 1955).

In experimental renal hypertension, Ledingham (1953) demonstrated a general body gain in extra-cellular fluid, and Laramore and Grollman (1950) showed a rise in sodium and a fall in potassium in the heart muscle of hypertensive rats. All this suggests mineralo-corticoid activity and makes it appear possible that there may be some direct connexion between the kidney and the adrenal electrolyte mechanism in experimental hypertension. Thus, by this mechanism of “conditioning”, ordinary mild anxieties may expose patients to vasopressor production and water retention, with promotion of glaucoma in cases predisposed thereto by structural factors. For example, a decrease of 20 per cent. or more in renal plasma flow may occur in patients with early essential hypertension when the subject of discussion turns to topics of traumatic significance in the life situation. This renal response is abolished by sympathectomy. Similar changes were effected in persons with normal tensions by unpleasant psychiatric interviews in four out of eleven young males, five out of eight older males, and five out of eight females.
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The inhibition of water diuresis by emotional stress is discussed by O'Connor and Verney (1942, 1945) and O'Connor (1947). It is suggested, therefore, that we may accept the V.E.M. mechanism as a natural concomitant of the involutionary process in the aged, and as a product of anxiety, stress, etc., in younger persons. In really young people the effects may be transient, e.g. the temporary rise in blood pressure found in members of the armed forces after sustained desert warfare.

But it is a familiar fact that in the middle-aged the changes that begin as temporary functional modifications become fixed, either as structural damage or as Selye's "conditioning".

Ocular Participation

These are all matters of general systemic scope. Cristini (1951) demonstrated a progressive reduction in the functioning capillaries in optic nerve atrophy and in the uvea in hypertension, including shunts between large vessels, and a reduction of the capillary bed with rise of pressure in the vessels still functioning. His histological illustrations are remarkably apposite to Franklin's description of areas that are undergoing vascular "sacrifice". They show inter alia that the vascular changes in an optic nerve with cavernous atrophy are the same as those seen in the uvea in glaucoma. These optic nerve vessels (which are not subject to intra-ocular pressure conditions) can be regarded as exemplifying the vascular changes of the glaucoma patient in their pure state. These findings gain some support from the work of Keeney and Leopold (1952), who reported a reduced response to histamine by the skin capillaries of glaucoma patients.

For other cases, the additional postulate of a local predisposition appears necessary, and increased outflow resistance (structural or episodic) has been suggested.

Therapy

Therapeutically, it is the vascular aspect that can be influenced by the agents available: at the three points already listed (central, ganglion, and effector), and now possibly at the fourth point, by reducing the output of V.E.M. or inhibiting its effect.

Our present armamentarium comprises the following drugs:

1. Central Sedatives
   - Phenobarbitone—no great value—too many deteriorating patients having already had it from their doctors for years.

2. Other Sedatives
   - Nembutal—very few cases—no special effect.
   - Largactil—few cases—some effect noted.
   - Serpasil—some apparent effect—we concluded this to be best in combination with other agents. If used in effective strength it appears to cause drowsiness and may impair activity in important respects. It also tends to cause miosis.

   Stillboestrol—where this can be used effectively for menopausal symptoms of vasomotor type (hot flushes) it has repaid use for concomitant intra-ocular imbalance.
(3) Drugs designed to prevent (or obstruct) the Propagation of Nerve Impulses

_Hydergine_-some definite effect—very variable between one case and another. This may be related to the extent of the neurogenic element. The patient’s feeling of relaxation of physical tenseness has some parallel effect in reducing mental tension.

(4) Drugs designed to reduce or possibly eliminate Activity of Presumed Humoral Agent (V.E.M.)

The immediate possibility of using mono-amine oxidase is negated by non-availability as a separated product (Blaschko, personal communication).

_V.D.M. (Ferritin)_ is so rapidly inactivated in the body that continuous infusion would be required, and antibody difficulties would arise.

_V.E.M._ cannot so far conveniently be neutralized in the body. It remains to reduce, if possible, the output of V.E.M._—and to this end to increase effective renal blood flow.

(a) _Vitamin A_ is, perhaps surprisingly, an effective agent (vitamin D has the opposite tendency). Thus, vitamin A should be given in a pure form. It has been used in therapy but not tested quantitatively. It has quite marked subjective effects in over half the patients who are given it. It is, however, interesting to recall the impairment of dark adaptation that is common to glaucoma and vitamin A deficiency, and that—apart from famine states—this deficiency can arise in dysfunction of the liver. While it would be speculative to infer some causal relationship here, the effects of vitamin A therapy on dark adaptation (Mutch and Griffith, 1937) and on renal blood flow (Herrin and Nicholas, 1940) provide a double justification for its use on glaucoma patients. The influence of vitamin A on the adaptation curve, as altered by glaucoma, demands early measurement. Oral medication is essential, the intramuscular route being ineffective (Wulf and Nibbe, 1955).

(b) _Increase in Body Temperature_ causes an increase of renal blood flow. Fig. I shows a decrease in ocular tension concomitant with an artificially induced rise in body temperature. It is unfortunate that this has little practical (therapeutic) application.

(c) _Isuprel_ (Corcoran and Page, 1947) is a vasodepressor resembling Sympathin 1, and has also an effect in increasing effective renal blood flow (not tested).

(d) _Hydralazine (Apresoline)_ offers a promising association of characteristics (Fig. 2, opposite; Figs 3 and 4b, overleaf). It reduces blood pressure while maintaining cardiac output and increasing renal blood flow, by which it should diminish the production of V.E.M. (MacKinnon, 1952; Moyer, Handley, and Huggins, 1951; Reubi, 1950; Freis, MacKay, and Oliver, 1951). It is alleged to operate perhaps centrally but certainly peripherally—possibly at the level of the pre-
Vaso-motor factor in glaucoma

37.5 mg. Apresoline daily

BLOOD PRESSURE (mm. Hg)

OCULAR TENSION (mm. Hg Schiotz)

Previous Range

*Patient treated by drops for 7 years before period covered by chart.

Fig. 2.—Effects of out-patient treatment with Apresoline 12.5 mg. three times daily for 6½ months in a woman aged 72. The intra-ocular pressure (below) was not parallel to the blood pressure (above). The therapeutic effect was slow and sustained. The range of ocular tension in the previous 7 years is shown at the right-hand side of the chart.

capillary sphincters. It is active against Hypertensin, Cerebrotonin, and Nor-adrenalin, and its action differs from that of the ganglion blockers, so that it is most effective in cases persisting or recurring after sympathectomy. Thus, Apresoline and Hydergine are convenient for use together to invoke the humoral and neurogenic mechanisms, respectively (Fig. 4c, overleaf).

In seeking a therapy to offset a humoral agent, there is a certain relevance in noting what is efficacious in the hypertension and toxaemia of pregnancy which are independent of neurogenic factors and respond very poorly to autonomic and adrenergic blocking agents. These hypertensions and toxaemias involve a placental and uterine ischaemia (down to one-quarter of normal), and possibly a reflex ischaemia of renal cortex (British Medical Journal, 1955). It is already clear that the vasoconstrictor element in these cases must be humoral. Here is evidence that it is associated with an ischaemia, later most precisely confirmed by Johnson and Clayton (1957). Apresoline has been used in these cases with good effects which tend to be sustained, with a rise in cardiac output, fall in blood pressure, acceleration of heart rate, and diminution of cerebral and renal vascular resistance (Assali and Suyemoto, 1952; Assali, Kaplan, Oighenstein, and Suyemoto, 1953; McCall, 1953).
Effects of in-patient treatment with one intravenous injection of 16 and 20 mg. Apresoline respectively on two consecutive days in a woman aged 64. The right-hand chart also shows the ocular tension on the third day (without treatment).

Evaluation of response to different therapies in a woman aged 68 who had experienced a previous acute congestive attack of glaucoma in the left eye. Holth's iridencleisis had been carried out in both eyes. Ocular tension had remained at about 40-45 mm. Hg despite the use of miotics.

(a) Diurnal variation without treatment
(b) 20 mg. intravenous Apresoline ▲
(c) One tablet Hydergine plus 20 mg. Apresoline ▲
(d) Rauwiloid and Veriloid ▼
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(e) *Veratrum (Veriloid)* is another therapeutic agent of proved value (McCall, 1953). This has a well-marked hypotensive effect, depressing the vasoconstrictor centre by direct stimulation of afferent nerve endings in the ventricular walls, acting centrally on the cerebral chemo-receptor system, and inhibiting Cerebrotonin; it also has a peripheral vasodilator action. It causes bradycardia with a lowering of blood pressure, but also tends to cause nausea. Hence, there is an obvious advantage in using it with Apresoline or with Rauwiloid (the alkaloid of Serpasil), diminishing the dose of each, reducing side-effects, and letting the tachycardia caused by Apresoline be offset by the bradycardia caused by Veratrum (Fig. 4d). This requires an in-patient trial to ascertain the response of each patient, followed by continued charting of the course and response in the out-patient department.

**Results**

Initial tests on out-patients without this previous in-patient trial had given encouraging results.

Hydergine and/or Apresoline were given in the glaucoma clinic to all old cases that had a persistent ocular tension of 40 mm. Hg Schiötz and upward despite operation and/or drops; if miotics were in use they were continued in unaltered frequency. These drugs were also given to new cases of glaucoma (a much smaller number) at first without miotics; where this proved inadequate, miotics were added. Numerically, the old cases greatly outnumbered the new cases. Reduction of the ocular tension to 30 mm. Hg was regarded as therapeutically significant (Figs 5 and 6, overleaf). On this basis, a reduction in ocular tension and an increase in the visual field and visual acuity were obtained in about half the cases, half of whom had also had miotics (Figs 7, 8, and 9, overleaf).

Reductions in ocular tension can usually be achieved under in-patient test conditions with intravenous therapy, but may be difficult to carry over into the essential out-patient phase. It was disappointing that successful in-patient trials did not appear to lead to a greater number of long-term successes than were obtained by direct trial and error in the out-patient department. This may be because the smaller doses that are practical for ambulant out-patients are inadequate for our present purpose. It is also obvious that a return to normal environment could restore psychological stresses that had been an important factor.

The results of various forms of treatment are summarized in Table II.

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TABLE II
SUMMARY OF SYSTEMIC THERAPY FOR GLAUCOMA

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<tr>
<th>Drug</th>
<th>Clinical Impression</th>
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<tr>
<td>Sedative...</td>
<td>Nembutal (very few)</td>
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<td></td>
<td>Serpasil or Rauwiloid</td>
</tr>
<tr>
<td></td>
<td>Largactil (few)</td>
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<tr>
<td></td>
<td>Stilboestrol (special indications)</td>
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<td>&quot;Neurogenic&quot; agent</td>
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<td>&quot;Humoral&quot; agent</td>
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<td>? Humoral agent</td>
<td>Veratrum</td>
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<td>&quot;Humoral&quot; (? and biochemical)</td>
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<td>Responses appreciable</td>
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<td>Combined therapy appropriate</td>
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*Factors of systemic therapy in glaucoma.*
Of the first eighty patients, most of whom had previously failed to respond to classical methods of treatment, a response of therapeutic value was seen in forty (50 per cent.), a slight but inadequate improvement in 29, and no improvement in eleven.

Experience and/or newer drugs may give greater success, but in any case these suggestions are directed to the vascular factor only. Failures may be due to (i) error in the argument, (ii) imperfect therapeutic tools, (iii) imperfect judgment in their use, (iv) the fact that outflow resistance is the chief factor.

**General Treatment**

It is essential to prevent glaucoma clinics from degenerating into an unthinking routine of "visual acuity—ocular tension—visual field—drops—operate if compelled". The patient must know that he is regarded as a prime responsibility of the clinic and be considered as a whole person and not as an ambulant framework with two eyes to be treated by miotics or surgical interference. His way of life and arrangement of work may need modification. The psychological aspects have been dealt with by Schoenberg.
(1940), Duke-Elder (1949), Hartmann (1949), and many others, and the psycho-sociological aspects by Armstrong (1952). Our own almoners have confirmed a high ratio of stresses in glaucoma patients.

The emotional associations of acute glaucoma are classical, but there are also less obvious ones. The apparently quiet, efficient person with glaucoma is often an over-conscientious, over-working perfectionist. He should be encouraged to abandon his over-zealous tendencies, to be more independent—even careless—towards others and their demands on him, and to accept his position and life achievement as adequate without further striving. He should shed responsibility but continue to exploit the acquired skills which usually give him pleasure.
Fig. 7.—Blood pressure recordings, accompanying improvement of visual fields from 20° to 45° in a patient aged 64, during treatment with Hydergine.

Fig. 8.—(i) Visual field loss caused by early Schnabel’s cavernous optic atrophy in a patient aged 56. There was slight cupping of the lower edge of the left optic disc, and the ocular tension was normal.

(ii) Pilocarpine gave initial response in one month.

(iii) With added Ronicol tablets further response occurred in one week.

(iv) With added Hydergine there was little further change.

The visual acuity improved from 6/12 to 6/9.
VASO-MOTOR FACTOR IN GLAUCOMA

Because sharp exercises diminish renal blood flow, only relatively gentle exercise is wise, and it should be free from stooping; anything rhythmic has a sedative value, archery, golf (if sufficiently adept), fishing, and many handyman activities. Such things as tight collars, which set up "provocative tests", must be avoided. Morning tea must be forbidden, as it is an excellent combination of the water-drinking test and the caffeine test. Work involving the handling of ice or fish, anything requiring the hands to be kept in cold water, or involving wet, cold feet, is a pressor test (Reiser and Ferris, 1948; Talso, Crossley, and Clarke, 1948). The cinema and television can reproduce a dark-room test plus emotional influences, and both have been known to precipitate attacks.

A small quantity of wine or spirits acts as a psychological sedative and mild vasodilator and so is good. It is a disappointing denial of tradition

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that Tinct. juniperi does not appear to increase renal blood flow (Smith, 1951). Beer is a "volume" drink and because of its resemblance to the water-drinking test is better avoided. Tobacco—believed to have vaso-spastic influences—should be discouraged. Many other physical influences will come to mind, for example, a hot bath at night will have a general vasodilator effect and promote good sleep.

It is perhaps possible to make a rough separation of cases into two types, in which senile involution is or is not significantly present. Where it is the main factor, palliation by vasodilators plus a high vitamin intake, especially of vitamin A, will be the chief line of therapy.

In the younger age group—the active, anxious, hard-working type, sometimes with an ill-defined glaucoma of doubtful diagnosis, but more often with a developed condition that varies considerably with general health and with pressure of work and responsibility—the general management of the patient’s life, the adjustment of demands to match his capacity without overtaxing his neurovegetative balance, will be the over-riding factors and drugs should be regarded only as adjuvants, however valuable. The sedatives of the pharmacopoeia may supplement and should not supplant those of psychology; the ganglion adrenergic blockers will probably be missed if not used, and physical factors of diet and avoidance of provocative influences should all help.

It has long been known that 40 per cent. of all glaucoma cases can be kept going on drops without operation (Schleih, 1906). In our experience, 50 per cent. of cases not controlled by drops and/or operation showed a significant response to the therapies described. If this were confirmed in general use, Schleih’s 40 per cent. could be raised to 66 per cent. and the frequency and extent of surgical intervention reduced.

I am indebted to many people for help. Most of the ideas stated are derived from others, but conscientious attributions are impossible. My colleague, Miss Hatherley, kindly allowed me to investigate and treat her glaucoma patients. I acknowledge much help, especially with in-patient evaluations, from my assistants, Dr. H. Hardy (who also did most of the Nor-adrenalin tests), Dr. R. Cowley, Mrs. Larway, and Dr. Kadir; from our Ward Sister, Miss Alsop; from Miss H. E. M. Carroll, lady almoner, for her reporting and continuing care for our patients; from Mr. Foster, hospital artist, for clarification of diagrams; and from Dr. Jordan (consultant biochemist) for providing the estimations of 17-ketogenic steroids.

Messrs. Ciba kindly supplied ampoules of the drug Apresoline, which is not yet generally obtainable in this form.

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Vaso-Motor Factor in Glaucoma


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ADDITIONAL BIBLIOGRAPHY

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1. Glaucomatosal Symptoms and Signs in Other Diseases.


2. Vascular Conditions in Glaucoma.


3. Circulatory and Vasomotor Conditions.

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4. Pharmacology.


5. Vitamin A.


6. Psychosomatic Aspects.


7. Stress.


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