DOYNE LECTURE
GLAUCOMA: FACTS AND FANCIES

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When I first began thinking about glaucoma, 23 years ago, life was much simpler. Dogma demanded treatment of any patient with an intraocular pressure consistently greater than 21 mmHg, while success was announced by a pressure consistently below 22 mmHg. Seven years later I returned to the subject and presented my planned studies to a small group of fellow clinical epidemiologists that I had gathered together from across the Johns Hopkins University faculty. My initial self-confidence was destroyed by a cardiologist who concluded from my presentation that glaucoma appeared to be a condition one could not define, could not diagnose, and for which there was little evidence that therapy materially altered the course of the disease. He was right then; he is, unfortunately, largely right today.

For too long glaucoma research has resembled the fabled story of the airline pilot whose voice boomed across the plane's intercom: 'I'm pleased to announce that we've reached 35 000 feet and a cruising speed of 540 nautical miles an hour. While we are *hopelessly lost*, we *are nonetheless* making excellent time.'

WHAT IS PRIMARY OPEN ANGLE GLAUCOMA?

Basically, we do not know – or, at best, lack a precise definition of primary open angle glaucoma (POAG). This presents a certain irony, since POAG is characterised by the most quantifiable parameters of any ophthalmic entity: intraocular pressure, aqueous outflow, a variety of geometric measurements of the optic disc and a myriad ways to test and describe the visual field. Probably the best we can do, without making unwarranted assumptions, is to note that POAG is 'a characteristic form of optic neuropathy among patients with open angles that is related, to some degree, to the level of intraocular pressure'.

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Given the imprecision of the overall definition I will not try to describe the modifier, 'characteristic', particularly as it relates to the appearance of the optic nerve head, nerve fibre layer or the visual field.

The bottom line: We presume to know it when we see it.

WHAT 'CAUSES' PRIMARY OPEN ANGLE GLAUCOMA?

At whatever level we enquire – whether it be the aetiology of a patient's intraocular pressure or the destruction of their optic nerve – the answer is that we do not know either what causes POAG. We are, however, increasingly gaining more data and greater insight about some of the parameters of potential importance.

Intraocular Pressure

No factor is more traditional or potentially amenable to treatment than the level of intraocular pressure (IOP). There is no question that, statistically, the risk of glaucomatous optic nerve damage is directly related to the height of the intraocular pressure:[1,2]

The prevalence of POAG increases with increasing IOP.[3]

The risk of subsequently developing glaucomatous field loss increases with increasing IOP.[1,4–7]

Among patients with asymmetrical IOP and visual field loss in one eye, the eye with the field loss almost invariably has the higher IOP. This is as true for patients with severe monocular elevations in IOP following trauma as it is for asymmetrical levels of IOP among patients with so-called normal tension glaucoma, where neither eye has an IOP greater than 21 mmHg.[8,9]

Dramatic reductions in IOP appear to reduce the risk of subsequent nerve damage. The greater and more consistent the reduction in pressure, the greater the reduction in risk.[10–14]

It is important to recognise that there is little if any

evidence that 21 mmHg represents a threshold level of any particular import. While it is a traditional 'cut-off', IOP levels above 21 mmHg conventionally being classified as 'abnormal' (as in 'ocular hypertension'), 21 mmHg is simply a statistical construct of *normality*; it was meant to represent 2 standard deviations above the mean IOP (approximately 16 mmHg) in the normal population at large.

In a normally distributed (Gaussian) population, roughly 3% of *normal individuals* would have higher IOP levels. In screening studies, however, the actual percentage is often closer to 8%.[3,15] By a twist of history, this normal construct became a mark of abnormality. Because only a relatively small population of normal individuals have an IOP greater than 21 mmHg and even fewer greater than 23 mmHg, these were considered useful cut-offs for concentrating potentially high-risk subjects, making screening for cases of actual glaucoma more efficient; they were *never* meant to be criteria for defining POAG. If there really is a minimal IOP threshold for glaucoma, observational data on treated[10,11,14] and untreated[1,4,5,16] subjects suggest it is closer to 16 mmHg.

While the risk of an individual developing glaucomatous optic nerve damage increases with increasing IOP, the risk is already evident at levels below 21 mmHg (Fig. 1). Since most people have an IOP below 21 mmHg, it is not surprising that a significant proportion, perhaps 20–30% of all patients with characteristic POAG, have IOPs consistently below 21 mmHg.[1,3,17]

The important point is that there is little scientific basis for the traditional distinction between 'high' and 'low' tension glaucoma. The relationship between IOP and glaucoma is a continuum, much like the relationship between systemic hypertension and stroke. Patients with an IOP in the high teens are already at increased risk.

Structure of the Optic Nerve

Clearly, IOP represents only one of the many factors determining the risk of glaucomatous optic nerve damage. We have all had patients with 'normal pressures' who develop characteristic glaucomatous optic nerve damage, and other patients with much higher pressures who do not.

One study suggests IOP may account for only 10% of such risk.[18] Exactly what accounts for differences in disc vulnerability remains obscure, but probably relates to the size, organisation and composition of the optic nerve and its supporting structures,[19] the size and shape of the scleral canal, and the vascular supply. The risk of POAG is at least 5 times greater in blacks than whites[20–22] but their levels of IOP are similar.[3,20]

On average, blacks have larger discs than whites.[19,23,24] Their cups are also larger in proportion to the larger size of their scleral canals. As the disc increases in size in normal individuals, the retinal rim area, thought to be the best index of the number of optic nerve axons, increases as well; but the increase is greater in whites than in blacks, suggesting blacks may have disproportionately fewer axons, for each size disc, than whites. This might well account for at least some of the increased risk of glaucomatous optic nerve damage among black subjects. Whether the apparent increase in vulnerability of the optic nerve in blacks is directly related to recognised differences in its structure are uncertain, but provides potentially important clues to a more general phenomenon.

Vascular Flow

There is growing evidence that vascular flow to the optic nerve may play an important role. Drance and co-workers, using sophisticated statistical analyses, have provided tenuous evidence for the existence of two distinct groups of patients: those with and those without a vasospastic component. Both groups contained patients characterised as having 'high tension' and 'normal tension' glaucoma.[25]

We recently evaluated the potential role of systemic blood pressure, and its derivative, pulse pressure, as determinants of glaucoma. We reasoned that the oft-reported lack of association between systemic hypertension and glaucoma made little biological sense.[26] Early in systemic hypertension, the higher head of pressure should force more blood through the vascular network serving the optic nerve; in late-stage hypertension, increased vascular resistance from narrowed vessels should reverse this advantage. When we pooled all our data, we found little association between systemic hypertension and the risk of existing glaucomatous damage. But when we dissected the data further, distinguishing the risk relationship among younger and older hypertensives

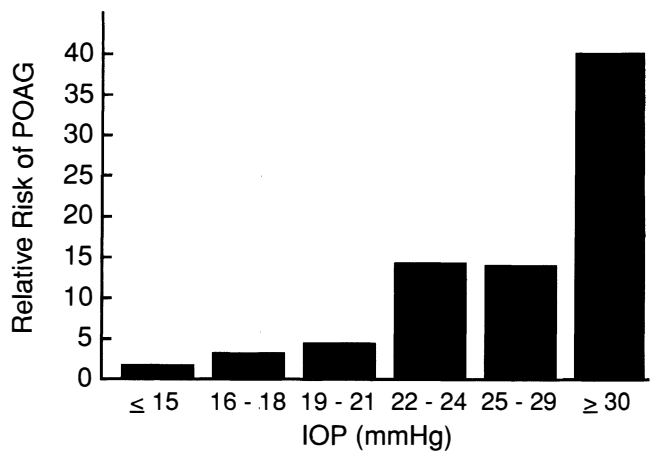

Fig. 1. *Relative risk of POAG at different levels of screening IOP among subjects studied in the Baltimore Eye Survey. After Sommer* et al.[3]

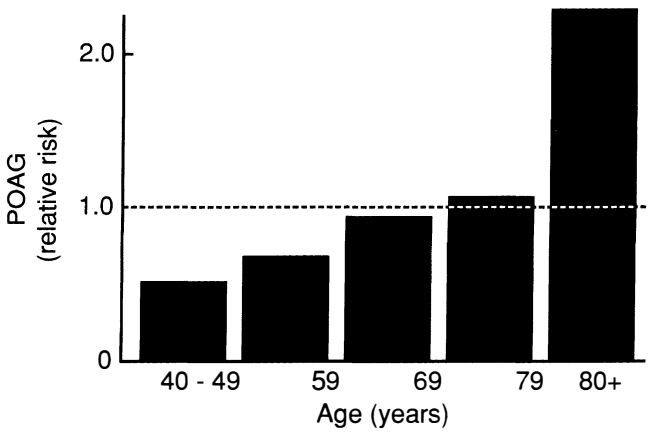

Fig. 2. *Relationship between systemic hypertension and the risk of having glaucomatous optic nerve damage. Systemic hypertension defined as systolic >160 mmHg or diastolic >95 mmHg or current use of anti-hypertensive medication. Data from the Baltimore Eye Survey.*[26]

(surrogates for early and late hypertension) independently, the data fitted our hypothesis exactly. Young hypertensives seem to be protected from glaucoma, having only half the risk of their normotensive, age-matched peers. In contrast, older hypertensives had double the risk of glaucoma of their age-matched peers (Fig. 2).[26] The risk of glaucoma increased in direct relation to the height of the systolic, diastolic and mean systemic blood pressures.[26]

The determinants of blood flow to the optic nerve are highly complex.[27] These include (but are not limited to) systemic blood pressure, IOP, 'perfusion pressure' (systemic blood pressure minus IOP, a better determinant of the gradient of pressure forcing blood through the vascular tree), vascular resistance and other factors affecting the quantity (rather than velocity) of blood flow, the latter measured, somewhat grossly, by Doppler studies.[28,29] A variety of potential perfusion pressure determinants were constructed: the most conclusive was the diastolic perfusion pressure (Fig. 3).

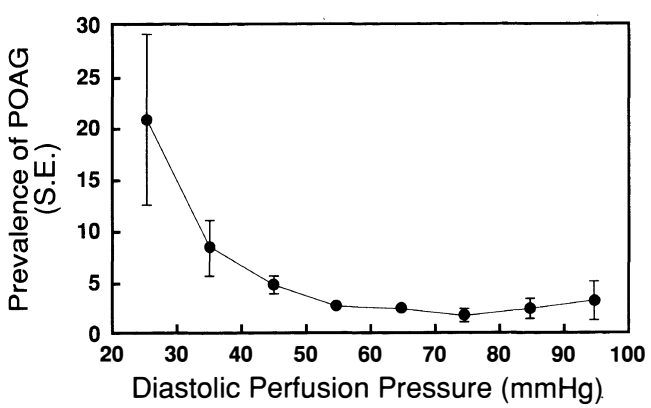

Fig. 3. *The risk of glaucoma declines sharply below a diastolic perfusion pressure of 50 mmHg. From Tielsch* et al.[26]

The relationship between pulse pressure and POAG held true for subjects below and above 65 years though, as anticipated, the absolute risk of POAG, as well as the relative risk associated with lower perfusion pressure, increased with age (Table I). Despite the rapid rise in risk of glaucoma with diastolic perfusion pressures below 50 mmHg, less than one-third of all subjects with POAG fell within this category. More refined measures of vascular perfusion, applied to individuals of different age and with different structural characteristics of their optic nerve, might well provide important clues to identifying those at greatest risk (and insights on how best to manage them).

While we could define a 'pulse pressure' that helped distinguish some glaucomatous from non-glaucomatous subjects,[26] repeat studies, in other populations, will be required to confirm and refine our results. Recent data from the Netherlands and elsewhere confirm the association between IOP and blood pressure observed in the Baltimore eye Survey.[26,30–32] However, this association between IOP and blood pressure is distinct from the association between POAG and perfusion pressure (except to the extent that the small increase in IOP accompanying an increase in blood pressure affects perfusion pressure) and would therefore not explain the inversion in risk between systemic hypertension and POAG observed with ageing in the Baltimore study.

The bottom line: Vascular flow to the optic nerve is probably an important and under-recognised determinant of optic nerve vulnerability, and perfusion pressure is one meaningful way of integrating the relationship between IOP and blood pressure. No doubt the real relationship is more complex – but what we know to date highlights the potential vulnerability of the optic nerve to aggressive reductions in systemic blood pressure, a warning sounded in the past.[33] Treatment of older patients for systemic

Table I. Diastolic perfusion pressure and risk of POAG

Diastolic perfusion pressure (mmHg)	Prevalence of POAG at age:	
	40–64 years	≥65 years
<30	0/6	5/18 (27.8%)
30–39	2/39 (5.1%)	7/68 (10.3%)
40–49	11/296 (3.7%)	20/338 (5.9%)
≥50	4/2882 (1.6%)	66/1591 (4.2%)
	Relative risk	
<40	2.44	3.36
≥40	1.00	1.00

The same monotonic trend between diastolic perfusion pressure and prevalence of POAG is seen among younger and older subjects. The higher the perfusion pressure, the lower the risk of POAG. The trend is more pronounced among older subjects, perhaps because flow through more stenotic vessels is less susceptible to autoregulation and more dependent upon the 'head' of pressure.

hypertension requires careful and considered ophthalmological input.

Age

It has long been known that the incidence and prevalence of POAG increase with age. What is not clear is whether older individuals have more vulnerable optic nerves or simply have suffered more frequent and prolonged insults over their lifetime. Probably both play a role. The biological evolution of hypertension may exemplify the former; the slow, persistent (though sometimes step-wise and incremental[18,34]) increase in optic nerve damage over many years, perhaps the latter. Whatever the basis, older people are at greater risk of developing demonstrable field loss than younger individuals, and deserve more frequent and aggressive investigation.

DETECTING PRIMARY OPEN ANGLE GLAUCOMA

We cannot prevent the underlying disease (POAG) itself, only its consequences. Such secondary prevention should obviously be instituted as soon as practicable. But how soon can that be (Fig. 4)? Treating individuals whose IOP simply exceeds a specified value (21 mmHg, 25 mmHg, etc.) incurs the risk of harming, or at least inconveniencing, large numbers of patients who never needed intervention in the first place. By the same token, it will result in failure to recognise, and therefore delay in treating, many patients who might benefit from intervention. Multiple studies have demonstrated that half of all adults with glaucoma will have a screening IOP less than 21 mmHg, while 8% of all normals will have higher pressures (Fig. 5).[3,15,35] One would end up referring 10–30 patients without glaucoma for each new patient detected as having glaucomatous damage.

At the other extreme, one cannot simply wait for

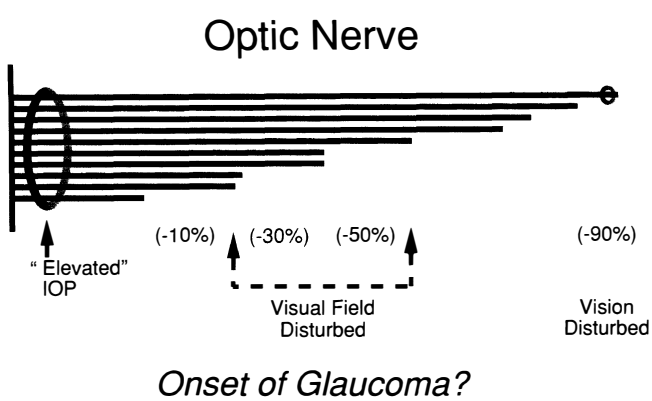

Fig. 4. *While one would prefer initiating therapy as early in the course of glaucoma as possible, available indices for definitive diagnosis of POAG await the demonstrable and irreversible loss of optic nerve axons. The proportion of axonal loss at each physiological transition is approximate.*

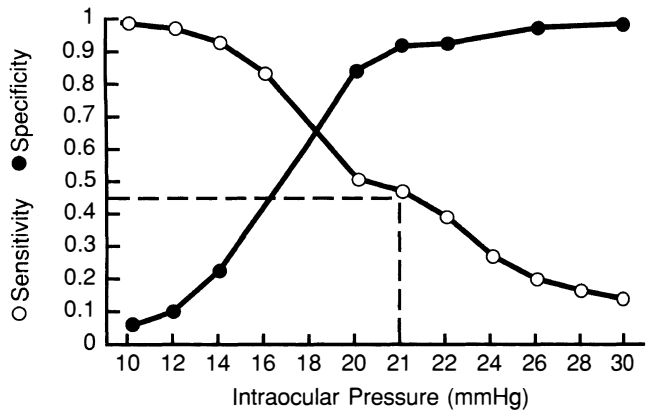

Fig. 5. *Sensitivity and specificity curves for differing levels of IOP in the Baltimore Eye Survey. Adapted from Tielsch* et al.[35]

patients to complain of significant loss of their visual fields. By then, probably 10% or fewer axons remain. Not only is the patient's ability to function already compromised, but there is little time or leeway to preserve the few remaining axons.

The commonest approach to detection and definitive diagnosis awaits the appearance of characteristic defects in the nerve fibre layer,[36–39] progressive enlargement of the optic cup,[40–42] or the development of characteristic visual field defects.[43] Data collected in the population-based Baltimore Eye Survey indicate that at a fixed level of specificity of 85%, traditional IOP screening identifies half the patients in need of treatment; suprathreshold perimetry (STP) almost two-thirds; and a combination of IOP, STP, cup geometry and other risk factors 83% (Table II) (A. Sommer and J. Tielsch, unpublished data).[35] Only detailed threshold perimetry is likely to identify nearly everyone with glaucomatous damage, and these will already have lost a third or more of their optic nerve.[44]

The bottom line: If we really want to identify all patients with significant glaucomatous optic nerve atrophy, we must include full threshold perimetry as an integral part of every routine examination.

Other diagnostic tools fall short of the mark.

Table II. Performance of alternative glaucoma 'screening' strategies

	Specificity[a] (%)	Sensitivity (%)
Suprathreshold visual field (STF)	85	65
Model[b]	85	63
Model I + STF	85	69
Model I + disc	85	76
Model I + STF + disc	85	83

At a fixed specificity of 85%, sensitivity varied from 51% for IOP alone (not shown) to 83% for a combination of factors developed in a step-wise logistic regression. Data from Baltimore Eye Survey.[35]

[a]Operator receiving curves artificially fixed at specificity of 85% for comparison.

[b]Model I: age, race, IOP, family history, diabetes.

Simplified, relatively rapid multiple presentation STP will miss a considerable number of glaucomatous subjects. Nonetheless it is quick, cheap, and likely to identify those with the most advanced disease and therefore in most urgent need of intervention (personal communication: W. E. Sponsel, R. Ritch, R. Stamper, E. J. Higginbotham, D. Anderson, T. Zimmerman T, for the Prevent Blindness America Glaucoma Advisory Committee. Prevent Blindness America visual field screening study).

MANAGEMENT OF PRIMARY OPEN ANGLE GLAUCOMA

It makes little sense to waste time and resources detecting glaucoma if one cannot influence its outcome. Despite anecdotal reports and uncontrolled observations, there is a dearth of definitive evidence that treatment reduces the risk of subsequent optic nerve damage.[45] It is not surprising that treating everyone with an 'elevated' IOP seemingly 'prevented' many from developing 'glaucomatous damage'. Most would never have developed glaucomatous damage in the first place!

Until recently, the best available data came from several observational studies of patients treated for glaucomatous damage: the better the control of their IOP the better their prognosis.[10,11,46] In two of these studies, patients whose IOP was maintained at or below 16 mmHg fared far better than those whose IOP ranged from the high teens to the low twenties.[10,11]

Topical IOP-lowering medication administered to patients with 'ocular hypertension' appears to reduce the risk of developing visual field loss when compared with untreated controls, although not all such studies have yielded similar, beneficial results.[16,47,48] Part of the variation may relate to sample size and selection, medications employed, the degree to which IOP was reduced, compliance, effects on the contralateral eye (when the contralateral eye served as the control), and systemic effects of the drug. While encouraging, these studies are hardly definitive.

Value of Reducing IOP

More recently, a series of increasingly sophisticated trials, many them from the United Kingdom, have been conducted on patients with pre-existing, well-documented glaucomatous field loss.[13,14] Perhaps the most convincing and definitive to date was the large, long-term Moorfields trial, comparing the relative value of medical, laser and surgical intervention.[14] Not only was the study well controlled but, encouragingly, the results were internally consistent. Surgery was more likely than laser or medical therapy to reduce IOP below 22 mmHg; among those patients in whom this target was achieved, the average IOP was 4 mmHg lower among patients receiving fistulising procedures than among patients receiving laser or medical therapy; and the stability of the visual field paralleled the degree to which the IOP had been lowered.

Half a dozen additional controlled trials are under way. One or two are likely to provide additional definitive data relating reduction in IOP to protection of the optic nerve.[49]

The bottom line: While the data are less than ideal, it is likely that by *significantly* lowering IOP one can effectively reduce the rate of optic nerve destruction. The relationship, however, is not simply linear – a small or even a modest reduction in IOP may provide little or no clinically significant benefit.

Choice of Therapy

We are in the midst of a therapeutic revolution. Although proclivities for pursuing non-invasive modalities were always greater on the American side of the Atlantic,[50] recent studies, and those just getting under way, are likely to draw us closer together. The American Academy of Ophthalmology's Quality of Care Committee, which I chaired, recommended the traditional, conservative approach to management: initiate therapy with topical agents, beginning with one and rising to three; add systemic carbonic anhydrase inhibitors if need be; progress to laser trabeculoplasty to augment the response; and finally, when all else fails, perform a fistulising procedure.[51] This 'stepped' therapy was formalised in the management principle of achieving an acceptable 'target pressure', a level of IOP deemed, on the basis of patient's history and physical findings, likely to prevent further optic nerve damage. Patients might fail to achieve this target IOP because therapy, compliance or both were inadequate; or the target itself might prove too high, damage progressing despite its having been 'achieved' (assuming the patient used their medicine and maintained the same 'target' pressure during the interval between examinations).

A famous glaucomalogist once said, 'You don't know how to treat glaucoma until you've been at it for at least ten years.' His underlying message was that one is easily deluded by short-term follow-up into believing you have been effective in halting further progression; it is only after following patients for ten or more years that one realises those seemingly transient and potentially inconsistent fluctuations in IOP, visual fields or the appearance of the disc, really represented deterioration, and the patient was getting progressively worse without anyone having recognised it or acted on it.

The bottom line: While we must await more data to be definitive, my twenty years of experience and the data at hand suggest surgery is probably the initial

treatment of choice for most cases of POAG. Successful filters result in the most marked, unwavering reduction in IOP (and potential increase in vascular perfusion),[52] and hence in the greatest reduction in risk of progressive optic nerve damage. Furthermore, results do not require careful, lifelong patient compliance and there is every reason to expect patients will be happier with their 'blebs' than with instilling drops or taking carbonic anhydrase inhibitors multiple times each day. Recent studies even suggest initial topical therapy might be harmful in the long term – it appears to increase conjunctival inflammation and fibrosis,[53–55] reducing the success rate of subsequent filtering surgery.[56,57] There is not yet a consensus on this point – but when there is, it will cause a true paradigm shift in therapeutic approach.

In Conclusion

1. Do not make the diagnosis of glaucoma lightly. Once made, we are duty-bound to do all in our power to reduce IOP to a 'safe' (i.e., 'target') level, which generally means the mid to low teens.
2. We should consider including detailed perimetry as part of our routine examination of all patients, particularly if they are black or elderly. The less detailed the perimetry, the more meagre the proportion of early glaucoma cases we will detect.
3. Once we have made the diagnosis of primary open angle glaucoma, we must treat the patient aggressively. I am convinced that almost as many people may have gone blind in the United States under careful but conservative management than from no management at all. If simple laser trabeculoplasty or a single topical agent does not bring the IOP into the target range, consider operating. Available data suggest it may be better to operate initially in any case.
4. We need to pay particular attention to glaucoma patients with systemic hypertension. Clearly their hypertension will need to be controlled, but an abrupt reduction in blood pressure could have a devastating impact on their optic nerve.
5. We eagerly await the results of the (few good) studies presently under way, and stand prepared to effect a whole new approach to glaucoma management.

REFERENCES

1. Sommer A. Intraocular pressure and glaucoma (editorial). Am J Ophthalmol 1989;107:186–8.
2. Anderson DR. Glaucoma: the damage caused by pressure. XLVI Edward Jackson Memorial Lecture. Am J Ophthalmol 1989;108:485–95.
3. Sommer A, Tielsch JM, Katz J, Quigley HA, Gottsch JD, Javitt J, Singh K, Baltimore Eye Survey Research Group. Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans: the Baltimore Eye Survey. Arch Ophthalmol 1991;109:1090–5.
4. Armaly MF, Krueger DE, Maunder L, Becker B, Hetherington J, Kolker AK, *et al.* Biostatistical analysis of the collaborative glaucoma study. I. Summary report of the risk factors for glaucomatous visual-field defects. Arch Ophthalmol 1980;98:2163–71.
5. David R, Livingston DG, Luntz MH. Ocular hypertension: a long-term follow-up of treated and untreated patients. Br J Ophthalmol 1977;61:668–74.
6. Sommer A. Epidemiology and statistics for the ophthalmologist. New York: New York University Press, 1980.
7. Perkins ES. The Bedford Glaucoma Survey. I. Long-term follow-up of borderline cases. Br J Ophthalmol 1973;57:179–85.
8. Cartwright MJ, Anderson DR. Correlation of asymmetric damage with asymmetric intraocular pressure in normal-tension glaucoma (low-tension glaucoma). Arch Ophthalmol 1988;106:898–900.
9. Crichton A, Drance SM, Douglas GR, Schulzer M. Unequal intraocular pressure and its relation to asymmetric visual field defects in low-tension glaucoma. Ophthalmology 1989;96:1312–4.
10. Odberg T. Visual field prognosis in advanced glaucoma. Acta Ophthalmol 1987;65(Suppl):27–9.
11. Mao LK, Stewart WC, Shields MB. Correlation between intraocular pressure control and progressive glaucomatous damage in primary open-angle glaucoma. Am J Ophthalmol 1991;111:51–5.
12. Werner EB, Drance SM, Schulzer M. Trabeculectomy and the progression of glaucomatous visual field loss. Arch Ophthalmol 1977;95:1374–7.
13. Jay JL, Murray SB. Early trabeculectomy versus conventional management in primary open angle glaucoma. Br J Ophthalmol 1988;72:881–9.
14. Migdal C, Gregory W, Hitchings R. Long-term functional outcome after early surgery compared with laser and medicine in open-angle glaucoma. Ophthalmology 1994;101:1651–7.
15. Hollows FC, Graham PA. Intra-ocular pressure, glaucoma, and glaucoma suspects in a defined population. Br J Ophthalmol 1966;50:570–86.
16. Schulzer M, Drance SM, Douglas GR. A comparison of treated and untreated glaucoma suspects. Ophthalmology 1991;98:301–7.
17. Dielemans I, Vingerling JR, Wolfs RCW, Hofman A, Grobbee DE, deJong PTVM. The prevalence of primary open-angle glaucoma in a population-based study in the Netherlands. The Rotterdam study. Ophthalmology 1994;101:1851–5.
18. Airaksinen PJ, Tuulonen A, Alanko HI. Rate and pattern of neuroretinal rim area decrease in ocular hypertension and glaucoma. Arch Ophthalmol 1992; 110:206–10.
19. Dandona L, Quigley HA, Brown AE, Enger C. Quantitative regional structure of the normal human lamina cribrosa. Arch Ophthalmol 1990;108:393–8.
20. Tielsch JM, Sommer A, Katz J, Royall RM, Quigley HA, Javitt J. Racial variations in the prevalence of primary open-angle glaucoma: the Baltimore Eye Survey. JAMA 1991;266;369–74.
21. Leske MC, Connell AMS, Schachat AP, Hyman L, the Barbados Eye Study Group. The Barbados Eye Study: prevalence of open angle glaucoma. Arch Ophthalmol 1994;112:821–9.
22. Mason RP, Kosoko O, Wilson MR, Martone JF, Cowan CL, Gear JC, Ross-Degnan D. National survey of the prevalence and risk factors of glaucoma in St

Lucia, West Indies. I. Prevalence findings. Ophthalmology 1989;96:1363–8.
23. Quigley HA, Brown AE, Morrison JD, Drance SM. The size and shape of the optic disc in normal human eyes. Arch Ophthalmol 1990;108:51–7.
24. Varma R, Hilton S, Tielsch JM, Katz J, Quigley HA, Sommer A. Neural rim area is inversely related to the level of intraocular pressure in urban Americans (abstract). Invest Ophthalmol Vis Sci 1995;36:S628.
25. Schulzer M, Drance SM, Carter CJ, Brooks DE, Douglas GR, Lau W. Biostatistical evidence for two distinct chronic open angle glaucoma populations. Br J Ophthalmol 1990;74:196–200.
26. Tielsch JM, Katz J, Sommer A, Quigley H, Javitt JC. Hypertension, perfusion pressure and primary open-angle glaucoma: a population-based assessment. Arch Ophthalmol 1995;113:216–21.
27. Williamson TH, Harris A. Ocular blood flow measurement. Br J Ophthalmol 1994;78:939–45.
28. Rojanapongpun P, Drance SM, Morrison BJ. Ophthalmic artery flow velocity in glaucomatous and normal subjects. Br J Ophthalmol 1993;77:25–9.
29. Hamard P, Hamard H, Dufaux J, Quesnot S. Optic nerve head blood flow using a laser Doppler velocimeter and haemorheology in primary open angle glaucoma and normal pressure glaucoma. Br J Ophthalmol 1994;78:449–53.
30. Leibowitz HM, Krueger DE, Maunder LR, Milton RC, Kini MM, Kahn HA, *et al.* The Framingham Eye Study monograph. Surv Ophthalmol 1980;24 (Suppl): 335–610.
31. Dielemans I, Vingerling JR, Algra D, Hofman A, Grobbee DE, de Jong PTVM. Primary open-angle glaucoma, intraocular pressure, and systemic blood pressure in the general elderly population: the Rotterdam Study. Ophthalmology 1995;102:54–60.
32. Klein BEK, Klein R, Sponsel WE, Franke T, Cantor LB, Martone J, Menage MJ. Prevalence of glaucoma: the Beaver Dam Eye Study. Ophthalmology 1992; 99:1499–504.
33. Richardson KT. Diagnostic evaluation and therapeutic decision in the glaucomas. Br J Ophthalmol 1972; 56:216–22.
34. Mikelberg FS, Schulzer M, Drance SM, Lau W. The rate of progression of scotomas in glaucoma. Am J Ophthalmol 1986;101:1–6.
35. Tielsch JM, Katz J, Singh K, Quigley HA, Gottsch JD, Javitt J, Sommer A. A population-based evaluation of glaucoma screening: the Baltimore Eye Survey. Am J Epidemiol 1991;134:1102–10.
36. Sommer A, Miller NR, Pollack I, Maumenee AE, George T. The nerve fibre layer in the diagnosis of glaucoma. Arch Ophthalmol 1977;95:2149–56.
37. Sommer A, Quigley HA, Robin AL, Miller NR, Katz J, Arkell S. Evaluation of nerve fibre layer assessment. Arch Ophthalmol 1984;102:1766–71.
38. Airaksinen PJ, Drance SM, Douglas GR, Mawson DK, Nieminen H. Diffuse and localized nerve fibre loss in glaucoma. Am J Ophthalmol 1984;98:566–71.
39. Sommer A, Katz J, Quigley HA, Miller NR, Robin AL, Richter RC, Witt KA. Clinically detectable nerve fibre atrophy precedes the onset of glaucomatous field loss. Arch Ophthalmol 1991;109:77–83.
40. Sommer A, Pollack I, Maumenee AE. Optic disc parameters and onset of glaucomatous field loss. I. Methods and progressive changes in disc morphology. Arch Ophthalmol 1979;97:1444–8.
41. Quigley HA, Katz J, Derick RJ, Gilbert D, Sommer A. An evaluation of optic disc and nerve fibre layer examinations in monitoring progression of early glaucoma damage. Ophthalmology 1992;99:19–28.
42. Coleman AL, Sommer A, Enger C, Knopf HL, Stamper RL, Caprioli J, *et al.* Interobserver and intraobserver variability in the detection of glaucomatous progression of the optic disc. Glaucoma (in press).
43. Katz J, Sommer A, Gaasterland DE, Anderson DR. Comparison of analytic algorithms for detecting glaucomatous visual field loss. Arch Ophthalmol 1991;109:1684–9.
44. Quigley HA, Addicks EM, Green WR. Optic nerve damage in human glaucoma. III. Quantitative correlation of nerve fibre loss and visual field defect in glaucoma, ischemic neuropathy, papilledema, and toxic neuropathy. Arch Ophthalmol 1982;100:135–46.
45. Rossetti L, Marchetti I, Orzalesi N, Scorpiglione N, Torri V, Liberati A. Randomised clinical trials on medical treatment of glaucoma. Are they appropriate to guide clinical practice? Arch Ophthalmol 1993; 111:96–103.
46. Grant WM, Burke JF. Why do some people go blind from glaucoma? Ophthalmology 1982;89:991–8.
47. Kass MA, Gordon MO, Hoff MR, Parkinson JM, Kolker AE, Hart WM, Becker B. Topical timolol administration reduces the incidence of glaucomatous damage in ocular hypertensive individuals. Arch Ophthalmol 1989;107:1590–8.
48. Epstein DL, Krug JH, Hertzmark E, Remis LL, Edelstein DJ. A long-term clinical trial of timolol therapy versus no treatment in the management of glaucoma suspects. Ophthalmology 1989;96:1460–7.
49. Tielsch JM. Catalyst Seminar II: Does lowering intraocular pressure benefit the glaucoma patient? Summary and recommendations. San Francisco, CA: Glaucoma Research Foundation, 1994.
50. Sherwood MB, Migdal CS, Hitchings RA (Part I). Sharir M, Zimmerman TJ (Part II). Schultz JS (Part III). Initial treatment of glaucoma: surgery or medications? I: Filtration surgery. II: Medical therapy. III: Editorial. Chop or Drop? Surv Ophthalmol 1993; 37:293–305.
51. AAO Quality of Care Committee (A. Sommer, chair). Primary open-angle glaucoma. Preferred practice pattern. San Francisco: American Academy of Ophthalmology, 1989.
52. James CB. Effect of trabeculectomy on pulsatile ocular blood flow. Br J Ophthalmol 1994;78:818–22.
53. Broadway DC, Grierson I, O'Brien C, Hitchings RA. Adverse effects of topical antiglaucoma medication. I. The conjunctival cell profile. Arch Ophthalmol 1994; 112:1437–45.
54. Broadway D, Grierson I, Hitchings R. Adverse effects of topical antiglaucomatous medications on the conjunctiva. Br J Ophthalmol 1993;77:590–6.
55. Nuzzi R, Vercelli A, Finazzo C, Cracco C. Conjunctiva and subconjunctival tissue in primary open-angle glaucoma after long-term topical treatment: an immunohistochemical and ultrastructural study. Graefes Arch Clin Exp Ophthalmol 1995;233:154–62.
56. Broadway DC, Grierson I, O'Brien C, Hitchings RA. Adverse effects of topical antiglaucoma medication. II. The outcome of filtration surgery. Arch Ophthalmol 1994;112:1446–54.
57. Lavin MJ, Wormald RPL, Migdal CS, Hitchings, RA. The influence of prior therapy on the success of trabeculectomy. Arch Ophthalmol 1990;108:1543–8.