A Critical Reevaluation of Current Glaucoma Management

International Glaucoma Think Tank, July 27–29, 2006, Taormina, Sicily

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Introduction

Advances in glaucoma research have provided a better understanding of its causes, the development and refinement of diagnostic techniques, and more efficient ways to manage the disease. However, barriers still exist to the successful diagnosis and treatment of glaucoma in the community. In the United States, recent findings indicate that despite numerous public policy initiatives developed by leading organizations such as the American Academy of Ophthalmology, Veterans Health Administration, and National Institutes of Health, additional efforts are needed to improve the detection of glaucoma and its care.

With increasing life expectancy, it is important that efforts be focused on maintaining the quality of life of patients and alleviating the social and economic burden of glaucoma. It is therefore essential that diagnostic and management practice be constantly reevaluated so that improvements can be brought about to ensure high-quality affordable care. This was the objective of the International Glaucoma Think Tank entitled "A Critical Reevaluation of Current Glaucoma Management" and held on July 27 to 29, 2006 in Taormina, Sicily. This meeting gathered a distinguished group of glaucoma clinicians and researchers from academic institutions around the world and was co-chaired by Drs Joseph Caprioli and David F. Garway-Heath.

This event was characterized by open discussions organized around 5 key themes relevant to glaucoma management. The meeting concluded with a session dedicated to future directions of glaucoma care, deriving from the discussions in the previous sessions, and a bonus session dedicated to eye disease depicted in art. This last session, although not a scientific one per se, added another dimension to the meeting, as it invited ophthalmologists to look at vision from a different perspective.

The chairs of the meeting briefly disclose pertinent details of the planning process, as this was a commercially supported meeting. The chairs alone controlled the design of the meeting and content of the agenda. Explicit discussions were held with the supporter, who readily agreed to relinquish all control over program content to avoid the introduction of commercial bias into the program. Nonetheless, there were two areas of discussion that could be perceived as benefiting commercial pharmaceutical interests: early diagnosis and the shortening of clinical trials. Early diagnosis would allow more patients to be treated, and shorter (and cheaper) clinical trials would benefit a pharmaceutical supporter. The chairs and participants were careful in not allowing significant bias to creep into the discussions, though the obvious influences remain. We hope that this short explanation has made the process transparent.

Session 1: Early Glaucoma Diagnosis

The first session of the meeting was co-moderated by B. Chauhan and D. Greenfield and was dedicated to the relevance of early glaucoma diagnosis in clinical practice. Prevention of glaucomatous damage is a key aim of disease management. Because glaucoma is a slowly progressing disease, some believe that early diagnosis, which allows for early treatment, may not be essential. It is not uncommon for ophthalmologists to think that early glaucoma rarely leads to blindness and that screening for early glaucoma, as opposed to very advanced glaucoma, is not relevant from a public health perspective.

Glaucoma is an optic neuropathy characterized by irreversible damage to the optic nerve that can lead to visual disability. Although disease progression is usually slow, it may be faster in individuals whose optic nerve is more susceptible to intraocular pressure (IOP)–related damage. The findings of a study conducted in Olmsted County, Minnesota indicated that the risk of unilateral blindness could be as high as 14% at 20 years in treated patients with ocular hypertension (OHT).[1] Using a mathematical model,

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*Think Tank participants available in "Appendix" on p. S41.

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risks of progression to unilateral blindness from OHT were estimated to be 1.5% to 10.5% in untreated patients and 0.3% to 2.4% in treated patients over a 15-year period.[2] It is therefore important that glaucoma be diagnosed early to allow for timely intervention to prevent irreversible damage to the optic nerve and to preserve vision.

Although the ultimate impact of delaying treatment is currently not known in detail, there is evidence to show that early treatment can prevent or delay progression to glaucoma. The findings of the first stage of the Ocular Hypertension Treatment Study (OHTS) showed that lowering IOP with topical hypotensive medication can prevent or delay progression to glaucoma in OHT patients without definite evidence of glaucomatous damage.[3] In this study, 1636 participants with OHT of 24 to 32 mmHg in one eye and 21 to 32 mmHg in the other eye, but with no certain evidence of glaucomatous damage, were randomized to either observation or treatment with commercially available ocular hypotensive medicines. At 5 years' follow-up, the cumulative probability of progression to glaucoma in the treated group was less than half that in the untreated group (Fig 1). The OHTS follow-up study (OHTS II) will provide information about the effect of delaying IOP-lowering treatment on progression to glaucoma in OHT patients (Fig 1). Early IOP-lowering intervention was also found to reduce the rate of conversion from OHT to glaucoma in the European Glaucoma Prevention Study.[4] The difference between the treated and untreated groups was not statistically significant, perhaps because of the less potent IOP-lowering effect of the drug used (dorzolamide alone).

Although findings suggest that the rate of conversion to glaucoma from OHT is relatively low,[5,6] it is essential that those in whom the disease progresses receive appropriate care. Available findings on conversion rates were only based on 5 years' follow-up, and these rates may be significantly higher over a longer period. It is accepted that glaucoma is a chronic progressive disease, and evidence of structural and/or functional progression is therefore important for diagnosis, particularly at the very early stages of the disease, in the absence of obvious damage from glaucoma.

Identification of progression reduces the number of false-positive and false-negative diagnoses of subjects incorrectly identified by cross-sectional measures. Measuring progression helps identify subjects who will never convert to glaucoma or who will convert only over a long time (e.g., 30 or 40 years), in which case conversion is unimportant in the context of the patient's life expectancy. Measuring progression also helps to identify patients who have developed glaucoma and require attention but were not diagnosed by cross-sectional tools because they were within predefined normal limits. The reason for this is that diagnosis is currently made based on the findings of published large randomized clinical trials, in which progression was deemed to occur only when a test reached a predefined threshold for damage (event-based analyses).[3,7–9] An important aspect to consider in clinical trials is the definition of damage. In addition, in the absence of an accepted standard of glaucoma progression, different criteria have been used in different studies, and it is not surprising that the outcomes from clinical trials show a great deal of variation.

There is currently no clear gold standard definition of glaucoma, and the decision as to what constitutes clinical disease is sometimes made in an arbitrary manner. This could result in a false dichotomy between detection of damage (going from no disease to disease) and disease progression (going from mild disease to more severe disease) depending on how clinical disease is defined (Fig 2).

In the absence of damage, the diagnosis of glaucoma may be defined by abnormalities of the optic nerve consistent with other ancillary structural tests, such as nerve fiber analysis or quantitative topography, or corresponding visual function loss. However, because there are several ancillary diagnostic tests, the question "What if those tests disagree with one another?" was proposed. For example, how should differences be reconciled in clinical practice and in clinical trials if an inspection of the optic disc does not correlate with a functional test, or if various structural tests disagree? Thus, evidence for progression in early disease becomes important.

Progressive optic disc change, in eyes with normal visual

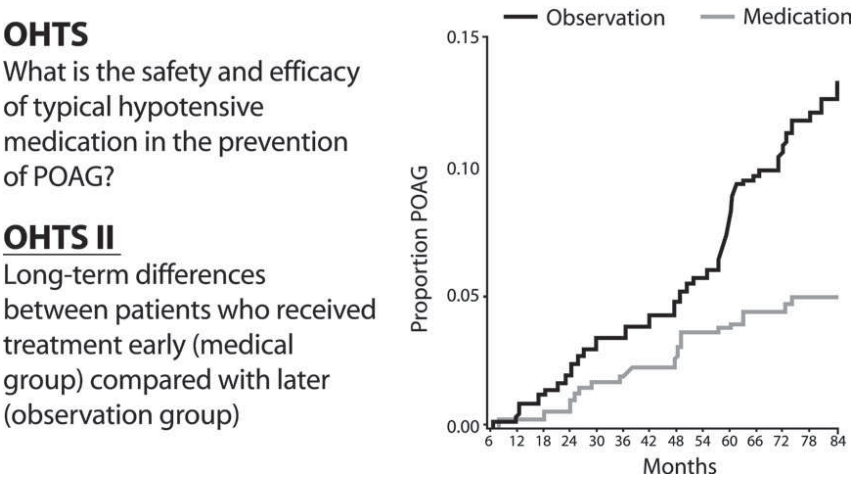

Figure 1. Effect of early treatment on progression to primary open-angle glaucoma (POAG) in ocular hypertension (OHT) patients over 5 years. OHTS = Ocular Hypertension Treatment Study. Cumulative proportion of participants who develop POAG compared among original observation and medication groups. Modified with permission from Kass MA et al. Arch Ophthalmol 2002;120:701–13.

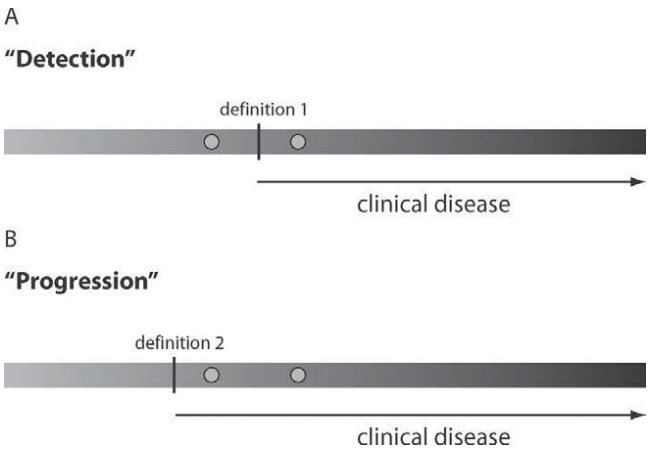

Figure 2. The definition of clinical disease is made in an arbitrary manner, potentially leading to a false dichotomy between detection of damage (**A**) and disease progression (**B**).

fields (VFs), has been used to define so-called pre-perimetric glaucoma.[10] A potential problem with using progression at the level of the optic disc as a requisite for early glaucoma diagnosis is that change is often slow and subtle and may be missed. Another consideration is to determine which optic disc features should be considered when defining pre-perimetric early glaucoma—for example, thinning of the neuroretinal rim only, development of optic disc hemorrhage, progression of peripapillary atrophy, or retinal nerve fiber atrophy. Should one also consider the confirmation of suspected structural change with repeat tests or ancillary tests to make the diagnosis of early glaucoma? Repeat testing was a requirement of the OHTS, where suspected change of the optic nerve head based on stereo photography required confirmation in a repeat set of photographs.

After the introduction, the comoderators invited the participants to a discussion focused on the following themes:

- Is early diagnosis important?
- When should damage be identified?
- When should treatment be started?
- What do we need to know to make this decision?

Summary Discussion

Is Early Diagnosis Important? Glaucoma is a leading cause of blindness worldwide, and early diagnosis certainly bears on the socioeconomic impact of the disease.[11] The burden of visual impairment is not distributed uniformly throughout the world; the least developed regions carry the largest share. Visual impairment is also unequally distributed across age groups, being largely confined to adults 50 and over.[12] Because early glaucoma is a silent condition without symptoms, many patients do not know they have the disease until it has progressed further. Current findings suggest that glaucoma may remain undetected in approximately 50% of the population until some loss of vision has occurred.[12,13] Thus, efforts should be dedicated to identifying those who are actually affected by the disease.

Some voiced the opinion that screening for early glaucoma may not be entirely practical from a public health viewpoint because the objective is to keep people from visual disability because this will help to preserve their quality of life. Case finding should identify those at risk of reduced quality of life.

An important concept that derived from the introduction and discussion was the importance of setting the boundaries of clinical disease. A definition of early glaucoma is needed to guide physicians in their diagnostic and management decisions. Based on this definition, the clinical importance or relevance of early diagnosis can be estimated. Early detection, together with appropriate management, can improve patient outcomes. Although decisions on treatment may not necessarily be made at an early stage, other appropriate measures, such as close monitoring, may be considered. It was generally agreed that early detection does not automatically imply early treatment, and that early detection and early treatment should be considered separately. However, it remains important to find ways to improve the identification of undiagnosed glaucoma in the population.

Early detection may benefit the physician–patient relationship. It is important that the physician educate and counsel the patient about his or her condition to ensure that the patient becomes engaged in the management of his or her condition. The surveillance of the patient should match the risk level. For example, a patient who is highly suspected of having glaucoma may be asked to come back for follow-up in 6 months, instead of the 1 to 5 years for patients in whom there is a lower likelihood of disease.

Among the factors that determine the clinical relevance of early diagnosis, patient age was judged to be important. As explained by A. Heijl, "early diagnosis is important in younger patients—that is, those who are 65 or younger. . . . Progression rates tend to be 0.5 to 1 decibels per year on average, so if you have a patient developing damage at 65, he or she has a fair chance of having quite serious problems before he or she dies." However, said Dr Heijl, "the average age of glaucoma patients in our department is 79, and at that age it's not important to detect the disease early." Monitoring the rate of progression would be more relevant in the typical older patient.

Indeed, focusing efforts on early diagnosis has financial and human resource implications, and ways should be sought to optimize the use of diagnostic resources; too much effort is being put into identifying the earliest signs of glaucoma in patients who are too old, whereas in the clinic the average glaucomatous damage detected in patients is too advanced. The fact that, in clinical situations, patients are found to have considerable damage indicates that detection of glaucoma in the community is often made too late. Late referral has important socioeconomic implications because existing evidence shows that late presentation is an important risk factor for subsequent blindness.[14]

There was a general impression that the identification of individuals with undetected glaucoma is an important public health issue that should be tackled by the appropriate agencies to ensure that effective strategies for screening glaucoma, when they become available, are effectively imple-

mented. Ophthalmologists should try to help these agencies drive this process.

It was also suggested that, perhaps, too many resources are being allocated in developing new technologies to diagnose the very earliest signs of glaucoma, and it may be more appropriate to reallocate some of these resources to identifying people who have their vision threatened by the disease. To do this, however, requires that clinicians have the ability to assess the risk of disease progression, but this is currently not easily achievable. As stated by D. Johnson, it is currently not possible to predict accurately which patients will develop blindness or will have significant vision loss in their lifetimes. The rate of progression is a fundamental consideration, because it drives treatment decisions. The fact that, even with treatment, some patients still go blind indicates that the intensity of treatment is insufficient or treatment is not initiated early enough. Monitoring glaucoma progression is therefore essential, as it allows appropriate clinical decisions to be made. In the view of some participants, diagnostic tools that permit an early detection of damage due to glaucoma will also enable a more precise assessment of the progression rate. In addition, as the ability to detect glaucomatous optic nerve damage varies considerably among physicians, the imaging devices can improve clinical practice by preventing or, at least, limiting any potential failure to detect glaucomatous damage by the clinician.

When Should Damage Be Identified? The boundary between normal and early glaucoma was discussed, and it was generally agreed that the most sound diagnosis of glaucoma is based on progressive damage. In more advanced cases, however, there is no need to demonstrate progression to make a diagnosis, and there is risk to the patient if diagnosis is delayed to observe progression. Evidence of progression is most useful for diagnosis in early, equivocal cases.

Definition of Damage. The difficulty in defining damage in early glaucoma lies in the fact that glaucomatous features are not as clear in early disease as they are in later disease. As pointed out by G. Cioffi, in very early stages of glaucomatous damage there is an overlap between normal and glaucomatous features, and the diagnosis may not be clear. Because of this, diagnosis of early glaucoma is not always straightforward. In the case of so-called glaucoma suspects, selective functional testing, such as short-wavelength automated perimetry or frequency-doubling perimetry, is needed to confirm the diagnosis. Generally, physicians can diagnose glaucoma with confidence, but the diagnostic difficulties here apply to a subgroup of patients with suspect glaucoma who represent 12% to 14% of a typical referral office's cases.

The definition of damage in clinical trials and its application to clinical practice were also discussed. This issue and how it impacts the translation of trial findings into clinical practice were addressed in an editorial by Cioffi and Liebmann.[15] Thus, it is important that the definition of damage be better established in clinical trials so that the trial outcomes can be effectively translated into clinical practice. Early diagnosis has implications regarding clinical management, and it is useful to have good scientific and clinical evidence on the impact of medical intervention at the very early disease stages, characterized by subclinical changes, which are not called glaucoma by clinical definition. This is an important concept that raised the question of how early a diagnosis can be made, because, even with the best tools currently available, it may not be possible to detect glaucoma at the earliest stages that would benefit from treatment.

On the other hand, a great deal of progress has been made in glaucoma diagnosis. For example, the functional defects that are currently picked up could not have been detected 40 years ago with Goldmann perimetry. Starting from the late stages of the disease, physicians have moved on to pick up earlier changes, and uncertainties between *normal* and *glaucoma* have been gradually reduced. Research progress over this period has also revealed that many patients who may require treatment are not being treated because their glaucoma is undetected. More efforts should be made to improve glaucoma detection. As stressed by R. Hitchings, it is important to find out why some patients are not identified and what can be done to enhance detection. It was recommended that it is also important to improve the rate of diagnosis early in the course of the disease because some patients who have undergone trabeculectomy and have an IOP of 10 mmHg still become blind, perhaps because of already severe damage at the time of surgery.

Approaches to Monitoring Progression for Early Diagnosis. The most appropriate approach for management of very early disease stages was discussed. Whereas no additional evidence is needed for diagnosis of patients at the end of the disease spectrum when decision to treat is appropriate, the management of patients with a low risk of conversion to glaucoma and an IOP of 25 mmHg is different. The participants were asked if it would be appropriate to follow up these patients for some time, such as 3 or 4 years, looking for change in the disc or field until evidence of progression is confirmed. This was seen as appropriate, but it was suggested that because glaucoma is accepted as a progressive disease, it is appropriate to monitor progression across the whole disease spectrum, not just in the earliest stages.

It was generally agreed that detection and treatment should be treated separately, and that treatment decisions should ideally be made based on progression rates. Practical considerations should therefore be given to this approach. There was uncertainty about how this could be ideally performed, because there is no clear agreement on the criteria used to establish progression. It was suggested that it might be possible to determine evidence of early damage in the absence of follow-up for progressive change, as it may not be clinically practical to follow up glaucoma suspects indefinitely. The diagnosis of glaucoma may be facilitated by other tests, such as electrophysiology (which determines the activity of the retinal ganglion cells [RGCs]).

When discussing early detection, there usually is a tendency toward dichotomizing whether the disease is present or absent. In reality, it is a question of probabilities, and our behavior in relation to a patient is based on the probability of that patient having glaucoma or the probability of progressing quickly. For example, a low probability can be

attributed to a person at very low risk for glaucoma (e.g., normal pressure and no family history) but with a questionable optic disc. There is a great deal of uncertainty in most cases of early disease, and the frequency of follow-up examinations and testing should vary with the level of disease (or progression) probability, increasing with a high probability and decreasing with a low probability. When asked about what probability threshold (e.g., 50%, 80%) he would set for diagnosis and whether progression would be required for him to decide if a person has glaucomatous damage, D. F. Garway-Heath said that he would not set a threshold for making his diagnostic decisions in early disease. "Setting a threshold," he said, "is more important when it comes to starting early treatment"; thresholds for treatment decisions also vary according to the individual (age, patient preference, family history). It was concluded that the best way of establishing whether or not a patient has glaucoma is change (progression).

The relevance of selective functional testing (such as short-wavelength automated perimetry or frequency-doubling perimetry) to confirm glaucoma diagnosis was discussed. It was thought that selective testing could increase the chance of false-positive results. Although, in clinical practice, additional testing is used to confirm the diagnosis when this is deemed necessary, this practice may increase the number of patients with false-positive results referred on and may lead to unnecessary treatment. The importance of the neural rim appearance as an indicator of early glaucoma was stressed. Confirmation of diagnosis with ancillary tests was suggested, as it can help to confirm diagnosis when there is a high clinical suspicion of glaucoma but negative conventional test results.

Factors Affecting the Rate of Change. There are similarities in progressive changes in the optic disc between healthy aging and glaucoma. B. Chauhan reported findings in normal subjects who were followed up for almost 15 years: the pattern of change of the optic disc in these subjects (e.g., sectoral disc rim change) is very similar to that in glaucoma patients; however, the rate of change is much slower. The rate of change in glaucoma may vary depending on the degree of damage. Several studies have shown that the risk of progression increases with more damage, although with perimetric analyses it becomes more difficult to confirm progression if there is already damage, because there is greater variability in damaged fields. In clinical trials, linear models best fit the pattern of progression. But because clinicians tend to increase treatment in advanced disease, progression would probably be greater if therapy were kept at the same level. Clinical practice is also to increase treatment if progression is suspected.

Retinal ganglion cell loss and rate of change. The potential artifacts of measuring progression rate with functional tests were discussed. Even with a constant rate of RGC attrition, the rate of VF progression may appear to increase because the loss of a constant number of RGCs represents a relatively larger proportion of the remaining RGCs in more advanced disease. The problem of identifying the pattern of progression is also caused by the amount of noise in the data. This can limit the detection and distort the pattern of progression in field tests and may have an important clinical impact because VF tests may reflect significant RGC loss. The work in rat models by J. Morrison was mentioned,[16] in which increases in RGC death subsequent to IOP elevation have not been found to be linear. These findings need to be taken into account when discussing the relevance of early diagnosis because clinical data have limitations: the loss of a great number of RGCs may not be detected by VF testing early in the disease.

Acceleration of RGC decline may also occur with normal human aging. This is why measurement of progression rates is an important consideration. The linear representation of VF loss over time is generally used because it is the simplest model, where rates of progression are inferred from VF data collected cross-sectionally (in individuals of different age groups). However, there is considerable interindividual variability. Statistical strategies are needed to predict at what point an accelerated rate of loss becomes abnormal (i.e., pathological). More data, especially longitudinal, are therefore required, and this entails more studies with new imaging and VF tools as they become available to clinical practice. The decline in RGC numbers in the aging process and in a pathological process such as glaucoma may follow similar patterns but at different rates. Another important aspect to consider is that in glaucoma the pattern of decline of RGCs in response to IOP elevation can vary considerably between individuals. As D. Greenfield said, some individuals may be able to tolerate IOP elevation for a much longer period; thus, the rate of progressive damage is considerably reduced. Factors that contribute to the variability of susceptibility to damage need to be further studied and better understood.

Progression rate is an important parameter in the disease process, and early diagnosis is critically important if there is a later acceleration of RGC decline. If, however, the rate of decline is linear, then early diagnosis may be less important. The pattern of RGC decline may depend on the intensity of stress on the optic nerve. Continuous low-level stress may lead to a low slope of linear progression, whereas higher-level changeable stress causes an accelerated slope of progression. Animal models of chronic IOP elevation may be more similar to a subacute model, with an accelerated sigmoidal pattern of RGC loss, even though the models are called chronic. The accelerated loss of RGCs may be related to secondary degeneration effected by the damaged retina.

Angle-closure glaucoma (ACG) is the type of glaucoma with such a progression pattern, in which IOP is the primary stress. In intermittent ACG, the stress to the optic nerve is subclinical, and there may be no progression. However, if the condition develops into a subacute or chronic condition, progression will be accelerated. An example of low-intensity stress is normal-tension glaucoma, where progression is often slow and, sometimes, episodic, and the relative influence of IOP stress may be less than that in high-tension glaucoma.

Role of Clinical Testing Devices in Glaucoma Diagnosis. There was general agreement among the participants that there should be a diagnosis before treatment decisions can be made, and the aim of treatment is to prevent people from developing significant visual impairment during their lifetimes. Based on this rationale, the rate of progression

then determines how treatment targets should be set. It was proposed that it should be possible to move toward an instrument-based definition of glaucoma (i.e., definition based on diagnostic devices) because this may improve the specificity and sensitivity over current clinical practice. However, this approach was judged to be impractical with current technology because of the complexity of the instruments, the variability of their measurements, and their different characteristics.

There was agreement that diagnostic devices could be used as an integral part of the diagnostic process, but that the onus for diagnosis should be put not on the devices themselves, but on the clinician. The devices cannot provide a patient's diagnosis, but their findings can guide estimates of the likelihood of the patient having a certain condition. What is required, therefore, is the integration of information from these devices into the diagnostic process, using sound clinical judgment. For example, by adopting this approach and combining the information from the Heidelberg Retina Tomograph (HRT; Heidelberg Engineering, Heidelberg, Germany) and IOP level, the predictive diagnostic probability of an HRT classification of outside normal limits can be increased from about 20% to 80%.[17] As there may be misconceptions about the role of diagnostic devices, education should be provided to ophthalmologists on how to use the information from these devices appropriately in the diagnostic process.

The findings from screening patients for the Early Manifest Glaucoma Trial (EMGT) showed that many glaucoma patients with normal IOP were left undiagnosed. This indicates that glaucoma detection, at least in Sweden, is too often based on IOP, and ophthalmologists do not examine patients for glaucoma if their IOP is normal. For this reason, some believe that diagnostic devices, used in a judicious way, will have a role in finding undiagnosed patients. High rates of false positives can be avoided by not setting sensitivity too high. This way, the devices can help detect patients who have early but established glaucoma.

When Should Treatment Be Started? With regard to the impact of early treatment on treatment outcome, one should consider if the intended outcome of treatment is prevention of field loss or prevention of disability; the former refers to visual function, whereas the latter is related to quality of life. Therefore, the effect of early treatment on these outcomes can be very different. Concerning treatment initiation, it was thought that treatment should be initiated if it is deemed necessary to preserve quality of life and that initiation of treatment should be considered on an individual basis. As recommended in the OHTS,[3] not all hypertensive patients should be treated, but several parameters should be taken into account, among which are the socioeconomic impact of long-term treatment, likelihood of the patient being helped by treatment, patient's health status and life expectancy, and patient's relative risk of developing glaucoma (see session 2's discussion on the clinical relevance of risk factors). Treatment decisions also depend on progression rate and confirmation of damage. Work over the last 20 years has been geared toward improving early detection, but more effort should be focused on measuring the progression rate, as this is more clinically valuable.

With increasing life expectancy, the number of people who develop glaucoma is increasing. J. Caprioli remarked, "in my practice, there are 6 or 8 people who are over 100 years of age, . . . we all may develop glaucoma if we live long enough." He stressed the importance of progression rate in making decisions on when to initiate treatment and how aggressive treatment should be: "It's a matter of how quickly the damage occurs, which determines when and how to treat, . . . it's less important to see where damage is along the spectrum of disease but more important to know how quickly it progresses along this spectrum."

Consideration was given to whether treatment should be initiated as soon as possible, because available findings have shown that considerable RGC death may go undetected. The rate of RGC death may be much more accelerated than usually thought, because research evidence has shown that RGC decline may not be linear but can increase steeply with further damage. In terms of clinical relevance of this observation, it was suggested that a follow-up study to the EMGT[18] should be conducted to investigate progression rates of patients who received early treatment, compared with those who received later treatment in this study. In the 6-year EMGT, early intervention delayed disease progression in the treatment group with early glaucoma compared with untreated patients (45% vs. 62%; $P = 0.007$). In other words, it needs to be determined if early treatment is beneficial for the long-term visual outcome or whether it is acceptable to observe progression behavior and then treat the patient on the basis of observed progression behavior. A. Heijl disclosed that the patient cohort from the EMGT is still being followed as long as the patients' health allows him and his team to do so. The aims of this follow-up study are to determine the long-term effect of delaying treatment until progression is detected and to find out if there is any difference between this approach and early treatment before progression is shown. He explained that most of the patients who were not treated initially have progressed. Although the initial findings from 6-year follow-up have shown no difference in VF or acuity between the two patient groups, it cannot be ascertained whether delaying treatment initially until progression has been confirmed will result in further damage over the longer term.

Concerning the OHTS II, which is the long-term follow-up of the OHTS, it was noted that in addition to providing information on the effect of delaying treatment on the conversion to glaucoma in patients with OHT, another two outcomes of great clinical interest are whether a lower rate of further progression will be seen in treated patients and if a higher rate of progression will be seen in treated or untreated patients who have reached a degree of damage sufficient to manifest as VF loss. These two outcomes would demonstrate the effect of early versus late treatment on disease progression.

The following conclusions were drawn by the comoderators to close the first session of the Think Tank:

- Glaucoma seems to be an acceleration of a normal aging process, in which there is an acceleration of RGC death that ultimately results in a recognizable

pattern of nerve fiber layer atrophy and optic nerve head damage, ultimately leading to vision loss.

- Change (progression) is an important element in the diagnosis of glaucoma, and resources should be appropriately allocated for a better identification of individuals at risk for ultimate visual disability and blindness.
- It is currently difficult to identify very early glaucoma, and more selective structural and functional tests may help establish an earlier glaucoma diagnosis, although it may introduce a greater rate of false positives.
- The impact of delayed treatment in OHT and early glaucoma diagnosis remains to be established by further follow-up of long-term studies.
- The findings of the OHTS II would help to improve resource allocation, because they would better identify individuals who require treatment, and to make decisions about when to initiate treatment.

Session 2: Detection of Progression in Glaucoma

The importance of progression, as well as the rate of progression, was highlighted in the first session. The second session, co-moderated by D. F. Garway-Heath and A. Heijl, was concerned with the detection of glaucomatous progression and quantification of its rate. The aim of glaucoma treatment is to slow the rate of progression so that the patient does not experience a loss of quality of life due to loss of vision. Because of this, it is important to know the rates of change, instead of simply whether or not change is taking place. The approaches for detecting and quantifying progression may differ among patients. For example, event-based methods may be more appropriate in an 85-year-old patient with a treated IOP of 20 mmHg and VF mean deviation (MD) of −7 decibels (dB), whereas trend-based methods may be more suitable in a 45-year-old patient with the same characteristics. Consideration also needs to be given to the most appropriate approaches for use in clinical trials, which may differ from the goals of routine clinical care. This is so because clinical trials are designed to answer certain usually specific questions and require the statistical rigor to prove or disprove a hypothesis based on how a group of subjects (rather than an individual) behave.

In the event-based approach, illustrated for VFs in Figure 3, the criterion for progression, or event, is defined at the start of the study, and progression is confirmed when changes in VF have dipped below the preset threshold. Information at baseline and that from the most recent test are used to decide whether an eye has progressed.

Trend-based (or rate-based) approaches can be adopted to improve progression rate measurement. These may be applied on the MD or VF sectors or at individual test locations over time by linear regression analysis (Fig 4). These approaches have been shown to be more sensitive for detecting progression than event-based analysis because all VF measurements over the course of follow-up are used in the analysis.

There are other factors to be considered. Although it would be ideal to know the rate of progression in all patients, this would entail frequent testing, which would have cost implications; it could cause inconvenience to patients and have a psychological impact on them. It was thought that resources ought to be concentrated on patients who are at the highest risk of vision loss, and the consequence of this approach would be to risk profile patients at the outset. Attempts would then be made to measure rates of change in patients at highest risk of vision loss, and a safety net approach would be used for others to identify patients in whom the risk profiling may have been inaccurate (i.e., false negatives).

Looking at the natural history of glaucoma, findings from various studies have shown that patients progress at different rates. In untreated patients, the proportions of patients that were detected as progressing (distinction needs to be made between detected progression and actual progression) were 54% in 10 years in St. Lucia[19]; 60% in 5 years, after

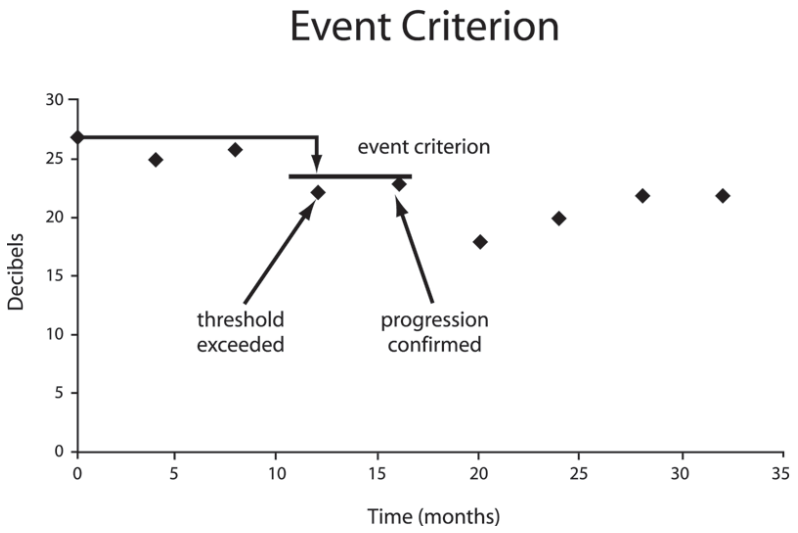

Figure 3. Illustration of event-based analysis of visual field change.

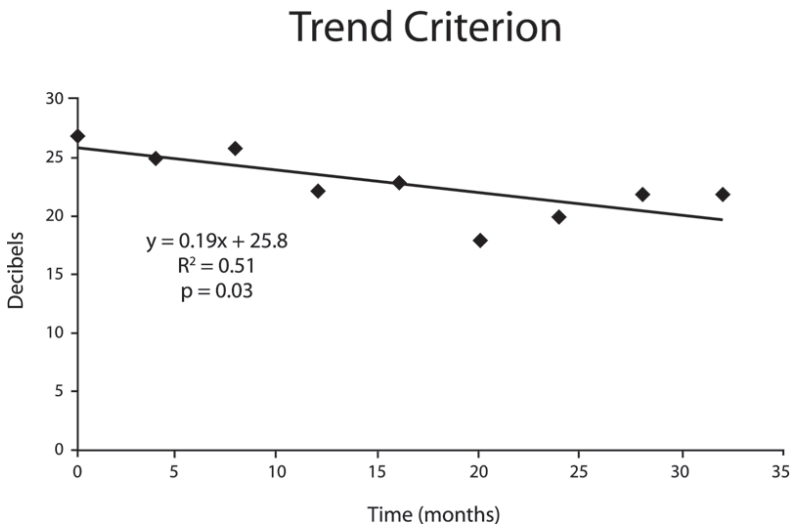

Figure 4. Illustration of trend-based analysis of visual field progression.

accounting for the influence of cataract, in the Collaborative Normal-Tension Glaucoma Study[7]; 62% in 6 years in the EMGT[19]; and 10% in 5 years in the OHTS.[3] The rate of progression, measured by visual function loss, was on average 0.8 to 0.9 dB/year in patients in St. Lucia. There may be considerable error in the estimate, however, as this average rate was obtained with only 2 VFs for each patient. In the Collaborative Normal-Tension Glaucoma Study, the average rate of visual function loss was 0.5 dB/year, and between 0.2 and 2.0 dB/year in patients who had significant progression. In the EMGT study, the average rate of progression was 0.6 dB/year.

Concerning rates of progression as measured by structural parameters, in a study looking at the rate and pattern of neuroretinal rim area decrease with follow-up from 5 to 15 years the rate of loss was about 0.2%/year in normal patients; nearly 0.5%/year and 3.0%/year in stable and deteriorating OHT patients, respectively; and almost 4.0%/year in patients with glaucoma.[20] Another study investigated the progression of optic disc and VF loss in early glaucoma with an average follow-up of 6 years.[21] Neuroretinal rim loss was found to be <2%/year for eyes without initial field loss and >2%/year in eyes with initial field loss.

The above information indicates that progression is slow in most patients, but progression rates vary greatly. Figure 5 shows data from the EMGT, which are used to illustrate the point at which a progression event can be identified. Using the end point criteria applied in this study, it was determined that a progression event occurred with a VF loss (MD) from baseline of about 2 dB on average, with a great variability around this value according to the field quality.

There are 2 approaches that can be adopted to identify which patients will progress quickly. One is to estimate the initial rate by measuring structure and/or function intensively in all patients at the outset, and the other is to risk profile patients and measure the initial rate only in those at high risk. For measuring structural progression rates, a number of instruments can be used, one of which is the HRT.[22] Measurements can be made of global parameters, such as rim area, or height parameters, such as surface height within the optic disc. For VF progression rates, measurements can be made on global parameters, such as MD over time, or pointwise to determine change at various locations within the VF.[23] The required frequency of testing depends on the rate of progression, and a lower frequency, for a fixed time, is required to detect faster rates of change.[24] The evidence suggests that quantitative structural and functional assessments require a similar frequency of testing to detect progression.

The time it takes to detect progression is an important consideration, and a parameter that is critically important is data quality. A study by Vesti et al compared the 4 methods for detecting VF progression in 76 patients with progressive glaucoma.[25] Visual fields were measured at the outset and end of a 7-year follow-up, and computer modeling was used to fill in the intervening fields at 6-month intervals, adding no-threshold, moderate-threshold, and high-threshold variability to the series. These series were then used to see how the various methods picked up progression in the absence or presence of high or moderate data variability. Time to detection of disease progression and method specificity

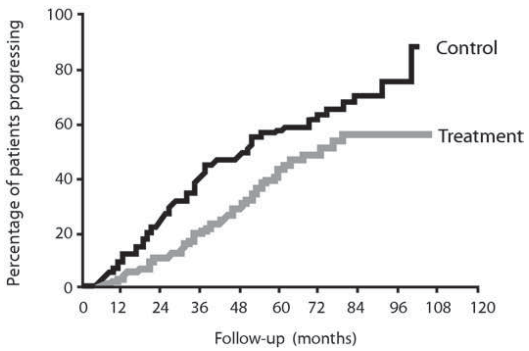

Figure 5. Data from the Early Manifest Glaucoma Trial showing the slope of change in the control and treatment groups. Modified with permission from Heijl A et al. Arch Ophthalmol 2002;120:1268–79.

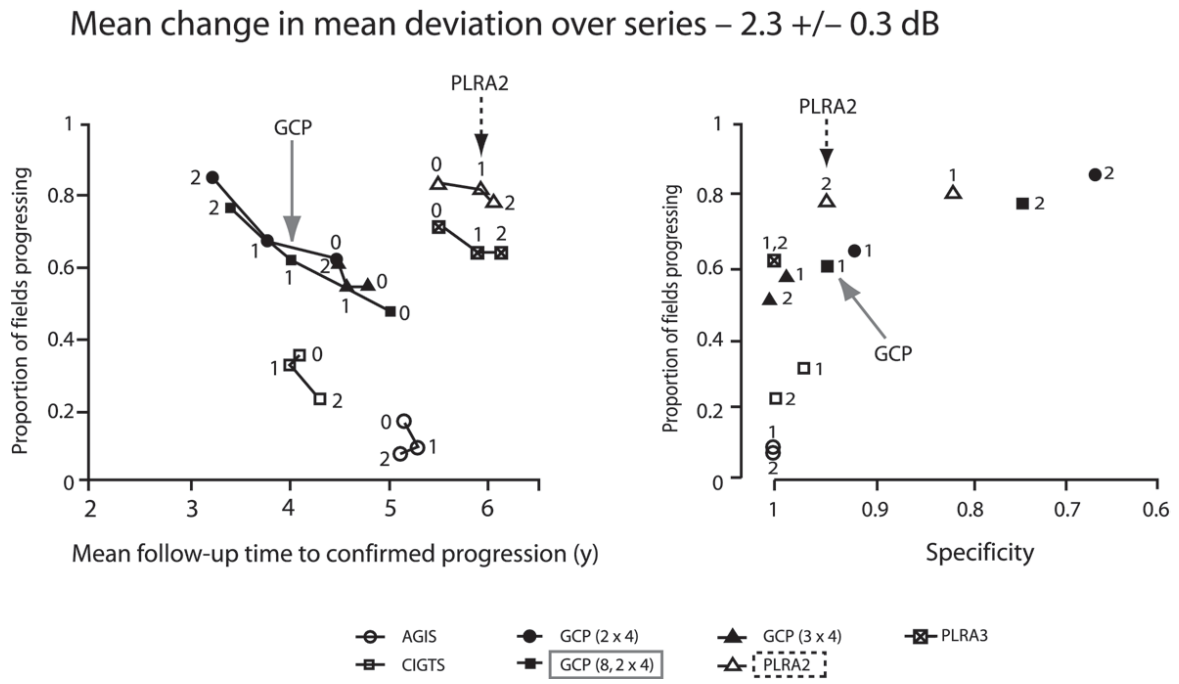

Figure 6. Comparison of the 4 visual field scoring systems in detecting progression. AGIS = Advanced Glaucoma Intervention Study; CIGTS = Collaborative Initial Glaucoma Treatment Study; GCP = glaucoma change probability; PLRA = pointwise linear regression analysis. 1, moderate data variability; 2, high data variability. Modified with permission from Vesti E et al. Invest Ophthalmol Vis Sci 2003;44:3873–9.

were the main outcome measures. Figure 6 shows that event-based analysis (glaucoma change probability) was good at detecting change early on but tended to be less specific in the presence of greater data variability. Although trend-based analysis (pointwise linear regression analysis) took longer to detect progression, it identified more progressing fields and had higher specificity in identifying changes in the VF.

The correlation between structural and functional changes has been investigated in a recent study in OHT patients.[26] Trend-based analysis was used to define progression in neuroretinal rim area and visual function. When specificity was set at 90%, almost equal numbers of patients progressed structurally and functionally, with a relatively small overlap between the two. Two thirds of the patients progressing by both structure and function changed in corresponding regions of the optic nerve head and VF. With more stringent criteria and specificity set at 97%, fewer cases were detected, but the very small overlap had 100% spatial congruity between structure and function (Fig 7). The most likely cause for the lack of correlation between structural and functional estimates of progression is that, in some patients, noise is greater for one modality than the other. It is also possible that some structural changes are not directly related to RGC loss or that functional loss is unrelated to RGC loss but is related to RGC dysfunction or cataract development. The findings from this study indicate that measurement of both structural and functional changes is needed in patients with OHT. Similar findings have been reported for manifest glaucoma.[27]

In clinical practice, therefore, one needs to take into account that measurements of change are affected by the rate of change, measurement variability, and frequency and spacing of tests. It is of clinical relevance to consider how measurements of structural change relate to those of functional change. The relationship between structure and function varies at different stages of the disease and looks very different in early disease compared with later disease (Fig 8).

One should also consider how best to summarize measurements of change. Currently, summary measures (e.g., MD) for progression or pointwise (from each field location) measurements across the VF are used. But perhaps sectors

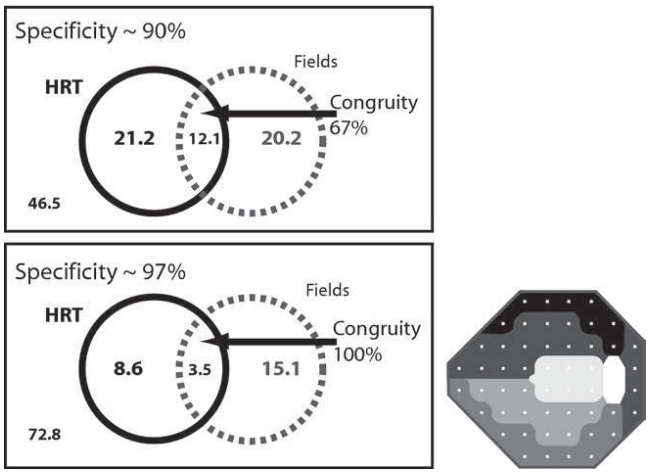

Figure 7. Specificity and congruity for the Heidelberg Retina Tomograph (HRT) and visual field examination in 192 patients with ocular hypertension. Reproduced with permission from Strouthidis NG et al. Invest Ophthalmol Vis Sci 2006;47:2904–10.

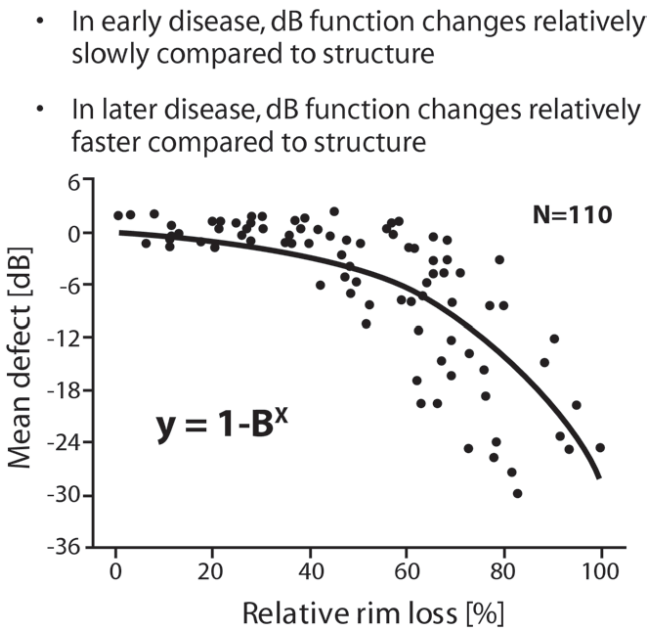

Figure 8. Structure–function relationship. dB = decibel.

of the optic nerve head related to the VF map (Fig 9) could be considered as an alternative to pointwise measurements. Measurements of progression in these sectors may be as sensitive as pointwise measurements, and it may be easier to derive summary measures of progression from them. In addition, using the sectors may make it easier to relate visual function change to structural change.

Other considerations of clinical relevance are the functional importance of the location of the loss. In other words, one needs to think about the possible impact of RGC loss in certain locations on visual function and the consequences on the patient's physical abilities and daily functions. In this respect, it would be appropriate to consider the importance of progression of binocular defects, as this can have an impact on the patient's quality of life and physical abilities (e.g., may cause falls or driving accidents).

The participants joined a discussion focused on the following points:

- Are rates of change more important than early detection?
- How can rates be best measured?
- The clinical relevance of structural and functional testing.

Summary Discussion

Rate of Change or Progression? There was some discussion about the terminology used to designate change in structural or functional defects. *Rate of change* was brought up as a more appropriate term to use than *progression.* G. Spaeth pointed out that the latter term may convey the idea of improvement because patients who progress are actually getting worse. From the physician's point of view, the disease progresses, but for the patient, his or her condition deteriorates, and so the term *progression* may confuse the patient. However, as with other terms used in medicine, although *progression* may not be the ideal term, it conveys the idea of disease advancement. There are often problems with medical terminology, and one may run into semantic difficulty trying to identify the ideal language to express certain ideas. For example, *positive test* may convey different concepts to doctors and patients.

Are Rates More Important than Early Detection? It was generally agreed that the assessment of rates of change is clinically more important than early detection of change, as management decisions should be based on these rates (see "Session 1: Early Glaucoma Diagnosis" for a related discussion). The extent to which data from clinical trials can be applied to clinical practice was discussed. It was generally agreed that the practice of medicine should be based on evidence. However, there may be cases where not enough data are available to provide guidance. For example, there are no trial data available that can be used to predict disease progression rates in newly diagnosed patients with early disease. This shortage of data is due to the fact that all trials have been designed to identify disease progression based on an arbitrary disease event. Future trials should therefore be designed to measure rates of change, which are more useful measures of disease progression.

Existing clinical trial data could be used to determine differential rates of progression at different stages of the disease so that they may be applied to clinical situations. However, an issue that was raised concerned the applicability of trial data to individual patients, as there is high interpatient variability. For example, within the 10% of untreated patients who progressed over 5 years in the OHTS[3] the rate of progression in some patients was much faster than in others: these individuals started with no visual function loss, and some ended up with significant visual loss. However, it was judged that if rates of progression in a clinical trial are estimated correctly with the appropriate statistical methods (e.g., correct confidence intervals [CIs]), then they can be extrapolated to single patients to provide guidance on management. Although data from clinical trials may not be generalized to all individuals, they do form the foundation of evidence-based medicine. The results of clinical trials specifically pertain only to those individuals who match the profiles of patients included in the trial and who

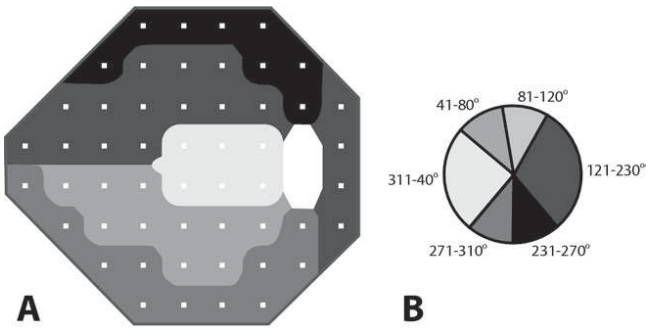

Figure 9. A division of the visual field (**A**) and optic nerve head (**B**) into mapped sectors according to the results of a study of defects in 69 patients with normal-tension glaucoma or suspected glaucoma. Reproduced with permission from Garway-Heath DF et al. Ophthalmology 2000;107:1809–15.

are treated exactly as they were according to the clinical trial protocols.

How Can Rates Best Be Measured? In the absence of trial data to provide guidance to clinical management decisions, an appropriate approach should be identified to assess progression rates in newly diagnosed patients. It was agreed that although assessment of risk would be an option, patients should be initially followed up for a certain period (e.g., several years) so that their rates of progression could be determined. It was recommended that, when working with newly diagnosed patients, the ophthalmologist have the important obligation to make sure that they are not progressing rapidly. Because of this, a thorough evaluation of the individual on his or her visit is needed. Although IOP has an important place, management decisions should not be based solely on IOP assessment.

As assessing progression rates was agreed by all the participants to be essential in clinical practice, it was suggested that practical considerations should be given to rate measurement, such as the period of follow-up needed to determine a patient's rate, the number and types of tests required to determine this rate, and the resources needed to perform rate measurement.

Is Measuring Rates Practical? The practicality of measuring progression rates was discussed. It was felt that a general agreement on a simple definition of progression was the first and essential step. This definition can be used to design end points for future clinical trials and is necessary to ensure that findings from these trials can be compared with each other. Approaches to measuring progression will be more accessible in the near future. In the meantime, ophthalmologists should evaluate the optic disc carefully, assess the risk of progression (because it determines the frequency of follow-up), and perform VF tests and assess VFs effectively.

Assessment of risk of progression. It was suggested that one way of establishing an initial risk assessment to assist decision making about treatment and follow-up would be through the use of information on risk factors from the EMGT[18] and OHTS.[3] It would be useful to know if the patients who showed evidence of the fastest progression in the EMGT were also the ones with the highest risk for progression in the OHTS. This information would help to identify which individuals require more frequent VF testing.

This view, however, was not entirely agreed upon. Concerning the relevance of risk factors in assessing progression rates, A. Heijl et al in the EMGT spent much time investigating the influence of risk factors on the rate and interpatient variability of progression. The conclusion they reached was that using all the risk factors that have been identified in combination, they could explain only about half of the interpatient variability. It is therefore not possible to use risk factors to accurately predict the rate of progression in an individual patient. For this reason, it is essential for clinicians to monitor the rate of progression in every patient to assess his or her risk of future progression. Progression rate assessment should be part of standard clinical care.

Regarding the use of risk factors to make initial decisions on frequency of VF testing, there was agreement that risk factors have some value but that only general, and not entirely precise, recommendations can be based on them. However, there are enough data available that can be used by clinicians, in combination with sound clinical judgment, to estimate initially how frequently a newly diagnosed patient needs to have his or her VF tested. It may also be possible to risk profile patients according to their likelihood of disease status and outcomes. Age, IOP, disease stage, presence of disc hemorrhage, family history, and exfoliation were identified as the most important risk factors to consider at the start. Disc hemorrhage and exfoliation have been found to be independent risk factors for glaucoma progression.

Assessing functional change. Frequent VF testing was judged to be of great importance, in particular at the beginning of a patient's follow-up, as it allows the rate of progression to be estimated. To obtain the rate of progression in a patient, a number of data points are needed. It was recommended that newly diagnosed patients have 3 field examinations a year for the first 2 years, after which time testing frequency is reassessed. For patients who do not progress or progress very slowly, the frequency is reduced to every year or longer.

Assessing structural change. The importance of structural change assessment was discussed. Examination of the optic nerve head should be conducted in newly diagnosed patients. Identification of change can be made with serial optic disc photographs, but measurement of the rate of change is better made with a quantitative method. Imaging devices have measurement errors but may provide a more impartial approach to progression as the variability in measurements can be quantified and the level of imprecision estimated. The approach based on optic disc photographs is more subjective, as it depends more on the observer's own experience and clinical judgment. Some ophthalmologists do not use disc photographs but have access to automated devices. Because of this, some would favor the use of more practical tools to help clinicians assess progression.

J. Morgan highlighted that currently there is a lack of education on how to recognize defects in the optic disc, and this is a cause for the failure to detect glaucoma in the community. Some patients referred to glaucoma specialists show surprisingly advanced disease. A further consideration is that some patients do not perform well on VF tests. For this reason, the quality of the fields obtained in the community and in general hospitals can be poor and does not reflect the data of clinical trials. There would be a considerable problem if clinical practice relied only on VFs, at least in earlier stages of the disease.

J. Caprioli asked G. Spaeth, who has had long-term experience with optic disc photography, for his opinion on the use of this method to assess progression rates and on the impact of quantitative measurements on this approach. Spaeth responded that he increasingly uses the disc damage likelihood scale, which is a simple technique to assess optic disc change from disc photographs. This method is based on the appearance of the neuroretinal rim of the optic disc corrected for disc diameter.[28] There are 8 stages of change, from no damage to very advanced damage, which are based on the width of the neuroretinal rim or the circumferential

extent of absence of the neuroretinal rim. Using this approach, it was found that most patients took 7 years to exhibit 2 stages of change and another 10 years to exhibit another 2 stages of change. G. Spaeth recommended that for making clinical decisions it is essential to estimate how much damage has occurred at diagnosis, what the rate of change is, and the patient's life expectancy.

Although optic disc photographs can be used to identify change, it would be clinically challenging to use them to quantify change. Stereoscopic disc photographs can be used in this approach, but one has to know how to make measurements from the photograph. It was conceded that it is more likely that the general clinician would use a method that provides him or her with the information required readily and in an objective manner. Clinicians should nevertheless be encouraged to take the photographs in the first place, as this encourages them to pay more attention to structural change. This approach has been widely adopted in the clinical setting. J. Morgan suggested that rate of change can be determined if enough photographs are taken. In terms of translating this approach to clinical management, measurements can be made from optic disc photographs by scaling them. However, this approach is not widely practiced because it is effort- and time-consuming. Any approach to assessing rate that is time-consuming would be difficult to achieve in the clinic.

Clinical Relevance of Structural and Functional Testing. The participants were asked to consider the clinical relevance of determining structural change, functional change, or both at different disease stages (i.e., before and after confirmation of visual function defects). An opinion was expressed that it seems better to focus on structure early in the disease and on function measurements later in the disease if resources are limited.

Reference Standard for Clinically Significant Change. There was further discussion on how best to determine the rate of progression within the context of clinical care. As a starting point, a reference standard should be decided and agreed upon. For this purpose, a measure of progression—for example, percentage of structural defect or MD in VF, over a certain period—could be used to define the threshold for clinically significant change. This criterion should be technique independent, so that it can be determined using different approaches (optic disc photographs or imaging devices). This is a simple approach that can be easily and widely adopted, but consideration should be given to the location of the change (i.e., where the VF or optic nerve change is occurring) because this has implications for the patient's function.

Importance of Assessing Structural Change. With respect to the clinical relevance of determining structural change, the participants were asked if they would initiate treatment in a patient in his or her 50s identified with progressive neuroretinal rim loss of the optic disc but with a normal VF. There was a clear consensus that treatment should be initiated. This general agreement indicates that, in the case of a normal VF, evidence of change in the optic nerve head is important for treatment decisions and that a VF examination should not substitute for an examination of the optic nerve head.

Another case scenario is when the patient has well-established glaucoma and is already receiving treatment. In this situation, guidance needs to be provided to the clinician on the approach(es) for identifying and confirming progression and for deciding whether to pursue medical treatment or to perform surgery. The physician's treatment decision has an important impact on the patient's quality of life. Education is needed on the importance of optic nerve head examination and how to conduct this appropriately. For example, the concept of cup-to-disc (C/D) ratio is not a useful approach for assessing glaucomatous disc progression. Better approaches include a careful inspection of the neuroretinal rim and retinal nerve fiber layer (RNFL) and for the presence of optic disc hemorrhage. Indeed, approaches to identifying progression need to be modified based on the patient's age and location of the VF defect—certainly, one that is close to fixation will have a very large impact on the quality of vision. Perhaps, with the exception of very late disease, some patients progress structurally and others progress functionally at any stage of the disease. Therefore, assessment of both structure and function is necessary.

Corroboration of Structural and Functional Change in Clinical Practice. Multiple testing. The necessity of performing multiple testing was discussed. Confirmation of progression in clinical practice may differ from that done in trials. When structural change confirms a change detected in the VF, repeated VF testing may not be required to confirm that progression has occurred.

It frequently happens that a defined threshold for field change is not reached in the same patient on subsequent visits, and multiple VFs are needed to confirm change. In addition, if a change in the optic nerve head does not correspond to a change in VF or vice versa, then confirmation of the VF change is also needed. An aspect that some have incorporated into their practices is never to examine a disc after looking at the field because doing so would influence the judgment of the disc. It was recommended, "Don't ever look at the field first before you look at the disc, because you'll see a change in the disc if you see a change in the field." This may bias one's opinion on the patient's disease status.

The future of structural change assessment. Because of the problems with assessing VFs, more objective methods (such as imaging) are being considered, certainly for early disease. When it comes to progressive disease in a patient with established glaucoma, there is still the need for VF testing at regular intervals. For early disease, serial optic disc photography is an option for monitoring disease progression. However, this view is not universally held because a drawback of optic disc photographs is that their interpretation is complex, and this would limit their use in the clinic. For this reason, some would prefer a method that provides an automated objective estimation of change (progression). The important considerations that should be given to a method chosen for recording and measuring progression rate are highest data quality possible, convenience for frequent use, ease of interpretation, and quickly available information.

According to P. Lee, the findings from 12 glaucoma

centers in the U.S. show an annual rate of only about 35% of patients having disc photographs taken. In community settings, documentation of the optic disc is under 40% within 2 years of the most recent examination, and even then it is usually only a vertical C/D ratio. Future glaucoma management may rely more heavily on automated image analysis of the disc, and appropriate means and guidance on how to use and interpret these images will have to be provided to ophthalmologists. T. Zeyen proposed that, while we wait for a more complete validation of imaging devices, stereophotography could be used to record baseline optic disc features. Although this technique is slightly cumbersome and requires pupil dilation, it offers good images that can be scanned and viewed using a stereoviewer system installed on a monitor.

Importance of corroboration between structural and functional change. It was generally agreed that corroboration between disc and field is important, and it should always be sought for diagnosis and management decisions. Evidence from clinical trials provides guidance to medical practice, but in the absence of evidence, sound clinical judgment and various clinical parameters contribute toward decision making. As explained by J. Liebmann, in routine clinical situations the physician has to deal with individual patients and to use a pragmatic approach to clinical decision-making. For example, multiple field testing to confirm progression may not always be needed if other factors (e.g., optic nerve head change, disc hemorrhage, IOP level) contribute to corroborate a finding in one test.

Corroboration between disc and field may not be found in very early or very late disease, but is useful mostly in early to moderate glaucoma. Corroboration in disc change may not be needed in very late disease stages (i.e., when there is major field loss) for making therapeutic decisions. However, multiple visual tests are required to confirm progression because of the presence of measurement noise. This avoids overemphasis on a single field test result. In addition, there is a spectrum of patients in whom VF tests provide different information; in other words, some eyes are noisier than others. Therefore, more fields should be obtained to average out the noise level and confirm test results. But, indeed, conducting more field tests also has financial implications.

The best evidence of the nature of progressive change is that from well-conducted prospective clinical studies, and it suggests that the coincidence of significant structural and functional progression is rare (i.e., the overlap between the two is poor). It was suggested that this small overlap might be because the changes sought in clinical trials are very small and usually early, and therefore, the chance of corroborating the 2 types of change might be reduced. A longer period of examination might increase the likelihood of increasing this overlap because, as in clinical situations, optic disc change is often corroborated by field change and vice versa. Glaucoma is a neuropathy that is very variable at different stages of disease, even within the same individual. In some patients, there may be a manifest change in the neuroretinal rim; in others, there is no visible change, but there is enough axonal loss to manifest as a field change. In the future, there may be advancements in research that allow for better predictions of the type of change that can be found in a patient. New technologies will take into account variations with age and in the structure of the optic nerve head to make these predictions. There is a strong need to perform both structural and functional assessments.

The second session of the meeting closed with a summary by the comoderators on the following points:

- Knowing the progression rate is essential in the clinical management of glaucoma, and future advances in research and technology will allow for a more efficient assessment of rates of progression and better dissemination of the tools to measure progression rates in clinical practice.
- Efforts should be focused on providing simple and effective education to practitioners on how best to examine the optic disc and how to perform and assess VFs effectively, to assess progression.
- There was consensus on the clinical role of both function and structure testing, although in very advanced disease, in which the patient is close to visual disability, it is more effective to measure progression with functional tests than with structural tests.
- A threshold for change will be useful for determining clinically significant change, and a percentage of loss of structural/functional status could be used for this purpose.
- Optic disc photography is not frequently practiced in the community setting, and the new imaging modalities that can provide objective estimates of change in an objective manner may become useful standards. Although the group believes that optic disc photography and evaluation are superb tools for the evaluation of the optic nerve head in glaucoma, their performance is somewhat cumbersome and costly and requires a skilled (and usually dedicated) photographer. These resources are often not available in community private practices, particularly small ones.

Session 3: Reevaluation of Treatment—Intraocular Pressure

This session focused on the reevaluation of glaucoma treatment with IOP reduction and was co-moderated by C. Burgoyne and P. Lee.

The key goal in glaucoma therapy should be preserving vision and the patient's quality of life. Persistent elevated IOP is the most significant risk factor for the development and progression of glaucoma, and IOP control is therefore a key aspect of glaucoma management. In the Advanced Glaucoma Intervention Study (AGIS), eyes with IOP < 18 mmHg at 100% of visits over 6 years had virtually no change from baseline in VF defect score during follow-up, whereas eyes with IOP < 18 mmHg at fewer than 50% of visits had an estimated worsening of 0.63 units of VF defect score per year ($P = 0.083$) (Fig 10).[8] Visual field worsening was greater at 7 years (1.93 units; $P<0.001$) than at 2 years (0.25 units; $P = 0.572$).

The findings from 2 studies investigating the effect of lowering IOP on VF loss progression were subsequently

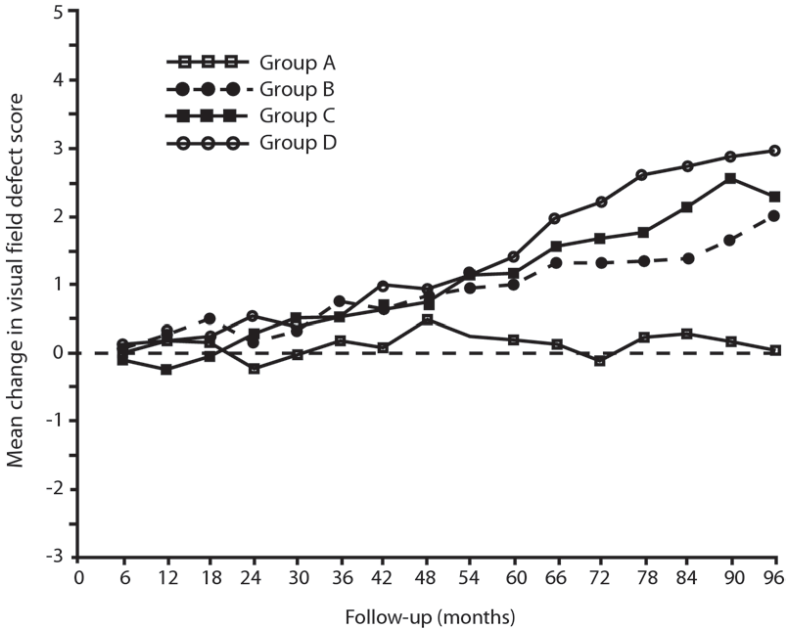

Figure 10. Effect of intraocular pressure (IOP) control on visual field change, compared with baseline, over time (group A, 0%–49% of visits with IOP < 18 mmHg; group B, 50%–74% of visits with IOP < 18 mmHg; group C, 75%–99% of visits with IOP < 18 mmHg; group D, 100% of visits with IOP < 18 mmHg). Reproduced with permission from AGIS Investigators. Am J Ophthalmol 2000;130:429–40.

incorporated into the American Academy of Ophthalmology preferred practice pattern in 1992. One of the studies on early VF loss was conducted by Mao et al, investigated the rate of progression of VF on an event basis, and showed that progression could be reduced if IOP was maintained at a low enough level.[29] Thus, all eyes with mean IOP higher than 21 mmHg during the follow-up period had progressive glaucomatous damage, whereas eyes with mean IOP < 17 mmHg remained stable, and approximately 50% of the eyes with mean IOP of 17 to 21 mmHg had progressive glaucomatous damage. A similar dose–response situation was seen in eyes with advanced VF loss, with the least progression seen in eyes maintained at an IOP of <16 mmHg.[30] However, the findings from another community-based study showed that, even when there was severe VF damage, an IOP of ≤16 mmHg was achieved in only about one third of the patients (Fig 11).[31]

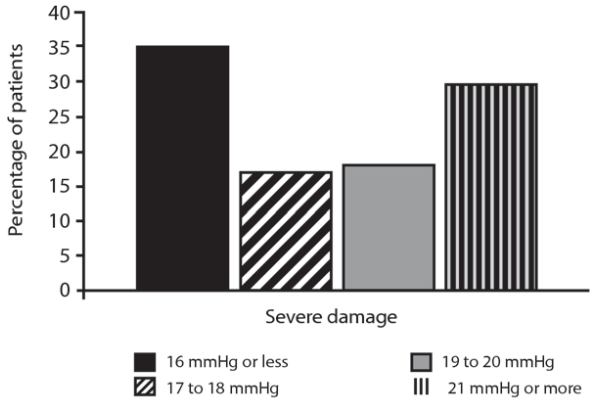

Figure 11. Intraocular pressure achieved in the community setting.

The data from a community-based longitudinal study of residents of Olmsted County, Minnesota showed that patients at greatest risk of blindness were those with preexisting moderate to advanced VF loss and greater intervisit IOP fluctuation.[32] The findings from another study by Quigley et al indicated that well over one third of patients presented with a level of VF damage that put them at a high risk for going blind in their lifetimes (Fig 12).[33]

Before discussing IOP fluctuation, a few caveats are in order. Intraocular pressure measurements are mere snapshots of true IOP over time, and our understanding of real IOP behavior is limited. Terminology is also confusing. What is IOP fluctuation? Do we measure it over hours, days, weeks, months, or years? Is it best measured by peak, range, standard deviation (SD), or some other summary parameter? We will use the terms *short-term IOP fluctuation* to indicate that which occurs over hours or days and *long-term IOP fluctuation* to indicate that which occurs over months to years. The parameters *peak* and *range* are not usually desirable, because they are sensitive to outliers and do not take into account the number of measurements. Standard deviation is a more robust measure, is less affected by outliers, and takes the number of measurements into account. Potentially confounding variables include treatment effects, compliance with therapy, frequency of measurements, and, of course, the difficulties in identifying true progression.

In a study by Mosaed et al,[34] the correlations between average office-hour IOP and peak nocturnal IOP were evaluated in healthy and glaucomatous eyes. Intraocular pressure was measured every 2 hours, with patients in the supine and sitting positions, between 7 AM and 11 PM, and in the supine position only in the sleep period. The patients in this study had early to late glaucoma and had had their medica-

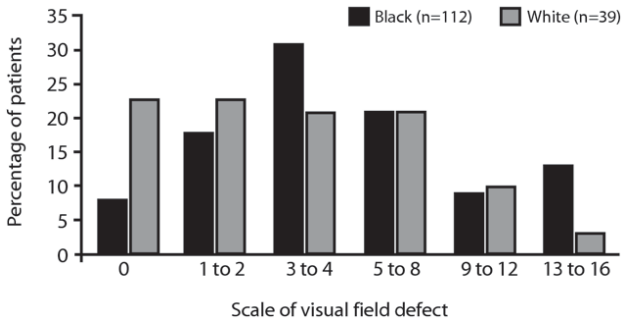

Figure 12. Visual field at presentation in the Baltimore Eye Study (scale of visual field defect was from 1 to 16, with 16 representing the worst defect).

tions washed out. Correlations between short-term IOP fluctuation and peak nocturnal IOP were strongest in the untreated glaucoma patients (ages 40–74), less strong in healthy subjects of a similar age group, and absent in younger healthy subjects (ages 18–25). Interestingly, the findings of this study did not confirm the principle commonly taught that 24-hour IOP fluctuations are greater in glaucoma but indicated that, although IOP was higher at all time points in glaucoma patients, the range of 24-hour IOP fluctuations was less in these patients than in healthy patients. Substantial fluctuations in healthy subjects were described in a previous study (Fig 13),[35] and the magnitude of fluctuation was greater than that seen in glaucoma patients.

The effect of IOP fluctuation on the progression of VF has been investigated in a number of studies. The study by Asrani et al examined the risk associated with short-term IOP fluctuation in patients with glaucoma.[36] This study was difficult to perform, had some weaknesses, yet yielded pertinent findings. Intraocular pressure measurements were obtained by home tonometry performed by the patients 5 times a day for 5 days (morning, noon, midafternoon, supper, and bedtime). The main limitation of the study was that the outcomes were based on a retrospective review of medical charts, at the time of home tonometry, to determine which patients had progressed over the last 5 years. Within the population of patients studied, it was found that despite an office IOP within the normal range, there were large fluctuations in diurnal IOP. These fluctuations were a significant risk factor for progression, even after adjusting for baseline office IOP, age, race, gender, and severity of VF damage at baseline, and may be relevant for management decisions. Cumulative risks of progression were 88% for eyes with the greatest amount of fluctuation and 57% for eyes with the lowest amount of fluctuation, within 8 years (Fig 14).

The effect of short- and long-term IOP fluctuation on the risk of developing glaucoma in high-risk OHT patients was studied by Bengtsson and Heijl.[37] The patients were examined prospectively for office diurnal IOP and VF every 3 months for 10 years or until glaucomatous VF loss could be demonstrated. Intraocular pressure was measured at 8 AM, 11:30 AM, and 3:30 PM. At 17 years, 34 of 90 patients progressed to VF loss. Univariate Cox regression analysis indicated that mean IOP of all measurements was a significant risk factor for developing glaucoma (95% CI, 1.08–1.39), and long-term IOP fluctuation was almost significant (95% CI, 0.98–1.93). With Cox multiple regression analysis to separate the effects of mean IOP level and mean IOP fluctuation, only IOP level came out as significantly (95% CI, 1.09–1.38) contributing to the risk, but not IOP fluctuations (95% CI, 0.80–1.60).

In a study by Nouri-Mahdavi et al of the predictive factors for VF loss in the AGIS,[8,38] 509 eyes from 401 patients from the AGIS were included. They had to have a baseline VF score of ≤16, at least 7 fields, and more than 3 years of follow-up. Pointwise linear regression was used to characterize field progression, with 2 progressing test points required within a glaucoma hemifield cluster. Intraocular pressure fluctuation was defined as the SD of IOP at all visits after the initial surgical intervention. Visual field progression was found in 151 patients. Older age, larger IOP fluctuation, increased number of glaucoma intervention, and longer follow-up all increased the risk of VF progression. When regression analysis was repeated for eyes with or without cataract, only age and long-term IOP fluctuation increased the risk of VF loss progression. Figure 15 shows the influence of IOP fluctuation on the change of VF, as determined by the AGIS score, over time: eyes with higher long-term IOP fluctuations had significant (regression slope, 0.026/year; $P = 0.0006$) field progression. Every 5-year increment in age and 1-mmHg elevation in IOP fluctuation increased the odds of VF loss progression by 30%.

In a recent study by Jonas et al in over 850 glaucoma or OHT patients' eyes, it was found that short-term IOP fluctuation was highly significantly correlated with IOP measurements but was not a separate significant risk factor for disease progression.[39] In this study, 24-hour IOP profiles were obtained in the sitting/standing position at 7 AM, noon,

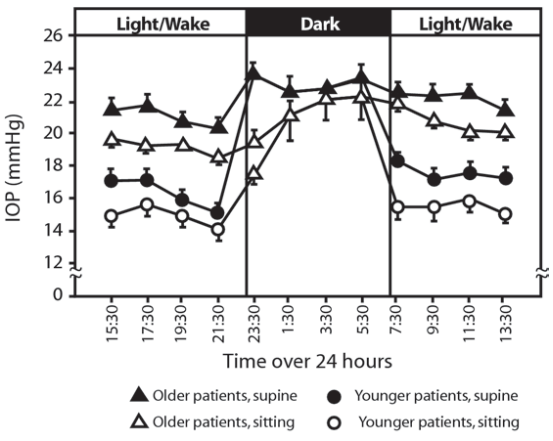

Figure 13. Diurnal and nocturnal intraocular pressure (IOP) in younger and older healthy subjects. Trough IOP occurred at the end of the light/wake period, and peak IOP occurred at the beginning of the dark period. Nocturnal IOP elevation appeared to be caused mainly by the shift from the daytime sitting position to the nighttime supine position. Adapted with permission from Liu JH et al. Invest Ophthalmol Vis Sci 1999;40:2912–7.

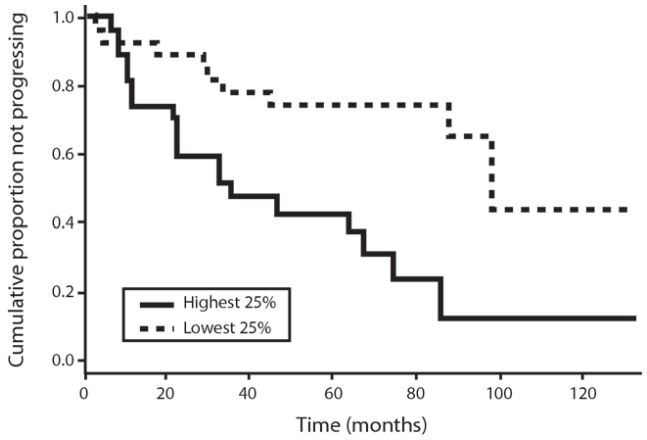

Figure 14. Cumulative risk for progression within the Caucasian population in function of intraocular pressure fluctuations. Vertical axis, cumulative proportion of the population that did not progress at each time point of the horizontal scale. Reproduced with permission from Asrani S et al. J Glaucoma 2000;9:134–42.

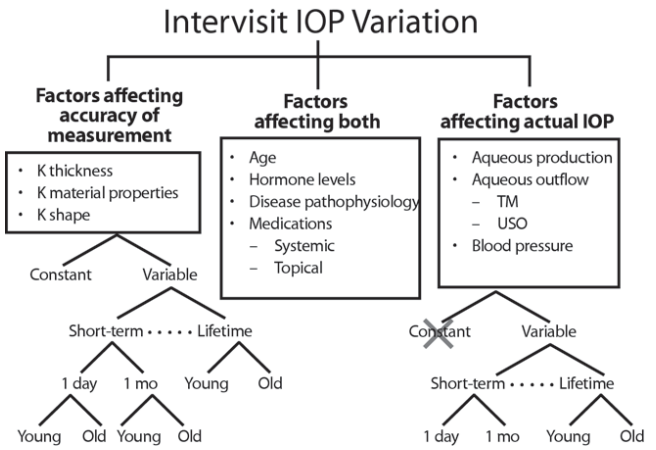

Figure 16. Factors directly and indirectly affecting intraocular pressure (IOP). K = cornea; TM = trabecular meshwork; USO = uveoscleral outflow.

5 PM, 9 PM, and midnight, and multifactorial analysis was performed to determine the correlation between IOP fluctuation amplitude and glaucoma progression. The findings showed that IOP itself, but not its amplitude, was associated with glaucoma progression rate. In light of these findings, J. Jonas suggested that the findings of previous studies could be reexamined to confirm if it was short-term IOP fluctuation itself, and not its correlation with IOP measurement, that was associated with glaucoma progression. This correlation, however, was not found by Nouri-Mahdavi et al.[38]

Many factors contribute to long-term IOP variation, and they may be divided into 3 groups (Fig 16). The first group consists of factors that affect the accuracy of IOP measurement. These factors, such as corneal thickness, are clinically relevant because they can affect clinical decisions regarding treatment options for glaucoma; however, they may be confounding variables, and some may be indicative of optic nerve susceptibility. This latter aspect is still controversial at the present time. The second group of factors affect IOP itself (such as aqueous production and outflow) and, indeed, need to be investigated and monitored appropriately. Finally, there are factors affecting both IOP itself and IOP measurement, such as disease and medication. The nature of the variability changes over the short term and lifetime of the patient, further complicating the measurement and characterization of IOP.

After the introduction, the participants were asked to participate in a discussion with the following questions:

- What is the clinical relevance of IOP fluctuations from clinical trials?
- How do we include IOP intervisit variation or 24-hour diurnal fluctuation in clinical care?
- Can numeric IOP targets for treatment be established to guide clinicians by severity of VF loss (e.g., 18 mmHg for early VF loss, 15 mmHg for moderate VF loss, 12 mmHg for late VF loss, single digits at end-stage disease)?

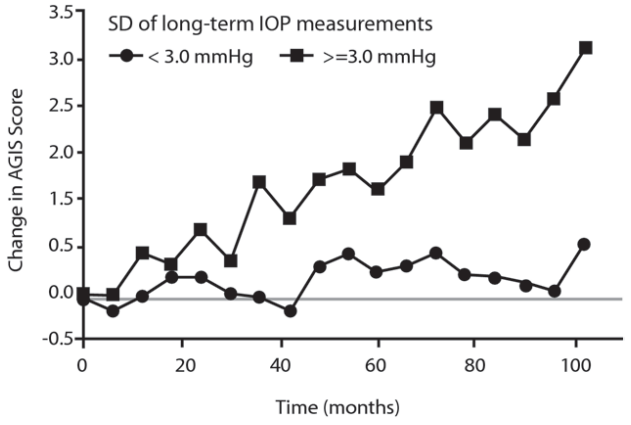

Figure 15. Influence of intraocular pressure (IOP) fluctuation on visual field progression, determined as the change in the Advanced Glaucoma Intervention Study (AGIS) score over time. SD = standard deviation. Reproduced with permission from Nouri-Mahdavi K et al. Ophthalmology 2004;111:1627–35.

Summary Discussion

Clinical Relevance of Intraocular Pressure Fluctuation from Clinical Trials. The role of IOP fluctuation in glaucoma progression and its clinical relevance were discussed. There is some evidence suggesting that both short- and long-term IOP fluctuations may have a role in disease progression, but further confirmation is needed to substantiate this evidence. Another aspect to consider is that in secondary open-angle glaucoma and, particularly, that due to pseudoexfoliation, IOP fluctuation is much higher than that usually seen in primary open-angle glaucoma and may reach 40 mmHg in certain cases. This exceptionally high IOP fluctuation amplitude may influence overall study findings, and the proportions of patients with secondary glaucoma in the studies need to be taken into consideration. Cerebrospinal fluid pressure can also influence the effect of IOP. Cerebrospinal fluid pressure is higher in the supine position than in the upright position. The cerebrospinal fluid

pressure may counterbalance the IOP across the lamina cribrosa.

The association of long-term IOP fluctuation and disease progression has also been suggested to be influenced by medical therapy. Intraocular pressure fluctuation was not found to be an independent risk factor for glaucoma progression in an unpublished follow-up study to the EMGT.[18] Similar to the findings by Jonas et al,[39] IOP itself was found to be a very significant risk factor for glaucoma progression. Intraocular pressure fluctuation became associated with disease progression after the patients had progressed and were given a more intensive treatment.

The discrepancies between the findings of this study and that by Nouri-Mahdavi et al[38] could be explained by the different patient populations and treatment regimens in the two studies. The patients in the AGIS were at a more advanced disease stage, and they may have had more damage at the level of the trabecular meshwork and optic disc. In addition, they had lower mean IOP. The AGIS's design was such that more interventions were administered to the patients if their IOP exceeded 18 mmHg, and not because they had progressed. Apart from the EMGT, all the large randomized clinical trials were designed so that an IOP above a certain target could not be reached, so all the peak IOPs were eliminated. This aspect probably has some effect on the final statistical analysis.

A subsequent analysis conducted on the data from the AGIS,[8] looking at disease progression across the entire study and also at time to event, revealed a highly significant difference between patients in the upper and lower quartiles of mean IOP. Interestingly, long-term IOP fluctuation as a risk factor for progression was not significant in the higher IOP group, whose mean pressure was about 18 mmHg, but was highly significant in the lower IOP group, whose mean pressure was about 10 mmHg. In the lower IOP quartile group, long-term IOP fluctuation was an important predictor of VF worsening, and the patients with the lowest progression rate were those with low IOP and low IOP variability.

As the intervention itself can make IOP vary, it would be more relevant to compare IOP variation in patients who have received the same number of interventions, because any additional treatment will have an impact on this variation. This way, the confounding effect of interventions can be controlled. A further analysis by A. Heijl et al on the data from patients in the EMGT before disease progression (i.e., when all the patients had the same treatment) indicated that it was the number of medications, and not the number of interventions, that was a risk factor for progression. There was also a relationship between higher IOP fluctuation and higher number of medications. Increasing the number of medications may lead to IOP fluctuation as a consequence of a reduction in patient compliance, which would subsequently lead to suboptimal control of the disease.

The clinical relevance of the findings by Mosaed et al[34] on nocturnal IOP variation was discussed. These data do not seem to corroborate those from a previous study by Anderson and Grant,[40] who reported that in glaucoma patients IOP increased by 1.5 mmHg in the supine position, which was no greater than that in healthy subjects. This value could increase much further in the presence of abnormalities in the episcleral venous pressure, such as in Sturge–Weber syndrome or carotid cavernous fistulas. Mosaed et al reported nocturnal IOP peaks 5 to 7 mmHg greater than daytime IOP. This discrepancy in IOP measurements could result from the different tonometry techniques used in the two studies, making the findings incomparable. J. Caprioli pointed out that the significance of nocturnal IOP peaks requires further investigation because IOP variation may just be part of the normal physiological process. These peaks may reflect regular rhythmic cycles in a way that preserves the integrity of the tissue in an organism. However, if the steady state of this variation is disturbed and there are irregular elevations of IOP at irregular times, damage may be more likely to occur.

Toward a Harmonization of Clinical Trial Methodologies. To make the findings from various studies more comparable, there are a few methodological aspects that should be addressed. Different approaches have been used to measure IOP fluctuation: intervisit IOP fluctuation, 24-hour IOP fluctuation (with or without nighttime IOP measurement), or office-hour IOP fluctuation. Study patient populations also differ between studies and vary from OHT patients to patients with glaucoma at different stages of the disease. Patient age can also impact the findings—for example, autoregulation to maintain a constant perfusion pressure to the optic nerve in reaction to dynamic changes in IOP and blood pressure (BP) differs in younger and older patients.

Part of the confusion that arises is caused by the different ways of calculating and expressing IOP fluctuation, and it is important to keep these consistent to make the comparison of study findings easier. For long-term IOP fluctuation, the range of measurements is not an optimal way to express fluctuation because it is very sensitive to outliers and does not take into account the number of measurements. Therefore, increasing the number of measurements is likely to increase the range. Standard deviation takes into account the number of observations and is less sensitive to outliers.

Other methodological considerations include the period during which IOP is measured and number of IOP measurements made in a day. For example, IOP was measured only during office hours in the study by Bengtsson and Heijl,[37] whereas it was measured during the day and at nighttime in the study by Jonas et al.[39]

In addition, it needs to be specified if IOP measurements are made in the supine or upright position. For clinical trials, it was suggested that measuring IOP in the upright and supine positions during the day and in the supine position at nighttime, as in the study by Mosaed et al,[34] would provide a more complete range of IOP measurements, which would be closer to the real-life situation.

Terminology is important. For example, it would be useful to determine how IOP amplitude in the study by Jonas et al can be related to IOP fluctuation in other studies. It was also suggested that the term *short-term diurnal IOP fluctuation* should be used to designate 24-hour variations in IOP measurements, such as those performed in the study by Jonas et al, whereas long-term IOP variation should be used to designate variations in IOP measurements over a large

number of visits over a long period (e.g., over a number of months or years).

From a technical point of view, the accuracy of IOP measurement can be affected by the type of tonometric instrument used. Various tonometry techniques are differently influenced by central corneal thickness and patient age,[41] and interobserver agreement varies between the instruments.[42] In the clinical setting, IOP measurements in the same patients are not always performed by the same observer, and this can affect the reproducibility of IOP measurement.

Another technical issue is that there is currently no method that allows 24-hour IOP to be monitored continuously. In D. Epstein's opinion, even multiple measurements of IOP provide only a brief snapshot of a patient's real IOP and so may not reflect the real IOP profile. However, there is the possibility that a high level of fluctuation in IOP reflects an underlying problem within the trabecular meshwork (i.e., outflow problem), and the only way to confirm this is by tonography, which is a cumbersome technique. It is conceivable that greater IOP fluctuation would have a detrimental effect on RGCs and the optic nerve. However, these variations would need to be confirmed to ensure that they were not due to methodological flaws (e.g., choice of tonometry instruments).

Inclusion of Short- and Long-term Intraocular Pressure Fluctuation in Clinical Care. Generally, glaucoma patients are not admitted to hospitals to get 24-hour readings in most centers. For this reason, it has been suggested that office diurnal IOP measurements would be, perhaps, more important than nocturnal measurements because clinicians perform IOP measurements in their patients during the daytime. Evidence from clinical intervention trials has shown that treating patients based on daytime IOP measurements provides beneficial outcomes. In the clinical setting, management decisions have been made based on these measurements and have been proven reasonably successful. Therefore, despite the fact that daytime IOP measurement is only a surrogate measure of the true IOP profile, this method still constitutes the basis of glaucoma management practice.

Intraocular pressure monitoring may not be optimally performed in general, mostly because of lack of resources. Thus, monitoring diurnal IOP variation is not widely done, and its practice is triggered only by certain clinical situations. An example of such situations is when progression is detected in a patient whose condition has been thought to be well controlled.

Concerning the suitability of measuring long-term IOP fluctuation as a clinical approach to monitoring IOP, P. Lee reported the findings from a retrospective analysis performed over at least 5 years within 12 U.S. health care centers, which indicated that this method was relevant. Both mean IOP and long-term IOP fluctuation from visit to visit (measured as the SD) were significantly related to the risk of disease progression determined by a 6-stage categorical field system. The same findings were confirmed if IOP was measured before or after treatment.

Clinical Relevance of Numeric Intraocular Pressure Targets for Treatment. The findings from the AGIS[8] strongly suggest that if IOP is maintained below 18 mmHg it is more likely that the patient's condition is stabilized over the long term, irrespective of the disease stage at baseline. These findings also show that long-term IOP SDs of 3 mmHg are indicative of an effective control of disease progression. This poses the question of whether a higher mean IOP (e.g., 17 mmHg) with less fluctuation would be more clinically desirable than a lower mean IOP (e.g., 14 mmHg) with higher variations. No general agreement was reached on this point.

It is known, however, that through the course of the disease and the aging process, the connective tissues of the optic nerve head and peripapillary sclera become more rigid. This increased stiffness means that the tissues will have less tolerance for IOP variation and will undoubtedly have clinically important implications, if not in all patients, at least in a subset. For example, this change can affect intraocular blood flow, and this may have clinically significant consequences. If intraocular blood flow is constant throughout a lifetime, then the amount of oxygen and nutrients that move from the laminar capillaries across the extracellular matrix of the laminar beams to the astrocytes ought to differ profoundly between a 30-year-old patient and an 85-year-old patient. Therefore, the factors that affect the volume of blood flow, such as IOP and IOP variation, potentially contribute to damage. In addition, older patients are more likely to have decreased BP at night and may experience vasospasm and episodes of hypoperfusion, which would interact with other parameters that adversely affect the amount of nutrition that is supplied to the optic nerve head. One can imagine that the normal 24-hour IOP fluctuation that is present in most subjects may have clinical importance for some patients, but this will need to be confirmed by further evidence from ongoing studies.

It was suggested that there is enough evidence to recommend that the lowest IOP should be achieved to ensure the best possible control of disease progression. Numeric targets have been proposed in light of emerging evidence to support their use. These are 18 mmHg for early VF loss, 15 mmHg for moderate VF loss, 12 mmHg for late VF loss, and single digits at end-stage disease. This step was perceived as potentially useful for improving current practice, but there are limitations that need to be taken into account. In theory, this approach may improve the current management of glaucoma but, perhaps, at the cost of overtreating some patients. Certain characteristics of the patient, such as age and general health, should be taken into account to avoid overtreating some patients and causing them unnecessary side effects from interventions. Examples where clinical judgment is required when using numeric IOP targets were pointed out. In the case of a patient with low-tension glaucoma presenting with an IOP of 19 mmHg and VF damage, the target IOP of 18 mmHg would not be low enough. Another example is that of a patient with secondary glaucoma due to pseudoexfoliation with early damage whose IOP has been reduced from 35 mmHg at baseline to 19 mmHg on maximum medical therapy. This borderline situation does not theoretically warrant surgical intervention but may cause some difficulties with reimbursement authorities (if they were to link reimbursement with treatment targets) because the IOP level achieved had not reached the

recommended target number of 18 mmHg. Patient compliance is another factor raised by A. Coleman, as this has an important impact on management decisions. In case of noncompliant patients, the numeric target IOP is not easily achieved, and reimbursement for the treatment might be jeopardized.

In general, there was agreement that recommendations based on numeric IOP targets could be useful for teaching purposes and to provide some guidance on glaucoma management. The factors to be taken into consideration include stage of the disease, starting (untreated) IOP, patient age, health condition, quality of life, and compliance. Numeric IOP targets should not be used for reimbursement purposes as in other medical fields. It was suggested that the target IOP for patients with achromatic field loss should be ≤18 mmHg, unless there are other mitigating circumstances and taking all relevant factors into consideration.

The comoderators concluded the third session of the Think Tank with the following summary, drawn from the key points discussed:

- Intraocular pressure fluctuation seems to have a role in disease progression, and further evidence may confirm this role, as well as the clinical relevance of these fluctuations. Further research is needed to elucidate whether IOP itself, its fluctuation, or both are associated with the rate of glaucomatous progression.
- Among factors that can influence the association of IOP fluctuation and disease progression is medical therapy. An increased number of medications has also been found to be a risk factor for progression.
- A few methodological aspects need to be addressed to make the findings from various studies more comparable, such as the methods used to measure IOP and the ways in which IOP fluctuation is expressed. The position of the patients (supine or upright) also influences IOP measurement. Another important consideration is whether nocturnal IOP should be included in 24-hour IOP monitoring. The choice of tonometric instruments is also relevant because it can affect the accuracy of IOP measurement.
- Long-term IOP fluctuation is associated with disease progression in some patients. Intraocular pressure fluctuation expressed as SDs takes into account the number of measurements and is less sensitive to outliers.
- In the clinic, nocturnal measurements may be less important than diurnal IOP measurements because it is during the daytime that patients have their IOP measured. Although daytime IOP measurement is a surrogate measure of the true IOP profile, it still constitutes the basis of glaucoma management practice.
- Numeric IOP targets could be useful for teaching purposes and for providing guidance on glaucoma management, but sound clinical judgment should be used, taking into consideration the patient's age, health condition, quality of life, and compliance. Numeric IOP targets should not be used for reimbursement purposes.

Session 4: New Avenues toward Optic Nerve Protection and Regeneration

Glaucoma is a chronic progressive neuropathy in which the optic nerve is irreversibly damaged and RGC loss is the key pathologic feature. Although elevated IOP is an important risk factor for neuronal damage, other factors can also contribute to the development of the disease. A treatment approach that addresses both IOP-dependent and IOP-independent risk factors would therefore be desirable. The concept of maintaining and regenerating the function of RGCs has gained interest in recent years[43,44] and was the subject of this session comoderated by R. Gross and S. Gandolfi.

In addition to elevated IOP, an important potential mechanism involved in neuronal injury is excitotoxicity, which is defined as excessive exposure to the neurotransmitter glutamate or overstimulation of its membrane receptors.[45] An underlying mechanism of excitotoxicity is an overload of glutamate in the microenvironment, which is caused by either its discharge in the environment from dying cells or a reduced clearance of it, particularly by Müller cells and astrocytes.[46] Excitotoxicity could also result from an overactivation of glutamate receptors by normal extracellular levels of glutamate.[45] Another mechanism that can lead to RGC damage is oxidative damage through the action of free radicals. Reactive oxygen species have been found to act as intracellular signaling molecules that initiate apoptosis in neurons deprived of nerve growth factor and in axotomized RGCs.[47] Deprivation of growth factors is another potential cause of neuronal damage. In primate models of glaucoma, it was found that, with increased IOP, blockage of neurotrophins and other target-derived growth factors, as well as other chemical signals, occurred at the level of the lamina cribrosa.[48] This blockage may induce RGC apoptosis or programmed cell death. Other mechanisms that may lead to RGC apoptosis include impaired regulation in the retinal microvasculature, which is thought to cause reduced delivery of nutrients to and reduced clearance of waste from the retina and RGCs.[49] Defects in endogenous neuroprotection can lead to an increased susceptibility to RGC injury and could be an important mechanism in glaucomatous damage.[50] Finally, structural deformation in the tissues of the optic nerve head has been suggested to influence susceptibility to the development and progression of glaucoma. In the eyes of young adult monkeys with early experimental glaucoma, there was deformation of the lamina cribrosa and anterior scleral canal wall.[51] This finding suggests that damage to the optic nerve head connective tissues occurs in the early stages of glaucoma. In human eyes with advanced optic nerve damage due to glaucoma, it has been found that the lamina cribrosa is thinner and deformed compared with normal eyes, which could lead to an increased risk of further progression; the relationship between cause and effect remains unclear.[52,53] Interestingly, decreased central corneal thickness has also been suggested to be a significant risk factor for the development of glaucoma.[6]

Several experimental animal models have been used to investigate the effects of potential neuroprotective agents on some of the mechanisms described; these models include

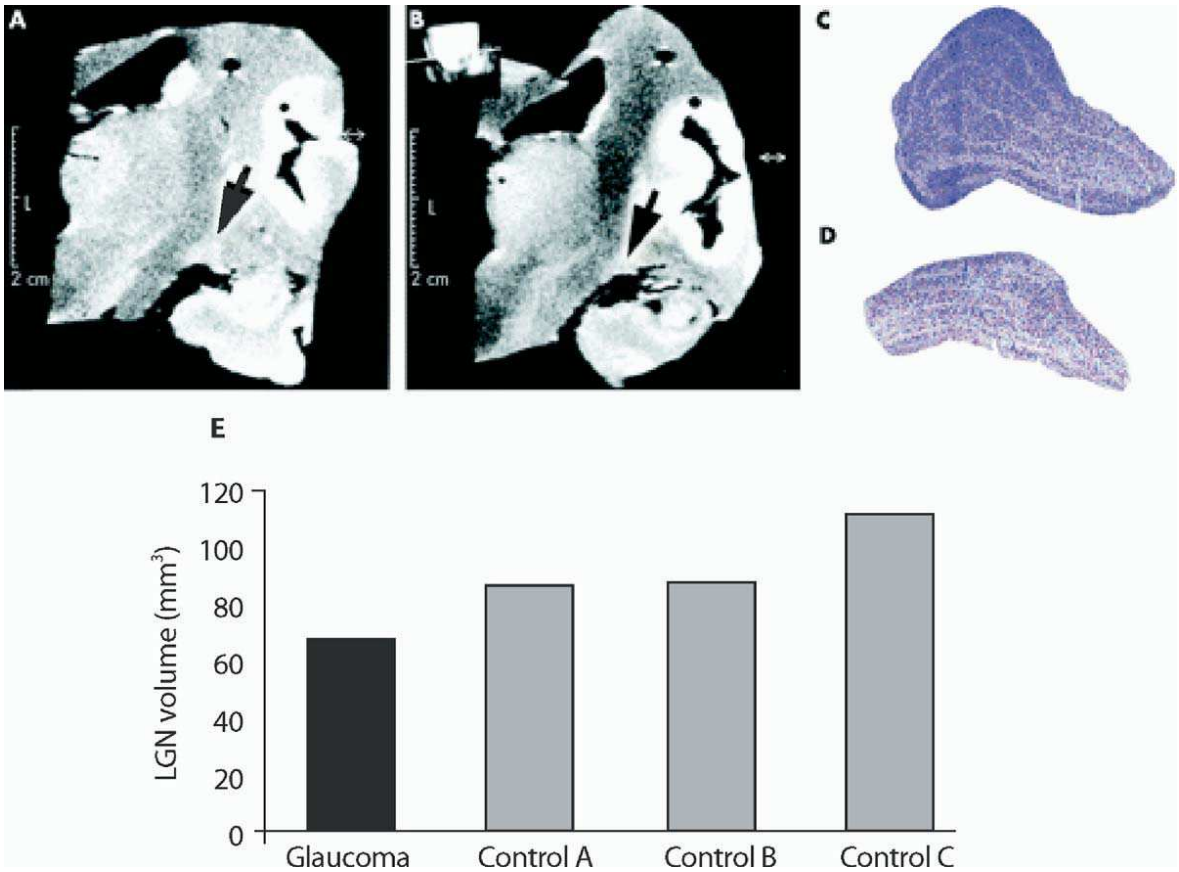

Figure 17. Reduced lateral geniculate nucleus (LGN) in glaucoma (**B**) compared with a control (**A**) seen with magnetic resonance imaging. Nissl staining reveals shrunken LGN in glaucoma (**D**) compared with the control (**C**). **E**, Lateral geniculate nucleus volume in glaucoma (black) is reduced compared with controls (gray). Reproduced with permission from Gupta N. Br J Ophthalmol 2006;90:674–8.

optic nerve transection (axotomy), optic nerve crush, induction of retinal ischemia followed by reperfusion (ischemia–reperfusion), and chronic elevation of IOP. Both primary and secondary RGC degeneration have been reported, and these are likely to occur in an optic neuropathy such as glaucoma. There may be events secondary to IOP elevation that could lead to self-perpetuating degeneration, or secondary degeneration, of RGCs even if the main risk factor (i.e., elevated IOP) is kept under control.[54] The self-destructive process eventually leads to a much greater loss of tissue than that caused by the initial trauma itself. Secondary degeneration of RGCs occurs when cells surrounding an injured or dead cell become injured as a result of factors released from the initially injured cell. This phenomenon has been demonstrated in animal models in which primary RGC death due to optic nerve transection was associated with secondary death of surrounding RGCs that were not directly injured.[55,56] Signaling pathways may be involved in this process.[57]

Systemic factors can also contribute to the development of glaucoma, and the immune system has been implicated in the onset and progression of the disease in some patients.[58] Autoimmune damage to the optic nerve may be elicited directly by autoantibodies or indirectly, by way of a mimicked autoimmune response to a sensitizing antigen that, in turn, injures RGCs.[59] Autoimmune-mediated glaucomatous injury has been suggested to occur in patients whose IOP has been found not to be elevated.[59] On the other hand, benign autoimmunity can be protective against glaucoma, as the immune system fights against agents that are responsible for secondary RGC degeneration.[60] It has been demonstrated that in normal animals suffering from glutamate intoxication, optic nerve injury, or elevated IOP it is possible to reduce RGC degeneration by vaccination with a well-tolerated antigen.[61]

Another important aspect to consider is the extent of optic nerve damage beyond the eye. Because 90% of RGCs project to the lateral geniculate nucleus (LGN) in humans, this damage may extend from RGCs to vision centers in the brain. Studies in experimental monkey models have shown that neurodegenerative changes due to glaucoma occur in the LGN cell layers, and the extent of these changes is related to the severity of optic nerve damage.[62] Changes seen in the primate glaucoma model are relevant to human glaucoma because findings from human brain tissue indicated overall shrinkage of the LGN in glaucoma, with additional significant changes in the intracranial optic nerve and visual cortex (Figs 17, 18).[63]

Neuroprotective therapeutic strategies should be designed to address the various pathways that lead to neuronal damage. From available findings, it seems that apoptosis is an important mechanism involved in RGC loss.[64] The

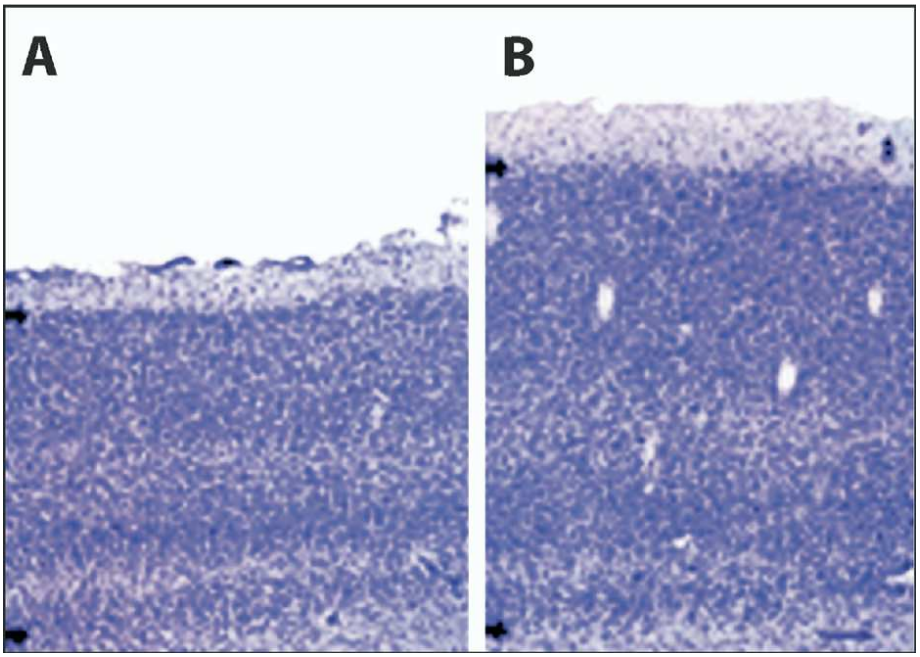

Figure 18. Thinning of the inferior bank of the visual cortex in glaucoma (**A**) compared with a control (**B**). Reproduced with permission from Gupta N. Br J Ophthalmol 2006;90:674–8.

mechanisms by which axonal damage signals apoptosis or programmed cell death are complex and involve various factors, summarized in Figure 19. In the optic nerve, some neurons are healthy, whereas others are affected by glaucomatous injury to varying degrees. Several approaches have been investigated to provide protection to or to rescue these cells, and these have been the subjects of many publications (Fig 20).

Among all neuroprotective agents so far investigated, memantine is the one being tested in a large randomized clinical trial as a treatment for glaucoma. Memantine is a selective blocker of the *N*-methyl-D-aspartate–type glutama-

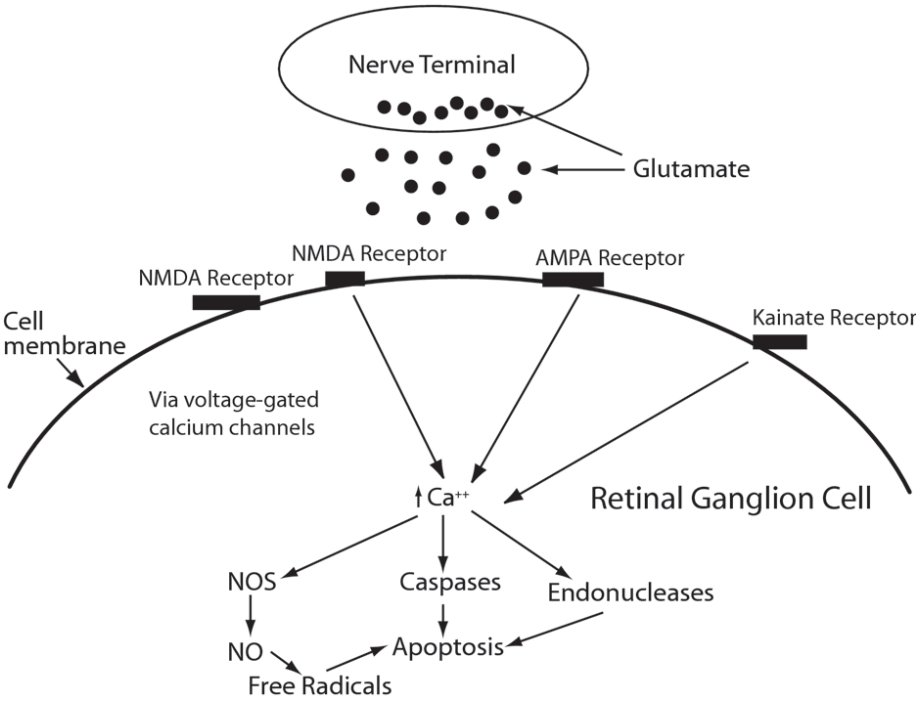

Figure 19. Factors in retinal ganglion cell apoptosis. AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate; NMDA = *N*-methyl-D-aspartate; NO = nitric oxide; NOS = nitroc oxide synthase.

Protective Approaches for At-Risk Axons and Retinal Ganglion Cells	Rescue Approaches for Marginally Damaged Axons and Retinal Ganglion Cells
NMDA/other excitatory amino acid antagonists	Lazaroids/21-aminosteroids
Antioxidants/free-radical scavengers	Upregulation of anti-apoptotic genes (e.g., Bcl-2)
Ca^{++} channel blockers	Antioxidants/free-radical scavengers
NO-synthase inhibitors	Ca^{++} channel blockers
Upregulation of heat-shock proteins	NO-synthase inhibitors
	Phospholipids, gangliosides, citicoline

Figure 20. Protective and rescue approaches. NMDA = *N*-methyl-D-aspartate; NO = nitric oxide.

Regeneration and Regrowth Approaches for Axons of the Optic Nerve Head	
Spanner neural grafts	cAMP
Growth factors	Gene therapy
Transglutaminases/ interleukin-2	Stem cell transplants
Complement C3	

Figure 22. Various strategies for nerve regeneration. cAMP = cyclic adenosine monophosphate.

tergic type ion channel, which has been approved for the treatment of moderate to severe Alzheimer's disease. It has specific open channel blocker properties that result in a preferential inhibition of excessive (excitotoxic) neuronal activation by glutamate without interfering with the channel's normal functions.[65] In a primate model, memantine was found to maintain and preserve RGCs[66] and to prevent LGN shrinkage (Fig 21).[67]

Finally, concerning nerve regeneration, various strategies have been investigated (Fig 22), and research findings from animal models seem to indicate that it is possible to regenerate optic nerve axons that have been damaged by stimulating the signaling cascade of growth factors.[68] In regenerated RGC axons, the reformed connections in the appropriate layers of the superior colliculus appear to persist for the life span of the animals.[69] Stem cell transplantation, particularly with embryonic stem-derived cells, has also shown promise for therapeutic repair after spinal cord injury.[70] Further work is needed to confirm the relevance of these findings to the human optic nerve.

The discussion that followed the introduction was based on the following topics:

- Relevance of findings on neuroprotection to clinical disease
- How to assess neuroprotective effects of potential treatments
- What can be learned from neuroregeneration?

Summary Discussion

Research in the field of neuroprotection for glaucoma has been conducted actively for approximately 10 years. Progress in understanding the mechanisms involved in the

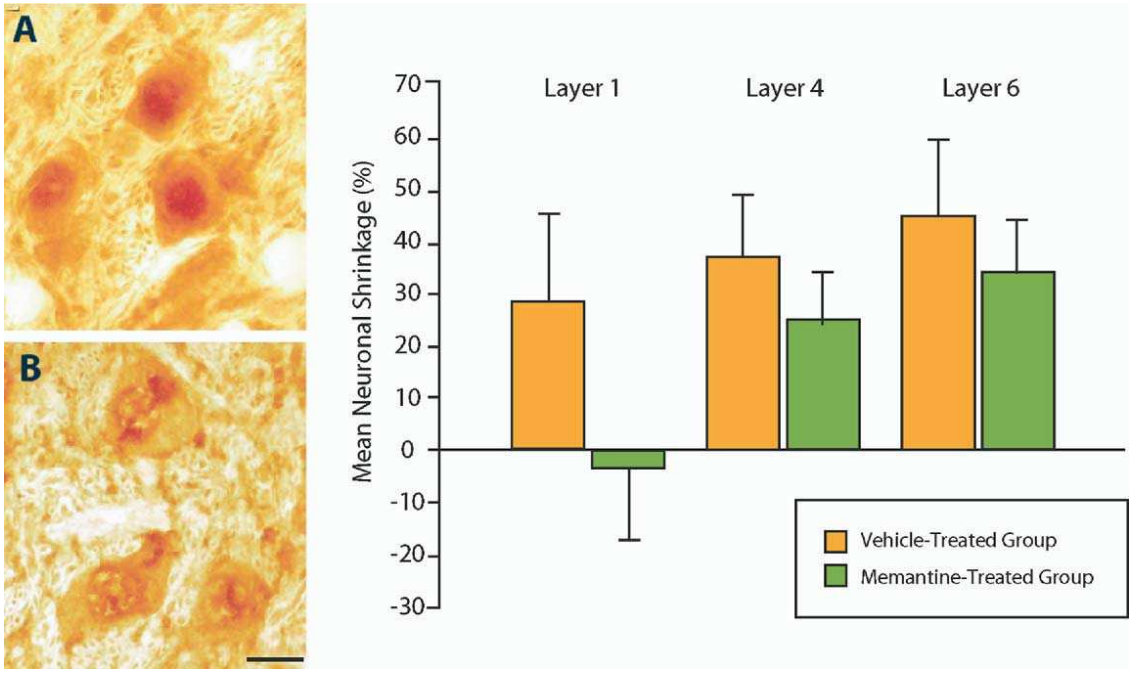

Figure 21. Effect of memantine on neuronal shrinkage in the lateral geniculate nucleus (LGN). The left LGN relay neurons (layers 1, 4, and 6) were examined after parvalbumin immunolabeling. **A**, Controls. **B**, Memantine-treated group. The bar graph summarizes the overall findings. Reproduced with permission from Yücel YH et al. Arch Ophthalmol 2006;124:217–25.

neurodegenerative processes of visual system neurons has been acquired from animal models and has been modest. In terms of neuroprotection, treatment should be aimed at recovering dysfunctioning RGCs subsequent to glaucoma-related damage. It is likely that these cells are damaged but do not die immediately, and the period of agony therefore represents a therapeutic window. Human data will soon be available from a large randomized clinical trial to determine the neuroprotective potential of memantine. It is expected that these data will provide insight into the mechanisms of optic nerve degeneration and protection in humans, which may confirm findings from animal studies and could have an impact on future research in this field.

Relevance of Findings on Neuroprotection to the Clinical Situation. The reproducibility of experimental findings in clinical trials was discussed. It was felt that research progress in glaucoma neuroprotection, as in neurodegenerative diseases of the CNS, has been much slower than in other fields. Although some progress has been made in understanding the mechanisms of neurodegeneration in glaucoma, the findings from animal studies on neuroprotection cannot be easily replicated in clinical trials. Because of this, it has been difficult to determine the clinical relevance of experimental findings.

Factors Influencing the Reproducibility of Animal Findings. The eyes of animal species used as experimental models do not have the characteristics of the human eye (e.g., absence of a well-developed lamina cribrosa in the rat). Most animal models should be referred to as models of elevated IOP. Another aspect to consider is that in humans it is difficult to focus on the therapeutic window that allows the therapeutic effects seen in animals to be magnified. Another explanation for the discrepancy between animal findings and clinical trial data is the heterogeneity of the study populations, which include patients at various stages of glaucoma, as opposed to the homogeneity of the animal models. In addition, absorption of the test agent into the circulation and distribution to the target tissue can vary depending on the mode of administration and the agent's ability to cross the blood–brain barrier and penetrate into the brain.

Influence of Intraocular Pressure–Lowering Drugs. Most important, however, is the fact that clinical trials in neuroprotection cannot be conducted without concurrently treating IOP. As pointed out by J. Caprioli, treatment with neuroprotective agents is conducted at the margins of IOP lowering. These margins can be seen from the OHTS and EMGT, in which some patients still progressed despite IOP treatment, and represent an opportunity for other types of treatment. Considerations should therefore be given to how a trial could be best planned so that the effect of a neuroprotective agent could be determined separately from the effect of IOP reduction. This is a key reason why the effect of neuroprotectants may not be as obvious in clinical trials as it is in animal studies. As explained by D. F. Garway-Heath, the effect of concomitant IOP lowering would "shallow the slope of the progression rate curve considerably, and the additional benefit of the neuroprotective agent that could be seen would be quite small." This would explain why the neuroprotective effects in clinical trials would be not as dramatic as those seen in animal models. For this reason, either very large study populations over a long trial period or very precise measurements of changes in the end points chosen would be necessary. For example, the approach proposed by S. Gandolfi, whereby a particular group of patients that are progressing more rapidly than normal was enrolled, would help to increase the glaucoma progression signal and may reveal a neuroprotective effect.

Role of Connective Tissues. The biomechanical properties of connective tissues and their role in maintaining the shape of the optic disc and survival of RGCs were discussed. In C. Burgoyne's opinion, it is possible that neuronal axons become less susceptible to further damage once IOP has been lowered in eyes that have more compliant connective tissues. The optic disc shape would be restored in these eyes, and axonal integrity would be strengthened. On the other hand, the degree of elasticity of connective tissues could influence the structure and function of astrocytes. In this respect, it is not known whether more rigidity or more flexibility in connective tissues would be more beneficial to astrocytes. It is possible that in the case of glaucoma-related injury some astrocytes and axons may be traumatized but not dead and may recover with appropriate treatment. Treatment effects may not be dramatic in patients who have many dead neurons but may be beneficial to the remaining viable cells in the long term.

How to Assess Neuroprotective Effects of Potential Treatments. *Impact of Noise on Data Interpretation.* An important aspect discussed was the impact of noise, or variability, in clinical data, which could mask the effects of neuroprotective agents and make trial findings difficult to interpret. For this reason, the choice of end points, measurement techniques, and data analysis is important to allow the efficacy of neuroprotective or neuroregenerative therapies to be assessed adequately. In large randomized trials, it is difficult to include a homogeneous study population, and patients at different stages of the disease are usually enrolled, which would increase the noise level in the data. Even if patients were at a similar disease stage, interindividual variability still contributes to this noise. Selecting subjects with specific phenotypes that increase the chance to detect changes in the end points chosen and using techniques that maximize the number of measurements in each patient may increase the signal-to-noise ratio of measurements and shorten the study.

Visual Field Test. It was generally agreed that the noise level can be very high in VF testing, and a high number of tests is always required to reveal the true trend. There is also the important consideration that trend-based analysis, as opposed to event-based analysis, should be used to improve the measurement of progression rates. The benefit of trend-based analysis, such as pointwise linear regression analysis, is that information from all VFs is used, so that the rate and magnitude of change over time can be assessed in each individual eye.

Use of Biomarkers. It was generally felt that the selection and incorporation of appropriate structural biomarkers into clinical trial end points is needed, especially because of the problems experienced with VF measurement. From an ethical point of view, the precision of the technique

used is important in clinical trials because this will improve the monitoring of disease progression so that adequate measures may be taken to prevent disease progression.

Potential biomarkers. A promising technique for imaging glaucoma-related RGC apoptosis in vivo was described by Guo et al.[71] This method is used to visualize and monitor the effect of therapy on the neuronal cells themselves, but its clinical relevance needs to be established. The extent to which the information provided by this technique could be used to make clinical management decisions would need to be determined. In addition, the relevance of these finding to clinical outcomes would need to be clarified. Other considerations with this technique include the need for a denominator that will give a precise indication of the number of apoptotic RGCs, because a low apoptotic rate may reflect a low rate of apoptosis but may also indicate that most of the RGCs are already dead. There is also the need to ensure that the labeling approach used is specifically targeted at the RGCs and does not affect other cells.

Another example of how the neurodegenerative process in RGCs can be more appropriately investigated, and not based only on apoptosis, is the work on neuronal pruning in glaucoma in the primate.[72] As explained by J. Morgan, the findings showed that RGC degeneration started with the dendritic arbor and ended with shrinkage of the cell soma. A global neuronal pruning effect on RGCs occurs before they die, with functional deficits affecting the cells. However, the cell membrane potentials are preserved, which means these cells could potentially recover. It is technically difficult to develop psychophysical tools for detecting changes in the activity of these cells. Imaging techniques that use spectral analysis to record optically the activity in the retina are being developed but are still in their infancy. (Optical recording is the process that records signals on a medium through the use of light.) Another potential biomarker mentioned was the early change in the distribution of *N*-methyl-D-aspartate receptors in the dendrites of the retina, which may be recorded at a single-cell level. This approach is also at its very early stage of development.

Detection of structural changes with new imaging modalities. The ever-increasing performance of imaging modalities may allow a high level of precision in the detection of structural changes in the optic nerve head. The completion of the validation of these techniques will allow their routine use in the clinic, and efforts should be made to gain regulatory approval for their use in clinical trials. It was suggested that ancillary existing imaging techniques could be used to confirm the efficacy end points of a clinical trial in case these could not be established by the current accepted methods for clinical trials (such as VF testing).

In addition to confocal scanning laser ophthalmoscopy (HRT), scanning laser polarimetry (GDx; Carl Zeiss Meditec, Inc., Dublin, CA), and optical coherence tomography, an imaging technique that has been attracting a great deal of interest is ultrahigh-resolution optical coherence tomography.[73] This technique represents a way forward for acquiring a large amount of data in vivo in clinical time. The resolution of this device is of histological precision (i.e., at a subcellular level), and the devices available provide images of structures of 3 to 4 μm. Images of organelles, such as the mitochondria, can be obtained, and changes in these organelles in the prodromal phase of cell death may be detected. Unlike other methods, ultrahigh-resolution optical coherence tomography does not focus on RGC apoptosis but has the potential to allow for an appreciation of the whole microenvironment, which may be a more accurate way of assessing the effects of neuroprotective agents on all the mechanisms that are involved in cell death.

The importance of optic disc structural changes was emphasized by G. Spaeth when he cited a recent retrospective study conducted by his group. Patients in whom an improvement of the optic disc was noted 10 years ago ended up with less long-term VF loss than those in whom this improvement was not seen. The influence of IOP lowering on this effect seemed to disappear over time, which suggests that other mechanisms may be involved in the improvement in VF.

What Can Be Learned from Neuroregeneration? This discussion was centered around neuroregenerative techniques that have shown the potential for application in the clinic. As pointed out by K. H. Park, the prospect of 2 methods of neuroregeneration in glaucoma, stem cell transplantation and nerve grafting, is significant. Research in stem cell transplantation in glaucoma has been generating a great amount of interest, and the technique looks promising. Stem cells can be injected directly into the vitreous while being viewed through the pupil, unlike in brain lesions, where direct visualization of stem cell injection is not possible. The other positive aspect of stem cells is the homing effect, through which stem cells may be able to replace damaged RGCs and integrate themselves into the damaged sites. To be functional, however, stem cells need to develop axons and make proper connections to their targets in the LGN.

The session ended with the following conclusions by the comoderators to summarize the key points discussed:

- Progress has been achieved in the field of neuroprotection, allowing further understanding of the mechanisms involved in optic nerve degeneration that will help advance therapeutic research.
- The choice of end points, measurement techniques, and data analytical methods is important in clinical trials in neuroprotection and, perhaps, more important than in clinical trials of IOP-lowering treatments.
- Because of the limitations of VF assessment, there is a need to incorporate precise structural end points into clinical trials in neuroprotection.
- The use of other biomarkers for identifying and assessing the neuroprotective or neuroregenerative effects of therapeutic methods may be useful in the future, but their clinical relevance is currently unproven.
- As far as visual function measurement is concerned, the main considerations are the length of the trial and number of patients needed, and trend-based analytical methods such as pointwise linear regression and related techniques could be used to improve the quality of the findings.

- Efforts should be made to improve experimental models of glaucoma to make them more relevant to human disease and, therefore, more relevant to neuroprotection in clinical trials.

Session 5: Risk Factors and Outcomes—Are We Looking at the Right Things?

Problems with Normative Data

This session, co-moderated by G. Spaeth and A. Coleman, looked at key concepts that underlie medical decision-making: medical knowledge and the basis of diagnosis and treatment. Much of our current medical knowledge is based on data averages and not data ranges. Something is held to be true if it is in line with a statistical theory based on the concept of normative data and the spread of data around a mean. For example, if IOP has an average of 15 mmHg and SD of 3 mmHg, then an inference from normal-distribution theory would suggest that values >2 SDs above the mean (i.e., >21) are rare and might be viewed as abnormal. This concept of knowing extends to virtually everything that medical practice now conceptualizes and actualizes. However, as is now recognized, IOP over 21 frequently does not lead to any disease, and IOP of 15 can be associated with disease. More extensive demographic data are needed because the optimal care of individual patients should not be based on normative data that are based solely on averages, as it may not be valid to suppose that IOP values for people without glaucoma are normally distributed. In particular, some individuals with IOP>21 may never exhibit nerve damage or vision loss even if left untreated.

Figure 23 is an illustration of when the use of means, or averages, should not be applied to the individual patient. As an example, mean optic disc cup sizes change according to the disease stage, but the data points that are used to make up those means (Fig 23, right) are clustered in different areas, and the patient with the smallest cup (Fig 23, right, bottom of third column) actually happens to have glaucoma. Therefore, even if cup size is predictive of glaucoma risk, estimated cup size is not a measure that in and of itself determines whether or not an individual has glaucoma or is abnormal. The critical word in the previous sentence is *determines*. It is possible, even common, to have a small cup, the size usually considered normal, such as a C/D ratio of 0.3, and yet still have glaucomatous damage. A disc that started with a C/D ratio of 0.1 and develops a ratio of 0.3 is unquestionably diseased, even though well within the range of normal. On the other hand, a person who is born with a large disc and large C/D ratio (e.g., 0.8) does not have a diseased optic nerve, even though the ratio is well above the normal range.

The definition of *normal* can also be problematic, as this term is now commonly used to designate healthy; an example is the use of normal eyes to designate healthy eyes or eyes that do not have glaucoma. A problem that comes up in this regard relates to so-called normal-pressure glaucoma, which can be viewed as contradictory because patients with this condition do have glaucoma and do progress while their IOP is termed normal. In this case, *normal* refers to the

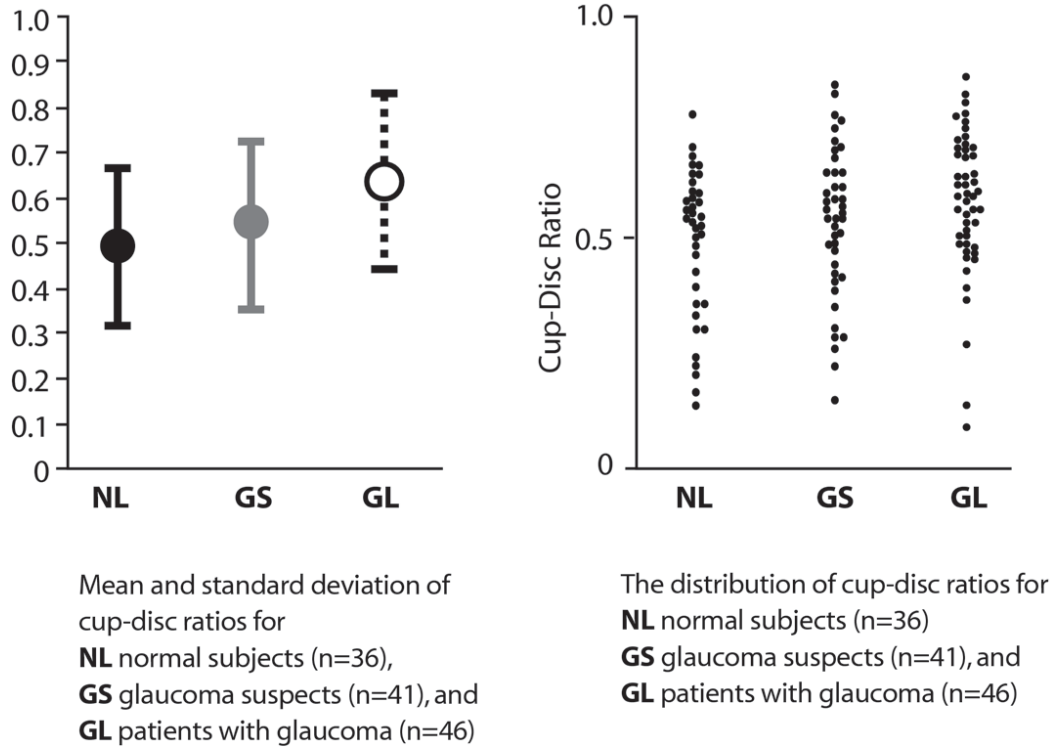

Figure 23. Statistically significant differences between the means of the normal and glaucoma groups and between the means of the glaucoma and glaucoma suspect groups. A large overlap of the values among the patient groups is apparent.

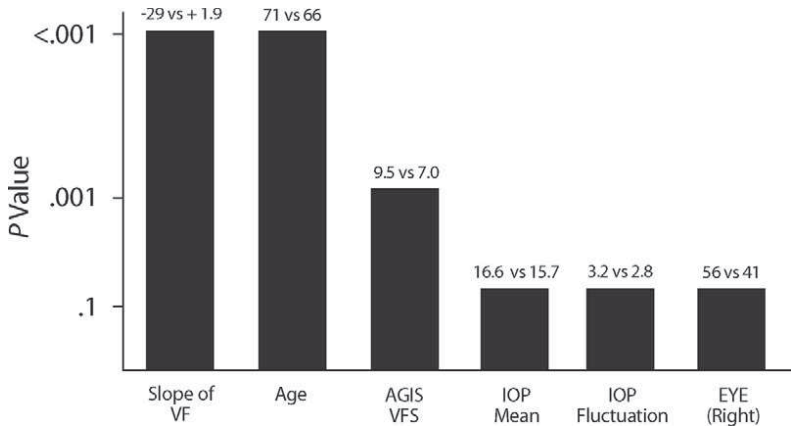

Figure 24. Determination of the probability of future glaucomatous visual field (VF) progression in the Advanced Glaucoma Intervention Study (AGIS) population with clinical and perimetric data. Data shown are mean values; the values at the top of the bars are the means of the 2 groups (those who got worse vs. those who did not). IOP = intraocular pressure; VFS = VF score.

finding that an IOP of 15 mmHg is average for the population, whereas *normal* is used elsewhere to mean healthy, but these 2 adjectives are not synonyms. Most findings from research rely on clinical characteristics to arrive at conclusions but do not provide clear guidance on how these characteristics relate to the health status of patients.

Traditionally, ranges are not commonly used in medicine, and points at the end of a range are often thought of as outliers and are often discarded from data sets. Figure 24 illustrates the findings from a study conducted on the AGIS population to determine the parameters that can be used to predict VF loss progression in glaucoma.[74] The slopes of VF change and age came out as powerful and statistically significant indicators of future VF progression ($P<0.001$).

However, when the individual data points that make up the mean values are considered (Fig 25), VF slope, but not age, is a very powerful predictor of VF worsening (almost 100% predictive power). The data also showed that the oldest people (i.e., at the end of the range) did not show any VF loss progression. The questions, therefore, are whether using information from means is valid for decision-making about individuals; so-called outliers should not be ignored. It may not be justifiable to exclude outliers because of their distance to the mean value, because they may have clinical significance.

Another way of making clinical decisions is to use the individual as his or her own control. This way, individual patient characteristics can be taken into account. This con-

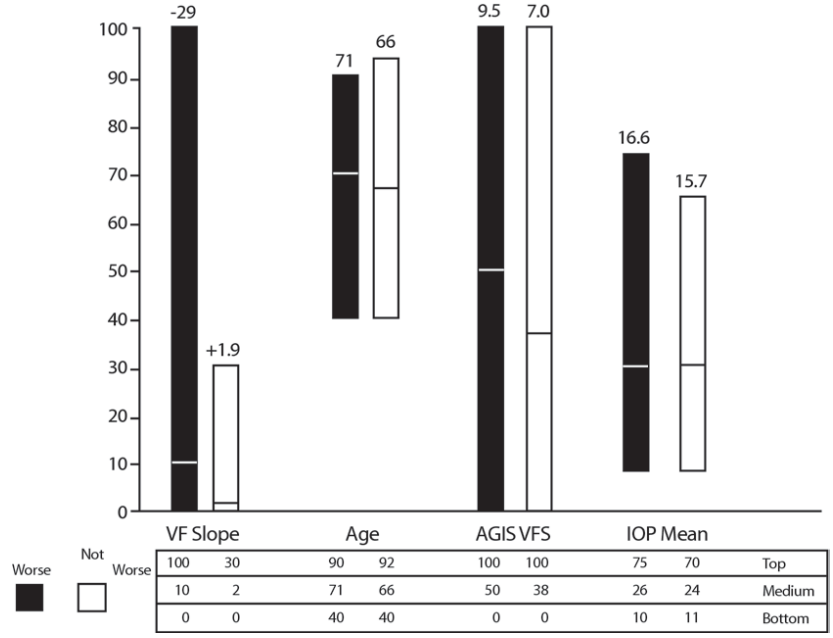

Figure 25. Prediction of future glaucomatous visual field (VF) progression in the Advanced Glaucoma Intervention Study (AGIS) population by clinical and perimetric data. The values at the top of the bars are the mean values for each group. Data were obtained with individual values that make up the mean values shown in Figure 24; the strongest predictive power is that seen with almost 100% predictive value in the top row of the figures beneath the graph. IOP = intraocular pressure; VFS = VF score.

cept introduces the idea of N-of-1 methodology. For example, in determining how a drug works in an individual, one could use crossover comparisons of an active drug against a placebo in the same patient.[75] This method allows for conclusions about the efficacy of the treatment based on the notion that transient factors, other than treatment, can be ignored.

Classic Statistical Analyses

The place of statistics is central in the decision-making process, as it represents a tool to help us make decisions on information that is available. Two situations in which statistical analyses are used are hypothesis testing and decision-making. The first situation involves the null and alternative hypotheses. The null hypothesis, or the innocent until proven guilty hypothesis, usually applies to some theory that has been put forward, either because it is believed to be true or because it is to be used as a basis for argument but has not been proved. For example, the null hypothesis in the OHTS was "lowering IOP does not decrease the risk of developing glaucoma." The alternative hypothesis was a statement of what the statistical test is set up to establish (e.g., "lowering IOP by 20% decreases the risk of developing glaucoma"). Hypothesis testing is frequently used in clinical trials and experimental work in glaucoma.

Minimization of the expected (or maximum possible) loss is an alternative rule for choosing an action that can provide information on the states of nature that are most plausible. This statistical approach is highly relevant for choosing among equally accepted treatment options. An example of the decision-making perspective can be found in the ophthalmic part of the Rotterdam population-based study.[76] In the study, a quantitative basis for diagnostic criteria of glaucoma was created by defining *glaucomatous optic neuropathy* as cupping of the optic nerve head greater than that found in 97.5% of the population. Indeed, there was an expected false-positive error rate associated with this decision rule, as some patients in this category did not have glaucoma. However, this error was limited by setting a 97.5% threshold. This approach, therefore, sought to detect as many people with glaucoma as possible by minimizing expected false-negative errors, subject to a small tolerance for false-positive errors.

It is important to realize that a causal effect for an individual is the difference in potential outcomes between 2 treatments. The extensive literature about causal effects indicates that the fundamental problem is that only the potential outcome of a treatment assigned, and not any other potential outcome, can be observed.[77] Thus, once a therapeutic intervention has been initiated, the outcome in case of nonintervention cannot be directly observed, and individual causal inference cannot be determined. Another problem is that the outcome of an intervention may be influenced by confounding factors (e.g., age, diet), and when groups of people are exchangeable, randomized controlled trials are conducted to assign potential confounders randomly, so that confounders cancel out. One way to handle causal inference is by assuming that there is temporal stability, which can be illustrated by the reasoning that if the light switch had not been flipped on, the light would have stayed off. It is therefore intuitively reasonable to make assumptions about how the course of the disease would have been affected by not initiating treatment, as long as there are no confounding factors. Thus, our knowledge of the natural history of the disease (untreated or unperturbed by any interventions) allows us to make assumptions about the course of the disease. There may be considerable variability in terms of temporal stability, as population-based studies of age-related macular degeneration (AMD) have shown: soft drusen disappear without treatment in about 5% of eyes. This finding indicates that not all individuals within the same group exhibit the same causal effect and that subgroup analyses are important because they may reveal differences in average causal effects. Because of interindividual variability, assigning trial results to individual patients requires stronger exchangeability assumptions than those required in randomized clinical trials.

It is important to bear in mind that assumptions are usually made and that study patient populations should be well described so that the relevance of trial findings to the clinical setting can be assessed. It is also important to realize that clinical decisions can never be made with complete certainty. Because of this, the level of uncertainty for each decision varies. The VF is currently used in clinical practice as a key outcome measure on which management and treatment decisions are made. However, health would be more relevant as an outcome to patient care because maintenance of quality-of-life and functional ability should be the purposes of clinical management. In clinical practice, patients are assessed in terms of risk, particularly that of developing monocular or binocular VF loss. In this respect, the idea of a risk calculator is an important concept, but its clinical relevance to health-related aspects (functional ability and quality of life) needs to be better determined.

The association between visual function and the ability to perform daily functions was recently reported.[78] High correlations were found between functional ability and, in descending order, contrast sensitivity, binocular visual acuity (VA), better-eye VA, and worse-eye VA. In conclusion, it is assumed that patients who have impaired vision have reduced quality of life and are affected by physical disability. However, it is still unclear what aspects of decreased vision have an influence on health.

The discussion that followed the introduction presented by G. Spaeth and A. Coleman was focused on the following points:

- Validity of evidence-based medicine.
- Are the right risk factors being evaluated in clinical practice?
- Are the right outcomes being measured in clinical practice?
  - How can functionally important vision be assessed?

Summary Discussion

Validity of Evidence-Based Medicine. The application of clinical trial findings to clinical practice forms the basis of evidence-based medicine, and it is therefore important to examine this process in some detail. Although evidence-based medicine is a desirable approach to health care prac-

tice and provides guidance to the clinician, its application to individual patients has limitations. There are 2 reasons for these limitations. As highlighted in "Problems with Normative Data," the data drawn from clinical trials cannot be universally applied to every patient, especially given eligibility restrictions that are important to ensure the internal validity of clinical trial comparisons. Furthermore, evidence is not available regarding some aspects of glaucoma management, in which clinical practice is conducted based on expert consensus by default or by custom. Bernadette Healy, former director of the National Institutes of Health, has said of the evidence-based movement, "By anointing only a small sliver of research as best evidence and discarding or devaluing physician judgment and more than 90 percent of the medical literature, patients are forced into a one-size-fits-all straitjacket. Ironically, this comes at a time when both human genomics and informed patients are demanding more tailored and personal prescriptions for care."[79]

Uncertainty in Decision Making. In making clinical decisions, the clinician is helped by clinical and scientific evidence, together with his or her professional experience and knowledge. However, there is a level of uncertainty that he or she has to face, as there is no single correct answer to every situation. For example, it is often difficult to predict with a high level of accuracy life expectancy, compliance with treatment, and disease evolution for any individual patient. The level of uncertainty that would be acceptable to a clinician depends on how comfortable he or she would feel with it and would be affected by the stakes of judgmental errors. If the benefits of treatment are high, then there would be more willingness on the clinician's part to accept more uncertainty in treating the patient. This would happen, for instance, in the case of diagnosed glaucoma. Because glaucoma is a gradual, chronic condition, follow-up is needed for assessing disease evolution, which will determine how management should be conducted. In this way, uncertainty is alleviated and the risk of making incorrect decisions minimized.

Uncertainty can be reduced by statistical methods, which are used to assess the probability of uncontrollable events, but cannot be completely removed. Thus, in applying evidence from clinical trials to individual patients, the clinician has to make assumptions. An example of an assumption that was made in the past was that treatment outcomes in women would be similar to those in men. For this reason, women were not always included in clinical trials until various research studies demonstrated the differences in disease behavior between the two sexes.

Individual Assessment of Patients. Consideration given to a patient at an individual level is essential. It is important to evaluate the data from an individual patient in a reliable manner so that the evolution of disease when no treatment is given can be better predicted. This information is necessary to justify treatment. As discussed earlier ("Session 1: Early Glaucoma Diagnosis"), the rate of progression is the key basis for management decisions, and it is important to identify ways of predicting this rate. Another concept emerging from the discussion is the applicability of the N-of-1 approach in clinical practice. This approach is valid in long-term follow-up, where each patient is used as his or her own control. In the case of a newly diagnosed patient, evidence from clinical studies on risk factors is used as the basis to assess the risk to the patient, and management decisions are made based on this assessment. Initial management decisions may be altered depending on the results of individual follow-up data compared with those obtained at baseline.

Clinical Significance of Outliers. An outlier is defined as a single observation, or data point, that is far from most of the rest of the measurements.[80] Outliers can indicate faulty data generated by biases in measurement or flawed procedures, or extreme cases where the theory tested may not be valid. Because outliers have a strong influence on the calculation of many statistics, there are methods that can be used to reduce this influence. Outliers may also have clinical significance, because their presence may indicate subgroups of patients or subpopulations.

Ranges versus Means. The validity of using data ranges was discussed. It might be more appropriate to use ranges of values, in addition to mean values, when assessing a patient in clinical practice. For example, when assessing risks, ranges could be taken into account to allow the entire spectrum of risk (i.e., mean risk and upper and lower limits of risk) to be assessed. In clinical trials, the assessment of ranges is also critical. An example from the OHTS data is helpful. Ocular Hypertension Treatment Study subjects, as defined in the study, were described as normal with respect to VF and disc cupping, but they may not correspond to normal in the sense of disease-free (see also session 1's "Summary Discussion"). The range of cupping values in OHTS subjects was skewed toward higher values compared with healthy subjects. Useful additional information can be obtained from evaluating critically the range of data from clinical trials.

Are the Right Risk Factors Being Evaluated in Clinical Practice? *Validity of Self-Reporting Methods.* The validity of using self-reporting questionnaires for assessing functional disability from vision loss was discussed. It was suggested that the outcomes of such approaches may be sensitive to the patients' subjective perception of their disability. For this reason, the impact of vision impairment on hard outcomes, such as falls or fractures, would more accurately reflect reality. For example, recent unpublished work conducted by A. Coleman et al has shown that greater binocular VF loss is associated with increased risk of falls and fractures. Patients' self-reports on their functional abilities often do not correlate with their VF measurements. An example of this poor correlation, even for VA and contrast sensitivity, can be found in the article by S. West et al on the findings from the Salisbury Eye Study.[81] This lack of correlation occurs because patients' perceptions of their abilities often differ from their actual abilities measured in a laboratory environment. Disease symptoms also have a powerful influence on self-reported functioning and are arguably more important than the presence of disease itself. Poor adaptability leads to an increase of perceived problems, which may lead to depression and anxiety, causing patients to perform less well on quality-of-life questionnaires.[82] Cognitive impairment also contributes to inade-

Figure 26. Left, *Water Lilies* (1903) by Claude Monet before cataract operation. **Right**, *Garden at Giverny* (1923) by Monet after cataract operation, with one eye still having cataract and low vision.

quate self-reporting and makes it difficult to ascertain disease status accurately from history alone.[83,84] Because of the potential problems associated with these various factors, models for disability testing were developed. The applicability of these models has been verified, and a reliable model can be used to test the ability of an individual to perform daily tasks.

Importance of Health-Related End Points. An obvious area where the patient's visual disability is important is driving. Driving ability is a quality-of-life end point that has been frequently used as a marker for a stage of glaucoma that clinicians try to prevent.[84,85] This stage is clinically important because of its associated visual disability, which may not be perceived by the patient but may lead to reduced quality of life (i.e., inability to perform daily activities). As explained by R. Hitchings, driving ability is an external end point that can be applied to many people, and the loss of this ability has tremendous societal effects. According to the work done by A. Hoste,[86] the brain can fill in visual defects caused by glaucoma. For this reason, most patients are unaware of their visual impairment until the advanced stages of glaucoma. As shown in a study conducted in Austria, many patients with glaucoma are driving without meeting the requirements for safe driving.[87] Thirty-six percent of the patients investigated had binocular defects within their central 30° VF. The binocular VF test is important as a screening tool to assess glaucoma patients' fitness to drive. To this end, a perimetric method has been developed to ascertain the binocular central field and visual functional capacity without additional perimetric examination.[85,88] The relationship between motor vehicle accidents and degree of binocular VF loss has been established. As

Figure 27. Left, *Field with Reaper* (1889) by Vincent van Gogh, showing xanthopsia. **Right**, *The Starry Night* (1889) by van Gogh, showing halos around the stars.

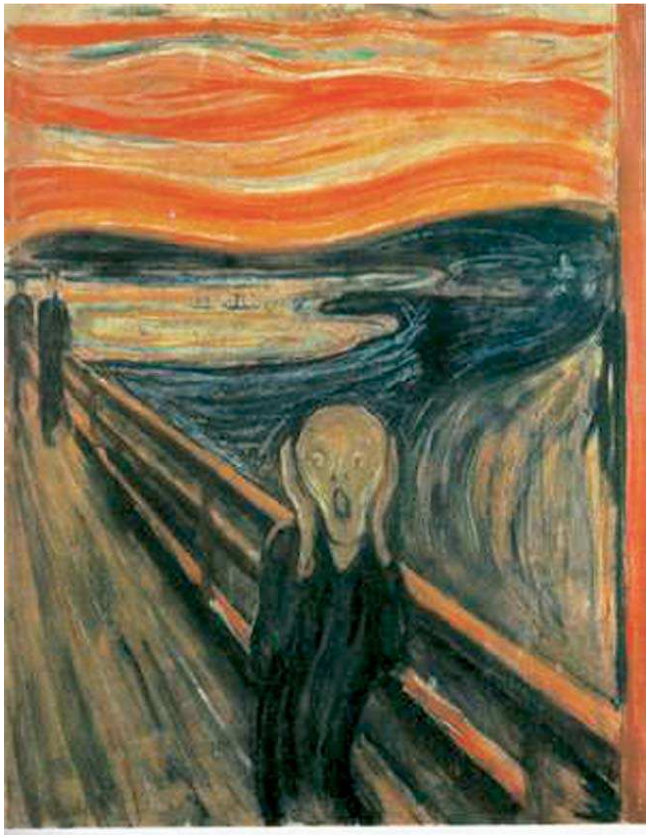

Figure 28. *The Scream* (1893) by Edvard Munch. The predominant grid of lines is used to record the artist's perceptions during his illness.

shown in a recent study,[89] glaucoma patients with binocular field loss are 6 times more likely to have been involved in a car crash, compared with subjects not affected by the disease. Another factor that can affect driving ability is the useful field of view in the midperipheral VF, which may be important in accident avoidance.[90]

In early to moderate disease stages, visual disability is not perceived by the patient but can have profound effects on quality of life. Perimetry is the standard method used to measure visual function but has limitations because its measurements do not correlate well with functional ability or perception of visual ability. Other sensitive approaches should be identified to determine the impact of glaucoma on actual visual function—that is, not that determined by standard perimetry alone. Assessment of contrast sensitivity was suggested to be important, because a change in this visual function would translate into reduced reading ability, which would be noticed by the patient.

More studies on the impact of glaucoma on quality of life are necessary. Unlike AMD, for which quality-of-life data are better established, more work is needed in glaucoma that will help to clarify various aspects that are not yet well understood and will raise awareness of the potential debilitating effects of glaucoma and the health care costs attributed to these effects. An important area for further research is the prevention of visual function loss that increases the risk of automobile accidents and falls.

The session was concluded by the comoderators with the following summary of key points discussed:

- Evidence-based medicine is a helpful tool to guide clinicians in their management of patients; however, it does not always provide the best treatment for every patient.
- In making clinical decisions on diagnosis and management, the physician must make assumptions and accept a certain level of uncertainty.
- Because glaucoma is a chronic and gradual disease, decisions are best made after a certain period of follow-up, so that each patient can be individually monitored and managed and serve as his or her own control.

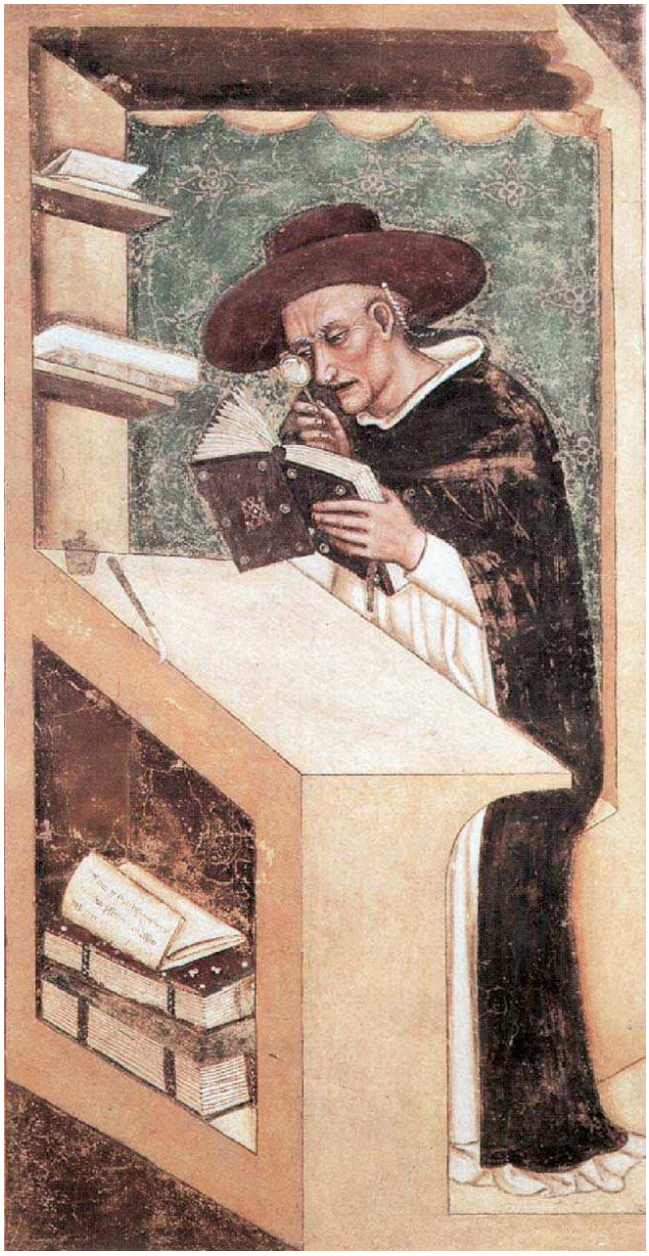

Figure 29. *Cardinal Nicholas of Rouen* (1352) by Tommaso da Modena.

- Other outcomes more closely related to quality of life, such as functional and driving abilities, should be considered besides those already being used.
- Better methods need to be developed to assess visual function related to quality of life and to measure the quality of life of patients with glaucoma.

Session 6: Future Directions—Where Will Glaucoma Care Be 5 and 10 Years from Now?

This interactive session was dedicated to defining the future priorities for research and management of glaucoma and was co-moderated by J. Caprioli and D. F. Garway-Heath.

Future Directions for Clinical Trials

Among the important topics discussed in the previous session, the refinement of clinical trial end points and identification of strategies to shorten clinical trial duration and to make better use of clinical data emerged as important issues for future clinical trials and development of new glaucoma treatments. For instance, in the OHTS VF data were generated over 10 years, and despite this long period, not all of the data were used. For each subject, only the information at study entry and at reaching an end point, and none of the data in between, was used. In addition to the long duration required to collect the data, not much information was obtained on the rate or magnitude of disease evolution between these 2 time points.

Importance of Trend-Based Analyses. To evaluate the effects of drugs in clinical trials in a more realistic manner, there is the need to use trend-based approaches to determine the rate of disease progression ("Session 2: Detection of Progression in Glaucoma"). However, event-based analysis is useful when follow-up periods are short and data are insufficient for trend-based analysis. The frequency of testing should be adequate to allow enough measurements to be obtained, and it is important that there be good data.

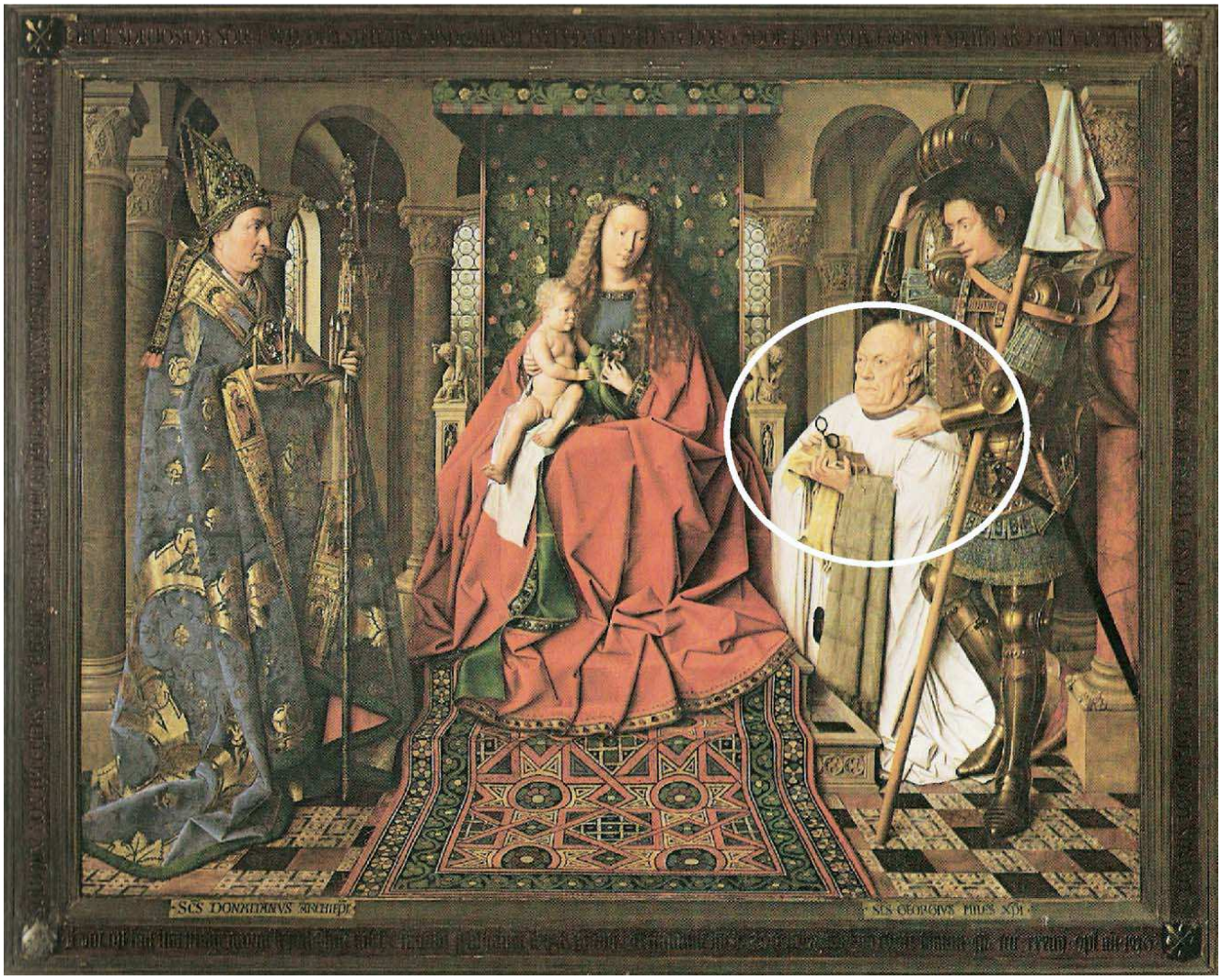

Figure 30. *Madonna with Canon van der Paele* (1436) by Jan van Eyck.

Importance of Structural Assessment. It is also important to choose an approach that allows progression to be detected earlier, because this will shorten the trial and help clinicians identify advancement of the disease process early. In this respect, the importance of performing both structural and functional measurements was stressed because this will optimize the detection of changes in early disease ("Session 2: Detection of Progression in Glaucoma"). A better integration of structural and functional measurements will make it possible to develop strategies that allow progression to be detected sooner.

New imaging devices were judged to be useful in structural assessment, and their use is expected to increase over the next 5 to 10 years. Despite the availability of sophisticated instruments that can provide reasonably reproducible information about the optic disc and RNFL, these devices are not being used optimally. Guidance should be provided to clinicians on how to use the imaging devices and how to interpret the results in an appropriate manner. The capacities and limitations of the techniques should also be clear to anyone using such devices to make clinical decisions.

Other Approaches to Reducing Trial Duration. Glaucoma clinical trials, because of the nature of the disease, are often long and very costly. Some are so long, in fact, that the answers may no longer be relevant, or the methodology may become outdated. Shorter clinical trials would offer increased relevance to clinical practice and reduce the huge costs of lengthy trials. Another consideration of how trial duration could be shortened would be through the use of mathematical modeling to predict changes over time. For example, a machine-assisted classifier, or artificial neural network, could be developed to evaluate information from clinical trials and provide predictions of disease evolution.[91,92] Trials could also be shortened by including selected at-risk patient populations in clinical trials, though this may come at the cost of reduced generalizability. With an improved knowledge of risk factors and risk assessment, it would be possible to select and include the highest-risk patients in clinical trials to maximize the chance of obtaining changes in a shorter time with fewer patients.

In defining more appropriate clinical end points, it is important to reevaluate whether current measurement techniques are adequate to detect and measure progression. For example, whether achromatic perimetry should still be the first choice to measure progression would have to be established. Also, data collected from patients (IOP, VF, structural changes, risk factors, etc.) are often not integrated efficiently by clinicians to monitor disease. Software that can present these data in an integrated manner, so that disease trends can be readily identified, would be helpful.

Figure 31. *Madonna with Canon van der Paele*, details of the printed text from the canon's book seen through his glasses.

Funding Requirements for Future Glaucoma Research and Management

All the participants agreed that substantially more financial support is needed for glaucoma research and management. Glaucoma is the second-leading cause of blindness worldwide,[93] and it has an important impact on patients' health-related quality of life, yet it does not occupy the place that it deserves in the health care system. It is therefore important that public awareness of the disease be raised. Clear messages are needed for health care providers and professionals so that the effects of undermanagement of glaucoma can be understood. Mismanagement of glaucoma can have deleterious effects on a patient's functional abilities and quality of life, which can increase utilization of health care resources considerably.

Education and Training Needs for Clinicians

Guidelines for clinicians were considered important, as they will set the standards for clinical practice and provide guidance for glaucoma management. As pointed out in "Session 5: Risk Factors and Outcomes—Are We Looking at the Right Things?," glaucoma management should be driven by evidence, but where evidence is not available there is the need for consensus to guide clinicians in their practice. In this respect, the American Academy of Ophthalmology's preferred practice patterns and European Glaucoma Society guidelines are examples of how future global guidelines can be set.[94] These documents provide guidance to clinicians based on the integration of existing scientific evidence and consensus on clinical practice for making recommendations on glaucoma management. Together with guidelines, continuing education for clinicians is critical because it will bear on the way glaucoma is managed. It is essential that appropriate methods be chosen for delivering the contents of educational programs to physicians. The most effective approaches will have the most impact on the learning process,[95] which will be reflected in the clinician's practice of glaucoma management. For example, randomized controlled trials about the effectiveness of continuing medical education have shown that standard continuing medical education with a lecture format, as is currently practiced, is not effective in changing physician behavior compared with evidence-based online continuing medical education.[95] A possible explanation for this difference may be the length of time allocated to the meetings, which may not be long enough for the teachers to provide sufficient information and to allow enough interaction between teachers and students. Group size may be another factor that could hinder teacher–student interaction.

Approaches to help physicians manage relevant information will also be necessary to help change their behavior. With the ever-increasing amount of information available,

Figure 32. *Madonna with Canon van der Paele*, details of the canon's head.

software to manage knowledge and provide decision support would be useful to guide physicians.

Potential Importance of New Trials and Techniques

The outcomes of the trial on the neuroprotective effect of memantine will be of considerable interest. If they confirm earlier experimental studies in humans, the findings from this study would have a large impact on clinical practice.

It is also expected that within the next 5 to 10 years adequate imaging techniques will be available that can give an indication of the health status of photoreceptors and other relevant cells of the retina ("Session 4: New Avenues toward Optic Nerve Protection and Regeneration"). The potential application of these new methods in clinical practice may lead to significant changes in clinical practice.

The session ended with the following conclusions by the co-moderators:

- The measurement of structural changes should be incorporated to a greater extent in clinical trials, especially in early disease.
- Software to integrate functional and structural measurements and to present data in an easy-to-use format would be helpful for clinicians.
- Trend-based approaches to measure progression are important for the determination of progression rates, on which to base clinical decisions.
- Event-based analyses are useful in detecting changes when follow-up is short.
- It is essential to ensure that the frequency of testing is adequate and that data be of the highest possible quality.
- Appropriate continued education should be provided to ophthalmologists and health care providers on the proper use of measurement techniques in the diagnosis and follow-up of glaucoma.

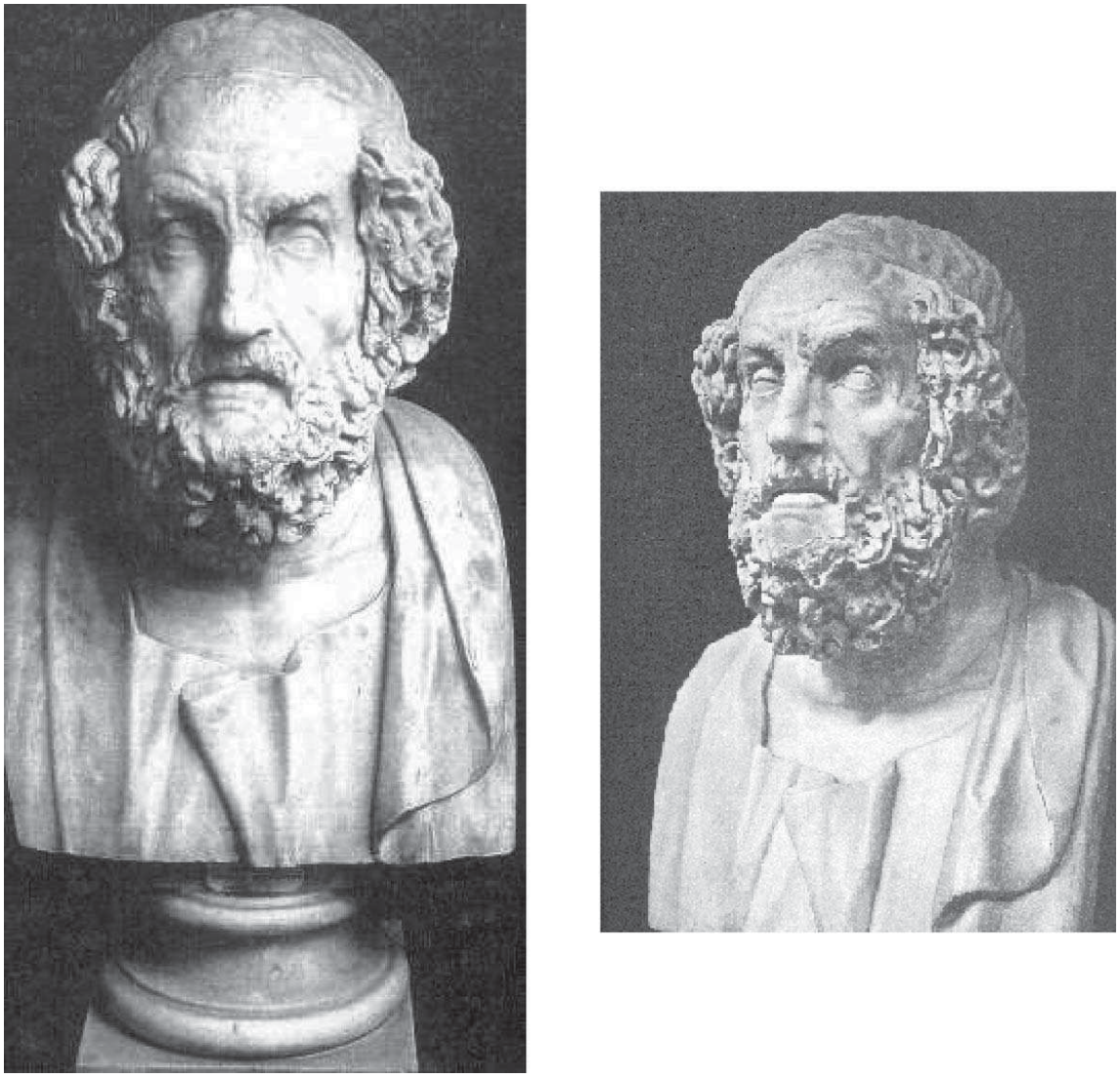

Figure 33. Bust of Homer. Roman sculpture of the first century AD, Naples, Italy.

Session 7: Eye Disease Depicted in Art

The presentation by T. Zeyen gave an overview of eye disease and art. It is known that eye diseases have affected the way in which some of the world's most famous artists express themselves. For example, some of the Impressionists working in France in the late 19th century suffered serious eye conditions, and it is interesting to look at their work to find out how the artists deal with their misfortune. But far from being resigned to their illness and by dealing with the difficulty, they created a new vision of art that has inspired many generations of artists. One glance at Monet's beautiful crisp lilies reveals the difference in the way that the artist perceived these objects before and after an unsuccessful cataract operation in one eye, while the other eye still had cataract and 20/200 vision (Fig 26).[96] The strong distinctive yellow color and halos in van Gogh's paintings may have been due to xanthopsia, a form of dyschromatopsia or color distortion that causes the sufferer to have the impression of seeing things through a yellow filter (Fig 27, left).[97] This condition can be caused by early cataract-induced lens opacity but, in van Gogh's case, may have been due to intoxication by the digitalis that he was prescribed for mania and depression.[93] The artist could also be suffering from glaucoma, and the halos nicely painted around the stars may have been created under the effect of IOP spikes (Fig 27, right).[97] El Greco's unique style of painting, in which the characters are obliquely elongated, could be purely stylistic but could also suggest that the artist was suffering from astigmatism.[98]

Finally, it is well known that the famous Norwegian painter, Edvard Munch, suffered from decreased vision and metamorphopsia subsequent to an intraocular hemorrhage of his right eye in his 60th year.[99] One of his most famous paintings, *The Scream* (Fig 28), shows his changing perceptions during this illness and his attempts to record these changes with a grid of lines.[100]

Interestingly, eye conditions or ophthalmic devices have also been depicted in works by artists who are not affected by ocular conditions themselves. Thus, the evolution of corrective eyeglasses has been commemorated in many paintings. Spectacles were an invention of medieval Europe and were first mentioned by the 13th century English Franciscan monk and scientist Roger Bacon in his writings about his experiments with convex lenses to correct vision.[101,102] The earliest spectacles had no sidepieces, and paintings from the 13th and 14th centuries showed readers holding them onto their face with their hands. The portrait of *Cardinal Nicholas of Rouen* as a Dominican monk reading and translating manuscripts by Tommaso da Modena in 1352 (Fig 29) is the first artistic depiction of corrective glasses. By the 14th and 15th centuries, spectacles were included in portraits of saints and scholars to denote piety and intellectualism.

In those times, glasses were dispensed not by opticians or ophthalmologists but by vendors of spectacles. By trial and error, the vendors identified the best glasses on hand for their clients. Myopic glasses were first described in the 15th century and were considered a status symbol exclusively destined for the elite. By the end of the 15th century, the use of glasses spread far outside the elite circle. Because of the widespread availability of books, the use of reading glasses

Figure 34. *The Parable of the Blind* (1568) by Pieter Bruegel the Elder. Scala/Art Resource, New York.

gradually reached the common people and became an important part of everyday life.

Another masterful painting depicting myopic glasses is that of *Madonna with Canon van der Paele* by the Flemish painter Jan van Eyck (ca. 1385–1441) (Fig 30). The glasses of the canon were meticulously drawn, with the print from his book seen through the lenses being smaller than that outside his glasses, emphasizing that these are myopic glasses (Fig 31). The prominent head of Canon van der Paele is interesting from another ophthalmologic point of view: on top of some discreet epiphora, the conjunctival vessels were delicately painted (Fig 32). Blue was used to depict scleromalacia and the prominent temporal veins. It was documented that Canon van der Paele was treated for arthritis and may have had sclero-uveitis and vasculitis.

A very important theme for artists is blindness, and a very important character in classical history who embodied this condition is Homer, the Greek author of the *Iliad* and the *Odyssey*. Tradition holds that Homer was blind, like many singing bards and poets of that time. The poet can be seen in several works of art, and among many sculptures of his bust, that shown in Figure 33 is certainly one of the most beautiful. One can appreciate the masterly shaped posture typical of a blind person. The body is bent forward, fumbling, but the head is tilted upwards with the eyes asymmetrically open, with the eyebrows elevated and frown lines in the forehead, in an attempt to seek the faintest perception of light.

A striking and very detailed painting dealing with blindness is that by Pieter Bruegel the Elder, *The Parable of the*

Figure 35. *Conversion of St Paul* (1600–1601) by Michelangelo da Caravaggio, depicting St. Paul struck blind and converted by lightning. Scala/Art Resource, New York.

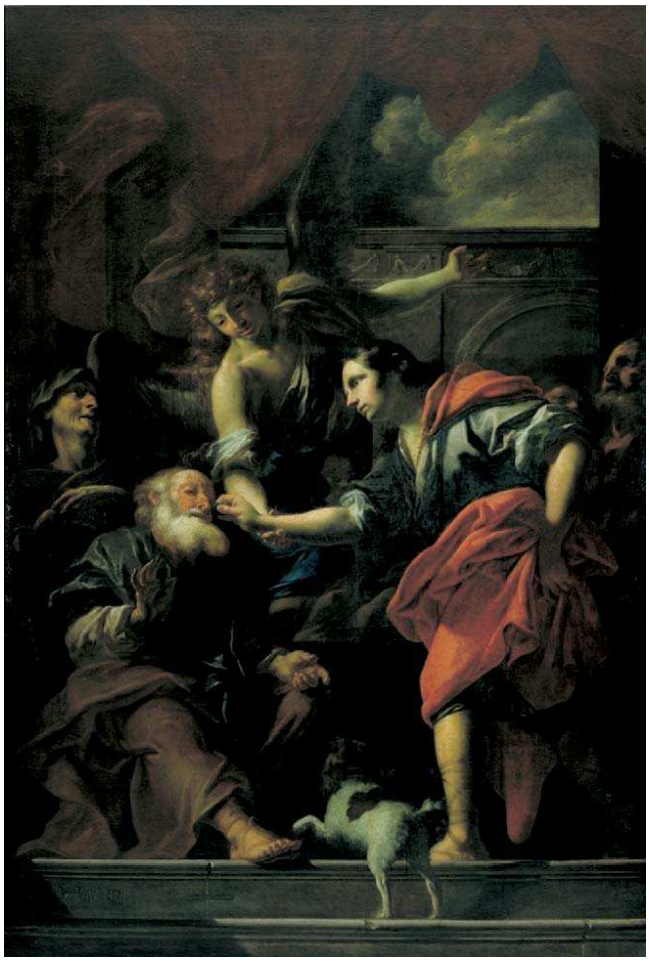

Figure 36. *Tobias Healing His Father from Blindness* (1705) by Peter Brandl.

Blind, which depicts the words of St. Matthew: "when the blind lead the blind, they will both fall into the ditch" (Fig 34). Some research has shown that the artist showed great interest in medicine, and Bruegel's detail has allowed physicians to analyze medical conditions in his paintings.[103] This can be seen in the eye conditions of the characters in *The Parable of the Blind.* The first one has pemphigus with corneal opacities; the second is heavily photophobic, possibly from uveitis; the third one has phthisis bulbi, possibly due to complicated surgery; the fourth one has corneal leukoma; and the last one has had bilateral orbital exenterations.

Another very inspiring theme for classical artists featuring blindness is *Christ Healing the Blind,* which portrays the words of the apostles of the New Testament. A great number of artworks have been created on this subject. *Healing blindness* was used to refer to Christ's authority over physical conditions and, metaphorically, to symbolize enlightenment of the apostles. One of the apostles, St. Paul, was struck blind by lightning, from which he recovered after 3 days, and converted to Christianity. The *Conversion of St. Paul* by Caravaggio is one of the many paintings depicting this biblical story (Fig 35). Many theories exist about the differential diagnosis of the blindness and recovery from blindness of St. Paul, varying from corneal burning associated with solar retinitis to a cerebrovascular accident.[104]

Blindness is reflected in the theme of Tobias returning to his father's side. From the Old Testament, the *Book of Tobias* tells the story of the holy man Tobias who, having lived to the age of 102 years, exhorted his son and grandson to piety. He became blind in his old age and sent his son Tobias away on a long journey to retrieve a long unpaid debt. In the beautiful baroque work by the Czech painter Peter Brandl, the young Tobias is shown healing his father from blindness, probably due to cataract (Fig 36). The technique used by Tobias is called couching, from the French word *coucher* (to lie down), and was practiced by the Egyptians, Greeks, and Romans and even in Rembrandt's time (i.e., 17th century). It was not until 1753 that the French surgeon Jacques Daviel published reports of his first 100 cases of extracapsular cataract surgery,[99] which was a major breakthrough in cataract surgery.

Another popular ocular theme in art is strabismus, which has been portrayed in various drawings and paintings, as shown here in a painting by Raphael (Fig 37). Last but not least is the beautiful painting by Hogarth that hangs above the staircase in the oldest hospital of London, St. Bartholomew's (Fig 38). In *Christ Healing the Lame Man at the*

Figure 37. Strabismus, as painted by Raphael or Raffaello Sanzio (1511), showing Cardinal Tommaso Inghirami.

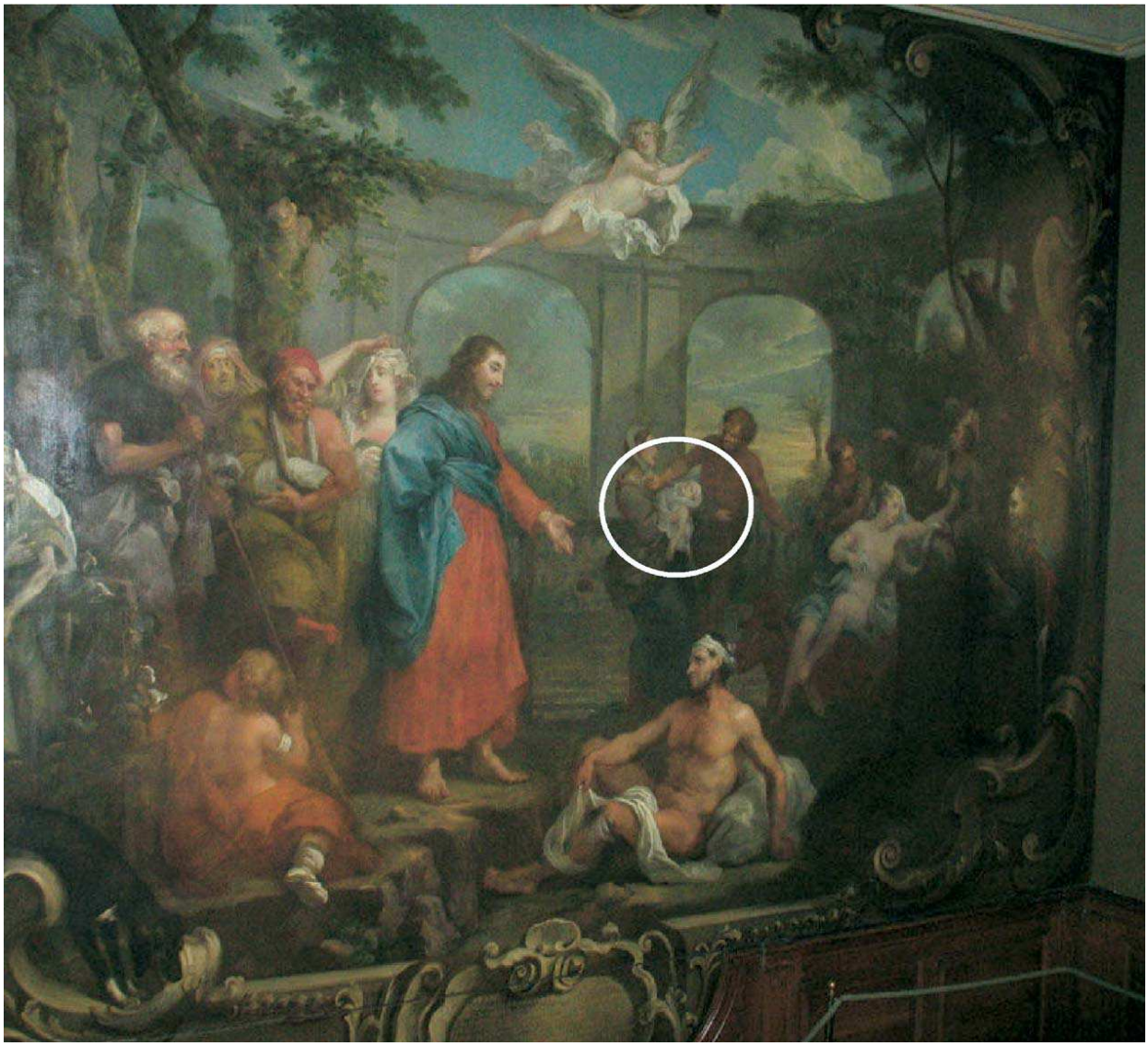

Figure 38. *Christ Healing the Lame Man at the Pool of Bethesda* (1736) by William Hogarth. © St. Bartholomew's Hospital Archives. Courtesy of St. Bartholomew's Hospital Archives.

Pool of Bethesda, Christ is pictured telling a lame man, "Rise, take thy bed and walk." Hogarth produced this painting in 1736 for the hospital, and all the figures surrounding Christ were patients of the hospital. One of them, a small baby, was blind from congenital syphilis.

Art and science are often complementary. It is fascinating for an ophthalmologist to witness how meticulously some artists, interested in medicine, depicted eye diseases in their art work and to understand how famous artists, affected by an eye disease, created a new vision of art.

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Appendix: Think Tank Participants

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