INTRODUCTION: WHY WAS THE STUDY DONE?
“Low tension glaucoma” is now more often called "Normal Tension Glaucoma" (NTG). These cases, perhaps heterogeneous, are people who had intraocular pressure (IOP) in the statistically normal range, but optic nerve damage and visual loss characteristic of that seen in patients with chronic glaucoma.

TWO HYPOTHESES WERE CONSIDERED
The first hypothesis (that the disease is IOP-independent) seemed in keeping with the frustration of clinicians in halting the nerve damage and visual loss by conventional treatments aimed at lowering the IOP. If this is the case, this clinical entity consists of etiologic and pathogenic factors that produce optic nerve injury that looks like that caused by an elevation of intraocular pressure (IOP), but in fact the IOP neither causes nor influences the process.

The second hypothesis (that IOP participates in producing the optic nerve damage in NTG) is that in both high pressure and normal pressure glaucoma, the impact of nerve-damaging factors is amplified by the level of IOP. Other etiologic and pathogenic factors are involved in the optic nerve damage, but the degree of insult or amount of harm depends on the level of the IOP.

A group of collaborators were of mixed intuition with regard to the question of whether IOP was or was not involved in NTG, and therefore whether aggressive efforts to lower IOP in patients with this condition was warranted. It was clear that support for either hypothesis was only anecdotal.

Clinical import: Most clinicians were in practice inclined to make some effort to lower the IOP in cases of NTG, but hesitated to use aggressive measures with potential untoward effects because of the uncertain benefit. Evidence was needed to help decide whether to be aggressive in lowering the IOP in cases of NTG.

METHODS: HOW WAS THE STUDY DONE?
Enrollment
230 patients were enrolled from 24 collaborating centers, each with Institutional Review Board approval. To be considered eligible patients had unilateral or bilateral NTG evidenced by glaucomatous cupping of the disc and a defined type and severity of field loss with a median IOP of 20 mm Hg or less in 10 baseline measurements.

Randomization
One eye of patients with NTG was randomized (a) to be followed without treatment until there was evidence of slight deterioration. The other eye could be treated at the discretion of the treating physician, except that systemic carbonic anhydrase inhibitors could not be used.

(b) to be placed on treatment with medication, laser trabeculoplasty, and filtration surgery as required to lower the IOP by 30%.

In both arms, neither eye could receive beta-adrenergic blockers or adrenergic agonists, because they might have systemic cardiovascular effects that could conceivably alter the course of the treated or untreated disease, confounding the analysis of data.

Some were randomized immediately: if the field defect threatened the point of fixation or there was previously documented progression of the disease.

The others were randomized later if there was visual field progression, progression of optic nerve head cupping, or a new disc hemorrhage.

By the end of the study, 145 eyes had been randomized: 66 to receive treatment and 79 eyes to serve as untreated controls.

Data collection
An important design consideration was the definition of progression. Some of the participating patients, who have a potentially blinding disease, would be followed without efforts to lower IOP -- ethical in the face of very uncertain benefit, but worrisome. For that reason, an effort was made to define the absolutely minimal field alteration that would be reasonably certain to be genuine. Four types of change were defined: deepening of an existing defect, expansion of the size of an existing defect, a new defect in a previously normal region, and a new or expanded threat to fixation. Replicate testing was used to be sure the small changes were reproducible and genuine. The endpoint criteria used for the study were shown to be reasonably specific and sensitive in identifying a small increment of progressive field change.

The somewhat complex criteria for field progression or change in the disc cupping confirmed by the reading committee guided the conduct of the study: the patient was released from protocol constraints. Those not receiving treatment could be treated, and drugs prohibited during the study could be used.

Some analyses of results were based on the
“endpoint” criteria used to determine when the patient was released from the protocol, but outcomes were also studied in terms of other variables as well. For the reports released in October 1998, data had been collected through June 1996. Upcoming reports will include additional data collected through September 1998.

REPORTS OF THE COLLABORATIVE NORMAL TENSION GLAUCOMA STUDY

[Detailed description of study design.]


A 30% lowering of IOP can be achieved in patients with NTG with medical therapy and laser trabeculoplasty about half the time, and perhaps this is even more feasible with medications not permitted in the NTG study protocol and with drugs that have more recently become available.


With repeated, frequent visual field examinations in search of very subtle changes or a slow rate of progression, in NTG or likely in any other chronic glaucoma, there is a risk of judging falsely that progression has occurred. Progression must be evident on at least one subsequent field to be sure it is genuine.


Once pressure has been successfully lowered 30% from baseline, rate of progressive field loss is slower than in a group that did not receive treatment.


Cataracts, which occur more frequently in treated patients who underwent filtration surgery, produce visual changes. In a clinical trial format with visual field as the sole outcome measure, correction for cataract effect must be made to uncover the benefit of lowering the IOP.


[Discussions of interpretation of findings.]


The rate of visual field progression in cases of untreated normal tension glaucoma is highly variable, some cases showing progression in a few months, but half not showing progression within five years.

Collaborative Normal-Tension Glaucoma Study Group. Natural history of normal tension glaucoma. Ophthalmology 2001; 108:000-00. (Accepted)

Risk factors involved in the pathogenesis or that can act as prognostic indicators are . . .

Collaborative Normal-Tension Glaucoma Study Group. Risk factors for progression of visual field abnormalities in normal tension glaucoma.

IMPLICATIONS OF NORMAL TENSION GLAUCOMA STUDY RESULTS

The natural course of NTG is quite variable, some cases slow enough that they may never need treatment, but others progressing rapidly to potential blindness.

Prediction of the untreated course is not yet possible except perhaps through observation of the course over time in the particular individual.

Meanwhile, it is known that as a group, progression is affected by the level of IOP.

Hypothetically it may do so more in some cases than others.

While a 30% lowering was used in this study, it is not known whether there is graded benefit, so that some patients may respond adequately with less IOP-lowering while others require more IOP-lowering.

This means that case selection for treatment and the IOP-target may depend on

* whether the person was one destined to have a disastrous natural course
* and hypothetically could depend on whether the person is one in whom IOP level matters (It is not known whether degree of benefit from IOP-lowering is variable among individuals or not - -
so this concept is speculative.] 

If a patient is placed on treatment an a 30% IOP-lowering goal is set, it can be achieved at least half the time without filtration surgery, and perhaps more often with use of types of medical therapy not used in the study.

Although filtration surgery achieved pressure lowering somewhat in excess of the 30% goal when it was used, and potentially had more benefit therefore, it came with the price of a higher incidence of cataract formation.

While following patient with NTG (or perhaps any glaucoma), with repeat testing of the visual field on many occasions, a field will someday be obtained by chance alone that seems worse than the baseline. Any field change needs to be confirmed before it can be judged genuine. Stability or instability of the case should correlate with other clinical findings, such as whether IOP-goal has been obtained, changes in the optic disc, and in advanced cases the subjective sense of patient.

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