PRIMARY THERAPY FOR CHRONIC OPEN-ANGLE GLAUCOMA:

THE ROLE OF LASER, MEDICINE AND SURGERY

by

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"Many are engaged in writing books and printing them
Many desire to see their name in print
Many read nothing but the race reports"

Choruses from "The Rock" III

T.S. Eliot

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PRIMARY THERAPY FOR CHRONIC OPEN-ANGLE GLAUCOMA: THE ROLE OF LASER, MEDICINE AND SURGERY

SECTION I

CHAPTER 1

INTRODUCTION

Glaucoma is a major public health problem worldwide. Although commonly affecting the elderly, it occurs in all sections of society, with significant social and economic consequences [1,2]. Left untreated, the condition may lead to irreversible blindness.

The prevention of blindness from glaucoma requires early detection and proper treatment. Various forms of therapy are now available. The effectiveness and goals of the various treatments need to be defined in relation to the disease itself, glaucoma being a chronic disease, pursuing a relentless course.

In primary open-angle glaucoma (POAG), there is abnormal resistance to aqueous humour outflow through the trabecular meshwork, resulting in elevation of intraocular pressure (IOP) that, depending on the susceptibility of the optic nerve head, leads to nerve fibre death. IOP elevation is not the sole abnormality in POAG, but it is the only modality we are currently able to treat. How effective, therefore, are the methods of treatment currently available?

That there is no previous published report of a randomised prospective study comparing the effect of laser, medicine and surgery on similar groups of patients with POAG is partially due to convention, over many years, having established medical treatment in its various forms, as the most frequently used primary therapy for the disease. However, this form of therapy has many well-documented disadvantages, with unending medications that do not reverse the disease process, are difficult and expensive to administer and may have significant morbidity.

Filtering surgery is nowadays a relatively safe procedure that successfully controls IOP in a large proportion of cases. There is no medical reason why surgery should not be used as a primary form of therapy, rather than after a period of medical treatment which has proved unsuccessful.

More recently, laser trabeculoplasty has been added to the therapeutic regime and is effective in reducing IOP. This method may be more effective than life-long multidrug therapy which so often leads to gross optic nerve damage after many years of borderline control and variable patient compliance, and is simple to perform and cost-efficient.

1.1 Purpose

This randomly allocated prospective clinical study has been designed to assess the relative efficacy of the three forms of therapy used as the primary treatment in POAG with particular regard to the level of IOP control and the amount of visual field decay. No patient had received any antiglaucoma therapy prior to entry into the trial.

1.2 Definition and Terminology

The Disease

Chronic open-angle glaucoma, in its typical form, is defined by the following three criteria:

1. An intraocular pressure consistently above 22 mmHg in at least one eye;

2. an open, normal-appearing anterior chamber angle with no apparent ocular or systemic abnormality that may account for the elevated IOP; and

3. typical glaucomatous visual field and/or optic nerve head damage.

Synonymous terms that also appear in the literature include "open-angle glaucoma", "primary open-angle glaucoma" and "chronic simple glaucoma". The specific minimum criteria required for inclusion in this trial are noted in Chapter 7.2.

The Treatment Groups

1. Medical patients had up to three topical antiglaucoma medications and/or a carbonic anhydrase inhibitor.
2. Surgical patients underwent a Cairn's type trabeculectomy.
3. Laser patients were treated over 360° of the trabecular meshwork in two separate sittings, using the argon laser. Pilocarpine 2% was considered permissible adjuvant therapy for those laser patients not controlled on laser alone. The treatments are detailed in Chapter 7.3.

Primary Therapy

All patients entered into the trial were newly-diagnosed and had not received any prior antiglaucoma therapy.

1.3 Natural History of Field Loss in Chronic Open-Angle Glaucoma

Open-angle glaucoma is a long-term disease, with gradual damage to disc and field occurring over a long time interval in untreated cases.

In a large population study, Leydhecker [3] noted that the incidence of

field loss was the same as the incidence of ocular hypertension in a population 20 years younger. His conclusion was that approximately 20 years elapse between the onset of pressure elevation and field loss developing. This concept may be erroneous, however, since the study did not show that the same individuals with elevated pressures were the ones who subsequently developed field loss.

Lichter & Shaffer [4], on the other hand, found that field loss in a group of ocular hypertensives observed for a period averaging 12.75 years, occurred earlier than Leydhecker had suggested, despite the fact that most received treatment during this time.

Grant & Burke [5], retrospectively analysing 750 patients blinded by glaucoma, found that some eyes with normal discs and fields tolerated IOP's of 30 mmHg for many years, but when abnormalities ranging from early glaucomatous cupping to advanced field loss were present on initial evaluation, progressive loss of field tended to occur at lower tensions. This reflects the increased susceptibility of the damaged eye.

In the typical case of chronic open-angle glaucoma with established visual field and/or optic nerve head damage, treatment to reduce the IOP is clearly indicated. To assess the results of this therapy, long-term clinical observations must be made, as the glaucoma affects the eye over extended periods of time. Few reports, however, detail the course of glaucoma patients treated for lengthy periods.

Chandler [6] reviewed the long-term results of glaucoma therapy in 20 patients followed for between 5 - 40 years and treated surgically and/or medically, and concluded that, while eyes with early disc changes withstand increased IOP relatively well, those with advanced glaucoma withstand increased tension poorly and require a tension below the average normal to prevent further loss of function. The ophthalmoscopic appearance of the optic disc may thus serve as an important guide in the management of glaucoma. He states that if the tension is reduced to a low enough level, there is an excellent chance of preventing further loss of function.

Kolker [7] reviewed the visual prognosis in advanced glaucoma in 101 eyes followed for a minimum of 4 years and compared the results of medical and surgical therapy. He found that loss of central vision occurred with equal frequency in the two treatment groups. The higher the IOP with medical therapy, the greater the risk of central field loss. In the surgical group, progression of field loss was rare in successfully treated patients, although cataracts developed in 32% of eyes.

Quigley & Maumenee [8] describe the findings in a group of glaucoma patients studied for 8 - 42 years and support the generally accepted belief that IOP reduction is important in preventing visual loss in glaucoma.

Redmond Smith [9], analysing the results of the Moorfields prospective surgical vs medical trial in POAG patients followed for up to 18 years, found, on the other hand, little correlation between the visual field and the level of IOP.

Other studies, such as those of Burke [10] and Kronfeld & McGarry [11] and, more recently, of Granström [12], Patkin et al. [13], Stavita et al. [14], and Werner et al. [15], also indicate that impressive numbers of patients in whom IOP is reduced (sometimes up to 50%) continue to lose field.

Several reports have dealt with the long-term results of trabeculectomy ([16 - 22]), and laser trabeculoplasty ([23 - 26]).

Allowing for the diversity of criteria in all these long-term reports, it would thus seem that there are two sub-groups in the 'syndrome' of glaucoma, with one that includes patients who are unresponsive to pressure reduction, perhaps even at the outset [27].

1.4 Risk Factors

Other than elevated IOP, there are additional risk factors significant for the development of glaucomatous damage. These include advancing age, a family history of glaucoma, cardiovascular/microvascular disorders and others [28-31]. However, no single risk factor or group of factors has yet been shown to predict the future development of glaucomatous damage with reasonable accuracy [32, 33].

Age

Statistically, the older the patient, the more likely damage will occur, with all other factors being equal. This may simply mean that the older persons are, the more fragile and susceptible they are to injury. An alternative interpretation, however, is that the older patient is more likely to have had an elevated IOP longer and therefore to have more damage. In the Bedford Glaucoma Survey of 3,000 individuals, the prevalence of POAG and low tension glaucoma by age group was 0.22% among persons in their 4th decade, rising to 2.81% for those in their 7th and 14.9% for patients over 80 years of age. [34].

Family History

Family history of glaucoma is generally accepted as a risk factor for the disease, but accurate estimates of the exact risk are lacking. Studies by Armaly et al. [35-37] indicated that IOP, facility of outflow and cup size appear to be genetically determined.

Cardiovascular/Microvascular Disease

There are many reports suggesting associations between diabetes and POAG [38]. Klein & associates [39] have presented data to suggest that diabetics may be at increased risk of glaucoma.

There is a strong association between blood pressure and IOP [40-42]. Leighton & Phillips [465] have hypothesized that the capillary circulation at the disc may be more precarious as blood pressure increases and that relatively high blood pressure may thus be a factor in producing POAG.

Race

The prevalence of glaucoma has been reported to be higher in blacks, develops at an earlier age and is more severe when compared with whites [43-49]. 81.6% of 140 patients with chronic glaucoma in the study by Martin, Sommer et al. [47] were black, compared to 48.7% prevalence of blacks from a random sample of the same population. In addition, blacks are said to have 6.8 - 8 times more blindness from glaucoma than whites [48, 49]. Recently, it has been reported that blacks have larger physiological cups than whites [50]. It is not known whether these cups are 'already on the way to glaucoma', or whether they are simply more susceptible to damage by higher IOP.

On top of this, lowered successful outcome of glaucoma surgery in blacks must considered.

The importance of racial differences in the risk factors of POAG may also relate to differential severity of the disease. Grant & Burke [5], in a retrospective analysis of patients blinded by glaucoma, reported a proportionately higher amount of blindness related to POAG among blacks than whites. Hiller & Kahn [48] indicated both a higher incidence and prevalence of blindness from POAG among blacks than whites.

Cup : Disc Ratio

The larger the cup : disc ratio, the greater the chance of field loss developing in a suspected glaucoma patient. Chandler & Grant [51] observed that a wide deep physiologic cup tolerates increased IOP poorly and the tendency is to enlargement and total cupping. In another study, 27 of 102 ocular hypertensives observed over 5 years who developed field loss , had significantly larger vertical cup : disc ratios than did those who did not develop field loss [52].

Stage of Disease

Grant & Burke [5] found that those patients diagnosed and treated early did well, while progressive field loss was relatively common in those who were not diagnosed and treated until they had reached a more advanced stage.

Shaffer [53,54] and Chandler [6, 55] have both pointed out that, if at first the disc and field are normal, the eye may tolerate a tension of 30 mmHG for many years without loss of function or necessity for treatment. On the other hand, eyes with early cupping or field loss are less resistant to damage and consequently lower tension is required. In eyes with advanced cupping and field loss, a reduction in IOP well below 20 mmHg is suggested to prevent further field loss. Similar evidence of the need for low tension in eyes with advanced disc changes and field loss is to be found in reports by Crick [56], Kolker [7], Lee [57] and Grant & Burke [5].

The particular risk factors investigated in this trial are IOP, age and stage of disease.

1.5 Aims of Treatment

The most significant risk factor in chronic glaucoma is the raised IOP. Current therapy is primarily aimed at reducing the IOP. (For explanation of this assumption see Chapter 9.1, 9.2.)

During the last couple of decades, we have witnessed the arrival of improved medications, improved surgical techniques and the use of lasers for the treatment of POAG. All of these are aimed at reducing IOP to the point that deterioration of the disc or field ceases, ideally with the minimum of complications or side-effects.

Glaucoma is not appropriately managed by simply attempting to lower IOP maximally, as all methods of pressure-lowering have possible side-effects, which (by and large) increase in severity and frequency the more one lowers the pressure.

To ascertain that deterioration has ceased requires the ability to recognise changes (e.g. perimetry, disc appearances, etc.). The documentation of change in the visual field or optic disc is the most certain criterion of control [58]. In problem cases, diurnal variations in IOP rather than simple readings may be a valuable finding. [59, 60].

1.6 Methods of Treatment Available

Over the past couple of decades, new and effective micro-surgical procedures, and laser therapy to the trabecular meshwork have been added to the time-honoured forms of medical therapy for POAG.

Glaucoma is a chronic disease; but civilised society now expects cures rather than the necessity of a lifelong burden of compliance with inconvenient, expensive and potentially hazardous medical therapies. In any event, medical treatment is probably still the most frequently used method of primary therapy, despite its many well-documented disadvantages and side-effects. Newer preparations have been developed which may limit

the latter.

Modern surgical techniques in the form of trabeculectomy, as described by Cairns [61], have been shown to control IOP successfully in over 80% of cases [62]. Primary surgical treatment could well have advantages over surgery used as a second resort after a period of medical therapy that has failed.

Following Wise & Witter's pilot study in 1979 [63], there have been numerous other reports of successful treatment of chronic POAG with argon laser trabeculoplasty [64-68]. It is a simple procedure to perform, is cost-effective and avoids the necessity for a general anaesthetic. However, there is some question as to the long-term efficacy of this form of treatment.

Chapter 2

CONCEPT OF 'CONTROL'

There still exists confusion as to what criteria constitute a satisfactory prediction of 'control' of glaucoma.

Regarding IOP, there has been no way of knowing at what level IOP is, in fact, satisfactory for each individual patient.

Six decades ago, when the indentation tonometer was still in its infancy, numerous authors provided a wide range of figures. These are listed in 'A Treatise on Glaucoma' by Elliot, published in 1922 [69]. Schiötz himself provided the figures of 15-25 mmHg as normal values. Cridland found a 'normal range' of 11.9-28.5 mmHg. McLean, using his own device, concluded that values between 22-40 mmHg were normal. Refinement of the indentation tonometer resulted in reduced normal values, with a mean of 15.5 mmHg provided by Leydhecker et al. Similar numbers have been provided by investigators using applanation tonometry. Using a non-contact tonometer, Carel & coworkers found the mean IOP in apparently healthy adults to be 13.5 $\pm$ 3.3 mmHg [70].

For many years it was believed that an IOP of 21 mmHg would guarantee control. but, as it has clearly been shown that many patients have progressive glaucomatous disease despite IOP's below 21 mmHg, this figure alone cannot be accepted as the sole criterion for control; such a pressure is not the boundary between health and disease.

The next criterion for control of glaucoma was stability of the visual field; that is, as long as the disc or field appeared unchanged, one assumed that the IOP was satisfactory. But changes in the disc and field can occur slowly. Further, as Quigley has shown, one third or more of the optic nerve axons may be lost before a defect in the visual field is detectable. [71]. In addition, both short-term and long-term fluctuations on the fields may make interpretation of deterioration difficult [58], particularly over the short term [72,73].

Automated threshold perimetry has been an important development in glaucoma management in terms of both the initial diagnosis of glaucoma and the subsequent detection of its progression. It provides detailed quantitative data, but this advantage has not, however, eliminated the traditional problem of interpretation. A variety of analytic strategies have been suggested for recognising glaucomatous or other visual field defects [74-79]. These newer methods of computerised perimetry, as well as methods of computerised disc image analysis [80, 81] and photogrammetry [82], may provide a more accurate estimate of disease 'control'.

Spaeth has suggested that the ideal definition of control of glaucoma is a lowering of ocular pressure associated with an improvement in the disc or visual field [83].

Having considered the basic principles of the natural history of POAG, the aims of treatment and the concept of 'control' of the disease, the three common methods of treatment currently available, namely medicine, surgery and laser, will now be reviewed.

Medical therapy as we know it, in the form of topical eyedrops, has been in use since the last century, with new preparations constantly being developed (seemingly all with improved pressure-lowering effects and other advantages over their rivals). The range of medications now available is vast, as is the literature on the subject.

Filtering surgery in the form of trabeculectomy was described by Cairns two decades ago, while laser trabeculoplasty is still more recent.

The literature review, given the constraints of length of this thesis, will attempt to provide a general understanding of the principles and problems of the three treatment methods, taking into account how they work, the techniques and complications. It cannot hope to be totally comprehensive because of the huge amount of published material dealing with the treatment of this disease.

Chapter 3

METHODS OF TREATMENT I : MEDICINE

The multitude of variables associated with medical therapy of glaucoma makes it a very complex subject to analyse and review. There is the need to consider, firstly, the patient himself, and the individual-related factors such as compliance, coincident systemic diseases, etc., and secondly, the drug, or combination of drugs, and the necessity in understanding the differing modes of actions, side-effects, duration of action of each preparation, etc.

The cost and inconvenience of medical therapy are clear disadvantages, and need to be compared with the other methods of therapy.

3.1 History of Medical Treatment

In olden days the medical treatment of chronic simple glaucoma was confined to the chronic and absolute phases of the disease when therapy consisted of bathing the eyes with vegetable derivatives, combined with the usual anti-inflammatory methods of depletion - purging, cupping, emesis, blood-letting and leeches.

The introduction of adequate treatment by drugs dates from the second half of the nineteenth century when almost simultaneously Adolf Weber of Darmstadt [Plate 1] advocated, in 1876, the use of extract of jaborandi (pilocarpine) [84] and Ludwig Laqueur of Strasbourg [Plate 2] in 1876 and 1877 [85, 86], that of the calabar bean (physostigmine, eserine). In later years, particularly towards the middle of the twentieth century, many cholinergic drugs and cholinesterase inhibitors have been synthesized, so that today a wide range of miotics has been introduced into the pharmacological armamentorium.

While the use of miotics remained the mainstay in the medical treatment of chronic simple glaucoma, other methods have been employed: the instillation of sympathomimetic drugs, initially by Darier [87], and strongly advocated by Hamburger in the 1920's [88, 89]; sympatholytic drugs introduced with compounds of ergot by Thiel in 1924 [90]; osmotic therapy, first by Cantonnet in 1904 [91] who administered sodium chloride by mouth and later by Hertel [92, 93] who gave intravenous injections of saline, a technique followed by the use of more effective substances such as sorbitol or urea intravenously or glycerol by mouth, and carbonic anhydrase inhibitors, initially acetazolamide by Becker in 1954 [94].

More recently, the use of beta-blockers has provided additional effective pressure lowering medications. Over 20 years ago, Phillips suggested that systemic or topical beta-blockers might have a therapeutic ocular effect [95]. The efficacy of topical propranolol was reported by Bucci et al. [96] in Italy, and Merté and Merckle in Germany [97]. This drug

was found to reduce IOP when given orally, topically or intravenously. Concerns over corneal anaesthesia following topical ·propranolol limited its general acceptance [98], as well as that of other beta-blockers, particularly practolol, another systemic beta-blocker, which caused reduced tear production. The introduction in 1976 of timolol was an important advance in the medical treatment of open-angle glaucoma [99-101].

3.2 General Considerations

A. Side Effects

The most common side-effects of medicines are neither life- nor vision-threatening : miotic-induced pain and dimming of vision, vasodilatation and the allergic tendency caused by epinephrine, potentiation of dry eyes, and effects on pulmonary function from timolol, and the acidosis syndrome induced by acetazolamide. Among the other multiple side-effects, more serious complications include aplastic anaemia after the use of carbonic anhydrase inhibitors, and retinal detachment associated with miotic therapy. However, many patients are able to tolerate one or more of these medications without side-effects.

B. Compliance

Another major problem cited with medical therapy is poor compliance which can lead to insidious visual loss. There is no doubt that the simple failure of patients to take effective medications is the most limiting factor in successful non-surgical therapy. A recent study by Granström [12] suggested that progressive glaucomatous visual field loss was no more common in patients whose compliance with pilocarpine therapy was poor, than in those whose compliance was good, and considered that non-compliance was less important for the outcome than were the type of glaucoma, the stage of the visual field defects and the mean IOP. However, compliance may well be very important, since progression occurred in six of the ten least-compliant patients in the study, but in none of the four most compliant patients.

Kass et al. [102], using an unobstrusive electronic eyedrop medication monitor to record pilocarpine compliance, showed a reduced rate of compliance compared with that claimed by the patient. Almost one quarter had at least one day per month with no administrations of pilocarpine.

Factors that influence compliance include: (1) the doctor-patient rapport, (2) the patient's understanding of the disease and/or its treatment, (3) the complexity of the medical regime (i.e. the number of medications and/or the frequency of their administration), and (4) the side-effects of the medications [103]. Considering these factors, the development of medications that are effective taken once or twice daily, as well as the introduction of medications and techniques that improve

the therapeutic index, are important.

C. Tachyphyllaxis

There are few long-term clinical studies that provide information about the relative contributions of decrease in the effect of medicine compared with the worsening course of the disease itself. It is sometimes proposed that medical treatment frequently leads to drug tolerance or immunity, but this diminished control of IOP may be due to a worsening of the disease.

D. Long-term Adverse Effects on the Meshwork

Watson & Grierson [62] put forward the hypothesis (with experimental support) that chronic medical therapy could lead to a detrimental effect on the trabecular meshwork. Using electron microscopy, detrimental ultrastructural damage to the whole trabeculum has also been demonstrated following experimental trabeculectomy in primate eyes [104].

3.3 Medical Control of Glaucoma

Control in terms of medical therapy often refers to multidrug therapy : if one drug is insufficient, then the concentration is increased, or other drugs added. Thus the patient may be subjected to borderline control for some time, increased numbers of clinic visits may be necessary, and the potential for side-effects may be increased.

A review of the literature of reports detailing the medical control of glaucoma is complicated by the fact that few long-term reports deal with medical treatment alone and that single or multi-drug therapy varies from individual to individual and from series to series, thus making comparisons impossible.

This chapter will therefore deal with the topical and systemic antiglaucoma drugs which will be analysed in terms of the method of action, administration, interaction with other drugs and the possible side effects, thus enabling an understanding of the complexities of treatment and a comparison to be made with the other two treatment modalities of surgery and laser.

The drugs used in this trial included pilocarpine, neutral adrenaline, guanethidine/adrenaline combinations (ganda), timolol maleate and acetazolamide. These will be considered in detail, but, for the sake of completeness, other commonly available preparations will be mentioned.

The topical antiglaucoma drugs act on the autonomic nervous system and include cholinergic stimulators and adrenergic stimulators and inhibitors. Systemic antiglaucoma agents include carbonic anhydrase inhibitors and hyperosmotics (Table I).

TABLE I

CLASSIFICATION OF ANTI-GLAUCOMA DRUGS

A. TOPICAL

a. Cholinergic system

1. Parasympathomimetics

i. Direct Parasympathomimetics
Pilocarpine

ii. Indirect Parasympathomimetics
Phospholine Iodide

b. Adrenergic system

1. Adrenergic stimulators
Adrenalin
Dipivefrin

2. Adrenergic antagonist
Guanethidine

3. Adrenergic inhibitors
Beta-blockers:
Timolol
Betaxolol
Carteolol

B. SYSTEMIC

1. Carbonic anhydrase inhibitors
Acetazolamide

2. Hyperosmotic agents
Mannitol
Glycerol

A. Topical Treatment

1. Cholinergic System

a. Parasympathomimetics (Miotics)

Over a century ago, several forms of glaucoma were recognised, but treatment was limited to surgery and was risky, painful and often ineffective.

As cited earlier, in 1876 Ludwig Laqueur reported on the successful use of "aqueous solutions of neutral sulphate of physostigmine" for the treatment of glaucoma in 5 patients [85].

This milestone, coupled with the introduction of topical pilocarpine one year later [105], heralded the concept of safe and effective medical treatment of the glaucomas for the next 100 years, with pilocarpine remaining for a long time the drug of reference.

i. Direct Parasympathomimetics

Pilocarpine

This direct-acting parasympathomimetic is the most frequently used of the miotics.

ii. Indirect Parasympathomimetics

Phospholine iodide (echothiophate)

This is the most commonly used anti-cholinesterase, but may cause intense miosis or cataract [106]. It should therefore only be used in aphakic eyes. The anti-cholinesterases tend to be more powerful and longer-acting than pilocarpine.

2. Adrenergic System

a. Adrenergic Stimulators

Adrenalin (epinephrine)

First used to treat glaucoma in 1903, this direct-acting sympathomimetic stimulates both α and β receptors, lowering IOP by means of a complex mechanism that primarily involves improved aqueous outflow.

Other Forms of Adrenalin Therapy

Diprivefrin (Propine)

Dipivalyl adrenalin is a modification of adrenalin in which two pivalic acid groups are added to the basic drug [107].

b. Adrenergic Antagonist

Guanethidine

This adrenergic antagonist causes an adrenergic supersensitivity by depleting stores of catecholamines [108]. It may lower the IOP when given alone, but is particularly effective when used in combination with adrenalin (gutt. Ganda).

c. Adrenergic Inhibitors

β-Adrenergic Blockers

These drugs lower the IOP by reducing aqueous production. They differ from one another primarily with regard to pressure-lowering efficacy and relative ocular and systemic side effects. Timolol, a β_1 and β_2 adrenergic antagonist, has a marked ocular hypotensive action with few ocular side-effects, although it may cause serious systemic reactions, especially on the cardiovascular (β_1) and pulmonary (β_2) systems. Betaxolol, a cardioselective β_1 blocker, lowers IOP and has the advantage of a reduced potential for pulmonary side effects. Other β blockers are also being evaluated for the treatment of glaucoma.

B. Systemic Treatment

1. Carbonic Anhydrase Inhibitors

The use of oral carbonic anhydrase inhibitors in the 1950's to lower IOP by reducing aqueous formation in the ciliary body [109] was another important development in glaucoma medication. These drugs are presently limited to systemic administration, although research is currently being conducted into effective topical forms. Systemic side effects are numerous. Drugs in this class include acetazolamide and dichlorphenamide.

2. Hyperosmotic Agents

These include mannitol and glycerol, but are not used for self-administration by patients.

MODE OF ACTION

1. Pilocarpine

a. Increased facility of outflow is the chief method of pressure reduction by pilocarpine. Stimulation of the ciliary muscle causes displacement of the scleral spur which leads to an increased facility of outflow of aqueous (presumably by altering the format of the trabecular meshwork, Schlemm's canal or both) [110]. Grierson et al. [111, 112] demonstrated a posterior, internal pull on the scleral spur, with widening of the trabecular spaces, distension of the endothelial meshwork, an increase in the number of giant vacuoles, a larger pores in the inner endothelium of Schlemm's canal. Primate studies suggest that the greater number of giant vacuoles is a result of increased aqueous flow through the outflow system.

b. Miosis, due to direct stimulation of the iris sphincter, does not appear to be related to the improvement of aqueous outflow facility in open-angle glaucoma [113].

c. Decreased aqueous formation. Whether this is significant in the pressure lowering effect of pilocarpine is controversial. Pilocarpine 0.1% was found to reduce aqueous formation in monkey eyes [114], while the increase in outflow facility was exceeded in normal human volunteers [115]. Bárány [116] suggested that prolonged treatment with miotics like pilocarpine may cause subsensitivity of the ciliary muscle, shifting emphasis to miotic inhibition of aqueous secretion by unknown mechanisms.

2. Phospholine Iodide

Acts by improving the facility of outflow of aqueous, as for pilocarpine.

3. Adrenalin

Theories of the mode of action of adrenalin have changed in recent years. Early observers suggested that the primary action was decreased aqueous production [117, 118]. An improved aqueous outflow facility was subsequently noted after prolonged use of adrenalin [119]. More recent studies have shown that increased outflow is an early and predominant feature [466].

Sears & Neufeld [120-122] have proposed a three-phase concept for the action of adrenalin on aqueous humour dynamics.

Phase I : Decreased aqueous production.

Due to the α-adrenergic vasoconstriction which reduces plasma ultrafiltration. This effect is transient.

Phase II : Early Increase in Outflow Facility

This phase overlaps with Phase I and is due to both an α-adrenergic and β-adrenergic response.

Phase III : Late Increase in Outflow Facility

Occurs weeks to months after the continued administration of adrenalin. The mechanism is uncertain.

4. Propine (dipivefrin)

The corneal penetration of this modified adrenalin preparation is greatly increased due to it being more lipophilic, and being a pro-drug, it undergoes a biotransformation to adrenalin after it enters the eye [123]. Clinical trials indicate that the pressure lowering effect of 0.1% dipivefrin is between that of 1% and 2% adrenalin [124-125].

4. Guanethidine

Clinical trials with the combined preparation of guanethidine/adrenalin have shown significant sustained IOP reduction [126-129]. The IOP lowering effect is reportedly equal to or better than adrenalin alone [130, 131], pilocarpine [131] or timolol [132].

5. Timolol

Timolol lowers IOP primarily by reducing aqueous humour production [133, 134], although a slight improvement in outflow facility has been suggested.

This drug acts directly on the ciliary processes, either on the non-pigmented epithelium causing decreased secretion, or on local capillary perfusion resulting in reduced ultrafiltration [135, 136]. Beta adrenergic receptors have been identified in the ciliary processes.

This non-selective beta-blocker has become the most commonly prescribed medication for glaucoma. It was found to have none of the adverse reactions described above for some of the other beta-blockers [99]. IOP was effectively lowered in normotensives [99], as well as patients with open-angle glaucoma [137, 138].

Comparative studies showed the pressure-lowering effect of timolol to be greater than that of adrenalin [139] (and as effective as adrenalin in the long term [140]), and equal to or slightly weaker than various concentrations of combined guanethidine/adrenalin [141]. Compared to pilocarpine, timolol had an equivalent or slightly greater pressure-lowering effect [142, 143].

As it lowers IOP by reducing aqueous production and does not alter the pupil or affect accommodation, timolol is useful in clinical situations when conventional aqueous outflow cannot be improved medically and in which miosis or mydriatics are to be avoided.

6. Other Topical Beta-blockers

Other newer topical beta-blockers effectively lower IOP in patients with chronic open-angle glaucoma [144, 145].

Betaxolol

Betaxolol hydrochloride is a cardioselective β_1 adrenergic antagonist. In early clinical trials, it resulted in a significant reduction in IOP when evaluated alone [146], or compared with a placebo [147, 148]. When compared with timolol, there was no statistically significant difference in the ocular hypotensive effect of the two drugs, although the lower IOP's provided by timolol may be clinically significant [149]. The advantage of betaxolol is the absence of β_2 adrenergic inhibition, thereby minimising the risks of respiratory side-effects. The drug causes no decrease in airflow in patients with proven airways disease [150].

Metipranolol

Metipranolol 0.3% has been compared to timolol 0.25% and the two drugs were found to be equal with respect to extent and duration of IOP reduction [151].

Carteolol

Carteolol has also been evaluated as a topical antiglaucoma agent with satisfactory preliminary results [152].

7. Acetazolamide

Carbonic anhydrase is an enzyme that is responsible for the catalytic hydration and dehydration of carbon dioxide:

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons HCO_3^- + H^+$$

Carbonic anhydrase inhibitors belong to the sulphonamide class of compounds and lower IOP by reducing aqueous production, probably through an alteration in ion transport associated with secretion of aqueous humour. Fluorophotometric studies suggest that acetazolamide decreases flow in the human eye by 27% [153].

ADMINISTRATION

1. Pilocarpine

Topical pilocarpine enters the eye mainly through the cornea [154]. Only a small percentage enters the anterior chamber, as the drug is largely complexed or degraded in the cornea [155-157]. To achieve the greatest

efficiency of ocular penetration, it is important to select the optimum drug concentration, frequency of administration and system of delivery.

The pressure lowering effect of pilocarpine is dose-related up to a concentration of 4% [158-159]. Higher concentrations may cause additional pressure reduction in darkly pigmented irides [160].

The frequency of administration is important in animals, the maximum concentration of pilocarpine in the aqueous and iris were reached in approximately 20 minutes [160], and had disappeared by 4 hours [156]. In ocular hypertensive humans, the maximal effect on IOP occurred within 2 hours and lasted for 8 hours, resulting in an IOP reduction of approximately 20% [161]. By the ninth hour, the pressure response began to decline, but a $\pm$ 15% reduction was still present 12-15 hours after installation [159].

To ensure adequate IOP control, standard pilocarpine drops are usually given four times daily. Newer drug delivery systems are attempting to improve efficiency.

An efficient delivery system in all the medical therapies aims to achieve the desired pharmacologic effect with the least amount of the drug. The volume of pilocarpine delivered by commercial droppers is significantly in excess of that needed to produce the desired response [162-163], resulting in an initial overdosing with associated side-effects, followed by an underdosing before the next installation. Vehicles for drug delivery have been developed which prolong the therapeutic effect, thereby needing less frequent installations with fewer associated side-effects [164].

Such delivery systems include soluble polymers (such as methylcellulose and polyvinyl alcohol) used in commercial preparations [165]; pilocarpine gel (pilocarpine 4%) in a high-viscosity acrylic vehicle) which is instilled once daily [166-168]; piloplex (aqueous emulsion of pilocarpine bound to a polymer vehicle) which is more effective in twice daily administration than four times daily standard pilocarpine [169-170]; ocuserts (pilocarpine between two polymeric membranes) provide a constant drug release comparable to 1-2% pilocarpine (ocusert P-20) and 4% pilocarpine (ocusert P-40) [171]; and soft contact lenses [172].

A one year multicentre study of once-daily pilocarpine gel concluded that there was no statistically significant difference in afternoon IOP control in 77 patients between pilocarpine gel and retrospective data on pilocarpine drops. However, 20% of patients who used the gel for more than 8 weeks developed a diffuse superficial corneal haze [168]. A single-dose study of piloplex demonstrated an IOP decrease of at least 14 hours' duration, which suggests its potential as a twice-daily therapy [169].

2. Phospholine Iodide

Usually given in strengths of 0.03 to 0.06% [467], but higher concentrations of 0.125% or 0.25% may have additional pressure-lowering effect in dark irides.

There is a long duration of action with the maximal effect in 4-6 hours, and substantial residual action present after 24 hours [468], allowing it to be used twice daily.

3. Adrenalin

Commonly used in a concentration of 1%. The pressure-lowering effect of adrenalin is proportional to the concentration of free base (active form of the drug) within the range 0.25% to 1% [120].

Twice-daily installation provides a continuous pressure-lowering effect in most cases.

4. Timolol

Timolol maleate is commercially available in 0.25% and 0.5% concentrations. Early experience indicated that the maximal pressure-lowering effect in open-angle glaucoma patients was achieved with 0.5% timolol [99]. A study by Mills, however, found the 0.25% concentration equally or more efficacious than the 0.5% [469].

Peak aqueous humour concentrations occur within the first 1-2 hours, as there is good corneal penetration of timolol [173]. The pressure-lowering effect peaks at approximately 2 hours after installation, and lasts for at least 24 hours [138]. The optimum frequency of administration in most cases is twice daily, although once daily treatment has been shown to be adequate in many cases [174], especially since timolol does not reduce the rate of aqueous flow during sleep.

Several long-term studies have confirmed the continued efficacy of long-term timolol therapy for many patients [175-181]. In a significant number of cases, however, the pressure responsiveness to timolol will decrease with continued administration. This occurs in two phases termed by Boger the "short-term escape" and the "long-term drift" [182, 183].

Short-term escape: Timolol may initially cause a dramatic reduction in IOP. However, in some patients, the effect partially wanes during the ensuing days of continuous therapy to plateau finally at a maintenance level [142, 182, 183].

Long-term drift: Although timolol continues to be effective after many months of therapy, a tendency for a slow rise of IOP has been noted in some patients, usually beginning 3 months to a year after starting treatment [175-181]. In a study by Sponsel et al., most cases whose IOP

control over a 3-year period was felt to be adequate, maintained stable visual fields, although progressive loss still occurred in some cases [184].

5. Acetazolamide

The commercially available carbonic anhydrase inhibitors are effective when given orally, intramuscularly or intravenously. The poor topical response to acetazolamide [185] may be due to limited ocular penetration. New carbonic anhydrase inhibitors which have enhanced corneal penetration have lowered IOP in experimental animals [186].

The dose-response curve for carbonic anhydrase inhibitors is very restricted, in that aqueous production is not significantly reduced until more than 90% of the carbonic anhydrase is inhibited. It is therefore important to use the drugs in adequate dosages [187].

The usual oral dosage for long-term medical therapy with acetazolamide is 250 mg every 6 hours, or 500 mg sustained release capsule twice daily. In tablet form, the ocular hypertensive effect peaks in 2 hours and lasts up to 6 hours, while that of the capsule peaks in 8 hours and persists beyond 12 hours. In emergency situations, the drug may be given intravenously.

DRUG COMBINATIONS

Possible drug interaction, when used in combination, is important.

1. Pilocarpine

a. Other miotics used in combination with pilocarpine not only fail to increase the pressure-lowering effect, but may also interfere with the action of pilocarpine.

b. Other antiglaucoma drops: Adrenalin [188, 189] and timolol [190] both have an additive pressure reduction effect when used with pilocarpine. The combination of pilocarpine and carbonic anhydrase inhibitors is also effective.

2. Adrenalin

a. Miotics and carbonic anhydrase inhibitors: Combination therapy with adrenalin and a miotic (as above) or carbonic anhydrase inhibitor usually results in an IOP reduction significantly greater than either drug given alone.

b. β-blockers: As adrenalin stimulates and timolol inhibits β-adrenergic receptors, the action of one drug may interfere with that of the other to a degree, although some additive effect on IOP may

be achieved with simultaneous use of the two drugs [191-192]. Timolol given to eyes pre-treated with adrenalin showed a significant additional pressure reduction for the first few weeks, after which the pressure-lowering effect of the combined regimen was only slightly greater than with timolol alone [193-195]. In the reverse sequence (adrenalin added to eyes receiving timolol), the additional reduction in IOP was small or absent.

3. Timolol: Long-term multidrug studies have shown that timolol will cause additional lowering of IOP in many cases when added to maximum tolerable antiglaucoma treatment [196, 197]. The combined effect of timolol and a miotic [198-200] or carbonic anhydrase inhibitor [198, 200, 201] is usually greater than the effect of either medication alone. The combination of timolol and adrenalin has less clinical value as reviewed earlier.

SIDE-EFFECTS

One of the major problems of medical therapy for glaucoma, is the possible adverse effects of the drugs. These may be systemic or ocular, and may contribute to poor compliance.

1. Pilocarpine

a. Systemic effects: Pilocarpine can produce systemic effects similar to those of muscarine, including perspiration, stimulation of glands such as salivary, lacrimal, intestinal and pulmonary mucosa, and contraction of smooth muscle. Systemic toxicity is rare with the usual therapeutic doses of pilocarpine for open-angle glaucoma.

b. Ocular side-effects are common with pilocarpine and can lead to poor compliance with therapy [202].

   i. Ciliary muscle spasm may cause browache which usually subsides with continued therapy. Induced myopia, due to shallowing of the anterior chamber with axial thickening and forward shift of the lens is more marked in younger patients [203-204].

   ii. Miosis may cause dimness of vision and alteration in the visual fields, particularly if cataracts are present [205, 206].

   iii. Retinal detachment from miotics has been suspected on circumstantial evidence, but a definite relationship has not been proven [207].

   iv Cataractogenic effect has been suggested from observing patients on long-term uniocular miotic therapy [208].

   v Corneal endothelial toxicity was dose-related in in-vitro

rabbit studies [209].

2. Phospholine Iodide

a. Systemic toxicity is related to cholinesterase depletion due to the pseudocholinesterase hydrolising succinylcholine. This can result in prolonged respiratory paralysis during general anaesthesia if succinylcholine is used in a patient depleted of cholinesterase.

Topical phospholine iodide may rarely cause diarrhoea, nausea, abdominal cramps and malaise.

b. A cataractogenic effect, which appears to be dose-related, has been found with the use of phospholine iodide in the management of chronic glaucoma [210, 211]. The drug is therefore reserved primarily for aphakic eyes.

c. Other ocular side-effects include cysts, retinal detachment and corneal epithelial toxicity.

All miotics have side-effects (Table II). As the glaucoma is often asymptomatic, the cure may feel worse than the disease. The side-effects tend to be more severe in younger patients and in myopic patients. They may work well in older patients, but can cause visual problems in those patients with cataracts [212].

3. Adrenalin

a. Systemic side-effects include elevated blood pressure, tachycardia, arrhythmias, headaches, tremor, nervousness and anxiety. Systemic absorption is 55-65% of the topically applied dose of both adrenalin and dipivalyl adrenalin [213].

b. Ocular: The extraocular side-effects are the most common and include burning, reactive conjunctival hyperaemia and adrenochrome pigmentation. Less commonly, tearing, photophobia, blurred vision and epidermalisation of the lacrimal puncta.

Cystoid macular oedema may occur in aphakic eyes on topical adrenalin [214, 215]. This is usually reversible and dose-related. Other side-effects include mydriasis, corneal endothelial changes [216] and ocular hypoxia [217].

4. Dipivefrin (propine)

Advantages over standard adrenalin include less burning and irritation and less systemic toxicity. Dipivefrin may be the most appropriate therapy for patients with obstructive airways disease, because its

systemic effects include bronchodilatation, and because it has fewer cardiovascular risks than its parent compound. However, it must be used with caution in such patients as propine contains sodium metabisulphite preservative to which an estimated 3-10% of the general asthmatic population is sensitive [218].

5. Guanethidine

Guanethidine may cause irritation, conjunctival hyperaemia, corneal epithelial changes, lid oedema and ptosis [219].

6. Timolol

Although the incidence of ocular and systemic side-effects is rare with timolol, these do occur.

a. Ocular toxicity is uncommon, although allergic and toxic reactions have been reported. Burning and conjunctival hyperaemia may occasionally occur and may be associated with superficial punctate keratopathy and corneal anaesthesia [220-222]. Tear production may be reduced in some cases [223]. Reduced central visual acuity (which may be associated with the discontinuation of miotic therapy) has been recorded in some patients [220-221].

b. Systemic toxicity is more frequently reported and is more significant [220, 221, 224, 225]. Measurable plasma levels of timolol are present within 8 minutes or less of topical administration.

   i. Cardiovascular: β_1 adrenergic blockade may cause bradycardia, arrhythmias, heart failure and syncope [220, 221, 224]. These effects usually do not cause problems in healthy patients, but may cause serious complications in patients with pre-existing heart problems, such as sinus bradycardia, greater than first degree heart block and congestive cardiac failure. In addition, even healthy individuals may be at risk under certain circumstances such as the stress of surgery [226] or strenuous exercise [227].

   ii. Respiratory: β_2 adrenergic blockade produces contraction of bronchial smooth muscle which may cause bronchospasm and airways obstruction, especially in asthmatics [220, 221, 224, 228, 229], and can lead to death in status asthmaticus [230].

   iii. Central Nervous System effects include depression, anxiety, confusion, dysarthria, hallucinations, light-headedness, drowsiness, weakness, fatigue and disorientation [220, 221, 224].

iv. Other systemic reactions include gastrointestinal disorders, dermatological disorders, sexual impotence and exacerbation of myaesthenia gravis.

7. Acetazolamide

Side-effects are common with carbonic anhydrase inhibitors, and may require discontinuation of the drug.

a. Paraesthesia of the fingers, toes and around the mouth, as well as urinary frequency from the diuretic action, are experienced by nearly all patients initially. However, these effects are usually transient.

b. Serum electolyte imbalances may cause more debilitating problems. These include metabolic acidosis and potassium depletion [230, 231]. A common symptom complex of malaise, fatigue, weight loss, anorexia, depression and decreased libido was correlated with the degree of metabolic acidosis [230].

c. Gastrointestinal symptoms are also very common and include vague abdominal discomfort, metallic taste, nausea and diarrhoea.

d. Renal calculi formation has been shown to be increased in patients receiving acetazolamide [232].

e. Blood dyscrasias are rare, but thrombocytopenia, agranulocytosis, aplastic anaemia and neutropenia have been reported [233].

f. Other adverse reactions include dermatitis, acute myopia, elevated uric acid and hirsutism.

C. Maximal Medical Treatment

The choice of drug or combination of drugs depends on the individual patient. Because young or myopic patients generally find the effects of miotics unacceptable, their choice is limited to the beta-blockers, adrenalin or carbonic anhydrase inhibitors.

Miotics are generally unsatisfactory for patients with cataracts.

In practice, the maximum possible medical therapy is usually restricted to maximum tolerated medical therapy, using the most effective drug or drugs with the least side effects, at the lowest concentration and as infrequently as possible.

Watson & Grierson [62] suggest that 'maximal medical therapy' is an outmoded concept.

TABLE II

ADVERSE EFFECTS OF EYEDROPS

1. Pilocarpine

Systemic effects	muscarinic effects (rare)
Ocular effects	ciliary muscle spasm miosis (retinal detachment) (cataract) (corneal endothelial toxicity)

2. Phospoline iodide

Systemic effects	cholinesterase depletion
Ocular effects	cataracts iris cysts retinal detachment corneal epithelial toxicity

3. Adrenalin

Systemic effects	BP tachycardia, arrhythmias, headache, tremor, nervousness, anxiety.
Ocular effects	burning, conjunctival hyperaemia, adrenochrome pigmentation (tearing, photophobia, blurred VA), cystoid macular oedema (aphakes), mydriasis, corneal endothelial changes, ocular hypoxia

4. Guanethidine

Ocular effects	irritation, conjunctival hyperaemia, corneal epithelial changes, lid oedema, ptosis.

5. Timolol

Systemic effects	Cardiovascular: bradycardia, arrhythmias, heart failure, syncope. Respiratory: bronchospasm and airways obstruction. CNS, gastrointestinal, dermatological, etc.

Ocular effects	uncommon (burning and conjunctival hyperaemia) (reduced tear production)

6. Carbonic Anhydrase Inhibitors

Systemic effects	paraesthesia serum electrolyte imbalance --> malaise, fatigue, weight loss, anorexia, depression, decreased libido gastrointestinal symptoms renal calculi blood dyscrasias

Chapter 4

METHODS OF TREATMENT II : SURGERY

The conventional operation most frequently used for open-angle glaucoma in adults is commonly referred to as a filtering procedure. Although a number of variations of this procedure have been described, all filtering operations share the same basic mechanism of action and general surgical principles.

4.1 History of Glaucoma Surgery

Filtering operations for glaucoma date back to the early nineteenth century.

William Mackenzie, in 1830, was the first surgeon to suggest draining fluid from the eye to relieve the tension. He performed a sclerotomy into the vitreous cavity, but this fistula was not permanent and did not improve the condition [234].

Albrecht von Graefe [235] found that an iridectomy helped in the treatment of some patients with glaucoma, especially acute glaucoma. George Critchet [236] from the London Hospital and Moorfields Eye Hospital further developed this idea and in 1857 created the technique of iris inclusion in his operation of iridodesis which allowed for "adjustment of normal tension, and perhaps the establishment of a communication between the anterior and posterior chambers". In the successful cases, it was probably producing a permanent drainage fistula.

De Wecker in 1869 [237, 238] described an anterior sclerotomy in the chamber angle area with an overlying conjunctival bridge flap as a means of producing a filtering cicatrix through which the intraocular fluid might leave the eye.

Argyll Robertson [239] introduced the sclerectomy using a posterior trephining procedure. The concept of fistula formation was expanded by Herbert [240] who performed a small flap sclerotomy combined with iris inclusion, and subsequently by Holth [241] who developed the technique of iris inclusion in his operation of iridencleisis.

Lagrange [242-244] in 1906 included the ideas of Argyll Robertson in a more anterior sclerecto-iridectomy. Fergus [245] performed Argyll Robertson's sclerectomy with a trephine in a more anterior position and combined it with cyclodialysis. A similar operation was performed by Elliot [Plate 3] [246] who was credited with the corneo-scleral trephining procedure.

Preziosi [247] in 1924 introduced a different method of producing a filtering bleb by using cautery to create a sclerotomy. This procedure was developed and improved by Scheie [248].

The most recent improvement was made in the trabeculectomy of Cairns [Plate 4] and Watson [61, 249] who described a partial thickness scleral flap which reduced the problems of overdrainage and protected the sclerectomy.

This chapter firstly considers the mechanisms of action of surgical filtering procedures, followed by a brief outline of the earlier types of fistulae and a more detailed discussion of the trabeculectomy procedure.

4.2 Mode of Action

A. Drainage Fistula

The basic mechanism of all filtering procedures is the formation of a fistula at the limbus, allowing aqueous to drain from the anterior chamber thereby bypassing the pathologic obstruction to outflow. The aqueous flows directly or indirectly into the sub-conjunctival space and is then removed by one or more routes.

B. Drainage bleb

Almost all successful glaucoma filtering procedures are characterised by an elevation of the conjunctiva at the filtering site, referred to as a drainage bleb. The clinical appearance of these blebs varies considerably with regard to diameter, elevation and vascularity. The blebs most frequently associated with good IOP control are avascular and either flat and diffuse [Plate 11], or elevated and cystic [Plate 12] [250, 251].

Histologically, both functioning and failed filtering blebs consist of normal epithelium with no encircling-type junctions between the cells that might limit fluid flow. Functioning blebs tend to have loosely arranged subepithelial connective tissue with histologically clear spaces, while the failed blebs have dense collagenous connective tissue [251]. An early light microscopic study suggested the presence of degenerate, hydrated collagen in successful blebs [252], although subsequent ultrastructural study found no evidence of degenerate or other forms of abnormal collagen [251].

C. Routes of Aqueous Drainage

Aqueous in the drainage bleb usually filters through the conjunctiva [253] and mixes with the tear film [254, 255], or is absorbed by vascular [253] or perivascular [252] conjunctival tissue.

Less commonly, a filtering procedure may be associated with IOP control in the absence of an apparent filtering bleb, especially when the fistula is covered by a partial thickness scleral flap. Suggested routes of

aqueous drainage in these cases include flow through lymphatic vessels, atypical newly incorporated aqueous veins or normal aqueous veins [252, 253].

D. Bleb Failure

Scarring of the drainage bleb is the most common cause of failure in glaucoma filtering surgery [256]. The increased amounts of collagen in failed blebs suggests that proliferation of fibroblasts with the associated production of collagen and glycosaminoglycans is an important response to filtering surgery [251].

Aqueous humour usually slows or fails to support the growth of conjunctival fibroblasts in tissue culture [257, 258]. This is either due to the possibility that aqueous may contain an inhibitory factor for fibroblast proliferation, or more likely, because aqueous lacks the nutrients to support the growth of fibroblasts, since aqueous obtained shortly after intraocular surgery does promote fibroblastic proliferation. It may be the alteration in aqueous content that leads to bleb failures in some cases [257, 258].

E. Inhibition of Fibroblast Proliferation

In order to reduce bleb failures, agents are being evaluated which inhibit the proliferation of fibroblasts. The anti-metabolic 5-fluorouracil has been extensively studied. The subconjunctival injection of this agent after filtering surgery has been associated with significantly more bleb formation in monkeys [259] and an improved rate of success in difficult clinical cases [260]. Common side-effects, however, include corneal epithelial defects and conjunctival wound leaks [259, 260].

4.3 Fistulising Techniques

The two basic types of fistulae either extend through the full thickness of the limbal tissue, or are covered by a partial thickness scleral flap.

A. Full-thickness Fistulae

This involves the creation of a direct opening through the full thickness of the limbal tissue. A variety of techniques have been used:

1. Sclerectomy

In 1906, Le Grange [243] described the technique of making a full-thickness incision and then excising a piece of tissue from the anterior lip of the wound to create a limbal fistula. Holth [261] modified this procedure 3 years later by performing the sclerectomy with a punch. A

variety of sclerectomy punches have since been developed [262-264]. The sclerectomy technique most often discussed in recent literature is the posterior lip sclerectomy of Iliff & Haas [265].

2. Trephination

In 1909, Elliot [246] and Fergus [245] both described a glaucoma filtering procedure in which the fistula is created with a small trephine placed just behind the corneo-limbal junction. Sugar advocated more posterior placement of the trephine which he called limboscleral trephination [266, 267].

3. Thermal sclerostomy

In 1924, Preziosi [247] described a filtering technique in which a limbal fistula was created by entering the anterior chamber angle with an electro-cautering instrument.

Scheie, in 1958 [248], described an operation which also used cautery, but differed from Preziosi's procedure in that a limbal scratch incision was first made, and the cautery was then used to retract the wound edges, thereby creating the fistula. Various modifications have since been described [268, 269].

Other forms of full-thickness filtering surgery have also been described, such as iridencleisis [270] and laser sclerostomies [271, 272].

B. Partial-thickness Fistulae

Full-thickness filtering procedures may be complicated by excessive aqueous drainage, which can lead to a prolonged flat anterior chamber, associated with corneal decompensation, synechiae formation and cataracts. Moreover, the drainage bleb itself may become thinned and may leak, creating the danger of endophthalmitis. To alleviate these problems, an operation was designed to place a partial thickness scleral flap over the fistula.

The first report of glaucoma surgery using a scleral lamellar flap to control filtration was by Sugar in 1961 [273]. He termed his procedure 'experimental trabeculectomy'. He carefully sutured the scleral flap to prevent excessive filtration, but the results were poor. In 1967, Koryllos [274] described an operative procedure for glaucoma in which he dissected out the trabeculum. This too did not achieve very promising results. Other descriptions include those of Phillips [275] and Linner [276]. Cairns, in 1968, subsequently reported good results with trabeculectomy [61], and his basic operation, with various modifications, is at present the most popular surgical procedure for adult glaucoma. Cairns' operation involves the dissection of an opening into the anterior chamber under a scleral flap. the opening extends from the limbus to the scleral spur, but does not go behind the scleral spur. At this level of

dissection, the tissue that is removed constitutes cornea, trabeculum and sclera.

Theories of the mode of action

Initially it was thought that aqueous might drain into the cut ends of Schlemm's canal [61]. Subsequent studies, however, showed fibrosis and closure of the cut ends of the canal in monkeys [277] and humans [278]. In addition, the presence of Schlemm's canal in the trabeculectomy wedge did not correlate with the outcome of the procedure [279-281]. Most successful cases have a filtering bleb [282], indicating that external filtration is the principal mode of IOP reduction.

Controversy still exists whether the route of external filtration is chiefly through or around the partial thickness scleral flap. The outer layers of limbus and sclera do not differ ultrastructurally from the inner layers in that they might facilitate the increased passage of aqueous [283]. However, a significant flow through the scleral flap was suggested in perfusion studies of human autopsy eyes in which a trabeculectomy was fashioned, and the margins of the scleral flap sealed with adhesive [284]. Fluorescein studies in eyes with successful trabeculectomies, on the other hand, showed the primary route of external filtration to be around the margins of the scleral flap [285]. External filtration may therefore occur by either route, depending on how tightly the scleral flap is sutured. Other possible mechanisms of IOP reduction by trabeculectomy include cyclodialysis [277] or drainage of aqueous via newly developed aqueous veins, lymphatics or pre-existing aqueous veins [286, 287].

Original trabeculectomy technique and its modification

Cairns' original method [61, 282] was to incise a 5 x 5 mm half-thickness scleral lamellar flap, fornix- or limbal-based, followed by the resection of a 1 x 4 mm block of tissue to include the trabecular meshwork. An iridectomy and approximation of the scleral flaps and conjunctiva followed. This technique has been modified in many ways.

Modifications include triangular [288] or semi-circular [289] flaps, variation in the flap thickness [290], the application of cautery to the lateral margins of the flap [285], omitting all sutures from the scleral flap or excising the distal 2 mm of the flap [291]. Limbal- and fornix-based conjunctival flaps have been used [292].

Watson [293, 294] modified Cairns' basic technique by starting the dissection of the deep tissue block posteriorly over the ciliary body, separating it from the underlying structure and excising it at Schwalbe's line.

Other techniques used to form the deep scleral fistula include trephination [289], posterior lip sclerectomy [295], thermal sclerostomy

[296] and sclerostomy using a carbon dioxide laser [297]. "Non-penetrating trabeculectomy" carried the dissection of the deep limbal tissue down to the Schlemm's canal, but leaves the trabecular meshwork intact [298]. The technique has been modified by perforating the meshwork postoperatively at the surgical site using the Nd:YAG laser [299].

C. Other Filtering Procedures

Based on the concept that the major obstruction to outflow was at the inner wall of Schlemm's canal, the canal itself was divided in the operation of trabeculotomy [300]. This procedure is no longer commonly used in adults.
See also Appendix 14.

4.4 Complications of Filtering Surgery

Unfortunately, surgery once had a very bad reputation because of the high complication rates both at the time of operation and later. It was so bad that Scheie [301], in his Snell Memorial Lecture in 1962, was forced to conclude that 'All filtering procedures ... are associated with such hazards that ophthalmic surgeons, quite properly, should advise surgery when convinced that no alternative exists." Moreover, in the first widely published paper by Cairns on trabeculectomy [61] which gave the results of 17 patients thus treated, all of whom had controlled IOP, it is surprising, for an initial report of an operation that later became so popular, how many complications the 17 cases had. There was one intraocular infection, one iris prolapse (no peripheral iridectomy had been performed), three flat anterior chambers, and nearly all had a small hyphaema. However, very few had uveitis, nor was there lasting hypotony of less than 10 mmHg, nor choroidal detachments.

With the introduction of the operating microscope, improved surgical instruments and materials and a better understanding of the underlying mechanisms of glaucoma, it has become possible to operate directly on the angle structures without damaging the surrounding tissues and, most importantly, leaving the eye anatomically almost intact, thus improving the results.

Nevertheless, complications do occur, although some operations and techniques appear to provide certain advantages over others.

The complications will first be considered in general, and then the merits of the various filtering procedures compared.

COMPLICATIONS

A. Intraoperative Complications

1. Hyphaema

These are not uncommon. Bleeding may occur from the ciliary body, iris or choroid. An expulsive haemorrhage is a particularly devastating complication that usually results from sudden decompression of the eye with rupture of a large choroidal vessel.

2. Choroidal detachment

This may occur during filtering surgery. It is seen frequently in eyes with prominent episcleral vessels, as in cases with the Sturge-Weber Syndrome [302]. The suprachoroidal fluid contains little protein, suggesting that the difference in pressure drives fluid and small molecules from the choroidal capillaries into the extravascular space [303].

3. Other Operative Complications

These include possible lens injury [304], stripping of Descemet's membrane [305], vitreous loss and conjunctival flap tears [306].

B. Post-operative Complications - Early

1. Hypotony

A low IOP is common during the early post-operative period. This hypotony could indicate hyposecretion, or, with a shallow anterior chamber, overdrainage; the former an indication of poor ocular health, the latter running the risk of a flat anterior chamber and complications. Over the first few days or weeks the IOP usually returns to the normal level (Mills [19] in reviewing 444 cases of trabeculectomy found that, irrespective of the presurgical IOP level, 76.4% returned to the physiological range after surgery), and the anterior chamber depth is restored. A prolonged flat anterior chamber may be due to the following possible causes:

a. Leaking conjunctival wound - this may require re-suturing [306, 307].
b. Choroidal detachment - in patients with hypotony and choroidal detachment, the aqueous humour flow through the anterior chamber may be low, and it has been suggested that choroidal detachment somehow causes hyposecretion of the ciliary body [308]. The alternative view has been put, however, supplemented by experimental data, which has shown that increased uveoscleral outflow is the cause of the

hypotony in such eyes [309], 303]. Additional factors, such as inflammation and venous congestion, also appear important [310]. It is rarely necessary to drain these choroidal detachments, as most resolve spontaneously.

c. Excessive filtration - may result from a large fistula or very large bleb. A scleral shell may be used as a tamponade to prevent the early flat anterior chamber after surgery [311] while additional sutures can be used for the scleral flap and cut with a laser if there is inadequate filtration [312]. Surgical bleb revision may be necessary [313].

2. Raised Intraocular Pressure

During the early post-operative stage this may be associated with either a flat anterior chamber (suggesting a malignant or pupil block mechanism), or a deep anterior chamber (suggesting inadequate filtration, either due to fistula obstruction or poor bleb formation).

In the latter case, pharmacologic alteration of wound healing after filtering surgery in eyes with poor surgical prognoses has been attempted by the administration of drugs such as corticosteroids, non-steroidal anti-inflammatory agents, beta-aminoproprionitrile (BAPN), and antimetabolites. A randomised clinical trial of post-operative corticosteroids demonstrated that the success rate of trabeculectomy was statistically significantly increased with pre- and post-operative topical prednisolone 1%; however, the addition of oral prednisolone to the regime resulted in no improvement in the success rate [314]. Subconjunctival triamcinolone given one week pre-operatively seemed to influence the outcome favourably in eyes with poor surgical prognoses [315]. Preliminary experience with postoperative BAPN, which interferes with collagen cross-linking, suggested that it may also have a role in the surgical management of difficult glaucomas [316]. Postoperative subconjunctival administration of 5-fluorouracil, an antimetabolite that inhibits the proliferation of fibroblasts in vitro and in vivo, increased the success rate of filtering surgery in a pilot study of patients with glaucoma in aphakia, glaucoma after unsuccessful filtering surgery and neovascular glaucoma, compared with earlier series at the same institution [259, 260, 317].

3. Other early complications

These include uveitis, dellen and hyphaema.

4. Loss of a central island of visual field

This is rare, but has been reported. O'Connell and Karseras [318] emphasize that abrupt changes in refractive error and lens opacity must be excluded before macular fixation is deemed lost. They found an increased incidence of maculopathy in late glaucoma cases. Lawrence [319] and Lichter and Ravin [320] consider this risk of central field

loss so low, that a residual central island is not a contraindication to glaucoma filtering surgery. In the latter series, of 52 eyes that underwent filtering surgery, all but 14 had field loss either involving fixation or within 5 degrees of fixation but none suffered sudden loss of central field after surgery. Another study of the field loss following surgery in late stage glaucoma patients, showed that a significant number, particularly those with residual field confined to a central island ± a small residual peripheral island, lost their central field post-operatively [321].

C. Post-operative Complications - Late

1. Late failure of filtration

This may develop within weeks of an initially successful operation [322] or months or years post-operatively [323]. The literature shows a wide range of success without medication from 10% [324] to 98% [325]. Most fall between 65% to 85% [326]. Comparison of the different series is further compounded by the varying definitions of 'success', the heterogenous groups of glaucoma patients treated and whether or not additional medication was allowed to control IOP. The time course of pressure control has two phases: a rapid decrease over the first 6 months, followed by a gradual decrease or stability [16, 17, 18, 19, 20, 327, 328, 329, 330, 331]. The general shape of the curve is similar whether or not cases with medication are included. In a retrospective study of 194 eyes that had undergone filtering surgery, Levene [332] found the percent success at 5 years to be 55.2 and that most of the failures occurred within the first 6 months.

In a large study of trabeculectomies in the Japanese, Inaba [20] also found that the time course of failure of IOP control after surgery was of the early failure type, with the probability of failure increasing rapidly within 1 year, particularly within 6 months, and subsequently showing a slow decrease. On the other hand, Lamping et al. [333] noted failed trabeculectomies between 9 months and 10 years after surgery (in the latter case, the IOP was controlled, but nasal field loss developed). Most other failures in this series occurred within 2 years. Jerndal and Lundström also noted a slight trend for the IOP to increase with time. Mills [19], however, found the IOP to remain relatively stable with extended follow-up and that there was no long-term 'drift or escape'. Ridgway [334], also reporting from Manchester, considered late failure to be rare.

At this stage, it would seem opportune to review the success rates of trabeculectomy in other published series. There are many papers in the literature reporting the results of this form of surgery. However,only a few reports compiled more than 100 eyes with a reasonable length of follow-up. These include those of Jerndal & Lundström (1980) [18], Mills (1981) [19], Watson & Grierson (1981) [62], Miller & Barber (1981) [335], Hashimoto et al. (1977) [336], Mochizuki et al. (1977) [337], Inaba

(1982) [20], Wilson (1977) [16], Honrubia et al. (1983) [338], D'Ermo et al. (1979) [17], Lamping et al. (1986) [333], Ridgway (1974) [334] and Zaidi (1980) [331]. The relevant details are summarised in Table III.

TABLE III

TRABECULECTOMY : REPORTED SERIES

Authors	No. of Patients	Type of Glaucoma	Success Rate	Length of Follow-up (yr)	Adjuvant Medication	Cataracts
Schwartz & Anderson (1974)	39	OAG/CNAG	74%	10/12	in 7	no
Jerndal et al. (1977)	330	many with PXF	79%	1.5 - 3	with/without	
Jerndal et al (1980)	281	many with PXF	56.8%	3 - 5.5	with/without	late complications
Mills (1981)	444	COAG + others	86.3% (71.9% without meds)	up to 5	with/without	15.2%
Watson & Grierson (1981)	424	COAG + others	98% (86% without meds)	2 - 10	with/without	16%
Hashimoto et al. (1977)	100	COAG + others	88%	0.16 - 3	with/without	
Mochizuki et al. (1977)	117	COAG + others	81%	0.6 - 2.3	with/without	
Miller & Barber (1981)	122	COAG + others	57%	> 1	with/without	
Inaba (1982)	427	COAG + others	75%	3/12 - 5	with/without	
Shirato (1982)	145	COAG + others	70%	0.5 - 3	with/without	38.6%
Wilson (1977)	309	COAG + others	87%	up to 7	with/without	
Honrubia (1983)	150	COAG + others	88% @ 1 yr 73.3% @ 4 yrs	4	with/without	
D'Ermo & Bonomi (1979)	90	Chronic glaucoma	71%	1 - 5	with/without	35%
Lamping et al. (1986)	71	COAG	76%	mean 4	with/without	21%

Ridgway (1974)	180	COAG + others	79%	1 - 3	with/without	4.7%
Zaidi (1974)	66	COAG	80% @ 4 yrs	up to 4	with/without	9.8%
Yamashita (1985)	145	COAG + others	61%	5	with/without	9.8%

It is not always possible to predict from the bleb appearance which cases will ultimately fail, although persistent inflammation and pre- or post-operative factors predisposing to an inflammatory response appear to play a relevant part [323].

The mechanism of failure is commonly related to scarring and cyst-like formation within the bleb [322, 323, 339]. The histopathologic study of failed blebs by Hitchings and Grierson [323] revealed a marked inflammatory response, abundant fibroblasts, a deposition of new collagen within the first few months after surgery. In the late failures, a hypocellular capsule of fibrous tissue lined by a thick layer of fibrin was seen beneath relatively normal conjunctiva and Tenon's capsule.

2. Leaking Bleb

A thin-walled bleb may rupture leading to loss of the anterior chamber and possible endophthalmitis.

3. Endophthalmitis

This is more common with thin-walled blebs as following trephinations [340, 341], but has also been reported after trabeculectomies [342, 343, 344].

4. Cataracts

The reported incidence of cataracts after filtering surgery varies with figures of between 30 - 40% quoted for some series [17, 18, 318, 345, 346] although the incidence was lower [19, 331] or not a problem [347] in others. A total of 76 of 252 eyes (30%) in the study by Lamping et al. [333] required cataract extraction which was indicated more often following full-thickness procedures, 34%, than trabeculectomies (21%). This is comparable to other reports that assess the incidence of cataract surgery following filtering operations [348-350].

It is difficult to determine the relationship between post-operative cataract formation and successful filtration surgery due to the problem of separating direct surgical causes of cataract formation from the metabolic and nutritive causes present in ageing. In a review of 83 successfully filtering eyes by Sugar [350], of 38% who developed cataracts, 20% were due to operative trauma, serious post-operative inflammation or persistent hypotony. The remaining 80% were considered to be due to a combination of ageing, relative hypotony, surgical trauma, the effects of the glaucoma itself and antiglaucoma drugs.

5. Other Late Complications

These include large overhanging blebs, spontaneous hyphaema, hypotony and choroidal detachment and eyelid changes.

4.5 Comparison of Trabeculectomy vs. Full-thickness Filtering Procedures

Before recommending an operation, it is important to establish whether the results are improved, or the complications reduced when compared with other procedures.

A. Glaucoma Control

Numerous studies reporting the results of trabeculectomy indicate successful control of IOP in approximately 75-95% of cases (i.e. similar to full-thickness procedures), but with a variable reduction in the incidence of complications [16-20, 61, 62, 282, 288, 289, 290-296, 328, 347, 351-355] compared with the thermosclerostomy.

Drance & Vargas [356] compared the results of trabeculectomy and thermosclerostomy and found comparable controls of IOP in both groups. However, the complications were worse in the thermosclerostomy group, with more flat anterior chambers, more uveitis and a greater reduction in visual acuity.

Bakker & Manku [357] had similar experience in a black population, performing primary surgery as they considered medical treatment unsatisfactory due to poor compliance in this group. Data was incomplete due to poor attendance, but the groups were well matched in that a trabeculectomy was performed in one eye and a thermosclerostomy in the other. IOP control was similar following both procedures. However, there was a fourfold increased risk of reduction in visual acuities, usually due to lens opacities, in the thermosclerostomy group. One case of endophthalmitis also occurred in the latter group.

Spaeth & Poryzees [358] randomly allocated to one eye a Scheie procedure and to the other a trabeculectomy in 15 patients requiring bilateral drainage surgery. IOP was lower in the Scheie group and fewer eyes required additional medication, although the overall control of the disease was similar in the two groups. Post-operative cataract occurred in similar proportions.

Blondeau & Phelps [327] had similar findings, with the IOP control at 1 and 5 years similar in each group. Flat or shallow anterior chambers occurred more frequently in the thermosclerostomy group, as did late complications such as cataract, hypotony and leaking or infected blebs.

Lewis & Phelps [359] reported an extension of the above study. At 5 years, the control of IOP without medication was statistically improved in patients treated by trabeculectomy. More cataracts occurred in the thermosclerostomy group.

B. Race

It is generally felt that glaucoma control among black patients is poorer than in Whites for most filtering procedures, although this has not been substantiated in all studies. For trabeculectomy, the control rate for Caucasian eyes ranged from 79-98% with or without the use of antiglaucoma medications [17, 19, 62, 282, 352]. In Japanese eyes, the control rate was reported to be 75-88% [20, 336, 337] and is felt to be slightly lower than in the Caucasian population. With regard to trabeculectomies in Blacks, the reported success rates have mostly been in the same range as those for whites [324, 332, 360-361], although some series have revealed less than 75% success with standard trabeculectomies[291, 335]. Welsh [291] achieved only a 28% success rate with the Cairns-type trabeculectomy in one group of Blacks, but found that the success was improved to 65% with a filtration trabeculectomy (modified trabeculectomy combined with intentional fistula formation) in a second group. Modifications have also improved pressure control in other reported studies in Blacks [362]. The report by Miller & Barber [335] showed that 43% of Blacks were uncontrolled one year after trabeculectomy. The low success rate in the black population has been attributed to intensive scar tissue formation in the subconjunctival tissue in this racial group [291].

Comparative studies of trabeculectomies and full-thickness filtering procedures within black populations have also been conflicting [357, 363, 364]. There appears to be a true biologic difference in the risk of glaucomatous optic nerve damage between Blacks and Whites, with the data compiled by Martin, Sommer et al. [365] strongly suggesting that Blacks suffer earlier and more severe increases in IOP than do Whites. Grant & Burke [5] investigated racial differences in blindness from glaucoma by reviewing 10 years of data on blindness from their institution. Although only 18% of their clinic population were black, between 33% and 51% of those who became blind from glaucoma were black. As the level and type of care offered to white and black patients were equal, they conclude that the glaucoma of these two racial categories may already have been different in some way when their treatment was started or that they responded differently to the treatment.

C. Age

Children do worse with filtering operations generally. However, young people who require filtering surgery constitute a heterogenous group, and variables other than age, such as previous surgery and the type of glaucoma, may influence the likelihood of success [20, 347]. In a study by Gressel et al. [366], none of the six trabeculectomies performed on patients under the age of ten years controlled the pressure. In patients aged between 10 and 29 years, 38% were successful, while in those between 30 and 49 years of age, 65% were successful. Other studies also show trabeculectomy to be more frequently successful in patients over the age of 40 years [367], or 60 years [20, 347], than in younger patients.

D. Primary or Secondary Therapy

Performing the procedure either as primary therapy, or following failed medical treatment had no influence on outcome in a report by Jay [368].

E. Complications

Virtually all studies agree that complication rates are lower with trabeculectomies as compared with full-thickness filtering procedures [16-20, 61, 62, 282, 285, 288-296, 327-329, 331, 347, 351-356, 358-359, 369].

Chapter 5

METHODS OF TREATMENT III : LASER TRABECULOPLASTY

5.1 Historical Background and Literature Review

The use of light energy to treat glaucoma has been one of the most exciting additions to the therapeutic management of this disease in recent years.

In 1960, Maiman [370] produced the first laser, using a ruby crystal. The following year, Zweng & Flocks [371] introduced the concept of applying light energy to the anterior chamber angle for the treatment of glaucoma. Using the xenon-arc photocoagulator of Meyer-Schwickerath, they selectively applied photocoagulation to the filtration angles of cats, dogs and monkeys, and reported subsequent lowering of IOP.

In the early 1970's, reports appeared from Krasnov [372] in Russia, Hager [373] in Germany, Demailly [374] in France and Worthen & Wickham [375] in the United States, of attempts to improve aqueous outflow by puncturing holes in the trabecular meshwork with laser energy. Although trabecular perforations were achieved, they eventually closed in the majority of cases, with only temporary IOP reduction.

The value of laser trabecular treatment was questioned when, in 1975, Gaasterland and Kupfer [376] reported the production of experimental glaucoma after applying laser energy to the trabecular meshwork of rhesus monkeys. However, the following year, Ticho & Zauberman [377] noted that long-term reduction in IOP occurred in some patients, despite the lack of permanent trabecular openings. Thus a new concept was considered in which lower energy levels were used to photocoagulate, rather than penetrate, portions of the meshwork.

In 1979, Wise [Plate 5] & Witter [63] described the first successful protocol of what has become known as laser trabeculoplasty. Many other studies have followed their preliminary work [23, 24, 25, 26, 64-68, 378, 379, 380-385], and laser trabeculoplasty has become one of the most frequently performed procedures for glaucoma.

In 1981, Wise [64] reported the control of 150 eyes with open angle glaucoma treated by argon laser trabeculoplasty (ALT) and followed for 6 - 48 months. He recorded a reduction in IOP between 10.5 - 13.29 mmHg, and claimed a success rate of 94%. It was noted that the results were poor in secondary glaucoma, but that the older patients and Blacks did well. As only 11 eyes were seen 4 years after treatment, this report is limited in establishing the long-term efficacy of ALT.

Schwartz et al. [65] reviewed 35 eyes from a mainly black population

followed for 18 months after undergoing ALT, and found 97% to be clinically controlled with pressure averaging less than 20 mmHg. The treated eyes showed a mean decrease in IOP of 10 mmHg at 4 months. The pre-treatment topical medications were not changed after therapy (all had been maintained on maximal tolerated medication). Good results were achieved in the Blacks. Peripheral anterior synechiae formation was the major complication encountered.

Wickham & Worthen [386], on the other hand, reporting on the follow-up of up to 5 years in 33 eyes treated with laser, found that only 20% had IOP's less than 20 mmHg up to 2 years after treatment. There were several end-stage glaucomatous eyes included in this series.

Wilensky & Jampol [66] followed 45 laser-treated eyes for 7 -14 months and noted an average IOP drop of 7.2 mmHg. Tonography showed increased facility of outflow. Complications encountered included raised IOP after treatment, uveitis and peripheral anterior synechiae formation.

Lichter [67] noted an average IOP reduction of 8.76 mmHg following ALT, and claimed successful control (viz. IOP reduction of 20%) in 37 out of 50 patients treated. As in many of these series discussed, many of the patients treated suffered from forms of open-angle glaucoma other than primary (e.g. pigmentary, pseudoexfoliation, aniridia, secondary).

Thomas et al. [68] found that it was possible to make the glaucoma worse with laser trabeculoplasty. The major complication noted was a rise in IOP after treatment (which could be reduced by treating only one half of the angle at each sitting). One patient lost the central island of visual field. The average pressure reduction obtained was 7.1 mmHg. Both primary and secondary open-angle glaucoma were treated. Good results were claimed in the secondary glaucomas. Almost half the patients developed peripheral anterior synechiae.

A report by Shirato et al. [385] showed a lower success rate of ALT among the Japanese with a probability of control at 38 months of 48%. All these patients still required topical medications in addition. An early failure pattern was noted, with few failures occurring if the pressure had been controlled for at least 6 months. Follow-up ranged from 7 - 38 months. The major complication was again raised IOP in the first few hours following treatment.

Horns et al. [380] found that a higher initial IOP usually resulted in a greater lowering of pressure after ALT. 19.2% of eyes required subsequent glaucoma surgery due to an inadequate lowering of IOP after laser. With an average follow-up of 36 weeks, they noted a mean overall pressure drop of 8.1 mmHg, although eyes with juvenile or inflammatory glaucoma responded poorly.

Pohjanpelto [23] reporting from Finland where a large number of patients treated had pseudoexfoliative glaucoma, noted that 23.6% of eyes with

POAG did not respond to treatment, as compared with 11.3% with pseudoexfoliation. Of those that did respond, treatment tended to remain effective for a period of at least 36 months. However, several late failures were noted, the new rise of IOP occurring 28 - 34 months after laser treatment. Late failures were commoner in the pseudoexfoliation group (10%). In some eyes with controlled pressure there was a deterioration of the visual field. In another study from Finland, Tuulonen & Airaksinen [381] found a similar success rate of 65% in simple glaucoma and 68%in pseudoexfoliation, although there was a greater mean IOP reduction in the latter group. IOP's were essentially stable throughout the follow-up of up to 18 months. In two eyes, a marked increase in IOP was noted after ALT.
Redmond Smith [387] noted that approximately 25% of the eyes treated with ALT were not improved over a short-term follow-up. In the 76% that were improved, the majority needed to carry on with treatment, but approximately 11% of the total were able to stop all treatments.

Moulin & Haut [382] initially reported a mean IOP drop of 8.9 mmHg achieved between 3 - 6 weeks after ALT, and that glaucoma surgery could be avoided in 93% of these eyes. However, three years later, with longer follow-up over a four-year period, 10% new failures per year were detected [388].

Schwartz & Kopelman [379] reported a mean success rate of 77% with an average follow-up of 2 years. An increased success rate was associated with a diagnosis of exfoliation syndrome or OAG, an age greater than 60 and a baseline pressure of less than 26 mmHg. Of the eyes that failed, failure occurred within 2 years in the majority. There appeared to be a decreasing pressure-lowering effect with time. Previous surgery and race had no influence on the outcome of ALT (56% in this series were Blacks).

A report of continued follow-up of this same group of patients [26] confirmed the decreasing pressure-lowering effect. The success rate after 5 years was reduced to 46% compared with the previous figure of 77%. Moreover, only 32% of black cases were successful compared with 65% of white cases.

Grinich et al. [383] also emphasize the progressive diminution of the effect of ALT with time, showing a cumulative success of 79% at 1 year, 69% at 2 years and 59% at 3 years. A significantly smaller IOP reduction was noted in patients under the age of 50 years after ALT, compared with those who are older.

Shingleton et al. [384] established that ALT was effective in reducing IOP in most of the 93 patients in their study followed up to 5 years. The mean final decrease for all eyes was greater than 6 mmHg, and the mean IOP reduction for all eyes changed only slightly over time. The probability of success at 4 years (defined as decrease in IOP $\geq$ 3 mmHg, IOP $\leq$ 19 mmHg, stable field, stable optic nerve, no further laser or

surgical intervention) was 52%. Failure was most common in the 1st year after treatment (23%).

Wise [389] in 1987 reviewed the long-term results of laser trabeculoplasty, and found that of the 110 patients followed for 6 years, 56% had an IOP < 21 mmHg, while 33 eyes had required filtering surgery. Of 10 eyes followed for 10 years, 8 had IOP's < 23 mmHg, 7 had IOP's < 21 mmHg, while 2 had required surgery. Eyes with advanced disc damage at the time of trabeculoplasty had a 51% rate of later glaucoma surgery. Of the 37 eyes of dead patients (average age 80 years), only one eye had required filtration surgery, and 33 of the remainder had had a last recorded IOP of < 21 mmHg before death. He concludes that laser trabeculoplasty may defer surgery for the remaining lifespan in the elderly patient, and may control POAG for over 10 years.

TABLE IV

LASER TRABECULOPLASTY SERIES

Author	No. of Cases	Follow-up (yrs)	Reduction in IOP	Success Rate
Wise (1981)	150	0.5 - 4	10.5 - 13.3	94%
Schwartz et al. (1981)	35	15	10	97% at 1 yr
Wilensky & Jampol (1981)	45	7 - 14/12	7.2	
Thomas, Simmons, & Bekker (1982)	334	1/52 - 21/12	7.1	87.5%
Grimrich, van Buskirk et al. (1987)	112	1 - 3	8.6	79% at 1 yr 69% at 2 yrs 59% at 3 yrs
Moulin et al. (1987)	194	2 - 4	6.3 - 7.8	72% at 2 yrs 64% at 3 yrs 59% at 4 yrs
Horns, Bellows, & Hutchinson (1983)	380	mean 9/12	8.1	80.8%
Schwartz & Kopelman (1983)	82	mean 24/12	9.7 at 2/12 5.9 at 4/12	77%
Pohjanpelto (1983)	180	18 - 42/12		88.7% in PXF 76.3% in COAG
Tuulonen & Airaksinen (1983)	131	1 - 1.5		65% in COAG 68% in PXF
Wickham & Worthen (1979)	33	5	10.3	20% at 2 yrs
Lichter (1982)	50	mean 7.2/12	8.7	74%
Shirato et al. (1982)	65	7 - 38/12		48% at 38/12

Schwartz, Love & Schwartz (1987)	82	5	9.7 at 2/12 7.3 at 2 yrs 6.8 at 4 yrs 4.9 at 5 yrs	46%
Shingleton et al. (1987)	118	mean 37/12	8.9 at 1 yr 9.3 at 3 yrs 10.3 at 5 yrs	52% at 4 yrs
Wise (1987)	110	6 - 10		

5.2 Mechanism of Action

The mechanism of action of laser trabeculoplasty in producing a lower IOP remains obscure. Wise & Witter [63] initially postulated that coagulation of the collagenous trabecular tissues resulted in "tightening" of the collagenous trabecular ring and the opening of Schlemm's canal, resulting in improved aqueous outflow. This theory has not been fully substantiated by laboratory studies.

Tonographic studies indicate that laser trabeculoplasty (LTP) reduces pressure by improving the facility of outflow of aqueous [378, 390-391], while fluorometric investigations show no significant influence on aqueous production [391-393].

Electron microscopic evaluation by Rodrigues et al. [394] of trabecular meshwork from human eyes obtained soon after trabeculoplasty showed that opening of Schlemm's canal as a result of fibrosis at the burn site, with inward bowing of the trabecular tissues does occur and is probably beneficial. They also point out that the histopathologic changes were confined to the superficial inner trabecular tissues and that scarring at the burn site resulted in the formation of a less permeable cellular lining, seen in specimens obtained several months after treatment. They believed that this was a deleterious effect. Furthermore, no "tightening" of the collagenous trabecular ring with an opening of the canalicular lumen was observed in humans treated with LTP when quantitative histologic methods of analysis were employed [395].

Alvarado [396] found that changes produced by the laser burn are very difficult to detect by histologic means, but that they can be observed clearly by scanning electron microscopy. Depending on the level of energy used and the absorption properties of a given meshwork, there is a shallow perforation created at the centre of the lesion. Here, a great deal of cellular debris and other particulate matter are found, as well as an intense area of coagulation of the deeper collagenous tissues. This central lesion is immediately surrounded by an annular area of less intense coagulation and shrinkage of trabecular tissues. The shrunken tissues pull the surrounding tissues, creating a separation of the corneoscleral lamellae, and a widening of the canal lumen. The net effect may be the production of aqueous channels, with increased conductivity and the opening of Schlemm's canal (which is partially collapsed in POAG).

Three potential mechanisms of action of LTP have been postulated by Van Buskirk et al. [397] who determined the effects of LTP on outflow facility, Schlemm's canal morphology, trabecular cellularity, and trabecular glycosaminoglycan composition in 33 pairs of eye-bank human eyes. These were mechanical (i.e. collagen shrinkage), cellular (i.e. reduction in trabecular cell density), and biochemical (i.e. an alteration of radioactive sulphate incorporation into the extracellular matrix in lasered eyes). After some cells are destroyed by laser, the

remaining cells may be stimulated to produce an altered extracellular matrix which may facilitate outflow.

5.3 Effect on Intraocular Pressure Control

A. Short-term IOP Control

Various studies have shown that argon laser trabeculoplasty produces a clinically significant decrease in IOP. Most series report a useful IOP reduction in approximately 85-90% of cases [63-68, 398, 399]. Some reports, however, have shown lower success rates [400, 401].

Although some patients show a pressure drop within the first few days, the full response may be delayed for as much as four weeks. The size of the pressure drop average 6 to 9 mmHg. In some cases it is then possible to reduce or stop medications [402-404]. Pollack et al. [403] found that 18% required no further medical treatment for control, whereas, of the remainder still requiring some medication, 39% required the same regimen to maintain control as before their laser treatment. Fink et al. [405] found that 94% of patients responded favourably to LTP as an alternative to carbonic anhydrase therapy.

A study by Greenidge et al. [406] showed that LTP reduces the diurnal pressure curve. The mean IOP fell 22%, the mean peak pressure fell 25%, the mean pressure range fell 30% and the pressure fluctuations fell 25%. Pressure spikes were frequent.

An early post-treatment pressure rise can be a problem (see Complications).

B. Factors Influencing the IOP Response

Many factors influence the IOP response to LTP. In general, the higher the initial IOP, the greater will be the decrease in response to treatment [401, 407, 408, 409]. However, a pre-treatment pressure above 30 mmHg has been associated with a higher frequency of failure [399, 410]. A useful IOP reduction may be achieved after LTP in eyes with low-tension glaucoma [411-412].

As regards the type of glaucoma, a favourable response is obtained in POAG, pigmentary glaucoma and the exfoliation syndrome [377, 399, 407, 410, 413-416], although the latter eyes may be subject to late failure [23]. Conditions responding to LTP less well than the above include aphakic open angle glaucoma and angle closure glaucoma following an iridectomy [413]. Poor responders include glaucoma secondary to uveitis, angle-recession or the congenital varieties [413, 414, 416].

In the study by Lieberman et al. [414] laser therapy was most successful in eyes without prior surgery or with only one prior operation. Tuulonen & Airaksinen [417] on the other hand found that, although the success rate in secondary glaucoma was only 23%, it was 83% in eyes with failed trabeculectomy treated with LTP. Fellman et al. [418] also reported a significant drop in IOP with LTP following failed trabeculectomy.

Tuulonen et al. [410] found that other factors which best predicted successful outcome of laser treatment included LTP performed as a primary procedure, low maximum pre-treatment IOP, no pre-operative treatment with pilocarpine and the surgeon's experience with LTP. Although no effect of age was seen in their study, poor results have been reported of LTP in young patients [399, 419]. Safran et al. [419] noted that 60% of patients under 40 years old had uncontrolled IOP after LTP and needed filtering surgery, compared to 7% in older patients. Older eyes also had greater decreases in IOP.

It is undetermined whether race affects either the short- or long-term IOP lowering effect of LTP. The long-term follow-up study by Schwartz et al. [26] demonstrated that the median time for IOP's to rise above 21 mmHg was statistically shorter for black patients (12 months) than whites (60 months). A more recent retrospective study by Krupin et al. [420] concluded that LTP was equally effective in black and white patients.

C. Long-term IOP Control

There is some concern as to the long-term results of LTP as regards IOP control. The studies of Schwartz et al. [26, 379] and others [23, 383, 388, 389, 420] report on the progressive diminution of the effect of LTP with time, despite good short-term control. This has already been discussed in detail.

Re-treatment trabeculoplasty in failed eyes results in pressure control in 1/3 - 1/2 of the cases, although 10 - 15% may have a sustained elevation of IOP [421, 422]. Another study by Richter et al. [423], however, found that re-treatment failed to control the IOP in 68%. The probability of successful IOP control 1.75 years after re-treatment was only 14%.

It is suggested that LTP may be effective in delaying the need for surgery, but that in many cases it does not prevent surgery [424].

5.4 Effect of Visual Field

The ability of LTP to lower IOP has been documented. However, the goal of glaucoma management is stabilisation of visual function. Several

studies on the short-term effect of LTP of the glaucomatous visual field have emanated from Scandinavia [425-427] which all showed that no change in the trend of visual field decay occurred after LTP compared with the period preceding intervention, despite good IOP control. In a study from Philadelphia [428], although 28% of eyes showed progression of the field defects, others either remained unchanged or improved (19%) over the short term. Schultz et al. [429] found that the mean IOP level after laser was a poor predictor of visual field progression, although patients with little fluctuation of IOP measurements after LTP had a better prognosis for field retention.

5.5 Laser Trabeculoplasty Technique

The original protocol of Wise & Witter [63] has remained the baseline approach to LTP, but there have since been many suggested variations in technique.

Argon laser settings of 0.1 second duration exposure and 50 micron spot size are used, with energy levels ranging between 500 to 1500 milliwatts, aiming to produce an area of depigmentation, or small gas bubble at the treatment site. Where there is a heavily pigmented trabecular meshwork, a lower energy level is usually sufficient, while higher levels are required with lightly pigmented meshworks. Treatment is carried out through a gonioscopy lens.

In the original description, laser burns were applied on or immediately posterior to the trabecular band with 100 applications evenly spaced around 360° of the meshwork [63]. However, this is often complicated by a transient rise in IOP immediately post-treatment.

A. Variations in Technique

These are mainly aimed at reducing the post-treatment IOP rise, as well as other complications.

1. Number of burns

The main advantage of a lesser number of laser applications during a single session, is a reduction in the transient post-treatment IOP rise [68, 430-435]. 25 burns over 90° of the meshwork was less effective than larger amounts of treatment [430, 436], but 50 burns over 180° or 360° had a similar effect to 100 burns over 360° of the meshwork [430-432]. A two-session treatment, each 180°, but one month apart, gave the same IOP reduction as the full 360° in one session [433]. One quadrant LTP gave approximately the same IOP control rate with less complications when compared to the standard 180° LTP [437].

2. Placement of burns anterior to the pigmented trabecular meshwork also diminishes the incidence of post-operative pressure rise [430, 432]

as well as peripheral anterior synechiae formation [438].

3. Post-operative treatment

a. Topical corticosteroids such as prednisolone 0.3% Q.I.D. is usually given for 3-4 days after treatment to reduce the mild anterior uveitis that may follow LTP.

b. Pilocarpine 4% STAT after the procedure has been shown to decrease the transient IOP rise [439].

c. Pre- and/or post-treatment with topical corticosteroids [440] or antiprostaglandins [441, 442] did not influence the IOP rise, or anterior uveitis [442].

5.6 Complications

A. Short-term

The most serious is the rise in IOP immediately after treatment [68, 435, 443-445]. This is usually mild and lasts only a few hours, causing no long-term problems. However, sometimes there is a marked pressure rise which can lead to further field loss, especially in advanced cases of glaucoma [68, 443, 444]. In most cases the pressure rise occurs within 2 hours after trabeculoplasty, but occasionally occurs later [445]. The mechanism of post-trabeculoplasty pressure rise is inflammatory, with fibrinous material and tissue debris occluding the meshwork [446]. There is a breakdown and re-establishment of the blood-aqueous barrier after LTP [447].

Other complications include mild iritis which is controlled with post-treatment topical steroids, and peripheral anterior synechiae formation (as discussed above). Corneal endothelial microscopy after LTP showed a significant increase in cell size in one study [448], but another showed no statistically significant changes [449].

B. Long-term

Theoretically, the changes produced by argon laser trabeculoplasty in the meshwork could eventually lead to an increase in resistance to aqueous outflow [394, 396, 450], making it more difficult to control the IOP. However, no recognised difference in the response to filtration surgery was found following failed LTP [451].

Chapter 6

PRIMARY VS. SECONDARY TREATMENT

In considering the question of primary versus secondary therapy, there is the need to take into account, firstly, whether each of the three treatment methods is equally effective when used as primary treatment, and, secondly, whether any of the three treatments used as initial therapy may affect the efficacy of the other treatments should they be necessary after primary therapy has failed.

Although the concept of maximum tolerated medical therapy before glaucoma surgery is a time-honoured one, recent clinical and histological evidence indicates that perhaps this concept deserves re-examination. The large retrospective study by Watson & Grierson [62] indicates that, although initial control of IOP is achieved in 74% of patients on maximum medical treatment, only 40% remain under adequate control with medication alone after a 5-year period.

In addition, experimental studies suggest that chronic underperfusion of the outflow system [452-455], which would be caused by inhibitors of aqueous secretion and the continuous use of strong miotics [456], can lead to progressive irreversible damage to the trabecular meshwork. These studies have been used to support early surgical intervention, if glaucoma is not controlled with minimal medical therapy, e.g. pilocarpine 2% TDS and/or timolol 0.5% BD [62]. Successful surgery does seem to lead to underperfusion of the remaining meshwork, but this does not matter if the filter remains patent. However, if further treatment is required, does this influence the outcome?

Jay [368] confirms that drainage surgery is more effective in lowering IOP than medical treatment in spite of the new drugs now available, and considers that early elective surgery protects visual function at least as well as the more conventional sequence.

In some parts of the world, socio-economic factors preclude the use of maximal medical therapy for the treatment of chronic open-angle glaucoma. The reasons are many, and include the great expense of the multi-medications of maximal medical therapy, impracticality of using such therapy in many parts of the world, poor patient compliance, and limited access to ophthalmologists. ALT has been suggested as a safe and effective initial therapy in these situations [457].

ALT was used as primary treatment in 33 consecutive phakic patients with newly diagnosed open-angle glaucoma by Rosenthal et al. [458] with successful lowering of IOP in 55%. Complications, however, included one case with plastic iritis and another with central retinal vein occlusion. The mean drop in pressure of 9 mmHg was not too dissimilar from that reported by other authors in the medically treated pre-surgical group of patients with chronic open-angle glaucoma [64-66], suggesting that ALT may be equally efficacious in lowering IOP whether or not the patient has

previously been treated with topical medication.

LTP was used as primary therapy in a series of 63 eyes treated by Tuulonen [459]. Control was maintained below 22 mmHg with no medication in 93.6% at 12 months and 88.4% at 18 months. After good initial response for 6 - 12 months, 6 eyes required additional medical therapy for control.

LTP was seen to be most successful in eyes without prior surgery or with only one prior operation in a study by Lieberman et al. [414]. In another series by Fellman et al. [418], ALT following failed trabeculectomy stabilised visual function in two thirds of eyes. Then out of 28 eyes in this series were considered treatment failures after ALT, six requiring further glaucoma surgery. The authors consider that alteration of the trabecular meshwork resulting from trabeculectomy does not appear to have an adverse effect on LTP.

Concern that post-laser inflammatory changes, or alteration of structural anatomy with damage to the trabecular meshwork may adversely affect the outcome of filtration surgery prompted an investigation of patients with failed ALT requiring filtration surgery by Schoenleber et al. [451]. The overall success rate of filtration surgery during the follow-up period was 92%. There was thus no recognised difference in response to filtration surgery following ALT.

ALT does show some reduction in effect with time [26, 379, 460], and it has been suggested that ALT may merely defer surgery [26]. Moreover, eyes with advanced disc damage at the time of trabeculoplasty had a 51% rate of later glaucoma surgery [389].

In two recent studies [333, 338], trabeculectomy showed a decrease in effectiveness with time, at rates which appear comparable to laser trabeculoplasty. Honrubia [338] found 15.5% of trabeculectomies required medical therapy after 4 years, and quoted post-trabeculectomy medical therapy rates up to 30%.

There is a suggestion that chronic conjunctival irritation from topical antiglaucoma medications may prejudice the results of a subsequent operation. The greatest suspicion must fall on the sympathomimetics. These can cause the development of reactive conjunctival follicles, together with the dilatation of the conjunctival blood vessels and pigmentation. Guanethidine and adrenalin preparations have been implicated in the development of subconjunctival fibrosis [461]. Pilocarpine [462] and timolol [462, 463] have been implicated in the conjunctival changes following long-term use both with [462] and apparently without [463] obvious clinical symptoms. These papers, however, do not differentiate between the effect of the preservative and the hypotensive agent.

In an attempt to assess the effect of prior medical treatment on the results of fistulising surgery, the conjunctival biopsy histology was compared in two groups of patients, one consisting of those undergoing a primary trabeculectomy, and the second, following multiple medical therapy [464]. Significant increases in the inflammatory cells, and a reduction in the number of goblet cells was seen in the patients who had previously undergone prolonged antiglaucoma topical treatment. In order to decide the safest and most effective course of management for the glaucoma patient, it is necessary to have a carefully-designed study comparing initial medical therapy with initial laser and initial surgery, with long-term follow-up and detailed documentation of visual function. No other studies have yet presented such data.

REFERENCES : SECTION I

1 Leske MC : The epidemiology of open-angle glaucoma. A review. Am. J. Epidemiol., 1983, 118, 166

2 Ghafour IM, Allan D, Foulds WS : Common causes of blindness & visual handicap in the west of Scotland. Br. J. Ophthalmol., 1983, 67, 209

3 Leydhecker W : Zur verbreitung des glaucoma simplex in der scheinbar gesunden, augenartzlich wicht behandetten bevolkerung. Doc. Ophthalmol., 1959, 13, 359

4 Lichter PR, Shaffer RN : Ocular hypertension & glaucoma. Trans Pacific Coast Oto-ophthalmol. Soc., 1973, 54, 63

5 Grant WM, Burke JF Jr : Why do some people go blind from glaucoma? Ophthalmology, 1982, 89, 991

6 Chandler PA : Long-term results in glaucoma therapy. Am. J. Ophthalmol., 1960, 49, 221

7 Kolker AE : Visual prognosis in advanced glaucoma : a comparison of medical and surgical therapy for retention of vision in 101 eyes with advanced glaucoma. Trans. Am. Ophthalmol. Soc., 1977, 75, 539

8 Quigley HA, Maumenee AE : Long-term follow-up of treated open-angle glaucoma. Am. J. Ophthalmol., 1979, 87, 519

9 Smith, RHJ : The Enigma of Primary open-angle glaucoma. Trans. Ophthalmol. Soc. UK, 1986, 105, 618

10 Burke JW : Field changes after satisfactory filtration operations for glaucoma. Trans. Am. Ophthalmol. Soc., 1939, 37, 147

11 Kronfeld PC & McGarry HI. Five-year follow-up of glaucoma. J.A.M.A., 1948, 136, 957

12 Granström PA : Progression of visual field defects in glaucoma : Relation to compliance with pilocarpine therapy. Arch. Ophthalmol., 1985, 103, 529

13 Patkin R, Krupin T, Kurata F et al. : Argon laser trabeculoplasty in black & white patients with primary open angle glaucoma. Invest. Ophthalmol. Vis. Sci., 1985, 26 (suppl.), 158

14 Starita R, Traverso C, Spaeth GL et al. : Short- & long-term effect of argon laser trabeculoplasty on the relationship between intraocular pressure & visual field. Invest. Ophthalmol. Vis. Sci., 1985, 26 (suppl.), 41

15 Werner EB, Krupin T, Bishop KI : Visual field behaviour following argon laser trabeculoplasty. Invest. Ophthalmol. Vis. Sci., 1985, 26, 41

16 Wilson P : Trabeculectomy : Long-term follow-up. Br. J. Ophthalmol., 1977, 61, 535

17 D'Ermo F, Bonomi L, Doro D : a critical analysis of the long-term results of trabeculectomy. Am. J. Ophthalmol., 1979, 88, 829

18 Jerndal T, Lundstrom M : 330 trabeculectomies. A long-time study (3 - 5 1/2 years). Acta Ophthalmol., 1980, 58, 947

19 Mills KB : Trabeculectomy : A retrospective long-term follow-up of 444 cases. Br. J. Ophthalmol., 1981, 65, 790

20 Inaba Z : Long-term results of trabeculectomy in the Japanese. An analysis of life table method. Jpn. J. Ophthalmol., 1982, 26, 361

21 Yamashita H, Eguchi S, Yamamoto T, Shirato S, Kitazawa Y : Trabeculectomy : A prospective study of complications and results of long-term follow-up. Jpn. J. Ophthalmol., 1985, 29, 250

22 Kidd MN, O'Connor M : Progression of field loss after trabeculectomy : a five year follow-up. Br. J. Ophthalmol., 1985, 69, 827

23 Pohjanpelto P : Late results of laser trabeculoplasty for increased intraocular pressure. Acta. Ophthalmol., 1983, 61, 998

24 Wickham MG, Worthen DM : Argon laser trabeculoplasty. Long-term follow-up. Ophthalmology, 1979, 86, 495

25 Wise JB : Ten-year results of laser trabeculoplasty. Does the laser avoid glaucoma surgery or merely defer it? Eye, 1987, 1, 45

26 Schwartz AL, Love DC, Schwartz MA : Long-term follow-up of Argon laser trabeculoplasty for uncontrolled open-angle glaucoma. Arch. Ophthalmol., 1985, 103, 1482

27 Sears ML : Clinical & scientific basis for the management of open-angle glaucoma. Arch. Opthalmol., 1986, 104, 191

28 Wilensky JT, Podos SM, Becker B : Prognostic indications in ocular hypertension. Arch. Ophthalmol., 1974, 91, 200

29 Drance SM : Chronic open-angle glaucoma - present & future. The second Spaeth lecture. Can. J. Ophthalmol., 1977, 12, 251

30 Drance SM, Schulzer M, Douglas GR, Sweeney VP : Use of discriminant analysis. II. Identification of persons with glaucomatous visual

field defects. Arch. Ophthalmol., 1978, 96, 1571

31 Kass MA, Hart WM Jr, Gordon M, Miller JP : Risk factors favoring the development of glaucomatous field loss in ocular hypertension. Surv. Ophthalmol., 1980, 25, 155

32 Armaly MF, Krueger DE, Maunder L, Becker B, Hetherington J Jr, Kolker AE, Levene RZ, Maumenee AE, Pollack IP, Shaffer RN : Biostatistical analysis of the collaborative glaucoma study. I. Summary report of the risk factors for glaucomatous field defects. Arch. ophthalmol., 1980, 98, 2163

33 Armaly, MF : Lessons to be learnt from the collaborative glaucoma study. Surv. Ophthalmol., 1980, 25, 139

34 Wright JE : The Bedford glaucoma survey. In: Glaucoma symposium. Hunt (Ed.), EJS Livingstone Ltd., Edinburgh, 1966, pg. 12

35 Armaly MF : The genetic determinants of ocular pressure in the normal eye. Arch. Ophthalmol., 1967, 78, 187

36 Armaly MF, Monstavicius BF, Sayegh RE : Ocular pressure and aqueous outflow facility in siblings. Arch. Ophthalmol., 1968, 80, 354

37 Armaly MF : Genetic determination of cup:disc ratio of the optic nerve. Arch. Ophthalmol., 1967, 78, 35

38 Becker B : Diabetes Mellitus and primary open angle glaucoma. Am. J. Ophthalmol., 1971, 71, 1

39 Klein BE, Klein R, Moss SE : Intraocular pressure in diabetic persons. Ophthalmology, 1984, 91, 1356

40 Leske MC, Podgor MJ : Intraocular pressure, cardiovascular risk variables and visual field defects. Am. J. Epidemiol., 1983, 118, 280

41 Bulpitt CJ, Hodes C, Everitt MG : Intraocular pressure and systemic blood pressure in the elderly. Br. J. Ophthalmol., 1975, 59, 717

42 Klein BE, Klein R : Intraocular pressure & cardiovascular risk variables. Arch. Ophthalmol., 1981, 99, 837

43 Hollows FC, Graham PA : Intraocular pressure, glaucoma and glaucoma suspects in a defined population. Br. J. Ophthalmol., 1966, 50, 570

44 Wallace J, Lovell HG : Glaucoma & intraocular pressure in Jamaica. Am. J. Ophthalmol., 1969, 67, 93

45 Wilensky JT, Gandhi N, Pau T : Racial influences in open angle glaucoma. Ann. Ophthalmol., 1978, 10, 1398

46 David R, Livingston D, Luntz MH : Ocular hypertension : a comparative follow-up of black and white patients. Br. J. Ophthalmol., 1978, 62, 676

47 Martin MJ, Sommer A, Gold EB, Diamond EL : Race and primary open-angle glaucoma. Am. J. Ophthalmol., 1985, 99, 383

48 Hiller R, Kahn HA : Blindness from glaucoma. Am. J. Ophthalmol., 1975, 80, 62

49 Wilson MR, Hertzmark E, Walker AM, Childs-Shaw K, Epstein DL : A case-control study of risk factors in open angle glaucoma. Arch. Ophthalmol., 1987, 105, 1066

50 Beck RW, Messner DK, Musch DC et al. : Is there a racial difference in physiologic cup size? Ophthalmology, 1985, 92, 873

51 Chandler PA, Grant WM : 'Lectures on Glaucoma'. Lea & Febiger, Philadelphia, 1965, p.13

52 Yablonski ME, Zimmerman TJ, Kass MA, Becker B : Prognostic significance of optic disc cupping in ocular hypertensive patients. Am. J. Ophthalmol., 1980, 89, 585

53 Shaffer RN : Open-angle glaucoma. Trans. Am. Acad. Ophthalmol. Otol., 1963, 67, 467

54 Shaffer RN, Hetherington J Jr : The case for conservatism in open-angle glaucoma management. Can. J. Ophthalmol., 1968, 3, 11

55 Chandler PA, Grant WM : Glaucoma. 2nd ed., Lea & Febiger, Philadelphia, 1979

56 Crick RP : Chronic glaucoma : a preventable cause of blindness. Lancet, 1974, 1, 205

57 Lee PF : Importance of status of visual field and optic disc in management of open-angle glaucoma. Am. J. Ophthalmol., 1962, 53, 435

58 Spaeth GL : The effect of change in intraocular pressure on the natural history of glaucoma : lowering intraocular pressure in glaucoma can result in improvement of visual fields. Trans. Ophthalmol Soc. U.K., 1985, 104, 256

59 Gloster J : Tonometry & Tonography. London, J & J Churchill Ltd., 1966, Pg. 170

60 Migdal C, Hitchings R : Control of chronic simple glaucoma with primary medical, surgical and laser treatment. Trans Ophthalmol. Soc. UK, 1986, 105, 653

61 Cairns JE : Trabeculectomy. Preliminary report of a new method. Am. J. Ophthalmol., 1968, 5, 673

62 Watson PG, Grierson I : The place of trabeculectomy in the treatment of glaucoma. Ophthalmology, 1981, 88, 175

63 Wise JB, Witter SL : Argon laser therapy for open angle glaucoma. A pilot study. Arch. Ophthalmol., 1979, 97, 319

64 Wise JB : Long-term control of adult open-angle glaucoma by argon laser treatment. Ophthalmology, 1981 88, 197

65 Schwartz AL, Whitten ME, Bleiman B, Martin D : Argon laser trabecular surgery in uncontrolled phakic open angle glaucoma. Ophthalmology, 1981, 88, 203

66 Wilensky JT, Jampol LM : Laser therapy for open angle glaucoma. Ophthalmology, 1981, 88, 213.

67 Lichter PA : Argon laser trabeculoplasty. Trans. Am. Ophthalmol. Soc., 1982, 80, 288

68 Thomas JV, Simmmons RJ, Belcher CD III : Argon laser trabeculoplasty in the presurgical glaucoma patient. Ophthalmology, 1982, 89, 187

69 Elliot RE : A Treatise on Glaucoma. 2nd Ed. London : H. Frowde, 1922, 91

70 Carel RS, Korczyn AD, Rock M, Goya I : Association between ocular pressure & certain health parameters. Ophthalmol., 1984, 91, 311

71 Quigley HA, Addicks EM, Green WR : Optic nerve damage in human glaucoma. Arch. Ophthalmol., 1982, 100, 135

72 Flammer J : Fluctuations in the visual field. In: Drance, SM, Anderson DR (Eds) : Automatic Perimetry in glaucoma. Grune & Stratton, Inc., Orlando, 1985

73 Flammer J, Drance SM, Augustiny L, Fankhauser A : Quantfication of glaucomatous visual field defects with automated perimetry. Inv. Ophthalmol. Vis. Sci., 1985, 26, 176

74 Heijl A : Automatic perimetry in glaucoma visual field screening. Grefes Arch. Clin. Exp. Ophthalmol., 1976, 200, 21

75 Li SG, Spaeth GL, Scimeca HA et al. : Clinical experiences with the use of automated perimeter (OCTOPUS) in the diagnosis & management of patients with glaucoma & neurologic disease. Ophthalmology, 1979, 86, 1302

76 Gloor B, Schmied U, Fassler A : Changes of glaucomatous field defects : Degree of accuracy of measurements with the automated perimeter OCTOPUS. Int. Ophthalmol., 1980, 3, 5

77 Heijl A, Drance SM, Douglas GR : Automated perimetry (Competer): Ability to detect early glaucomatous field defects. Arch. Ophthalmol., 1980, 98, 1560

78 Flammer J, Drance SM, Augustiny L et al. : Quantification of glaucomatous visual field defects with automated perimetry. Invest Ophthalmol Vis. Sci., 1985, 26, 176

79 Enger C, Sommer A : Recognising glaucomatous field loss with the Humphrey STATPAC. Arch. Ophthalmol., 1987, 105, 1355

80 Nagin P, Schwartz B, Namba K : The reproducibility of computerised boundary analysis for measuring optic pallor in the normal optic disc. Ophthalmology, 1985, 92, 243

81 Nagin P, Schwartz B : Detection of increased pallor over time; computerised image analysis in untreated ocular hypertension. Ophthalmology, 1985, 92, 252

82 Takamoto T, Schwartz B : Reproducibility of photogrammetric optic disc cup measurements. Invest. Ophthalmol Vis. Sci., 1985, 26, 814

83 Spaeth GL : Control of glaucoma : a new definition. Ophthalmic Surg., 1983, 14, 303

84 Weber A : 'Pilocarpine and intraocular pressure'. Korresp-Bl. Med. Wiss., 1876, 14, 986

85 Laqueuer L : A new therapeutic indication for physostigmine. Zentralbl. Med. Wissensch., 1876, 14, 421

86 Laqueuer L : Ueber Atropin & Physostigmin und ihre Wirkung auf den intraocularen Druck. V. Graefes ARch. Ophthalmol., 1877, 23, 14

87 Darier P : De l'extrait de capsules surrenales en therapeutie oculaire. Clin. Ophtal., 1900, 6, 141

88 Hamburger C : Experimentale glaukomtherapie. Med. Klin, 1923, 19, 1224

89 Hamburger C : Zu der neuen Glaukombehandelung, Praktisches und Theoretisches. Klin. Mbl. Augenheilk., 1924, 72, 47

90 Thiel R : Die medikamentose Beeinflussung des Augendruckes. Ber. dtsch. Ophthal. Ges., 1924, 44, 118

91 Cantonnet A : Essai de traitement du glaucome par les substances osmotiques. Arch. Ophthal., 1904, 24, 1

92 Hertel E : Uebaveranderung des Augendruckes durch osmotische vorgange. Klin. Mbl. Augenheilk., 1913, 57, 351

93 Hertel E : Klinische Untersuch ungen uber die Abhangigkeit des Augendrucks von der Blutbeschaffenheit. V. Graefes Arch. Ophthal., 1915, 90, 309

94 Becker : Acta XVII lnt. Congress Ophthal. Montreal - NY, 1954, 2, 1109

95 Phillips CI, Howitt G, Rowlands PJ : Propranolol as ocular hypotensive agent. Br. J. Ophthalmol., 1967, 51, 222

96 Bucci MG, Missiroli A, Pecori Geraldi J et al. : La somministrazione locale del Propranolol nella terapia del glaucoma. Bell. Ocul., 1968, 47, 51

97 Merte H.J., Merkle W : Propranolol - Augentrofen in der Glaukom-Dauer Therapie. Klin. Monatsbl. Augenheilkd., 1980, 177, 437

98 Draeger J : "Corneal sensitivity. Measurement and clinical importance." New York, Springer-Verlag, 1984, 78

99 Katz IM, Hubbard WA, Getson AJ : Intraocular pressure decrease in normal volunteers following timolol ophthalmic solution. Invest. Ophthalmol., 1976, 15, 489

100 Katz IM : Beta-blockers and the eye : an overview. Ann. Ophthalmol., 1978, 10, 847

101 Katz IM : Treatment of chronic open-angle glaucoma with timolol maleate ophthalmic solution. Efficacy & safety of long-term maintenance. In 'Timolol maleate ophthalmic solution in the treatment of glaucoma'. Symp. on Glaucoma. XXIII Int. Congress of Ophthalmology, Kyoto, Japan, 1978, pp. 29

102 Kass MA, Meltzer DW, Gordon M, Cooper D, Goldberg J : Compliance with topical pilocarpine treatment. Am. J. Ophthalmol., 1986, 101, 575

103 Kass MA, Meltzer DW, Gordon MO : The compliance factor. In: Drance SM, Neufeld EH (Eds) : Glaucoma: Applied Pharmacology in Medical Treatment. Grune & Stratton, Orlando, 1984, 537

104 Lutjen-Drecoll E, Baranyś EH : Functional and electron microscopic changes in the trabecular meshwork remaining after trabeculectomy in cynomologus monkeys. Invest. Ophthalmol. Vis. Sci., 1974, 13, 511

105 Weber A : Das calabar und seine therapeutische verwendung. Albrech v. Graefes Arch. Klin. Exp. Ophthalmol., 1877, 23, 1

106 Shaffer RN & Hetherington J : Anticholinesterase drugs & cataracts. Trans. Am. Ophthalmol. Soc., 1966, 64, 201

107 Kaback MB, Podos SM et al. : The effects of dipivalyl epinephrine on the eye. Am. J. Ophthalmol., 1976, 81, 768

108 Sneddon JM, Turner P : The interactions of local guanethidine and sympathomimetic amines in the human eye. Arch. Ophthalmol., 1969, 81, 622

109 Becker B : Decrease in intraocular pressure in man by a carbonic anhydrase inhibitor, Diamox. Am. J. Ophthalmol., 1954, 37, 13

110 Barany EH : The mode of action of pilocarpine on the outflow resistance of the eye of a primate (cercopithecus etiops). Invest. Ophthalmol., 1962, 1, 712

111 Grierson I, Lee WR, Abraham S : Effects of pilocarpine on the morphology of the human outflow apparatus. Br. J. Ophthalmol, 1978, 62, 302

112 Grierson I, Lee SR, Moseley H, Abraham S : The trabecular wall of Schlemm's canal : a study of the effects of pilocarpine by scanning electron microscopy. Br. J. Ophthalmol., 1979, 63, 9

113 Kaufman PL : Aqueous humor dynamics following total iridectomy in the cynomolgus monkey. Invest. Ophthalmol. Vis. Sci., 1979, 18, 870

114 Miichi H, Nagasaki S : Effects of pilocarpine, salbutomol and timolol on aqueous humor formation in cynomolgus monkeys. Invest. Ophthalmol. Vis. Sci., 1983, 24, 1269

115 Gaasterland D, Kupfer C, Ross K : Studies of aqueous humour dynamics in man. IV. Effects of pilocarpine upon measurements in young normal volunteers. Invest. Ophthalmol., 14, 848, 1975

116 Barany EH : A pharmacologist looks at medical treatment in glaucoma - in retrospect and in prospect. Ophthalmology, 1979, 86, 80

117 Weekers R, Prijot E, Gustin J : Recent adances and future prospects in the medical treatment of ocular hypertension. Br. J. Ophthalmol., 1954, 38, 742

118 Becker B, Ley AP : Epinephrine and acetazolamide in the therapy of the chronic glaucomas. Am. J. Ophthalmol., 1958, 45, 639.

119 Becker B, Pettit TH, Gay AJ : Topical epinephrine therapy of open-angle glaucoma. ARch. Ophthalmol., 1961, 66, 219

120 Sears ML : The mechanism of action of adrenergic drugs in glaucoma. Invest. Ophthalmol., 1966, 5, 115

121 Sears ML, Neufeld AH : Adrenergic modulation of the outflow of aqueous humor. Invest. Ophthalmol., 1975, 14, 83

122 Sears ML : Autonomic nervous system : Adrenergic agonists. In: Sears ML (Ed) 'Handbook of Experimental Pharmacology' Vol. 69, Springer Verlag, Berlin, Heidelberg, 1984, 1939

123 Mandell AI, Stentz F, Kitabchi AE : Dipivalyl epinephrine. A new prodrug in the treatment of glaucoma. Ophthalmology, 1978, 85, 268

124 Kass MA, Mandell AI, Goldberg I, Paine JM, Becker B : Dipivefrin and epinephrine treatment of elevated intraocular pressure. A comparative study. Arch. Ophthalmol., 1979, 97, 1865

125 Kohn AN, Moss AP, Hargett NA, Ritch R, Smith H Jr, Podos SM : Clinical comparison of dipivalyl epinephrine and epinephrine in the treatment of glaucoma. Am. J. Ophthalmol., 1979, 87, 196

126 Nagasubramanian S, Tripathi RC, Poinoosawmy D, Gloster J : Low concentration guanethidine and adrenalin therapy of glaucoma : a preliminary report. Trans. Ophthalmol., Soc. UK, 1976, 96, 179

127 Mills KB, Ridgway AEA : a double blind comparison of guanethidine-and-adrenaline drops with 1% adrenaline alone in chronic simple glaucoma. Br. J. Ophthalmol., 1978, 62, 320

128 Romano J, Patterson G : Evaluation of a 5% guanethidine and 0.5% adrenalin mixture (Ganda 5.05) and of a 3% guanethidine and 0.5% adrenaline mixture (Ganda 3.05) in the treatment of open angle glaucoma. Br. J. Ophthalmol., 1979, 63, 52

129 Murray A, Glover D, Hitchings R : Low-dose combined guanethidine 1% and adrenalin 0.5% in the treatment of chronic simple glaucoma : a prospective study. Br. J. Ophthalmol., 1981, 65, 533

130 Hitchings RA, Glover D : Adrenaline 1% combined with guanethidine 1% versus adrenaline 1% : a randomised prospective double-blind cross-over study. Br. J. Ophthalmol., 1982, 66, 247

131 Romano JH, Nagasubramanian S, Poinoosawmy D : Double-masked cross-over comparison of Ganda 1.02 (guanethidine 1% and adrenalin 0.2% mixture) with gutt. adrenaline 1% (Simplene 1%) and with pilocarpine 1% (Sno-Pilo 1%). Br. J. Ophthalmol., 1981, 65, 50

132 Heilmann K : Course of intraocular pressure during long-term treatment with a combination of guanethidine and epinephrine. Klin. Monatsbl. Augenheilkd., 1983, 183, 17

133 Sonntag JR, Brindley GO, Shields MB : Effect of timolol therapy on outflow facility. Invest. Ophthalmol. Vis. Sci., 1978, 17, 293

134 Coakes RL, Brubaker RF : The mechanism of timolol in lowering intraocular pressure in the normal eye. Arch. Ophthalmol., 1978, 96, 2045

135 Neufeld AH : Experimental studies on the mechanism of action of timolol. Surv. Ophthalmol., 1979, 23, 363

136 Neufeld AH, Bartels SP, Liu JHK : Laboratory & clinical studies on the mechanism of action of timolol. Surv. Ophthalmol., 1983, 28, 286

137 Zimmerman TJ, Kaufman HE : Timolol : A beta-adrenergic blocking agent for the treatment of glaucoma. Arch. Ophthalmol., 1977, 95, 601

138 Zimmerman TJ, Kaufman HE : Timolol : Dose response and duration of action. Arch. Ophthalmol., 1977, 95, 605

139 Sonntag JR, Brindley GO, Shields MB, Arafat N-IT, Phelps CD : Timolol & epinephrine. Comparison of efficacy and side effects. Arch. Ophthalmol., 1979, 97, 273

140 Alexander DW, Berson FG, Epstein DL : A clinical trial of timolol and epinephrine in the treatment of primary open-angle glaucoma. Ophthalmology, 1988, 95, 247

141 Hoyng PFJ, Verbey NLJ : Timolol v. guanethidine - epinephrine formulation in the treatment of glaucoma. An open clinical trial. Arch. Ophthalmol., 1984, 102, 1788

142 Boger WP III, Steinert RF, Puliafito CA, Pavan-Langston D : Clinical trial comparing timolol ophthalmic solution to pilocarpine in open-angle glaucoma. Am. J. Ophthalmol., 1978, 86, 8

143 Hass I, Drance SM : Comparison between pilocarpine and timolol on diurnal pressures in open-angle glaucoma. Arch. Opthalmol., 1980, 98, 480

144 Anon : New, topical beta-blockers for Glaucoma. In 'Drugs & therapeutics Bulletin', 1987, 25, 63

145 Novack GD : Ophthalmic beta-blockers since timolol. Surv. Ophthalmol., 1987, 31, 307

146 Berrospi R, Leibowitz HM : Betaxolol. A new beta-adrenergic blocking agent for treatment of glaucoma. Arch. Ophthalmol., 1982, 100, 943

147 Radius RL : Use of betaxolol in the reduction of elevated intraocular pressure. Arch. Ophthalmol, 1983, 101, 898

148 Caldwell DR, Salisbury CR, Guzek JP : Effects of topical betaxolol in ocular hypertensive patients. Arch. Ophthalmol., 1984, 102, 539

149 Berry DP, Van Buskirk EM, Shields MB : Betaxolol & timolol. A comparison of efficacy and side-effects. Arch. Ophthalmol., 1984, 102, 42

150 Schoene RB, Abuan T, Ward RL, Beasley CH : Effects of topical betaxolol, timolol and placebo on pulmonary function in asthmatic bronchitis. Am. J. Ophthalmol., 1984, 97, 86

151 Merte HJ, Stryz JR, Mertz M : Comparative studies on initial pressure reduction using metipranolol 0.3% and timolol 0.25% in eyes with open-angle glaucoma. Klin. Monatsbl. Augenheilkd., 1983, 182, 286

152 Negishi C, Kanai A Nakajima A et al. : Ocular effects of beta-blocking agent carteolol on healthy volunteers and glaucoma patients. Jpn. J. Ophthalmol., 1987, 25, 464

153 Dailey RA, Brubaker RF, Bourne WM : The effects of timolol maleate and acetazolamide on the rate of aqueous formation in normal human subjects. Am. J. Ophthalmol., 1982, 93, 232

154 Doane MB, Jensen AD, Dohlman CH : Penetration routes of topically applied eye medications. Am J. Ophthalmol., 1978, 85, 383

155 Krohn DL, Breitfeller JM : Transcorneal flux of topical pilocarpine to the human aqueous. Am. J. Ophthalmol., 1979, 87, 50

156 Asseff CG, Weisman RL, Podos SM, Becker B : Ocular penetration of pilocarpine in primates. Am. J. Ophthalmol., 1973, 75, 212

157 Chrai SS, Robinson JR : Corneal penetration of topical pilocarpine in the rabbit. Am. J. Ophthalmol., 1974, 77, 735

158 Harris LS, Galin A : Dose response analysis of pilocarpine induced ocular hypotension. Arch. Ophthalmol., 1970, 84, 605

159 Drance SM, Bensted M, Schulzer M : Pilocarpine and intraocular pressure. Duration of effectiveness of 4% and 8% pilocarpine instillation. Arch. Ophthalmol., 91, 104, 1974

160 Harris LS, Galin MA : Effect of ocular pigmentation on hypotensive response to pilocarpine. Am. J. Ophthalmol., 1971, 72, 923

160 Lazare R, Horlington M : Pilocarpine levels in the eyes of rabbits following topical application. Exp. Eye Res., 1975, 21, 281

161 Drance SM, Nash PA : The dose-response of human intraocular pressure to pilocarpine. Can. J. Ophthalmol., 1971, 6, 9

162 Patton TF, Francoeur M : Ocular Bioavailability and systemic loss of topically applied ophthalmic drugs. Am. J. Ophthalmol., 1978, 85, 225

163 File RR, Patton TF : Topically applied pilocarpine. Human pupillary response as a function of drop size. Arch. Ophthalmol., 1980, 98, 112

164 Fraunfelder FT, Hanna C L: Ophthalmic drug delivery systems. Surv. Ophthalmol., 1984, 29, 117

165 Shell JW : Ophthalmic drug delivery systems. Surv. Ophthalmol., 29, 117, 1984

166 March WF, Stewart RM, Mandell AI, Bruce LA : Duration of effect of pilocarpine gel. Arch. Ophthalmol., 1982, 100, 1270

167 Goldberg I, Ashburn FS Jr, Kass MA, Becker B : Efficacy and patient acceptance of pilocarpine gel. Am. J. Ophthalmol., 1979, 88, 843

168 Johnson DH, Epstein DL, Allen RC, Boysmith J, Campbell D, Rosenquist R, Van Buskirk EM : a one-year multi-center clinical trial of pilocarpine gel. Am. J. Ophthalmol., 1984, 97, 723

169 Klein HZ, Lugo M, Shields MB et al. : A dose-response study of piloplex for duration of action. Am. J. Ophthalmol., 1985, 99, 23

170 Ticho U, Blumenthal M, Zonis S, Gal A, Blank I, Mazor ZW : Piloplex, a new long-acting pilocarpine polymer salt. A: Long-term study. Br. J. Ophthalmol., 1979, 63, 45

170 Mazor Z, Ticho U, Rehany U, Rose L : Piloplex, a new long-acting polymer salt. B: Comparative study of the visual effects of pilocarpine and piloplex eyedrops. Br. J. Ophthalmol., 1979, 63, 48

171 Quigley HA, Pollack IP, Harbrin TS Jr : Pilocarpine Ocuserts. Long-term clinical trials and selected pharmacodynamics. Arch. Ophthalmol., 1975, 93, 771

172 Ruben M, Watkins R : Pilocarpine dispensation from the soft hydrophilic contract lens. Br. J. Ophthalmol., 1975, 59, 455

173 Phillips CI, Bartholomew RS, Kazi G, Schmitt CJ, Vogel R : Penetration of timolol eye drops into human aqueous humour. Br. J. Ophthalmol., 1981, 65, 593

174 Soll DB : Evaluation of timolol in chronic open-angle glaucoma. Once a day vs. twice a day. Arch. Ophthalmol., 1980, 98, 2178

175 Krieglstein GK : A follow-up study on the intraocular pressure response of timolol eyedrops. Klin. Monatsbl. Augenheilkd., 1979, 175, 627

176 Merte HJ, Merkle W : Results of long-term treatment of glaucoma with timolol ophthalmic solution. Klin. Monatsbl. Augenheilkd., 1980, 177, 562

177 Steinert RF, Thomas JV, Boger WP III : Long-term drift and continued efficacy after multiyear timolol therapy. Arch. Ophthalmol., 1981, 99, 100

178 Bischoff P : Long-term results with timolol. Klin. Monatsbl. Augenheilkd., 1980, 176, 551

179 Airaksinen PJ, Valle O, Takki KK, Klemetti A : Timolol treatment of chronic open-angle glaucoma and ocular hypertension. A 2.5 year multicenter study. Graefe's Arch. Ophthalmol., 1982, 219, 68

180 Vesti Nielsen N : The ocular hypotensive effect of timolol in long-term treatment of glaucoma. A 4-year study. Acta. Ophthalmol., 1982, 60, 961

181 Maclure GM : Chronic open-angle glaucoma treated with timolol. A four year study. Trans. Ophthalmol. Soc. UK, 1983, 103, 78

182 Boger WP III : Timolol : short-term 'escape' and long-term 'drift'. Am. Ophthalmol., 1979, 11, 1239

183 Boger WP III : Short-term 'escape' and long-term 'drift'. The dissipation effects of the beta adrenergic blocking agents. Surv. Opthalmol., 1983, 28, 235

184 Sponsel WE, Dallas NL, Burbridge L : Visual field survival : The response to timolol therapy in open-angle glaucoma. Br. J. Ophthalmol., 1983, 67, 220

185 Becker B : The mechanism of the fall in intraocular pressure induced by the carbonic anhydrase inhibitor Diamox. Am J. Ophthalmol., 1955, 39, 177

186 Stein A, Pinke R, Krupin T, Glabb E, Podos SM, Serle J, Maren TH : The effect of topically administered carbonic anhydrase inhibitors on aqueous humor dynamics in rabbits. Am. J. Ophthalmol., 1983, 95, 222

187 Becker B : Misuse of acetazolamide. Am. J. Ophthalmol., 1957, 43, 799

188 Kronfeld PC : The efficacy of combination of ocular hypotensive drugs. A tonographic approach. Arch. Ophthalmol., 1967, 78, 140

189 Harris LS, Mittag TW, Galin MA : Aqueous dynamics of pilocarpine-treated eyes. The influence of topically applied epinephrine. Arch. Ophthalmol., 1971, 86, 1

190 Knupp JA, Shields MB, Mandell AI, Hurvitz LM, Spaeth GL : Combined timolol and epinephrine therapy for open-angle glaucoma. Surv. Ophthalmol., 1983, 28, 280

191 Keates EV : Evaluation of timolol maleate combination therapy in chronic open-angle glaucoma. Am. J. Ophthalmol., 1979, 88, 565

192 Smith RJ, Nagasubramanian S, Watkins R, Poinoosawmy D : Addition of timolol maleate to routine medical therapy : a clinical trial. Br. J. Ophthalmol., 1980, 64, 779

193 Thomas JV, Epstein DL : Timolol and epinephrine in primary open-angle glaucoma. Transient additive effect. Arch. Ophthalmol., 1981, 99, 91

194 Thomas JV, Epstein DL : Study of the additive effect of timolol and epinephrine in lowering IOP. Br. J. Ophthalmol., 1981, 65, 596

195 Goldberg I, Ashburn FS Jr, Palmberg PF, Kass MA, Becker B : Timolol and epinephrine. A clinical study of ocular interactions. Arch. Ophthalmol., 1980, 98, 484

196 Ashburn FS Jr, Gillespie JE, Kass MA, Becker B : Timolol plus maximum tolerated antiglaucoma therapy : a one-year follow-up study. Surv. Ophthalmol., 1979, 23, 389

197 Sonty S, Schwartz B : The additive effect of timolol on open-angle glaucoma patients on maximal medical therapy. Surv. Ophthalmol., 1979, 23, 381

198 Keates EV : Evaluation of timolol maleate combination therapy in chronic open-angle glaucoma. Am. J. Ophthalmol., 1979, 88, 565

199 Smith RJ, Nagasubramanian S, Watkins R, Poinoosawmy D : Addition of timolol maleate to routine medical therapy. A clinical trial. Br. J. Ophthalmol., 1980, 64, 779

200 Kass MA : Efficacy of combining timolol with other antiglaucoma medications. Surv. Ophthalmol., 1983, 28, 274

201 Kass MA, Korey M, Gordon M, Becker B : Timolol and acetazolamide. A study of concurrent administration. Arch. Ophthalmol., 1982, 100, 941

202 Granström PA, Norell S : Visual ability and drug regimen. Relation to compliance with glaucoma therapy. Acta. Ophthalmol., 1983, 61, 206

203 Abramson DH, Chang S, Coleman DJ : Pilocarpine therapy in glaucoma. Effects on anterior chamber depth and lens thickness in patients receiving long-term therapy. Arch. Ophthalmol., 1976, 94, 914

204 Poinoosawmy D, Nagasubramanian S, Brown NAP : Effect of pilocarpine on visual acuity and on the dimensions of the cornea and anterior chamber. Br. J. Ophthalmol., 1976, 60, 676

205 McCluskey DJ, Douglas JP, O'Connor PS, Story K, Ivy LM, Harvey JS : The effect of pilocarpine on the visual field in normals. Ophthalmology, 1986, 93, 843

206 Van Buskirk EM : Hazards of medical glaucoma therapy in the cataract patient. Ophthalmology, 1982, 89, 238

207 Beasley H, Fraunfelder FT : Retinal detachments and topical ocular miotics. Ophthalmology, 1979, 86, 95

208 Levene RZ : Uniocular miotic therapy. Trans. Am. Acad. Ophthalmol. Otol., 1975, 79, 376

209 Coles WH : Pilocarpine toxicity. Effects on the rabbit corneal endothelium. Arch. Ophthalmol., 1975, 93, 36

210 Axelsson U, Holmberg Å : The frequency of cataract after miotic therapy. Acta. Ophthalmol., 1966, 44, 421

211 Thoft RA : Incidence of lens changes in patients treated with echothiophate iodide. Arch. Ophthalmol., 1968, 80, 317

212 Van Buskirk EM : Hazards of Medical Glaucoma Therapy in the cataract Patient. Ophthalmology, 1982, 89, 238

213 Anderson JA : Systemic absorbtion of topical ocularly applied epinephrine & dipivefrin. Arch. Ophthalmol., 1980, 98, 350

214 Kolker AE, Becker B : Epinephrine maculopathy. Arch. Ophthalmol., 1968, 79, 552

215 Michels RG, Maumenee AE : Cystoid macular edema assocated with topical applied epinephrine in aphakic eyes. Am. J. Ophthalmol., 1975, 80, 379

216 Waltman SR, Yarian D, Hart W Jr, Becker B : Corneal endothelial changes with long-term topical epinephrine therapy. Arch. Ophthalmol., 1977, 95, 1357

217 Stefansson E, Robinson D, Wolbarsht ML, Landers MB III, Walsh A : Effect of epinephrine on PO_2 in anterior chamber. Arch. Ophthalmol., 1983, 101, 636

218 Schwartz HJ, Sher TH : Bisulphite intolerance manifest as bronchospasm following topical dipivefrin hydrochloride therapy for glaucoma (letter). Arch. Ophthalmol., 1985, 103, 14

219 Gloster J : Guanethidine & glaucoma. Trans. Ophthalmol. Soc. UK, 1974, 94, 573

220 McMahon CD, Shaffer RN, Hoskins HD Jr, Hetherington J Jr : Adverse effects experienced by patients taking timolol. Am. J. Ophthalmol., 1979, 88, 736

221 Van Buskirk EM : Adverse reactions from timolol administration. Ophthalmology, 1980, 87, 447

222 Van Buskirk EM : Corneal anaesthesia after timolol maleate therapy. Am. J. Ophthalmol., 1979, 88, 739

223 Coakes RL, Mackie IA, Seal DV : Effects of long-term treatment with timolol on lacrimal gland function. Br. J. Ophthalmol., 1981, 65, 603

224 Fraunfelder FT : Interim report : National Registry of possible drug-induced ocular side-effect. Ophthalmology, 1980, 87, 87

225 Zimmerman TJ, Baumann JD, Hetherington J Jr : Side effects of timolol. Surv. Ophthalmol., 1983, 28, 243

226 Caprioli J, Sears ML : Caution on the pre-operative use of topical timolol. Am. J. Ophthalmol., 1983, 95, 561

227 Doyle WJ, Weber PA, Meeks RH : Effect of topical timolol on exercise performance. Arch. Ophthalmol., 1984, 102, 1517

228 Jones FL Jr, Ekberg NL : Exacerbation of asthma by timolol. N. Engl. J. Med., 1979, 301, 270

229 Schoene RB, Martin TR, Charan NB, French U : Timolol-induced bronchospasm in asthmatic bronchitis. JAMA, 1981, 245, 1460

230 Van Buskirk EM, Fraunfelder FT : Ocular beta blockers & systemic effects. Am. J. Ophthalmol., 1984, 98, 623

230 Epstein DL, Grant WM : Carbonic anhydrase inhibitor side-effects. Serum chemical analysis. Arch. Ophthalmol., 1977, 95, 1378

231 Spaeth GL : Potassium, acetazolamide and intraocular pressure. Arch. Ophthalmol., 1967, 78, 578

232 Kass MA, Kolker AE, Gordon M, Goldberg I, Gieser DK, Krupin T, Becker B : Acetazolamide & urolithiasis. Ophthalmology, 1981, 88, 261

233 Grant WM : Antiglaucoma drugs : problems with carbonic anhydrase inhibitors. In: Leopold IH (Ed.) 'Symposium on Ocular Therapy', Vol. 6., CV Mosby Co., St Louis, 1972, p. 19

234 Mackenzie W : Practical treatise of the diseases of the Eye. London, Longman, Orme, Brown, Green & Longmans, 1st Ed. 1830, 2nd Ed. 1835, 3rd Ed. 1839

235 Von Graefe A : Uber die Iridectomie bei Glaucoma und uber den glaucomatosen process. V. Graefes Arch., Ophthalmol., 1857, 3, 456

236 Critchet G : Illustrative of a new method of treating deep seated inflammation of the globe or acute glaucoma. Roy. Lond. Ophthal. Hosp. Rep., 1857, 1, 57

237 De Wecker : Ber Dtsch Ophthal. Ges., 1867, 11, 297

238 De Wecker : Die Skerotomie als Glaukomoperation. Klin. Mbl. Augenheilkd., 1871, 9, 305

239 Robertson DA : Trephining the sclerotic - a new operation for glaucoma. Roy. Lond. Ophthal. Hosp. Rep., 1876, 8, 404

240 Herbert H : Subconjunctival fistula formation in the treatment of primary chronic glaucoma. Trans. Ophthalmol. Soc. UK, 1903, 23, 324

241 Holth S : Iridencleisis antiglaucomatosa. An.. d'Occul., 1907, 137, 345

242 Lagrange F : De l'iridectomie et de la sclerotomie combinees dans le traitment du glaucoma chronique. Procede nouveau pour l'establissement de la cicatrice filtrante. Bull. Soc. Franc. Ophtal., 1906, 23, 477

243 Lagrange F : Iridectomie et sclerotomie combinees dans le traitment du glaucoma chronique. Arch. d'Ophtal., 1906, 26, 481

244 Lagrange F : Traitment du glaucoma chronique par l'iridectomie et la sclerotomie combinees. ARch. d'Ophtal., 1907, 27, 439

245 Fergus F : Treatment of glaucoma by trephining. Br. Med. J., 1909, 2, 983

246 Elliot RH : A preliminary note on a new operation for the establishment of a filtering cicatrix in the treatment of glaucoma. Ophthalmoscope, 1909, 7, 804

247 Preziosi CL : The electro-cautery in the treatment of glaucoma. Br. J. Ophthalmol., 1924, 8, 414

248 Scheie HG : Retraction of scleral wound edges as a fistulizing procedure for glaucoma. Am. J. Ophthalmol., 1958, 45, 220

249 Watson P : Trabeculectomy. A modified ab extremo technique. Ann. Ophthalmol., 1970, 2, 199

250 Migdal C & Hitchings R : The developing bleb : Effect of topical antiprostaglandins on the outcome of glaucoma fistulising surgery. Br. J. Ophthalmol., 1983, 67, 655

251 Addicks EM, Quigley HA, Green WR, Robin AL : Histologic characteristics of filtering blebs in glaucomatous eyes. Arch. Ophthalmol., 1983, 101, 795

252 Teng CC, Chi HH, Katzin HM : Histology & mechanisms of filtering operations. Am. J. Ophthalmol., 1959, 47, 16

253 Benedikt O : The effect of filtering operations. Klin. Monatsbl. Augenheilkd., 1977, 170, 10

254 Kronfeld PC : The chemical demonstration of transconjunctival passage of aqueous after antiglaucomatous operations. Am. J. Ophthalmol., 1952, 35, 38

255 Galin MA, Baras I, McLean JM : How does a filtering bleb work? Trans. Am. Acad. Ophthalmol. Otol., 1965, 69, 1082

256 Maumenee AE : External filtering operations for glaucoma : The mechanism of function & failure. Trans. Am. Ophthalmol. Soc., 1960, 58, 319

257 Herschler J, Clafin AJ, Fiorentino G : The effect of aqueous humor on the growth of subconjunctival fibroblasts in tissue culture and its implications for glaucoma surgery. Am. J. Ophthalmol., 1980, 89, 245

258 Radius RL, Herschler J, Clafin A, Fiorentino G : Aqueous humor changes after experimental filtering surgery. Am. J. Ophthalmol., 1980, 89, 250

259 Gressel MG, Parrish RK II, Folberg R : 5-fluourouracil & glaucoma filtering surgery I : An animal model. Ophthalmology, 1984, 91, 378

260 Heuer DK, Parrish RK II, Gressel MG, Hodapp E, Palmberg PF, Anderson DR : 5-fluorouracil & glaucoma filtering surgery II : A pilot study. Ophthalmology, 1984, 91, 384

261 Holth S : Sclerectomie avec la pince emportepiece dans le glaucome. Ann. d'Ocul., 1909, 142, 1

262 Gass JDM : Anterior lip sclerectomy. A microsurgical technique for filtering operation for control of glaucoma. Ann. Ophthalmol., 1970, 2, 355

263 Potts AM : Some rationalizations on chronic open-angle glaucoma. Am. J. Ophthalmol., 1978, 86, 743

264 Gershen HJ : Lateral lip sclerectomy. Arch. Ophthalmol., 1971, 86, 534

265 Iliff CE, Hass JS : Posterior lip sclerectomy. Am. J. Ophthalmol., 1962, 54, 688

266 Sugar HS : Limboscleral trephination. Am. J. Ophthalmol., 1961, 52, 29

267 Sugar HS : Limboscleral trepanation. Eleven years' experience. Arch. Ophthalmol., 1971, 85, 703

268 Wadsworth JAC : Corneoscleral cautery. Pathology & technique. Arch. Ophthalmol., 1976, 94, 633

269 Shaffer, RN, Hetherington J Jr, Hoskins HD Jr : Guarded thermal sclerostomy. Am. J. Ophthalmol., 1971, 72, 769

270 King JH, Wadsworth JAC : An atlas of ophthalmic surgery, 2nd edition. J.B. Lippincott, Philadelphia, 1970, 418

271 Litwin RL : Successful argon laser sclerostomy for glaucoma. Ophthalmic Surg., 1979, 10, 22

272 March WF, Gherezghiher R, Koss MC et al. : Experimental YAG laser sclerostomy. Arch. Ophthalmol. 1984, 102, 1834

273 Sugar HS : Experimental trabeculectomy in glaucoma. Am. J. Ophthalmol 1961, 51, 623

274 Koryllos K : Trabeculectomy : a new glaucoma operation. Bull. Soc. Hellen. Ophthalmol., 1967, 35, 147

275 Phillips CI : Trabeculectomy 'ab externo'. Trans. Ophthalmol. Soc. UK, 1968, 88, 681

276 Linner E : Some experiences of microsurgical trabeculotomy & trabeculectomy ab externo in chronic simple glaucoma. Adv. Ophthalmol., 1970, 22, 132

277 Rich AM, McPherson SD : Trabeculectomy in the owl monkey. Ann. Ophthalmol., 1973, 5, 1082

278 Spencer WH : Histologic evaluation of microsurgical glaucoma technique. Trans. Am. Acad. Ophthalmol. Otol., 1972, 76, 389

279 Schmitt H : Histological examination on disks obtained by goniotrephining with scleral flap. Klin. Monatsbl. Augenheilkd., 1975, 167, 372

280 Taylor HR : A histologic survey of trabeculectomy. Am. J. Ophthalmol., 1976, 82, 733

281 Lalive d'Ephinay S, Reme C, Witner R : Influence of different topographical locations of trabeculectomy specimens on regulation of intraocular pressure and the quality of the filtering bleb. Klin. Monatsbl. Augenheilkd., 1983, 182, 387

282 Cairns JE : Trabeculectomy. Trans. Am. Acad. Ophthalmol. Otol., 1971, 75, 1395

283 Shields MB, Bradbury MJ, Shelbourne JD, Bell SW : The ultrastructure of human limbal collagen. Invest. Ophthalmol. Vis. Sci., 1977, 18, 864

284 Shields MB, Bradbury MJ, Shelbourne JD, Bell SW : The permeability of the outer layers of limbus and anterior sclera. Invest. Ophthalmol. Vis. Sci., 1977, 16, 866

285 Shields MB : Trabeculectomy vs. full-thickness filtering operation for control of glaucoma. Ophthalmic Surg., 1980, 11, 498

286 Benedikt O : The mode of action of trabeculectomy. Klin. Monatsbl. Augenheilkd., 1975, 167, 679

287 Benedikt O : Demonstration of aqueous outflow patterns of normal and glaucomatous human eyes through the injection of fluorescein solution in the anterior chamber. Graefe's Arch. Ophthalmol., 1976, 199, 45

288 Krasnov MM : A modified trabeculectomy. Ann. Ophthalmol., 1974, 6, 178

289 Dellaporta, A : Experiences with trepano-trabeculectomy. Trans. Am. Acad. Ophthalmol. Otol., 1975, 79, 362

290 David R, Sachs U : Quantitative trabeculectomy. Br. J. Ophthalmol., 1981, 65, 457

291 Welsh NH : Trabeculectomy with fistula formation in the African. Br. J. Ophthalmol., 1972, 56, 32

292 Shuster JN, Krupin T, Kolker AE, Becker B : Limbus- v. Fornix-based conjunctival flap in trabeculectomy. A long-term randomized study. Arch. Ophthalmol., 1984, 102, 361

293 Watson PG : Surgery of the glaucomas. Br. J. Ophthalmol., 1972, 56, 299

294 Watson PG, Barnett F : Effectiveness of trabeculectomy in glaucoma. Am. J. Ophthalmol., 1975, 79, 831

295 Smith BF, Schuster H, Seidenberg B : Subscleral sclerectomy : A double-flap operation for glaucoma. Am J. Ophthalmol, 1971, 71, 884

296 Schimek RA, Williamson WR : Trabeculectomy with cautery. Ophthalmic Surg., 1977, 8, 35

297 Beckmann H, Fuller TA, Boyman R, Mandell G, Nathan LE Jr : Carbon dioxide laser surgery of the eye and adnexa. Ophthalmology, 1980, 87, 990

298 Zimmerman TJ, Kooner KS, Ford VJ et al. : Effectiveness of non-penetrating trabeculectomy in aphakic eyes with glaucoma. Ophthalmic Surg., 1984, 15, 44

299 Weber PA, Keates RH, Opremcek EM, Kapetansky FM, Szymanski C : Two stage Nd : YAG laser trabeculotomy. Ophthalmic Surg., 1983, 14, 591

300 Smith R : A new technique for opening the canal of Schlemm. Br. J. Ophthalmol., 1960, 44, 370

301 Scheie HG : Filtering operations for glaucoma : a comparative study. Am. J. Ophthalmol., 1962, 53, 571

302 Bellows AR, Chylack LT Jr, Epstein DL, Hutchinson BT : Choroidal effusion during glaucoma surgery in patients with prominent episcleral vessels. Arch. Ophthalmol., 1979, 97, 493

303 Bellows AR, Chylack Lt Jr, Hutchinson BT : Choroidal detachment. Clinical manifestation, therapy & mechanism of formation. Ophthalmology, 1981, 88, 1107

304 Swan KC, Lindgren TW : Unintentional lens injury in glaucoma surgery. Trans. Am. Ophthalmol. Soc., 1980, 78, 55

305 Kozart DM, Eagle RC Jr : Stripping of Descemet's membrane after glaucoma surgery. Ophthalmic Surg., 1981, 12, 420

306 Petursson GJ, Fraunfelder FT : Repair of an inadvertent buttonhole or leaking filtering bleb. Arch. Ophthalmol., 1979, 97, 926

307 Sugar HS : Treatment of hypotony following filtering surgery for glaucoma. Am J. Ophthalmol., 1971, 71, 1023

308 Chandler PA, Maumenee AE : A major cause of hypotony. Am. J. Ophthalmol, 1961, 32, 609

309 Pedersen JE, Gaasterland DE, MacLellan HM : Experimental Ciliochoroidal detachment. Effect of intraocular pressure and aqueous humor flow. Arch. Ophthalmol., 1979, 97, 536

310 Brubaker RF, Pederson JE : Ciliochoroidal detachment. Surv. Ophthalmol., 1983, 27, 281

311 Simmons RJ, Kimbrough RL : Shell tamponade in filtering surgery for

glaucoma. Ophthalmic Surg., 1979, 10, 17

312 Hoskins HD Jr, Migliazzo C : Management of failing filtering blebs with the argon laser. Ophthalmic Surg., 1984, 15, 731

313 Hutchinson BT : Choroidal detachment and flat anterior chamber after filtering surgery in open angle glaucoma. In : 'Controversy in Ophthalmology'. Brockhurst RF, Boruchoff SA, Hutchinson BT, Lessell S, eds. WB Saunders Co., Philadelphia, 1977. Pg. 248

314 Starita RJ, Fellamn RL, Spaeth GL et al : Short- and long-term effects of post-operative corticosteroids on trabeculectomy. Ophthalmology, 1985, 92, 938

315 Giangiacomo J, Dueker DK, Adelstein E : The effect of pre-operative subconjunctival triamcinolone administration on glaucoma filtration. I. Trabeculectomy following subconjunctival triamcinolone. Arch. Ophthalmol., 1986, 104, 838

316 Moorhead LC, Stewart R, Kimbrough R et al. : Effects of topically applied beta-aminoproprionitrile after glaucoma filtrations surgery. ARVO Abstracts. Invest. Ophthalmol. Vis. Sci., 1984, 25 (Suppl.), 44

317 Heuer DK, Parrish RK/II, Gressel MG et al. : 5-fluoro-uracil & glaucoma filtering surgery. III. Intermediate follow-up of a pilot study. Ophthalmology, 1986, 93, 1537

318 O'Connell EJ, Karseras AG : Intraocular surgery in advanced glaucoma. Br. J. Opthalmol., 1976, 60, 124

319 Lawrence GA : Surgical treatment of patients with advanced glaucomatous field defects. Arch. Ophthalmol., 1969, 81, 804

320 Lichter PR, Ravin JG : Risks of sudden visual loss after glaucoma surgery. Am. J. Ophthalmol, 1974, 78, 1009

321 Aggarwal SP, Hendeles S : Risk of sudden visual loss following trabeculectomy in advanced primary open-angle glaucoma. Br. J. Ophthalmol., 1986, 70, 97

322 Van Buskirk EM : Cysts of Tenon's capsule following filtration surgery. Am. J. Ophthalmol., 1982, 94, 522

323 Hitchings RA, Grierson I : Clinico-pathological correlation in eyes with failed fistulising surgery. Trans. Ophthalmol. Soc. UK, 1983, 103, 84

324 David R, Freedman J, Luntz MH : Comparative study of Watson's & Cairn's trabeculectomies in a Black population with open angle glaucoma. Br. J. Ophthalmol., 1977, 61, 117

325 Cairns JE : Trabeculectomy. Trans. Am. Acad. Ophthalmol. Otol., 1972, 76, 384

326 Shaffer RN : Microsurgery on outflow channels. Trans. Am. Acad. Ophthalmol. Otol., 1972, 76, 411

327 Blondeau P, Phelps CD : Trabeculectomy vs. thermosclerostomy. A randomised prospective clinical trial. Arch. Ophthalmol., 1981, 99, 810

328 Shirato S, Kitzawa Y, Mishima S : A critical analysis of the trabeculectomy results by a prospective follow-up design. Jpn. J. Ophthalmol., 1982, 26, 468

329 Watkins PH Jr, Brubaker RF : Comparison of partial-thickness and full-thickness filtration procedures in open-angle glaucoma. Am. J. Ophthalmol., 1978, 86, 756

331 Zaidi AA : Trabeculectomy : A review & 4-year follow-up. Br. J. Ophthalmol., 1980, 64, 436

332 Levene RZ : Glaucoma filtering surgery : Factors that determine control. Ophthalmic Surg., 1984, 15, 475

333 Lamping KA, Bellows R, Hutchinson BT, Afran SI : Long-term evaluation of initial filtration surgery. Ophthalmology, 1986, 93, 91

334 Ridgway AEA : Trabeculectomy. A follow-up study. Br. J. Ophthalmol., 1974, 58, 680

335 Miller RD, Barber JC : Trabeculectomy in black patients. Ophthalmic Surg., 1981, 12, 46

336 Hashimoto M, Okinami S, Ohkuma M : Trabeculectomy. A follow-up study. Acta. Soc. Ophthalmol. Jpn., 1977, 81, 1847

337 Mochizuchi M, Takase M,Kitazawa Y : Trabeculectomy. A follow-up study. Jpn. J. Clin. Ophthalmol., 1977, 31, 797

338 Honrubia FM, Grijalbo P, Gomez L, Tamargo D : A long-term study of trabeculectomy. Glaucoma, 1983, 5, 284

339 Cohen JS, Shaffer RN, Hetherington J Jr, Hoskins D : Revision of filtration surgery. Arch. Ophthalmol., 1977, 95, 1612

340 Hattenhauer JM, Lipsich MP : Late endophthalmitis after filtering surgery. Am. J. Ophthalmol., 1971, 72, 1097

341 Tabbara KF : Late infections following filtering procedures. Ann. Ophthalmol., 1976, 8, 1228

342 Paglen PG : Abbott RL, Webster RG Jr : Late onset bilateral endophthalmitis after trabeculectomy. Ocul. Ther. Surg., 1982, Jan - Feb, 33

343 Lobue TD, Deutsch TA, STein RM : Moraxella nonliquifaciens endophthalmitis after trabeculectomy. Am. J. Ophthalmol., 1985, 99, 343

344 Freedman J, Gupta M, Burke A : Endophthalmitis after trabeculectomy. Arch. Ophthalmol., 1978, 96, 1017

345 Haas J : Surgical treatment of open-angle glaucoma. In 'Symposium on Glaucoma', New Orleans Ophthalmologic Society, CV Mosby Co., St. Louis, 1967, p. 183.

346 Sugar HS : Cataract and filtering surgery. Am. J. Ophthalmol., 1970, 69, 740.

347 Schwartz AL, Anderson DR : Trabecular surgery. Arch. Ophthalmol., 1974, 92, 134

348 Marion JR, Shields MB : Thermal sclerotomy & posterior lip sclerotomy : a comparative study. Ophthalmic Surg., 1978, 9, 67

349 Bellows AR, Chylack LT Jr, Hutchinson BT : Choroidal detachment : clinical manifestation, therapy and mechanism of formation. Ophthalmology, 1981, 88, 1107

350 Sugar HS : Postoperative cataracts in successfully filtering glaucomatous eyes. Am. J. Ophthalmol., 1970, 69, 740

351 McPherson SD Jr, Chine JW, McCurdy DL : Recent advances in glaucoma surgery, trabeculotomy and trabeculectomy. Ann. Ophthalmol., 1978, 9, 91

352 Jerndal T, Lundstrom M : 330 trabeculectomies - a follow-up study through 1/2 - 3 years. Acta Ophthalmol., 1977, 55, 52.

353 Loewenthal LM : Trabeculectomy as treatment for glaucoma : A preliminary report. Ann. ophthalmol., 1977, 9, 1179.

354 Jay JL, Murray SB : Characteristics of reduction of intraocular pressure after trabeculectomy. Br. J. Ophthalmol., 1980, 64, 423

355 Busse H, Kuchle HJ, Wahning A : Long-term follow-up after goniotrepanation with scleral flap. Klin. Monatsbl. Augenheilkd., 1984, 184, 261

356 Drance SM, Vargas E : Trabeculectomy and thermosclerotomy : a comparison of two procedures. Can. J. Ophthalmol., 1973, 8, 413

357 Bakker NJA, Manku SI : Trabeculectomy versus Scheie's operation : a

comparative retrospective study in open-angle glaucoma in Kenyans. Br. J. Ophthalmol., 1979, 63, 643

358 Spaeth GL, Poryzees E : A comparison between peripheral iridectomy with thermal sclerostomy and trabeculectomy : a controlled study. Br. J. Ophthalmol., 1981, 65, 783

359 Lewis RA, Phelps CD : Trabeculectomy vs. thermosclerotomy. A 5-year follow-up. Arch. Ophthalmol., 1984, 102, 533

360 Freedman J, Sher E, Ahrens M : Trabeculectomy in a Black American population. Br. J. Ophthalmol., 1976, 60, 573

361 Ferguson JG Jr, MacDonald R Jr : Trabeculectomy in Blacks : a two-year follow-up. Ophthalmic Surg., 1977, 8, 41

362 Thommy CP, Bhar IS : Trabeculectomy in Nigerian patients with open-angle glaucoma. Br. J. Ophthalmol., 1979, 63, 636.

363 Sandford-Smith JH : The surgical treatment of open-angle glaucoma in Nigerians. Br. J. Ophthalmol., 1978, 62, 283

364 Kietzman B : Glaucoma surgery in Nigerian eyes : a five-year study. Ophthalmic Surg., 1976, 7, 52

365 Martin MJ, Sommer A, Gold EB, Diamond EL : Race & primary open-angle glaucoma. Am. J. Ophthalmol., 1985, 99, 383

366 Gressel MG, Heuer DK, Parrish RK : Trabeculectomy in young patients. Ophthalmology, 1984, 91, 1242

367 Stewart RH, Kimbrough RL, Bachh H, Allbright M : Trabeculectomy & modifications of trabeculectomy. Ophthalmic Surg., 1979, 10, 76

368 Jay JL : Earlier trabeculectomy. Trans. Ophthalmol. Soc. UK, 1983, 103, 35

369 Spaeth GL, Joseph NH, Fernandes E : Trabeculectomy : a re-evaluation after three years and a comparison with Sheie's procedure. Trans. Am. Acad. Ophthalmol. Otol., 1975, 79, 349

370 Maiman TH : Stimulated optical radiation in ruby. Nature, 1960, 187, 493

371 Zweng HC, Flocks M : Experimental photocoagulation of the anterior chamber angle. A preliminary report. Am. J. Ophthalmol., 1961, 52, 163

372 Krasnov MM : Laser puncture of the anterior chamber angle in glaucoma. Vesta Oftal, 1972, 3, 27

373 Hager H : Besondere mikrochirurgische Eingriffe II. Erste

Erfahrungen mit der Argon-laser-gerat 800. Klin. Monatsbl. Augenheilkd., 1973, 163, 437

374 Demailly, P, Haut J, Bonnet-Boutier M : Trabeculotomie au laser a l'argon (note preliminaire). Bull. Soc. Ophthalmol. Fr., 1973, 73, 259

375 Worthen DM, Wickham MG. Argon laser trabeculotomy. Trans. Am. Acad. Ophthalmol. Otol., 1974, 78, 371

376 Gasterland D, Kupfer C : Experimental glaucoma in the rhesus monkey. Invest. Ophthalmol., 1975, 14, 455

377 Ticho V, Zauberman H : Argon laser application to angle structures in the glaucomas. Arch. Ophthalmol., 1976, 94, 61

378 Pohjanpelto P : Argon laser treatment of the anterior chamber angle for increased intraocular pressure. Acta. Ophthalmol., 1981, 59, 211

379 Schwartz AL, Koppelman J : Four years experience with argon laser trabecular surgery in uncontrolled open-angle glaucoma. Ophthalmology, 1983, 90, 771

380 Horns DJ, Bellows AR, Hutchinson BT, Allen RC : Argon Laser Trabeculoplasty for open-angle glaucoma. A retrospective study of 380 eyes. Trans. Ophthalmol. Soc. UK, 1983, 103, 288

381 Tuulonen A, Airaksinen PJ : Laser trabeculoplasty. I. In simple & capsular glaucoma. Acta. Ophthalmol., 1983, 61, 1009

382 Moulin F & Haut J : Results of treatment by argon laser in 100 eyes with primary open-angle glaucoma (Trabeculoplasty - Trabecular Retraction). J. Fr. Ophthalmol., 1983, 6, 661

383 Grinich NP, Van Buskirk EM, Samples JR : Three-year efficacy of argon laser trabeculoplasty. Ophthalmology, 1987, 94, 858

384 Shingleton BJ, Richter CV, Bellows AR, Hutchinson BT, Glynn RJ : Long-term efficacy of argon laser trabeculoplasty. Ophthalmology, 1987, 94, 1513

385 Shirato S, Yakamoto T, Kitazawa Y : Argon laser trabeculoplasty in open-angle glaucoma. Jpn. J. Ophthalmol., 1982, 26, 374

386 Wickham MG, Worthen DM : Argon laser trabeculoplasty. Long-term follow-up. Ophthalmology, 1979, 86, 495

387 Smith RJH : Laser trabeculoplasty : a report on fifty-three patients. Klin. Monatsbl. Augenheilkd., 1984, 185, 9

388 Moulin F, Haut J, Abi Rached J : Late failures of trabeculoplasty.

Int. Ophthalmol., 1987, 10, 61

389 Wise JB : Ten year results of laser trabeculoplasty. Does the laser avoid glaucoma surgery or merely defer it? Eye, 1987, 1, 45

390 Lichter PR : Argon laser trabeculoplasty. Trans. Am. Ophthalmol. Soc., 1982, 80, 288

391 Brubaker RF, Liesegang TJ : Effect of trabecular photocoagulation on the aqueous humor dynamics of the human eye. Am. J. Ophthalmol., 1983, 96, 139

392 Araie M, Yamamoto T, Shirato S, Kitazawa Y : Effects of laser trabeculoplasty on the human aqueous humor dynamics. Am. J. Ophthalmol., 1984, 16, 540

393 Yablonski ME, Cook DJ, Gray J : A fluorophotometric study of the effect of argon laser trabeculoplasty on aqueous humor dynamics. Am. J. Ophthalmol., 1985, 99, 579

394 Rodriques MM, Spaeth GL, Donohoo P : Electron microscopy of argon laser therapy in open-angle glaucoma. Ophthalmology, 1982, 89, 198

395 Van Buskirk EM, Rosenquist RC, Pond V : Laser trabeculoplasty : studies on mechanism of action. Ophthalmology, 1983, 90 (August Suppl), 60

396 Alvarado JA : Laser photocoagulators for glaucoma research and therapy. Arch. Ophthalmol., 1984, 102, 1004

397 Van Buskirk EM, Ponud V, Rosenquist RC, Acott TS : Argon laser trabeculoplasty : studies of mechanism of action. Ophthalmology, 1984, 91, 1005

398 Zink H, Kampik A, Lund O-E : Argon laser trabeculoplasty : initial results of a prospective study. Klin. Monatsbl. Augenheilkd., 1984, 184, 278

399 Forbes M, Bansal RK : Argon laser goniophotocoagulation of the trabecular meshwork in open-angle glaucoma. Trans. Am. Ophthalmol. Soc., 1981, 76, 257

400 Nesterov AR, Mamedov NG : Argon laser trabeculostretching in open-angle glaucoma. Glaucoma, 1985, 7, 116

401 Raitta C, Letto I : Laser trabeculoplasty in open-angle glaucoma. Acta Ophthalmol., 1983, 61, 673

402 Pollack IP, Robin AL : Argon laser trabeculoplasty : its effect on medical control of open-angle glaucoma. Ophthalmic Surg., 1982, 13, 637

403 Pollack IP, Robin AL, Sax H : The effect of argon laser trabeculoplasty on the medical control of primary open-angle glaucoma. Ophthalmology, 1983, 90, 785

404 Fink AI, Jordan AJ : Laser trabeculoplasty and decay effects on glaucoma patients. J. Roy. Soc. Med., 1984, 77, 97

405 Fink AI, Jordan AJ, Bunke A, Fong D : Argon laser trabecular surgery as an alternative to carbonic anhydrase therapy. Trans. Ophthalmol. Soc. UK, 1982, 102, 125

406 Greenidge KC, Spaeth GL, Fiol-Silva Z : Effect of argon laser trabeculoplasty on the glaucomatous diurnal curve. Ophthalmology, 1983, 90, 800

407 Brooks AMV, Gillies WE : Do any factors predict a favourable response to laser trabeculoplasty? Aus. J. Ophthalmol., 1984, 12, 149

408 Belcher CD, Thomas JV, Simmons RJ : Photocoagulation in glaucoma & anterior segment disease. Baltimore, Williams & Wilkins, 1984, p. 83

409 Zborowski L, Ritch R, Podos SM, Boas R : Prognostic features in laser trabeculoplasty. Acta. Ophthalmol., 1984, 62, 142

410 Tuulonen AN, Airaksinen J, Kuulasmaa K : Factors influencing the outcome of laser trabeculoplasty. Am. J. Ophthalmol., 1985, 99, 388

411 Schwartz AL, Petman K, Whitten M : Argon laser trabeculoplasty in progressive low-tension glaucoma. Ann. Ophthalmol., 1984, 16, 560

412 Sharpe ED, Simmons RJ : Argon laser trabeculoplasty as a means of decreasing intraocular pressure from 'normal' levels in glaucomatous eyes. Am. J. Ophthalmol., 1985, 99, 704

413 Robin AL, Pollack IP : Argon laser trabeculoplasty in secondary forms of open-angle glaucoma. Arch. Ophthalmol, 1983, 101, 382

414 Lieberman MF, Hoskins HD Jr, Hetherington J Jr : Laser trabeculoplasty and the glaucomas. Ophthalmology, 1983, 90, 790

415 Lunde MW : Argon laser trabeculoplasty in pigmentary dispersion syndrome with glaucoma. Am. J. Ophthalmol., 1983, 96, 721

416 Strasser G, Hauff W : Argon laser trabeculoplasty (ALT) in secondary glaucoma. Klin. Monatsbl. Augenheilkd., 1984, 185, 412

417 Tuulonen A, Airaksinen PJ : Laser trabeculoplasty. II. In secondary glaucoma and after failed trabeculectomy in primary open-angle glaucoma. Acta Ophthalmol., 1983, 61, 1016

418 Fellman RL, Starita RJ, Spaeth GL, Poryzees EM : Argon laser trabeculoplasty following failed trabeculectomy. Ophthalmic Surg., 1984, 15, 195

419 Safran MJ, Robin AL, Pollack IP : Argon laser trabeculoplasty in younger patients with primary open-angle glaucoma. Am. J. Ophthalmol., 1984, 97, 292

420 Krupin T, Patkin R, Kurata FK et al. : Argon laser trabeculoplasty in black & white patients with primary open-angle glaucoma. Ophthalmology, 1986, 93, 811

421 Brown SVL, Thomas JV, Simmons RJ : Laser trabeculoplasty re-treatment. Am. J. Ophthalmol., 1985, 99, 8

422 Starita RJ, Fellman RL, Spaeth GL, Poryzees E : The effect of repeating full-circumference argon laser trabeculoplasty. Ophthalmic Surg., 1984, 15, 41

423 Richter CU, Shingleton BJ, Bellows AR, Hutchinson BT, Jacobson LP : Retreatment with argon laser trabeculoplasty. Ophthalmology, 1987, 94, 1085

424 Gilbert CM, Brown RH, Lynch MG : The effect of argon laser trabeculoplasty on the rate of filtering surgery. Ophthalmology, 1986, 93, 362

425 Heijl A, Bengtsson B : The short-term effect of laser trabeculoplasty on the glaucomatous visual field. A prospective study using computerized perimetry. Acta. Ophthalmol., 1984, 62, 705

426 Holmin C, Bauer B : Laser trabeculoplasty in open-angle glaucoma. a short-term study using computerised perimetry. Acta. Ophthalmol., 1984, 62, 337

427 Holmin C, Krakau CET : Trabeculoplasty and visual field decay : a follow-up study using computerized perimetry. Current Eye Res., 1984, 3, 1101

428 Traverso C, Spaeth GL, Fellman RL, et al. : The effect of argon laser trabeculoplasty on the visual field of patients with glaucoma. Proc. of the 6th Int. Vis. Field Sympos., 1985, Publ. W. Junk, Eds. Heijl A & Greve EL, p.365

429 Schultz JS, Werner EB, Krupin T, Bishop KI, Koelle J : Intraocular pressure and visual field defects after argon laser trabeculoplasty in chronic open-angle glaucoma. Ophthalmology, 1987, 94, 553

430 Schwartz LW, Spaeth GL, Traverso C, Greenridge KC : Variations of techniques on the results of argon laser trabeculoplasty. Ophthalmology : 1983, 90, 781

431 Weinreb RN, Ruderman J, Juster R, Wilensky JT : Influence of the number of laser burns administered on the early results of argon laser trabeculoplasty. Am. J. Ophthalmol., 1983, 95, 287

432 Lustgarten H, Podos SM, Ritch R et al. : Laser trabeculoplasty. A prospective study of the treatment variables. Arch. Ophthalmol., 1984, 102, 517

433 Heijl A : One- and two-session laser trabeculoplasty. A randomized prospective study. Acta. Ophthalmol., 1984, 62, 715

434 Klein HZ, Shields MB, Earnest JT : Two-stage argon laser trabeculoplasty in open-angle glaucoma. Am. J. Ophthalmol., 1985, 99, 392

435 Weinreb RN, Ruderman J, Juster R, Zweig K : Immediate intraocular pressure response to argon laser trabeculoplasty. Am. J. Ophthalmol., 1983, 95, 279

436 Wilensky JT, Weinreb RW : Low-dose trabeculoplasty. Am. J. Ophthalmol., 1983, 95, 423

437 Takenaka Y, Yamamoto T, Shirato S : One-quadrant argon laser trabeculoplasty and its indication. Jpn. J. Ophthalmol., 1987, 31, 483

438 Traverso CE, Greenidge KC, Spaeth GL : Formation of peripheral anterior synechiae following argon laser trabeculoplasty. A prospective study to determine relationship to position of laser burns. Arch. Ophthalmol., 1984, 102, 861

439 Ofner S, Samples JR, Van Buskirk EM : Pilocarpine and the increase in intraocular pressure after trabeculoplasty. Am. J. Ophthalmol, 1984, 97, 647

440 Ruderman JM, Zweig KO, Wilensky JT, Weinreb RN : Effects of corticosteroid pre-treatment on argon laser trabeculoplasty. Am. J. Ophthalmol., 1983, 96, 84

441 Weinreb RN, Robin AL, Baerveldt G et al. : Flurbiprofen pretreatment in argon laser trabeculoplasty for primary open-angle glaucoma. Arch. Ophthalmol., 1984, 102, 1629

442 Pappas HR, Berry DP, Partamian L, Hertzmark E, Epstein DK : Topical indomethacin therapy before argon laser trabeculoplasty. Am. J. Ophthalmol., 1985, 99, 571

443 Hoskins HD Jr, Hetherington J Jr, Minckler DS, Lieberman MF, Shaffer RN : Complications of laser trabeculoplasty. Ophthalmology, 1983, 90, 796

444 Levene R : Major early complications of laser trabeculoplasty. Ophthalmic Surg., 1983, 14, 947

445 Krupin T, Kolker AE, Kass MA, Becker B : Intraocular pressure the day of argon laser trabeculoplasty in primary open-angle glaucoma. Ophthalmology, 1984, 91, 361

446 Greenidge KC, Rodrigues MM, Spaeth GL, Traverso CE, Weinreb S : Acute intraocular pressure elevation after argon laser trabeculoplasty and iridectomy : a clinico-pathological study. Ophthalmic Surg., 1984, 15, 105

447 Feller DB, Weinreb RN : Breakdown and re-establishment of blood-aqueous barrier with laser trabeculoplasty. Arch. Ophthalmol., 1984, 102, 537

448 Hong C, Kitazawa Y, Tanishima T : Influence of argon laser treatment of glaucoma on corneal endothelium. Jpn. J. Ophthalmol., 1983, 27, 567

449 Traverso C, Cohen EJ, Groden LR, Cassel GH, Laibson PR, Spaeth GL : Central corneal endothelial cell density after argon laser trabeculoplasty. Arch. Ophthalmol., 1984, 102, 1322

450 Van der Zypen E, Fankhauser F : Ultrastructural changes of the trabecular meshwork of the monkey (Macaca speciosa) following irridation with argon laser light. Graefe's Arch. Ophthalmol., 1984, 221, 249

451 Schoenleber DB, Bellows AR, Hutchinson BT : Failed laser trabeculoplasty requiring surgery in open-angle glaucoma. Ophthalmic Surg., 1987, 18, 796

452 Grierson I, Lee WR : The fine structure of the trabecular meshwork at graded levels of intraocular pressure. II. Pressure outside the physiological range (0 & 50 mmHg). Exp. Eye Res., 1975, 20, 523

453 Grierson I, Johnson NF : The post-mortem vacuoles of Schlemm's canal. Graefe's Arch. Clin. Exp. Ophthalmol., 1981, 215, 249

454 Lee WR, Grierson I : The effects of hypotension and blood overload on the outflow system. In Naumann Gott, Gloor B (Eds) : 'Wundheilung des auges und ihre Komplikationen'. Munich, Bergman Verlag, 1980, 89

455 Lutjen-Drecoll E, Baranys EH : Functional and electron microscopic changes in the trabecular meshwork remaining after trabeculectomy in cynomologus monkeys. Invest. Ophthalmol. Vis. Sci., 1974, 13, 511

456 Lutjen-Drecoll E, Kaufman PL : Echothiophate-induced structural alterations in the anterior chamber angle of the cynomologus monkey. Invest. Ophthalmol. Vis. Sci., 1979, 18, 918

457 Thomas JV, EL-Moftyi A, Hamdy EE, Simmons RJ : Argon laser trabeculoplasty as initial therapy for glaucoma. Arch. Ophthalmol., 1984, 102, 702

458 Rosenthal AR, Chaudhuri PR, Chiapella AP : Laser trabeculoplasty primary therapy in open angle glaucoma : a preliminary report. Arch. Ophthalmol., 1984, 102, 699

459 Tuulonen A : Laser trabeculoplasty as primary therapy in chronic open angle glaucoma. Acta. Ophthalmol., 1984, 62, 150

460 Fink AL, Jordan AJ, Lao PN : The therapeutic limitations of argon laser trabeculoplasty. Trans. Am. Ophthalmol. Soc., 1985, 83, 236

461 Wright P : Cicatrising conjunctivitis. Trans. Ophthalmol. Soc. UK, 1986, 105, 1

462 Dvetkovic D, Parlinovic A, Kontic D : Conjunctival changes in local long-term medical glaucomatous therapy. Ophthalmology, 1986, 83, 407

463 Varga M, Follman P : Electron microscopic studies of the conjunctival surface after long-term timolol application. Ophthalmology, 1986, 83, 153

464 Hitchings RA, Sherwood MB, Grierson I, Migdal C : Chronic glaucoma therapy : does it affect the conjunctiva? Poster presentation. American Academy of Ophthalmology, 1988

465 Leighton DA, Phillips CO : Systemic blood pressure in opan-angle glaucoma, low tension glaucoma and the normal eye. Br. J. Ophthalmol., 1972, 56, 447-453

466 Krill AE, Newell FW, Novak M : Early & long-term effects of levo-epinephrine on ocular tension and outflow. Am. J. Ophthalmol., 1965, 59, 833

467 Harris LS : Dose-response analysis of echothiophate iodide. Arch. Ophthalmol., 1971, 86, 502

468 Barsam PC : Comparison of the effect of pilocarpine and echothiophate on intraocular pressure and outflow facility. Am. J. Ophthalmol., 1972, 73, 742

469 Mills KB : Blind randomised non-crossover long-term trial comparing topical timolol 0.25% with timolol 0.5% in the treatment of simple chronic glaucoma. Br. J. Ophthalmol., 1983, 67, 216

SECTION II

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Chapter 7

MATERIAL & METHODS

7.1 Purpose of Study

This randomly allocated prospective clinical study was designed to assess the relative efficacy of the three forms of therapy used as primary (i.e. initial) therapy for chronic open-angle glaucoma, with particular regard to the level of IOP control and the amount of visual field decay. No patient had received any antiglaucoma therapy prior to entry into the trial.

Although chronic open-angle glaucoma is a 'long-term' disease, and the full effects of therapy need to be assessed over a long period, specific conclusions can be reached over the shorter term, and trends established. This study commenced in March 1983. The period of follow-up at the time of compiling this thesis ranged from a minimum of 3 years to a maximum of 5 years.

7.2 Design

A. Numbers

168 patients presenting to Moorfields Eye Hospital, London, with untreated chronic open angle glaucoma were entered into the trial. These patients were either picked up routinely when they attended the Casualty Department for some other complaint, or had been referred by their optician or general practitioner following either a routine screening or the development of visual symptoms. (See Appendix 13 for details of informed consent.)

The three treatment groups were as follows: 56 patients who received medical treatment, 57 surgery and 55 laser. These numbers allowed for statistically relevant conclusions to be drawn when comparing the performance of the three groups.

B. Minimum criteria necessary for inclusion in the trial

1. IOP $\geq$ 24 mmHg on two occasions.

2. Cup : disc ratio > 0.6, and/or notching, and/or pallor of the neuroretinal rim.

3. Glaucomatous field loss using the Friedmann Field Analyser (Mark I). The minimal acceptable defect was the loss of at least 3 adjacent

spots at intensities 0.4 log units greater than threshold up to maximum intensity and/or one absolute defect.

4. Open drainage angle.

C. Selection / randomisation

Once the inclusion criteria had been satisfied, the patients were randomly allocated, using computer selection, into one of the three treatment groups.

In bilateral asymmetrical disease, the 'worse' eye was entered into the trial. In symmetrical disease, there was random allocation, with conventional glaucoma therapy being given to the second eye.

In order to eliminate bias as much as possible when carrying out the follow-up measurements, treatments and the trial/non-trial eyes were coded on the follow-up record sheet.

7.3 Principles of the Three Types of Treatment

A. Medical

Treatment with pilocarpine, and/or a sympathomimetic, and/or timolol was give as the initial treatment, increasing to maximum tolerated medical therapy which could, in individual cases, require three topical medications and a carbonic anhydrase inhibitor.

Pilocarpine was used in strengths of 2% and 4% given four times daily. Gutt. Neutral Adrenalin 1% (Eppy) was given twice daily. A combination of Guanethidine and Adrenalin (Ganda) was given twice daily in strengths 1% + 0.2% or 3% + 0.5%, while timolol maleate (Timoptol) was given twice daily in a concentration of 0.25%. Acetazolamide (Diamox) was given in tablet form either 125 mg or 250 mg four times daily.

Medical therapy was altered if the patient complained of significant side effects or if the pressure was not adequately controlled. Other medications or combinations of medications were tried up to maximum tolerated medical treatment.

B. Surgical

A Cairn's-type trabeculectomy was performed using either a fornix- or limbal-based conjunctival flap.

The technique was briefly as follows: After the conjunctiva had been reflected, a 4 x 4 mm scleral flap based on the limbus, half scleral thickness, was fashioned. No paracentesis was performed. A block of

tissue 3 x 2 mm anterior to the scleral spur (including Schwalbe's line) was then excised and a peripheral iridectomy performed. The scleral flap was re-sutured using 2 10.0 nylon sutures and the conjunctiva closed using continuous or interrupted sutures. [Plate 6]

Post-operatively, the patients received Gutt. Dexamethazone 0.1% Q.I.D., Gutt. Atropine 1% B.D. and Gutt. Chloramphenicol Q.I.D. for four weeks.

The surgery was performed by the consultant, residents or fellows at Moorfields in a random fashion, under general anaesthesia. (To remove any bias on follow-up, none of the operations in this study were performed by C.S.M.)

C. Laser

Two treatments, each consisting of 50 burns over 180° of the anterior trabecular meshwork, were carried out separated by an interval of two weeks. A spot size of 50 microns, exposure time 0.1 seconds and power 0.5 - 1 watt were used, aiming to achieve transient blanching or minute gas-bubble formation. [Plate 7]

Patients were given Gutt. Pilocarpine 4% immediately pre-treatment in an attempt to prevent the post-operative pressure spike. Post-treatment, the patients were given Gutt. Predsol 0.3% Q.I.D. for four days.

Because of ethical considerations, patients in the laser group were given Gutt. Pilocarpine 2% Q.I.D. for the first two weeks after treatment. This was then tailed off, provided the IOP remained normal. However, Gutt. Pilocarpine 2% Q.I.D. was regarded as permissible adjuvant therapy for patients not controlled by laser alone. Any further requirement to maintain a normal pressure, was regarded as a laser failure.

7.4 Methods of Measurements & Analysis

A. Intraocular pressure

IOP's were measured with the Goldmann applanation tonometer fitted to the Haag-Streit slit-lamp, following the instillation of a mixture of Gutt. benoxinate and fluorescein.

B. Visual fields

At the commencement of the trial, the visual fields of all patients were assessed using the Friedmann Field Analyser (Mark I). This method was chosen as it was felt that the relatively gross defect picked up by the

instrument would guarantee there being a definite glaucomatous field defect present. The first field was used for diagnosis and entry into the trial. Progress of the patient was compared using the initial field as a baseline.

Using the Friedmann apparatus, the patient's retinal threshold was calculated and the test was carried out at intensities 0.4 log units greater than threshold intensity, then at steps of 0.2 log units, up to maximal intensity.

A field score was allocated to each eye at each visit [Plate 8]. This was achieved by counting the number of spots missed at light intensities between 0.4 log units greater than threshold and maximum (i.e. the relative field defects), and those spots missed at maximum intensity (i.e. the absolute field defects). This gave two numerical values for each eye at each test. Due to frequent inaccuracies with the eight most peripheral spots in the upper and lower quadrants, these were subtracted and an "adjusted" score thus obtained (see example of field scoring [Plate 8]).

After the first year, Goldmann fields were also carried out, alternating with the Friedmann fields. For the last 18 months, the Humphrey Automated Visual Field Analyser was substituted for the Goldmann apparatus. Only the results of the Friedmann fields will be discussed in this report because of the short follow-up period thus far of the Humphrey fields.

C. Optic discs

Disc photography was carried out at regular intervals, after dilatation of the pupils. The optic discs were photographed on entry into the trial and thereafter at yearly intervals. [Plate 9] Progression was estimated by careful comparison of successive photos for increasing neuroretinal rim loss.

A Kowa RC-XV fundus camera with 20° field and a magnification of 3 - 7 x was used. The film was Ektachrome 64.

In addition, the cup : disc ratio was estimated clinically.

D. Phasings

In an attempt to assess the diurnal variation in IOP, the patients were admitted for a daytime phasing on an annual basis, when the IOP's were measured at two hourly intervals between 9.30 a.m. and 3.30 p.m. These times were chosen due to the practical logistics of transporting the patients to and from a hospital in central London.

E. Visual acuity

This was tested on the Snellen chart with corrective refraction where applicable. If a reduction in the visual acuity was noted at follow-up, a pin-hole aperture was used to ascertain whether this improved the acuity to the previous level, and the patient was instructed to see his local optician for a check refraction.

7.5 Documentation

A. Initial visit

At the first visit, the patient's age, medical history, family history of glaucoma and drug therapy were documented.

The visual acuities, IOP's, cup : disc ratios and Friedmann fields were charted, and the optic disc photographed.

B. Follow-up

All patients were seen for regular follow-up. After treatment had been commenced, the patients were seen monthly for the first three months, and then at 3-monthly intervals.

The visual acuity, IOP and cup : disc ratio were measured at each clinic visit.

Friedmann fields were plotted at three, six and twelve months during the first year, and then every 6 months (alternating with a Goldmann or Humphrey field).

The discs were photographed annually.

A daytime phasing was carried out at the beginning of each year of follow-up.

The results were tabulated on a follow-up sheet in a numerical fashion, which included a 'score' calculated from each Friedmann field. These figures were transferred onto the computer at the Institute of Ophthalmology for further analysis.

7.6 Failures

A. Definition of success and failure

Treatment was considered successful if the pressure had been reduced to < 22 mmHg by three months and kept below that level.

Treatment was considered unsuccessful if the pressure was > 22 mmHg after 3 months.

Because of short-term fluctuations, the visual fields were averaged over a minimum of five successive fields to assess whether a deterioration in the field had occurred.

B. Treatment of failures

In the event of failure, the second line of treatment was undertaken, again randomly allocated by computer selection from the two remaining treatments.

Follow-up was continued in the standard fashion.

7.7 Other Documented Details

A. Risk factors

At the initial visit, the patient's general medical history was assessed with particular regard to relevant medical illnesses such as diabetes, hypertension, heart disease, etc., systemic drugs and family history of glaucoma.

B. Race

The majority of the patients in the trial were Caucasian (152). Of the remainder, 14 were Black and 2 were Asians.

C. Staging of glaucoma

The disease in each patient was staged according to the degree of field loss at presentation:

Early: Field score of < 2 absolute defects (commonly in the arcuate region).
Middle: Field score of 2 - 12 absolute defects.
Late: Field score > 12 absolute defects.
(see examples) [Plate 10]

7.8 Statistical Methods

Mean values were routinely compared using the t-test. Analysis of variance was used to discover the relevance (and significance) of factors where there was more than one variable of interest. The significance of differences in proportions showing some effect between two groups was evaluated using the Fisher Exact Test. Descriptions of these tests can be found in Armitage (1971). The time to failure curves were constructed

using the life table method first described by Kaplan and Meier (1958), with significance between groups being determined using the logrank test (Peto et al., 1977). All p-values quoted are two-tailed.

Armitage P : An Introduction to Medical Statistics, Blackwell, Oxford, 1971

Kaplan EL, Meier P : Nonparametric estimation from incomplete observations. AM. Stat. Assoc. J., 1958, 53, 457-481.

Peto R, Pike MC, Armitage P & 7 others : Design and analysis of clinical trials requiring prolonged observation of each patient : II Analysis and examples. Br. J. Cancer, 1977, 35, 1-39

Chapter 8

RESULTS

The results of the trial will be divided into four sections:

1. Initial composition of the 3 groups.
2. Individual treatments:
   - A. Laser
   - B. Medicine
   - C. Surgery
3. Comparison of the 3 treatments.
4. Results of secondary therapy (in the failed cases).

8.1 Initial Composition of the 3 Groups

A. Of the total number of 168 patients entered into the trial, 55 underwent a primary laser trabeculoplasty, 56 received medical therapy and 57 were treated surgically by means of a trabeculectomy.

B. Mean age (in years) of the 3 groups was as follows:

Laser	64.6 ± 11
Medicine	62.4 ± 10.5
Surgery	62.3 ± 11.1

There were no significant differences between the 3 groups (t-test).

Ages ranged from 27 to 80 years (Fig. 1).

(± when used throughout this chapter refers to the standard deviation.)

C. Mean starting pressure (mmHg) on entry into the trial:

Laser	35 ± 8.7		
Medicine	35 ± 7.9	}	
		}	> t = 0.59 p = 0.28
Surgery	34.3 ± 5.4	}	
Overall	34.8 ± 7.4		

There were no statistically significant differences between the 3 groups for starting IOP.

D. Mean visual acuity score on entry:

Laser	11.91	p-values
Medicine	11.27	laser v. medicine = 0.17
		laser v. surgery = 0.10
Surgery	11.14	medicine v. surgery = 0.73
		i.e. non-significant

(Visual acuity measured on a scale of 1 - 20 where 6/5 = 9. NPL = 20.) – see Appendix 16

E. Mean visual field score on entry:

	L	M	S
Threshold (db)	1.55 ± 0.66	1.68 ± 0.6	1.67 ± 0.6
0.4 > threshold	23.6 ± 9.70	20.4 ± 10.5	20.1 ± 10.5 (no. of spots missed)
maximum intensity (no. of spots missed)	17.6 ± 12.1	14.1 ± 11.6	13.7 ± 12.6

p-values	0.4 > threshold	L v M + S	p = 0.08
		L v S	p = 0.15
	maximum	L v M + S	p < 0.06
		L v S	p = 0.09

Therefore no significant differences.

The distribution of the fields is shown in Fig. 2.

The field score was adjusted by excluding the eight most peripheral superior and inferior spots in the Friedmann fields, due to frequent

inaccuracies in these regions.

F. Mean cup:disc ratio on entry.

	mean	SE
Laser	7.75	0.15
Medicine	7.61	0.15
Surgery	7.54	0.12

p-values L v M p = 0.53
L v S p = 0.97

i.e. no differences between the starting CD values in the 3 groups.

G. Race

There were 152 Caucasians, 14 Blacks and 2 Asians who were entered into the trial. They received treatment in the following fashion:

	Caucasians	Blacks	Asians
Laser	50	5	0
Medicine	49	6	1
Surgery	53	3	1

H. Diseases / Family History / Drugs

	General illness (e.g. diabetes, hypertension)	Family history of glaucoma	Drugs (e.g. anti-hypertensives)
Laser	8	9	6
Medicine	15	14	11
Surgery	11	8	9

I. Staging of glaucoma on entry.

Early = ≤ 2 absolute defects on Friedmann field.

Mid = 2-12 absolute defects on Friedmann field.

Late = > 12 absolute defects on Friedmann field.

	L	M	S
Early	18	18	17
Mid	12	9	18
Late	33	29	22

L v M	$p = 0.87$	$(x^2 = 0.28)$
M v S	$p = 0.14$	$(x^2 = 3.98)$
L v S	$p = 0.21$	$(x^2 = 3.14)$

L v M = laser versus medicine

M v S = medicine versus surgery

L v S = laser versus surgery

J. Mean Age (in years)

Laser	64.6 ± 11
Medicine	62.4 ± 10.5
Surgery	62.3 ± 11.1

No significant differences between the 3 groups (t-test).

	Age	
	< 65 years	>65 years
Laser	24	31
Medicine	27	29
Surgery	25	32

$x^2 = 0.3$ p = 0.86 i.e. no differences

K. Dropouts during the course of the study

	Laser					Medicine					Surgery				
year	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Deaths	4	2	2	1	0	0	2	0	0	0	0	1	0	0	0
Dropouts	0	3	2	0	0	2	0	2	0	0	0	1	0	0	0
Failures	6	4	4	2	0	5	1	0	2	0	1	0	0	0	0
Total	10	9	8	3	0	7	3	2	2	0	1	2	0	0	0

L. The initial composition of the 3 groups is summarised in Table V.

TABLE V

INITIAL COMPOSITION OF THE 3 GROUPS

	LASER	MEDICINE	SURGERY	SIGNI-FICANCE
NUMBER OF PATIENTS	55	56	57	
MEAN AGE (YEARS)	64.6	62.4	62.3	NS
SEX - MALE	38	37	45	
FEMALE	18	18	12	
MEAN STARTING IOP (mmHg)	35 + 8.7	35 + 7.9	34.3 + 5.4	NS
MEAN VISUAL ACUITY (scale 1 - 20)	11.91	11.27	11.14	NS
MEAN VISUAL FIELD				
- THRESHOLD	1.55	1.68	1.67	
- 0.4 > THRESHOLD	23.6	20.4	20.1	NS
- MAXIMUM	17.6	14.1	13.7	NS
MEAN CUP:DISC RATIO	7.75	7.61	7.58	NS
RACE - CAUCASIAN	50	49	53	
- BLACK	5	6	3	
- ASIAN	0	1	1	
STAGE OF GLAUCOMA				
- EARLY	18	18	17	NS
- MID	12	9	18	NS
- LATE	33	29	22	NS

8.2 Individual Treatments

A. LASER

1. Laser sub-groups

Of the total of 55 patients treated with laser trabeculoplasty, 19 patients were controlled with laser alone, 20 required the addition of pilocarpine 2% to maintain control, while the treatment failed to control the IOP in 16 patients over the period of follow-up.

LASER SUB-GROUPS

CONTROL laser alone	CONTROL laser + pilo	FAILURES
19	20	16

2. Intraocular pressure

The mean IOP at diagnosis of the group of laser patients was 35.0 mmHg (± 8.7). The mean IOP at the end of each year of follow-up was:

year	1	2	3	4	5
Mean IOP (mmHg)	21.2	18.5	18.3	17.8	16.3
	n = 46	n = 39	n = 28	n = 11	n = 4

(These figures must be considered in the light that failed patients (i.e. with IOP's > 22 mmHg) had been removed from the calculations following failure.)

The distribution of the laser IOP's can be seen in Appendix 1.
The features of the 3 laser sub-groups will now be compared:

3. Staging

	CONTROL (laser alone)		CONTROL (laser + pilo)		FAILURES		TOTAL
	No.	%	No.	%	No.	%	
EARLY	8	(38.1)	2	(11.1)	4	(25)	14
MID	5	(23.8)	4	(22.2)	1	(6.25)	10
LATE	8	(38.1)	12	(66.7)	11	(68.75)	31

The preceding table shows that there were a higher proportion of late glaucoma cases in both the group that required additional pilocarpine and the failures, compared with a higher percentage of early cases in the group controlled by laser alone.

4. IOP Reduction (starting vs. IOP at 3 years)

	CONTROL (laser alone)	CONTROL (laser + pilo)	FAILURES
Starting IOP (mmHg)	29.1	37.4	42.5
IOP at 3 years	18	16.5	22.7 (n=4)
Mean reduction in IOP (at 3 years)	11.1	20.9	-
% IOP reduction at 3 years	38.1%	55.9%	-

There was a higher mean starting IOP in the failure group compared with the patients controlled by laser alone (41.6 mmHg vs. 28.7 mmHg; p = 0.000001 t-test). The group controlled by laser + pilocarpine was intermediate between these two (35.7 mmHg) and significantly different to both other groups (p = 0.002 and p = 0.04 respectively).

The percentage reduction in IOP at 3 years (compared with starting IOP) was 38.1% in the patients successfully treated with laser alone.

As might be expected, the combination of laser and pilocarpine achieved a greater percentage reduction in IOP.

5. Field performance (laser)

	year			
Mean no. of spots missed 0.4 log units above threshold	1	2	3	4
	21.73	23.44	22.86	16.17
maximum intensity	16.98	17.56	17.38	11.08
	(n=45)	(n=34)	(n=29)	(n=12)

i.e. losing failures (high values) bring mean down at 4 years - the 12 successfully treated patients, when analysed separately over the 4-year period, do not appear to have changed:

Field performance of the 12 successes (at 4 years)

	year			
Mean no. of spots missed 0.4 log units above threshold	1	2	3	4
	15	16.1	14.2	16.2
maximum intensity	10.9	12.6	11	11.1

i.e. no change.

For fuller details of the visual field data, see also Appendix 2-A and 2-B.

6. Phasings

		Mean IOP's at			
		9.30 am	11.30 am	1.30 pm	3.30 pm
Year	1	21.33	21.76	19.67	19.57
	2	19.61	20.11	17.17	17.71
	3	18.20	17.90	17.48	16.90
	4	17.33	16.86	16.14	17.14

The decrease in mean IOP's with successive years could be explained on the basis of the removal of the failures from the calculations. See also Appendix 3.

7. Visual acuity

The visual acuity scores in the laser group (VA measured on a scale of 1 - 20) can be seen in Appendix 10. see also Appendix 16

8. Laser failures

The cumulative survival (Kaplan-Meier) can be seen in Figure 3.

The pattern of the laser failures was as follows: 2 failed before 6 months after treatment, 4 between 6 months and 1 year, 4 between 2 and 3 years and 2 between 3 and 4 years. The mean time of failure was 19.25 months after LTP.

The mean length of follow-up of the successfully treated patients was 42.8 months in the laser plus pilocarpine group.

81% of the patients were successfully controlled (either by laser alone, or with laser and pilocarpine) at 3 years. This was reduced to 61% at 4 years.

The relationship of the time of laser failure to the stage of glaucoma can be seen in Figure 4.

9. Factors affecting outcome of laser

The 3 subgroups were further analysed to assess whether there were any additional factors which might affect the outcome of LTP:

	CONTROL (laser alone)	CONTROL (laser + pilo)	FAILURES
AGE (years)	63.5	64.9	65.9
NEGRO RACE	3	1	1
PXF	0	1	3

The degree of angle pigment and the width of the drainage angle did not appear to be related to the outcome of treatment. There were 5 Blacks in the group as a whole, with only one that failed. These numbers are too small to comment on. On the other hand, of the 4 patients with pseudoexfoliation in the group as a whole, 3 failed (at 27, 29 and 41 months respectively after LTP), despite a good initial response.

10. Deaths

There were 9 deaths in the laser group as a whole over the course of follow-up. Three of these cases had failed and required a secondary form of therapy prior to their deaths.

11. Complications

A post-treatment spike in IOP is a well-documented complication of LTP. In this series, no patient experienced a rise in IOP > 30 mmHg (the IOP was checked 1 hour after treatment, and monitored for a longer period of the pressure had risen above the pre-treatment level). However, one patient did suffer a significant loss of field after treatment, despite no recorded significant spike in IOP.

B. SURGERY

1. Success/failure

Of the 57 patients who underwent a primary trabeculectomy, 56 were controlled with IOP's < 22 mmHg over the period of follow-up. There were no specific features related to the patient that failed to suggest why failure had occurred (cf. Section 9). The surgical procedure and post-operative course were uncomplicated. Failure to control the IOP below 22 mmHg occurred at 3 months.

The Kaplan-Meier survival curve for the surgical group is seen in Figure 5.

2. Intraocular Pressure

The mean IOP at diagnosis of the surgical group was 34.3 mmHg (± 5.4).

The mean IOP at the end of each year of follow-up was:

year	1	2	3	4	5
Mean IOP (mmHg)	14.1	13.4	13.4	13.3	12.5
	n = 56	n = 54	n = 36	n = 18	n = 4

It is noteworthy when evaluating these figures that there were no

failures after 3 months - i.e. no removal of cases with higher IOP's.

The range of IOP's in the surgical group can be seen in Appendix 4.

3. Staging

There were 17 early-, 18 mid- and 22 late-stage glaucoma patients in the surgical group.

The one case that failed was classified as a late-stage glaucoma.

4. IOP Reduction (starting vs. IOP at 3 years)

	Surgery Group
Starting IOP (mmHg)	34.3 mmHg
IOP at 3 years	13.6 mmHg
Mean reduction in IOP (at 3 years)	20.7 mmHg
% IOP reduction at 3 years	60.3 %

5. Follow-up

The median length of follow-up for the surgically treated patients was 39 months.

98% of the surgically treated patients were successfully controlled at 4 years.

6. Field performance (surgery)

	year			
Mean no. of spots missed 0.4 log units above threshold	1	2	3	4
	10.75	12.23	14.10	12.67
maximum intensity	16.56	18.58	19.87	17.13

See also Appendix 5-A and 5-B.

7. Phasings

		Mean IOP's at			
		9.30 am	11.30 am	1.30 pm	3.30 pm
Year	1	15.31	15.00	14.69	14.07
	2	14.46	14.15	13.24	13.26
	3	14.26	15.52	13.13	14.26
	4	14.33	14.20	13.80	13.15

See also Appendix 6.

8. Visual acuity

The VA scores in the surgery group (VA measured on a scale of 1 - 20) can be seen in Appendix 11.

9. Factors affecting the outcome

There were 3 Blacks and 1 Asian in the surgical group. All their operations were successful.

The failed case was Caucasian, aged 56. The starting IOP was 43 mmHg and the C:D ratio 0.8. The only possible factor which might have contributed to failure was an excessive amount of pigment dispersion in the post-operative period. No pseudoexfoliation was present.

10. Deaths

The one surgical patient that died during the course of the trial was controlled up to the time of death.

11. Complications

Minor and major complications may occur after trabeculectomy, which may result in a temporary or permanent disability. These have been listed in Chapter 4.

The most feared complications after trabeculectomy are intraocular infection and loss of vision, the latter due either to cataract formation or eclipse of the central island of visual field.

In this series, 1 patient developed an infected drainage bleb. The infection responded well to therapy, but the patient developed a secondary cataract. Despite cataract surgery and intraocular lens implantation, the visual acuity was not improved in the long term due to co-incident macular oedema following a retinal branch vein occlusion. However, there was an initial short improvement to the preoperative level immediately after surgery, before the branch vein occlusion occurred.

No complications related to the general anaesthetic were encountered in the surgical group.

The second patient that developed a dense cataract, had postoperative loss of the anterior chamber with definite lens endothelial touch. Cataract extraction and lens implantation restored the visual acuity to the pre-operative level.

One patient required reformation of the anterior chamber and resuturing of the bleb due to a leaking section.

Cataract is difficult to quantify accurately. Moreover, with the average age of the patients being 62.3 years, senile as opposed to surgically-induced lens opacities also need to be considered. Comparing the pre-operative to the most recent visual acuity, only 5 patients showed a reduction of more than 2 lines on the Snellen Chart. (This included the patient with cataract and macular oedema above. In addition, senile macular changes and other retinal pathology must be considered in any patient who drops their vision.)

19 of the 57 surgical patients had an hyphaema recorded post-operatively. All of these settled spontaneously.

Hypotony (defined as an IOP < 8 mmHg) at some stage after trabeculectomy is very common and occurred in 87% of the patients in this series. 29% had prolonged hypotony with an IOP < 8 mmHg for longer than 2 weeks post-operatively. 52.2% of the patients with both prolonged and transient hypotony were seen to have choroidal effusions. A positive Seidel test was noted in 11 patients immediately post-operatively. Shallow post-operative anterior chambers were recorded in 23.4%.

C. MEDICINE

1. Drugs

The medical group of patients received any one or combination of the following drugs. Also listed are the number of patients receiving each of the drugs at 1 years.

Drug	No. of patients receiving the drug at 1 years
	n = 46
Pilocarpine 2%	10
Pilocarpine 4%	30
Eppy 1%	14
Timolol 0.25%	8
Ganda 1 + 0.2%	5
Ganda 3 + 0.5%	5
Diamox (tablets)	2

2. Intraocular pressure

The mean IOP at diagnosis of the medical group was 35 mmHg (± 7.9).

The mean IOP at the end of each year of follow-up was:

year	1	2	3	4	5
Mean IOP (mmHg)	20.4	18.5	18.5	16.8	18.3
	n = 48	n = 46	n = 32	n = 17	n = 6

These figures reflect the fact that the failed cases had been removed from the calculations. See also Appendix 7.

3. Staging

There were 18 early-, 9 mid- and 29 late-stage cases in the medical group.

4. IOP Reduction (starting vs. IOP at 3 years)

	Medical Group
Starting IOP (mmHg)	35.0 mmHg
IOP at 3 years	18.8 mmHg
Mean reduction in IOP (at 3 years)	16.2 mmHg
% IOP reduction at 3 years	46.3 %

5. Follow-up

The median follow-up period for the medical patients was 39 months.

89% were successfully controlled at 3 years, compared with 82% at 4 years.

6. Field performance (medicine)

	year			
Mean no. of spots missed	1	2	3	4
0.4 log units above threshold	19.77	21.30	19.00	19.50
maximum intensity	14.75	14.95	11.88	10.00

See also Appendix 8-A and 8-B.

(The explanation for the reduction in field scores at year 4 is that there were only 10 patients at this point, compared with 24 at 3 years.)

7. Phasings

		Mean IOP's at			
		9.30 am	11.30 am	1.30 pm	3.30 pm
Year	1	21.05	22.09	19.58	19.36
	2	20.45	20.34	17.44	17.52
	3	19.00	20.04	18.92	20.00
	4	20.88	19.56	15.88	16.33

See also Appendix 9.

8. Visual acuity

The visual acuity scores in the medical group (VA measured on a scale of 1 - 20) can be seen in Appendix 12.

9. Failures

There were 8 failures in the medical group. The pattern of failures was as follows:

3 failed before 6 months

2 failed between 6 months and 1 year

1 failed between 1 and 2 years

2 failed after 2 years

The Kaplan-Meier cumulative survival curve is shown in Figure 6.

The time of failure related to the stage of glaucoma in the medical patients is seen in Figure 6-A.

10. Factors affecting the outcome

Width of the drainage angle and the degree of angle pigment did not bear any relation to the outcome. Two of the failures had pseudoexfoliation. Of the 6 Blacks in the group as a whole, 2 failed. C:D ratios in the failures varied from 0.6 to 0.9.

11. Complications / side-effects / compliance

Compliance is a major problem amongst the medically treated patients. It is difficult to assess accurately in the individual case. Numerous patients attending the clinic had forgotten to instil their drops on the day of attendance, or had run out of drops a few days previously. On the other hand, it is difficult to know if patients are not taking extra care to instil their drops because they are attending the clinic, and that at other times their application may be less diligent. One patient who failed secondary medical therapy was very unreliable and appeared totally incapable of instilling his drops as instructed.

The side-effects of the various medical preparations are well documented and have been listed in Chapter 3. The side-effects that occurred most

commonly were the visual effects of pilocarpine, particularly in the younger patients, the topical irritative effect of adrenalin and ganda, and the systemic effects of acetazolamide. No adverse effects were encountered in patients receiving timolol.

44 patients required modification of their therapy, either due to side-effects or due to poor IOP control.

17 required 1 modification

14 required 2 modifications

13 required > 2 modifications

8.3 Comparison of the three treatments

As has been shown, the 3 treatment groups were very similar for age, starting IOP, stage of disease, etc.

The results of the 3 treatments will be compared in terms of the following:

A. IOP

B. Fields

C. Phasings

D. C:D ratios

E. Patterns of failures

F. Visual acuity

A. Intraocular Pressure

1. Mean IOP

	MEAN IOP (mmHg)		
TIME (years)	L	M	S
Pre-treatment	34.98 n=55	35.05 n=56	34.30 n=57
1	21.15 n=46	20.42 n=48	14.07 n=56
2	18.54 n=39	18.46 n=46	13.41 n=54
3	18.25 n=28	18.50 n=32	13.44 n=36
4	17.82 n=11	16.82 n=17	13.33 n=18

p-values	year 1	2	3	4
L v. M	0.34	0.44	-	-
M v. S	<<0.00001 (t=8.5)	<<0.00001 (t=6.75)	<<0.00001 (t=6.98)	<0.0001 t=4.07)
L v. S	<<0.00001	<<0.00001	<<0.00001	<0.0001 (t=4.3)

The mean IOP's in the 3 groups are displayed graphically in Fig. 7.

2. Distribution of IOP levels

The distribution of the IOP levels at 3 years is shown in Fig. 7-A.

3. IOP reduction

The relationship between the pre-treatment IOP and the IOP reduction at 1 year is seen in Fig. 8 (laser), Fig. 9 (medicine) and Fig. 10 (surgery).

The starting IOP is correlated with IOP at 1 year. Correlation coefficient of all three groups combined = 0.683. Correlation coefficient is a measure, in this case, of how the IOP values at 1 year are related to the starting values (e.g. correlation coefficient of 0 shows no correlation, i.e. random, while correlation coefficient of 1.0 = highly predictable).

IOP reduction after treatment

	L	M	S
Mean pre-Rx IOP	33.5	34.7	34.2
Mean post-Rx IOP at year 1	21.1	20.4	14.1
Mean reduction in IOP	12.6	14.3	20.1
Mean % reduction	36.3%	38.9%	57.7%

These figures are based on those patients still on primary treatment at 1 year (laser : n=44; medicine : n=48; surgery n=56).

B. Visual fields

1. Field scores : (Friedmann Fields) - excluding failures

a. Relative defects (no. of spots missed at 0.4 depression isopters).

	Mean field scores				
TIME (years)	Pre-op	1	2	3	4
Laser	23.34	21.73	23.44	22.86	16.17
Medicine	19.96	19.77	20.14	18.78	18.95
Surgery	20.25	16.56	18.44	19.22	17.95
p-values					
Laser v. Medicine	0.11	0.41	0.19	0.17	0.55
Laser v. Surgery	0.14	0.02	0.04	0.17	0.68
Medicine v. Surgery	0.89	0.16	0.48	0.86	0.80

b. Absolute defects (no. of spots missed at maximum intensity)

	Mean field scores				
TIME (years)	Pre-op	1	2	3	4
Laser	17.60	16.98	17.56	17.38	11.08
Medicine	13.47	14.75	14.68	13.27	12.85
Surgery	13.26	10.75	12.94	12.00	12.05
p-values					
Laser v. Medicine	0.10	0.38	0.32	0.19	0.71
Laser v. Surgery	0.08	0.01	0.09	0.06	0.84

Medicine v. Surgery	0.93	0.10	0.51	0.65	0.85

The field performance of the 3 groups is plotted graphically for the relative defects (Figs. 11A,B,C) and the absolute defects (Figs. 12A,B,C).

2. Field scores : (Friedmann Fields) - including failures

a. Relative defects (no. of spots missed at 0.4 depressions isopters).

	Mean field scores				
TIME (years)	Pre-op	1	2	3	4
Laser	23.34	21.98	23.34	23.64	19.00
Medicine	19.96	19.77	20.85	19.38	19.86
Surgery	20.25	16.56	18.44	19.22	18.91

b. Absolute defects (no. of spots missed at maximum intensity)

	Mean field scores				
TIME (years)	Pre-op	1	2	3	4
Laser	17.60	17.66	17.33	17.94	13.93
Medicine	13.47	14.79	15.41	13.50	14.05
Surgery	13.26	10.75	12.94	12.00	12.78

The above tables, when compared with the previous set, demonstrate the effect of the removal of failures on the later results.

3. Field correlations (maximum adjusted score v. time)

Laser	r = -0.09	(p=0.0)
Medicine	r = -0.04	(NS)
Surgery	r = 0.01	(NS)
All	r = 0.02	(NS)

i.e. no effect on the fields with time.

4. Field regression

We will now proceed to arrive at a definition of what constitutes significant visual field regression in terms of change in the Friedmann Field score.

(The following calculations refer to all three treatments together, and includes those going on after failure.)

A number of different possibilities were investigated using the size of change in field score > 4 spots in the absolute defects.

a. Using one instance of change > 4 spots:

45/168 showed at least one improved score

67/168 showed at least one deterioration

	Improvement	No improvement
Deterioration	11	56
No deterioration	34	67

Since 11 patients showed both an improvement and a deterioration, one instance of change > 4 spots is probably within the random variation of field score measurements. It was thus necessary to consider 2 instances of change > 4 spots.

b. Using two instances of change > 4 spots:

	Improvement	No improvement
Deterioration	0	43
No deterioration	23	102

Since no patients showed deterioration and improvement, this can be used as the definition of significant change (viz. two instances of change in absolute field score > 4 spots).

So, using > 2 instances of change > 4 spots in the absolute field scores, we have:

43 deteriorations

23 improvements

102 no change

Broken down into the treatment groups:

	Field score			
	Deterioration	No change	Improvement	Total
Laser	17	29	9	55
Medicine	20	30	6	56
Surgery	6	43	8	57
	43	102	23	168

It is worth noting the larger proportion of laser and medicine 'deteriorations', the high proportion of surgical 'unchanged' and the similar numbers of 'improvements' in all 3 groups.

5. Correlation of field change:

a. With the starting field score

	Starting field score (mean absolute field score)	
Improvement (23)	24	
		$p << 0.0001$
No change (100)	11.1	
		$p < 0.01$
Deterioration (43)	16.4	

(2 patients excluded as only had 1 field score)

It would therefore appear that the higher starting values (i.e. worse fields) show changes (either for the better or worse).

b. With IOP reduction

To relate the field changes to IOP reduction it was decided to use the IOP level at the 3 month visit as a baseline value, as in all 3 treatments, the pressure fall had been achieved by this time, and it allows the maximum number of patients to be included in the assessment.

i. Overall correlation (between field score and IOP reduction)

Using means

	IOP reduction	
Fields	mean	SD
Improved	17.3	8.6
No change	16.9	9.5
Deterioration	14.2	11.3

No significant difference (AOV)

(improved + no change) v. deterioration $p = 0.16$ (t-test)

Using cutoffs

	IOP reduction	
Fields	< 8 mmHg	> 9 mmHg
Improved	4	19
No change	21	79
Deterioration	13	30

$x^2 = 1.91$

p = 0.38 (NS)

With a larger IOP reduction

	IOP reduction		
Fields	< 20 mmHg	> 21 mmHg	
Improved	16	7	) NS
No change	70	30	) NS
Deterioration	30	13	) NS

Thus, no correlation between the IOP reduction (as achieved at 3 months) and absolute field changes.

ii. IOP deterioration

If the IOP deteriorates by 3 months (n=5)

	IOP	
Fields	Deterioration	No deterioration
Deterioration	4	39
No change	1	99
Improvement	0	23

4/43 v. 1/123 p = 0.02

So, if IOP deteriorates with treatment, fields will probably have deteriorated too.

6. Correlation with starting IOP

There was no correlation between the starting IOP and the number of changes in the field > 4 spots.

There was, also, no correlation between starting IOP in any of the 3 following groups:

1. Improvement in fields
2. Deterioration in fields
3. No change

7. Correlation by treatment group

i. Laser

	IOP reduction (mmHg)		
Fields	<8	>9	
Deterioration	4	13	4/17 v. 11/38
No change	9	20	p = 0.75
Improved	2	7	

ii. Medicine

	IOP reduction (mmHg)		
Fields	<8	>9	
Deterioration	8	12	8/20 v. 11/36
No change	9	21	p = 0.56
Improved	2	4	

iii. Surgery

	IOP reduction (mmHg)		
Fields	<8	>9	
Deterioration	1	5	
No change	3	40	NS
Improved	0	8	

Thus no relationship within the 3 treatment groups either.

C. PHASINGS

1. Mean Phasing IOP i.e. mean of 4 daytime IOP recordings

	Mean phasing IOP			
year	1	2	3	4
Laser	20.59	18.66	17.65	16.89
Medicine	20.51	19.04	19.46	17.99
Surgery	14.82	13.75	14.29	13.97
p-values				
Laser v. Medicine	0.91	0.64	0.05	0.47
Laser v. Surgery	0.000	0.000	0.0002	0.07
Medicine v. Surgery	0.000	0.000	0.000	0.007

The mean diurnal curves for laser, medicine and surgery are shown in Fig. 13.

2. Mean peak IOP i.e. highest recorded pressures on phasing

Mean peak IOP

year	1	2	3	4
Laser	23.54	21.42	19.67	19.00
Medicine	23.18	29.98	21.88	21.00
Surgery	16.84	15.43	16.35	15.40
p-values				
Laser v. Medicine	0.68	0.59	0.07	0.18
Laser v. Surgery	0.000	0.000	0.003	0.05
Medicine v. Surgery	0.000	0.000	0.000004	0.001

3. Range of IOP's i.e. maximum minus minimum recorded (mean values) IOP's

Phasing IOP range

year	1	2	3	4
Laser	5.30	5.42	3.95	4.00
Medicine	5.09	6.00	5.28	6.33
Surgery	3.75	3.28	4.39	3.00
p-values				
Laser v. Medicine	0.75	0.42	0.12	0.02
Laser v. Surgery	0.006	0.000	0.53	0.20
Medicine v. Surgery	0.03	0.000	0.22	0.0009

D. CUP : DISC RATIOS

These figures refer to the primary therapy only - failures extracted at time of failure.

1. C:D ratio v. time

C : D ratio

	Starting		Year 3		Year 4	
	x	SE	x	SE	x	SE
Laser	7.75	0.15	7.7	0.2	8.0	0.2
Medicine	7.61	0.15	6.9	0.23	7.7	0.31
Surgery	7.74	0.12	7.94	0.16	7.9	0.23

The relationship of the 3 groups is shown graphically in Fig. 14.

2. C:D ratio related to post-op. IOP

	C:D 0.8 +			C:D < 0.8		
	L	M	S	L	M	S
No. of eyes	15	6	25	8	15	10
Mean Post-op. IOP (3 year)	18.3	20	13.6	19.5	17.5	13.4

The medical group appears to have proportionately lower C:D ratios than laser and medicine.

E. VISUAL ACUITY

Mean VA scores

TIME (years)	Pre-op	1	2	3	4
Laser	11.91	11.07	10.36	10.75	10.00
n =	55	46	39	28	11
Medicine	11.27	10.44	10.67	10.75	11.12
n =	56	48	46	32	17
Surgery	11.14	11.41	11.54	11.72	11.50
n =	57	56	54	36	18

Note that these figures exclude the failures.

See also Appendix 9-A.

The visual acuity scores are shown graphically in Fig. 15.

The change in visual acuity between the starting V.A. and the last recorded V.A. is shown in Fig. 15-A.

F. FAILURES

1. Pattern of failures

The Kaplan-Meier Cumulative Survival curve for the 3 treatment groups is seen in Fig. 16.

2. Percentage success

Year	L	M	S
1	89	91	98
2	81	89	98
3	71	89	98
4	61	82	98

3. Failures related to age at start

This is seen in Fig. 17.

The cumulative survival related to a cutoff age of 65 is seen in Fig. 17-A.

4. Failures related to stage of disease

	Failures		
	L	M	S
Early	4	2	0
Mid	1	0	0
Late	11	6	1

5. Failures related to starting IOP

	Starting IOP		
	Failures	Successes	p-value (t-test)
Laser	41.6 + 8.2	32.3 + 7.2	0.0001
Medicine	38.6 + 5.5	34.5 + 8.1	0.17) NS
Surgery	39	34.2 + 5.4	0.39) NS

Laser chance of success related to starting IOP

> 40	4/13	= 31%	success rate	
				p = 0.0007
< 40	35/42	= 83%	success rate	
> 45	3/7			
		less significant		
< 45	36/48			
> 35	8/21	= 38%	success rate	
				p = 0.00004
< 35	31/34	= 91%	success rate	

i.e. best cut-off = starting IOP < 35 mmHg.

G. FOLLOW-UP

12 patients died during the follow-up period under study.

10 patients dropped out for reasons which included failure to attend, illness, or moving away.

Patients available for study at end of each year

At end of year	No. available for study			No. dead			Lost to follow-up		
	L	M	S	L	M	S	L	M	S
1	45	49	56	4	0	0	0	2	0
2	36	46	54	2	2	1	3	0	1
3	28	44	54	2	0	0	2	2	0
4	25	42	54	1	0	0	0	0	0
5	25	42	54	0	0	0	0	0	0

8.4 Results of Secondary Treatment

Should primary treatment fail, each patient was again randomly allocated to one of the two remaining treatment groups for secondary therapy.

A. Numbers requiring secondary therapy

Laser	16
Medicine	8
Surgery	1

B. Time when secondary therapy required

	L	M	S
In year 1	6	5	1
In year 2	4	1	0
In year 3	4	0	0
In year 4	2	2	0

C. Outcome of secondary therapy

	No.	No. successful	No. failed
Laser Group 2° Rx			
Medicine	8	7	1
Surgery	8	8	0
Medical Group 2°			
Surgery	4	3	1
Laser	4	4	0
Surgery Group 2°			
Medicine	1	1	0
Laser	0	0	0

D. Mean IOP's for secondary therapy

These are shown graphically in Fig. 18

Chapter 9

DISCUSSION

Chronic open-angle glaucoma is a long-term disease, and a prolonged follow-up is therefore necessary before the success (or otherwise) of the treatment can be fully assessed. Nevertheless, over the shorter term, trends in performance are established which provide useful information as to the final outcome.

This trial was aimed at investigating the effect of 3 different treatment modalities when used as primary therapy in 3 similar groups of patients with open-angle glaucoma. The prospective nature and random allocation of treatment make it the only trial of its kind yet published.

9.1 Effectiveness of Therapeutic Approaches to Glaucoma

A basic fact in medicine is the identification of the diseased tissue and the cause of the abnormality. The therapeutic ideal is to reverse the basic defect.

Glaucoma pursues a relentless course with the customary need for perpetual medical therapies that do not reverse the process, are a nuisance to administer and may have significant morbidity. However, the past couple of decades have witnessed the marketing of new anti-glaucoma drugs, the development of new surgical procedures, and the advent of laser trabeculoplasty, all with the aim of providing improved glaucoma control.

The chronic course of glaucoma must be assessed by observing a number of ocular parameters, including IOP, vision and the visual fields, over an indefinite period of time.

To establish an exact IOP that will ensure preservation of vision is difficult in the individual case, but it is clear that lowering the IOP with medicines or surgery can often arrest the progression of visual loss [1]. It is also evident that very low IOP's are sometimes necessary to prevent additional loss of vision in patients with extensive optic atrophy and field loss [1]. On the other hand, the role of high IOP in causing optic nerve damage has been questioned [67].

One of the most difficult tasks in determining whether a glaucoma treatment (whether medical, surgery or laser) is effective, is the need to arrive at an adequate definition of success.

9.2 Definition of Glaucoma 'Control'

The definition of glaucoma 'control' is complex. It can be considered in terms of a number of modalities:

A. Intraocular pressure

For a long time it was believed that IOP's less than 21 mmHg would guarantee control. However, it is now well known that many patients have progressive glaucomatous nerve damage despite IOP's below 21 mmHg.

Although it has been shown that the majority of patients with 'elevated IOP' may never develop glaucomatous nerve damage [2, 3], short-term studies strongly indicate a relationship between intraocular pressure and visual function [4-8], with worsening of visual function noted on induced elevation of IOP.

There are few guidelines as to the degree to which IOP must be reduced in order to prevent further damage. A mean decrease of 51% in Kolker's [9] and 59% in Quigley & Maumenee's [10] surgically treated patients was associated with a low incidence of further progression. In the series of Werner et al. [11], the mean reduction in pressure was only 36%, but the post-operative average IOP was almost the same as the above two studies. In the latter study, despite a mean average post-operative IOP of 16.8 mmHg, 10 of 24 patients studied showed a progressive loss of field. There was no difference in mean post-operative IOP's of those eyes that maintained stable IOP's and those that progressed. The decisive factor in the eyes that continued to deteriorate seemed to be a greater variability of IOP [11]. No doubt individual factors that we do not yet fully understand, govern the susceptibility of optic nerve heads to damage mediated by IOP. While accepting this individual variation to optic nerve damage from different pressure levels, it must also be considered that IOP itself is not a stable characteristic, with resultant periodic changes in the IOP level (the latter will be investigated in the section on Phasing).

In this series, despite no significant difference in the mean starting IOP's for the 3 treatment groups, surgery achieved a 60.3% reduction at 3 years, compared with 47% for the laser group as a whole, and 46.3% for the medically-treated patients. In addition, the IOP's in the surgical group were consistently lower than the other two groups, with no evidence of increase in IOP over time (this despite the fact that there was only 1 surgical failure removed at 3 months, compared with the exclusion of many more failed cases with high IOP's from the calculations in the other two groups).

When reviewing the progress of a patient retrospectively, it may be possible to state that a particular IOP level was 'too high' for that patient due to the fact that progressive nerve damage / field loss had occurred. However, in the day to day management, it is necessary to set an IOP level for 'successful control', and for the purposes of this study, the level was set at less than 22 mmHg.

It is also accepted that the stage of the disease may be important in defining the upper level of IOP necessary to prevent ongoing damage, with

the late stage patients requiring a lower mean IOP [9, 12, 13, 14, 15]. Although there was no significant difference between the number of early, mid and late stage cases in each of the three groups in this series, it is interesting to note that the majority of failed cases in both the laser and medical groups were late stage glaucoma.

In terms of IOP, therefore, the surgical group performed better than laser or medicine with lower mean IOP's throughout the period of follow-up, a higher mean reduction in IOP, and higher percentage reduction in IOP. There was no tendency for the mean IOP of the trabeculectomies to increase with time, unlike the experience of Jerndal et al. [16].

B. Phasings

The diurnal variation in unoperated glaucoma eyes has been shown to exceed significantly the normal diurnal variation [17-19]. Because of this abnormal variability and because, as we have discussed above, it is believed that elevated IOP is related to loss of visual function, measurement of the variance of IOP is considered useful in the management of patients with glaucoma.

Despite good average IOP measurements taken infrequently in the clinic, peak pressures may occur at other times of the day. This was seen frequently when the patients in this series were phased. Mean phasing IOP's for the 3 groups correlated reasonably well with the mean clinic IOP's, laser and medicine being similar, with surgery being significantly lower. Although the ranges of phasing IOP's for the 3 groups were similar, laser and medicine both showed significantly higher peak pressures than surgery when phased.

Thus diurnal curves are necessary in the assessment of the effectiveness of therapeutic regimes. Studies performed after pilocarpine administration [19] and after surgery [20] have documented a lowering and blunting effect on the diurnal curve. Greenidge et al. [21] studied the effect of ALT on the glaucomatous diurnal curve and noted a statistically significant reduction in mean daily pressure, peak pressure, pressure range and minimal pressure. These parameters have previously been associated with glaucoma damage [22].

C. Visual fields

Treatment in open-angle glaucoma is aimed at preventing further damage to the optic nerve head and hence further loss of visual field. But in attempting to assess this modality as a measure of control from one visit to the next, the ophthalmologist is beset by the problem that, like IOP, visual field is not a stable characteristic [23-29]. Both show continuing fluctuation. These fluctuations in the visual fields have been termed 'short-term' and 'long-term' fluctuations [30]. Such

variability from one moment to the next is an expression of several possible factors:

1. Limits of accuracy of the testing technique.
2. Variation in patient response related to factors such as concentration, fatigue, the desire to please, anxiety, pupil size, etc.

3. Skill and patience of the field technician.

These fluctuations result in periodic changes in field, resulting in differences between one field when compared with the next. Changes in the testing situation can result in improvement or deterioration of the visual field that is 'real', but does not represent a change in the state of health of the optic nerve, or similarly, an increase in pupil size due to the cessation of pilocarpine will result in a real improvement in the field which is unrelated to the optic nerve status [31, 32]. As regards the effect of pilocarpine on the visual field scores in this trial, it was felt that once therapy had commenced, the degree of miosis was likely to remain constant, thus not contributing to an ongoing change in the field score.

On the other hand, changes in the visual field may be a manifestation of disease or a manifestation of the intervention altering the course of that disease. The problem is differentiating normal from pathologic change. The former can differ from individual to individual.

The ultimate goal in the treatment of glaucoma patients is to halt the progression of their pathologic visual field defects.

It has been shown by Greve et al. [33] that fluctuation always takes place in visual field testing and can be quite considerable. Short-term fluctuation has been shown to be greater than long-term fluctuation [25] using the Octopus automated perimeter. Glaucoma patients tend to have a larger short-term fluctuation than other groups [30].

Thus, a major difficulty with visual fields is the definition of progressive visual field change. Some older studies have used arbitrary definitions of change which, for the most part, simply reflect the author's clinical impressions of what constitutes significant change. More recently, a variety of statistical techniques have been applied to the visual field as measured with computerised perimetry [35-41].

But computerised fields, too, have their limitations, and there is no general agreement on what constitutes significant visual field change with automated perimetry, nor any generally accepted technique for detecting it. A combination of analysis of variance and trend analysis was suggested by Schultz et al. [34]. Mikelberg and Drance [42] described progression and concluded that there is no statistical difference between those visual fields that progress and those which do

not as far as IOP level is concerned. There may, however, be some relationship between the highest IOP and progression. Some defects may become denser, some larger, or new defects may develop.

For the purposes of this report, we chose to analyse the data obtained from the Friedmann fields in an attempt to analyse the effect on visual function as a response to the three methods of therapy.

A field score allocated to each patient at each visit yielded a numerical value for the relative and the absolute defects. Because of inaccuracies in the upper- and lowermost spots on the chart, these spots were removed from the calculations, giving the so-called 'adjusted' scores. The scoring system itself is open to some comment: not always were the same spots missed in successive fields in an unreliable patient, and yet the field score could be the same. Moreover, the analysis of successive fields in individual patients showed some to be extremely reliable and the fields reproducible, whereas others were exactly the opposite. Comparing these same individuals' behaviour on the more sophisticated Humphrey computerised perimeter showed that similar problems were encountered in some individuals. Thus the relatively basic and simple field-testing method used was, to some extent, vindicated - the individual patient rather than the machine was all-important. Another point of note was that patients with late stage glaucoma who had lost central fixation, often gave more unreliable results on the sophisticated computerised perimeter, probably due to the anxiety induced by the machine offering so many unseen stimuli.

There were no significant differences between the mean field scores, both for relative and absolute defects, of the three treatment groups at the time of entry into the trial. The reduced mean field scores in year four of follow-up which occurred in both the laser and medical groups can be accounted for by the removal of failed cases from the calculations. If the failed cases had been included, it is possible that there would have been no reduction in the score with time. No obvious significant difference was shown between the mean field scores of the 3 groups as a whole over the 4 year follow-up.

An attempt was made, using statistics and mathematical modelling, to arrive at a definition of what constitutes significant visual field regression for the individual patient in terms of the change in the Friedmann field score. The most satisfactory definition appeared to be two or more instances of change in absolute field score of $\geq$ 4 spots.

Of the 43 patients who showed field deterioration, by far the majority consisted of laser (17 patients) and medically-treated (20 patients) cases. Only 6 surgical cases showed a deterioration according to this definition. The number of 'improved' cases was similar for the 3 treatment groups, while the largest number of 'unchanged' fields existed in the surgical group (43 for surgery, compared with 29 cases for laser and 30 for medicine).

There appeared to be no correlation between starting IOP or IOP reduction (as achieved at 3 months) and absolute field changes. However, correlating the amount of IOP reduction in the 3 treatment groups with field behaviour, it is worth noting the large number of unchanged fields in the subgroup of surgical patients whose IOP had been reduced $\geq$ 9 mmHg following treatment. This study nevertheless compares with that of Werner, Drance & Schulzer [11] who were not able to predict the behaviour of the field of an individual patient on the basis of IOP level or the amount of pressure reduction obtained after treatment, although it may well suggest that the greater IOP reduction and lower mean IOP's in the surgical group may slow down visual field regression.

D. Visual Acuity

The visual results following treatment for glaucoma must be viewed against a background of (1) the decay of visual acuity in the elderly, (2) the glaucomatous decay, (3) the effect on visual acuity of drugs, e.g. miotics.

The problems of cataract induced after filtering surgery are well documented [43-47] with the incidence of cataract formation ranging between 6% and 38%. Cataracts are difficult to quantify with any degree of accuracy, however, making comparison difficult.

In this series, only 2 patients developed clinically significantly lens opacities. Both had experienced a complicated post-operative course, one having developed a flat anterior chamber with lens endothelial touch, and the other an infected bleb with endophthalmitis. Following cataract extraction, the visual acuity returned to the pre-operative level in both cases. (See Chapter 8 pg. 14)

Miotic drugs, particularly in the presence of pre-existing cataracts (the mean age for the patients in this trial was the mid-sixties), may also reduce the visual acuity. Watson & Barnett showed an increase in acuity after trabeculectomy in 6% of cases and presumed this was due to a less miotic pupil [48].

Visual acuity in advanced glaucoma patients may be reduced due to loss of the central visual field. Although some authors have stressed the dangers of performing surgery in patients with advanced field loss [49], others have suggested that the risks are low [50].

Other causes of loss of visual acuity, independent of the glaucoma, are not uncommon in the elderly, and these include senile cataract, maculopathy, vascular occlusions, etc. In addition, it is important to exclude a possible change in refraction, particularly after surgery, or miotics.

In this series, there appeared to be a slight improvement in the mean

visual acuity score in the laser group, with that of surgery showing a slight decline over the 4-year period. In the latter, however, this amounted to less than one line on the Snellen chart. The medical group remained essentially unchanged.

Looking at individual cases and assessing the change in visual acuity between the first and last recorded visits, the surgery group showed significantly more patients with a reduction in visual acuity compared with the initial visit.

E. Optic Disc

The morphologic features of the optic disc are important in determining the status of the disease control. In particular, the change in the disc appearance is important and the value of serial photographs is stressed. These were performed annually on each patient in this series. In practical terms, however, in the short- as opposed to the long-term management of an individual case, they do not aid much in the assessment of adequate control. The evaluation of disc changes can be difficult. Lichter [51] made a number of eminent glaucoma specialists classify a set of pictures obtained from both normals and from manifest glaucoma cases. The unanimity was not impressive.

Nevertheless, several studies support the idea that change in the disc occurs before change in the field, particularly using the older methods of perimetry [52, 53], and there is certainly a correlation between disc and field changes [54].

Recent studies [55] have employed computer graphics to create a solid model display of the optic cup, along with pallor.

In all three treatment groups in this series, a slight increase in the mean cup : disc ratio was noted when comparing the measurement on entry into the trial with that at 4 years. The fact that many failed cases had been removed by this stage from the calculations in the laser and medical groups may have masked an even greater deterioration in these two groups.

In practical terms, therefore, the management of the patient with open angle glaucoma depends very much on the IOP (as this is easy to measure), aided by changes in the visual fields, and assessment of the diurnal variation in IOP's if the former two do not correlate. It is important to stress the variation in individual patients, particularly regarding fields, and to estimate the change in the modalities being measured.

9.3 Performance of each Group as a whole

The 'end point' of therapy is reached when the IOP has been lowered to a safe level so that no change occurs in the signs of damage being monitored. As discussed above, the theoretically safe IOP may vary from eye to eye; an IOP of 21 mmHg may be safe for one patient and blinding for another. Treatment therefore never replaces the need for careful follow-up.

In all the patients in this trial, the initial IOP at diagnosis was > 24 mmHg with a mean of 34.8 mmHg. Treatment was considered successful when the IOP had been reduced below 22 mmHg, i.e. in most cases a significant lowering of IOP. Whether the pressure level reached in each individual case was sufficiently low to prevent further damage, was then assessed by careful monitoring of visual fields, etc.

A. Laser trabeculoplasty

Using a similar laser treatment technique to that of Wise & Witter [30], a clinically significant lowering of IOP was produced in the laser group of patients (from 35 mmHg pre-treatment to 18.3 mmHg at 3 years). A mean reduction in IOP at 3 years of 12.6 mmHg was obtained.

Pilocarpine 2% was regarded as permissible adjuvant therapy for those laser patients not controlled at an IOP < 22 mmHg with laser alone. Nevertheless, over the period of follow-up, 38.2% of the laser group as a whole were controlled by laser alone. 32.7% required the addition of pilocarpine for control. The remainder were uncontrolled on this regime and regarded as failures. Pollack et al. [56] found that most patients were dependent on medications after laser trabeculoplasty. It might be argued that those lasered eyes that require additional medical therapy to control their pressure will suffer all the potential problems of medical therapy, such as compliance, expense and side-effects.

Phasings showed that, despite apparent IOP control when monitored at 3-monthly clinic visits, some patients were spiking high IOP's well above the normal limit. As failures were removed from the calculations over the passage of time, these mean phasing peaks diminished in magnitude.

The visual field scores in the laser patients were maintained over the period of follow-up, with an apparent improvement in both the relative and absolute scores at year four. This phenomenon could be explained on the basis of the removal of the 16 failed cases during the follow-up period, there being a preponderance of late stage cases amongst the failures.

The pattern of laser failures is very important. The laser treatment subgroup showed a continual tendency to failure over the period of follow-up (89% success at 1 year, reducing to 61% at 4 years). As

referred to above, the failure group contained a high proportion of late stage cases (11 out of 16). In addition, there was a significantly higher starting IOP amongst the laser failures compared with those whose treatment outcome was successful. It was calculated that LTP had the best chance of success in those patients with starting IOP's $\leq$ 35 mmHg. To this could also be added early stage glaucoma.

Wise [57] has suggested that, despite a tendency to failure with time, the majority of patients who died during the course of follow-up were controlled until the time of death. One third of the laser patients that died in our series required secondary therapy before they died in order to control their IOP.

The visual acuity scores in the laser group showed a slight improvement with time, while the IOP range on phasing showed a reduction with time, both probably as a result of the removal of the failures from the calculations.

Laser trabeculoplasty is simple to perform and cost-effective - more than one third of the patients in the laser group were controlled on primary LTP alone. This rose to almost three quarters if pilocarpine was supplemented. Moreover, no major complications of treatment were encountered, in particular post-treatment inflammation reaction or IOP spike. This could perhaps be due to the fractionated treatment carried out. However, with the apparently ongoing tendency to loss of IOP control, careful and continued follow-up of these patients is essential.

B. Medical therapy

Many topical and systemic drugs have been tried in the treatment of glaucoma. Although the cholinergic agents have a more physiologically desirable action of increasing facility of outflow, the beta-blockers have risen in popularity due to their efficacy in reducing pressure, as well as their low incidence of ocular and systemic side-effects.

In this study, the commonly used drops were pilocarpine 2% and 4%, epinephrine 1%, guanethidine/adrenalin combination (Ganda 1 + 0.2% and Ganda 3 + 0.5%) and timolol 0.25%. These were used either singly or in combination depending on the individual's tolerance and response to treatment. Only rarely was oral acetazolamide necessary if topical therapy alone did not control the IOP.

In order to maintain the IOP within normal limits, changes in therapy were necessary in many patients, with the commencement of stronger concentrations of the drug or additional combinations of drops, thus necessitating extra clinic visits. The financial considerations of extra medical time and the cost of long-term medical therapy must also be taken into account in these times of cost-awareness.

Side-effects which required a change in the drops used included miosis, brow-ache or visual disturbance associated with pilocarpine, and the discomfort caused by epinephrine or Ganda. No patient on beta-blockers developed significant side-effects. The problems of compliance as related to individual patients have been discussed above.

The medically-treated patients thus comprise a diverse collection of individuals susceptible to the wide variety of possible side-effects associated with the different drugs, to the problems of compliance or varying durations of drug action which may influence the control of IOP levels, to the effect of the pupil, and thus, indirectly, on the visual acuity or fields.

The mean IOP's of the medical group remained constant over the period of follow-up once failures had been removed from the calculations. Medical therapy resulted in a mean reduction in IOP at 3 years of 16.2 mmHg. Annual phasings again showed that numerous patients had peak pressures well above the normal limit, despite apparent control at clinic visits. These must be considered in the light that the patient would be more likely to use his treatment when attending the hospital and that compliance at other times might be even worse.

Visual acuities remained virtually unchanged during follow-up, as did the mean visual fields scores (with failures removed).

The pattern of failure was different from that of laser, with most (75%) of the failures occurring before 2 years. The percentage success in the medical group was 91% at 1 year, reducing to 83% at 4 years. There was no relationship of failure to starting IOP.

C. Surgery

Trabeculectomy achieved the lowest mean IOP's of the three treatment groups, with a mean IOP at 3 years of 13.4 mmHg. (This represented a mean IOP reduction of 20.7 mmHg.) IOP control in the surgical group was maintained with the passage of time (and this despite the fact that there was only one failure which was removed from the calculations).

The one failure in the surgical group occurred at 3 months, giving a percentage success of 98% throughout the period of follow-up. The low incidence of failure in this series can perhaps be attributed to the fact that all these patients had undergone primary surgery with the result that their conjunctiva had not been exposed to eyedrops which in turn, as discussed previously, might influence the healing response [58] following trabeculectomy. This 'early failure' pattern concurs with a study by Inaba [59] which showed that the time course of failure of IOP control following trabeculectomy was most likely to occur within one year of surgery.
Lack of a common specific definition of success and the variation in surgical procedures used, makes it very difficult to compare the results

of this trial with those of other studies [44-47, 60-65]. None of these studies used trabeculectomy as the primary procedure, it was sometimes permissible to add medication after surgery to achieve IOP control, not all cases were primary open-angle glaucoma, some of the studies included full-thickness procedures, and different IOP levels were used as a criterion of control.

Mean visual field scores showed no gross change (despite the removal of only one failure from the calculations). Using our definition of significant visual field change (i.e. 2 instances of change in the absolute field score $\geq$ 4 spots), relatively few surgical patients showed deterioration (6 patients) with by far the majority (43) remaining unchanged. This could perhaps be related to IOP, as 40 of the surgical patients showing 'no change' had IOP's reduced by $\geq$ 9 mmHg and the surgical group as a whole had significantly lower mean IOP's (this pattern of field change was not seen in the other two treatment groups). Some workers have suggested that 'control' may be lost with time in individual cases, regardless of the procedure [11, 36]. This may be related to the fact that as the human eye ages, it become more susceptible to decreased filtration, as well as decreased bleb formation. Also, it is suggested that decreased IOP may not safeguard against progression [11, 36].

In addition, on phasing, the surgical group showed lower mean IOP's and lower peak IOP's. (The highest mean peak IOP recorded in this group was 20.77 mmHg).

Potential surgical complications are all-important to take into consideration, particularly those that might threaten visual function. A low incidence of clinically significant cataracts was encountered in this series and the implications of this complication have already been discussed. The mean visual acuity for the group as a whole showed only a slight decrease with time, but this was equivalent to less than one line on the Snellen chart. The early post-operative complications encountered included hyphaema, shallow anterior chamber, leaking blebs (two required re-suturing), choroidal detachments and hypotony [66]. No obvious lasting adverse effect on visual function was noted in most cases (although one patient with lens-endothelial touch did develop lens opacification). The one serious complication encountered was a patient who developed endophthalmitis secondary to a bleb infection. This responded well to antibiotic therapy.

9.4 Comparison of the three treatments

To compare the response to three different forms of therapy, the groups of patients treated require to be the same, the outcome monitored in an identical fashion and the results calculated in the same way. With random allocation by computer into the selected treatment groups and

adequate numbers in each group to enable satisfactory statistical analysis, there appeared to be no statistical difference in the composition of the 3 groups at the commencement of the trial in terms of starting IOP, age, stage of disease, degree of field loss, CD ratio, etc.

One important aspect that does need to be considered when assessing the results, is that data from the failed cases was excluded from the calculations at the time of failure. As failed cases were often late-stage glaucoma with perhaps extensive field loss, higher IOP's and poor central visual acuity, this would result in a skewing of the results towards the better. This applied in particular to laser, with 16/55 failures which occurred intermittently throughout the follow-up period, and medicine, where 8/56 failures occurred, especially within the first two years of treatment. There was also a high 'drop-out' rate in the laser group, and to a lesser extent the medical group. Nevertheless, the very obvious difference in the 3 groups is the level of IOP obtained in the surgery group which was significantly lower than laser and medicine. Importantly, the low mean IOP in the surgery group was maintained throughout the period of follow-up, despite the fact that no additional failures were removed after 3 months - i.e. no adjustment of the means for the better as in the other two groups. This is important from the management point of view - good long-term control appears to have been achieved following primary surgery, compared with the continual possibility of late failure in the laser group and to a certain extent in the medical group. The percentage reduction in IOP at 1 year in the surgery group was 57.7%, compared with 36.3% in laser and 38.9% in medicine.

As might be expected, the lower mean IOP's in surgery resulted in lower phasing IOP's and lower peak IOP's in this group (although the range of phasing IOP's was similar for the 3 groups). It is possible that the higher peak IOP's in absolute terms are responsible for ongoing damage in the laser and medical patients.

Visual fields in terms of mean field scores appeared similar in the 3 groups (although, as discussed previously, an improvement existed in laser and medicine at 4 years which could be explained on the basis of removal of the failures). More notable, in terms of deterioration/improvement, the surgical group showed a significantly larger proportion of unchanged fields which also appeared to correspond with the greater IOP reduction.

Optic disc appearances are not a very reliable monitor of change when assessed clinically. Nevertheless, a slight increase in CD ratio was noted in all 3 groups, although it must also be pointed out that the medical group appeared to have lower mean CD ratios. In practical terms, when a medical patient is on pilocarpine, it is difficult to assess the CD ratio without dilating the pupil (all pupils were dilated for disc photography at least once a year in this series).

The change in visual acuity from the start of the trial to the most recent visit, showed a similar pattern of change in the 3 groups, but surgery contained more patients who had registered a reduction in visual acuity than laser or medicine. In terms of the mean reduction in visual acuity score, this was less than 1 line on the Snellen chart.

As regards the outcome of secondary therapy after any one of the primary treatments which had failed, there is nothing to suggest from the results of this study that any of the primary treatments had an adverse effect on the second method of therapy used. However, the numbers that required secondary therapy are small.

9.5 Individual vs. the group

When considering the role of different treatment modalities in the management of patients with glaucoma, the individual patient as well as the group as a whole needs to be taken into account.

As discussed previously, a whole host of variables may affect the outcome of each specific method of treatment and these in turn may be influenced by factors in the patients themselves. Thus certain individuals right from the outset may be suspected as being likely poor compliers as regards the instillation of eyedrops and thus unlikely to succeed with medical treatment. Certain patients may heal aggressively following surgery (e.g. Blacks) and may therefore be expected to have a poor surgical outcome. Patients with end-stage glaucoma and thereby severely damaged drainage angles may respond badly to trabeculoplasty. Equally, tests used to monitor the treatment may be less reliable in some patients than others, e.g. visual fields, and this must be assessed accordingly.

Nevertheless, for statistical purposes, the analysis of a minimum number of patients in each group is necessary. Providing the groups (as in this series) are comprised of equal numbers of similar variables (e.g. age, stage of glaucoma, etc.), the final analysis is of clinical significance.

From the clinical point of view in day-to-day management, each patient needs to be assessed on an individual basis both as regards treatment and follow-up.

Chapter 10

CONCLUSION

The management of glaucoma still requires clinical judgement and the assessment of the needs of every individual patient based on his age, his occupation, his lifestyle and his requirements for vision. What may be the right treatment for one is almost certainly not the correct treatment for another.

This study resulted in some notable findings:

1. High success rate of primary surgery.

2. Significantly lower mean intraocular pressures following surgery.

3. Maintenance of this lower IOP on follow-up.

4. Lower peak IOP's on phasing in the surgical group - the whole mean of the diurnal curve being lowered.

5. Low incidence of cataract / diminished visual acuity following trabeculectomy.

6. Little difference in the mean field scores over the follow-up period in the 3 groups, but surgery showed less individual patient field deterioration than laser or medicine.

7. Laser trabeculoplasty was simple to perform with few complications and in more than one third of patients, laser alone controlled IOP.

8. Tendency to late failure in the laser group. This can occur suddenly with a marked increase in IOP. Therefore regular follow-up is essential.

9. Better chance of success of LTP in early stage glaucoma and starting IOP < 35 mmHg.

10. In over 80% of medical patients, it is possible to control the IOP with a combination of the modern drugs available.

11. Extra clinic visits may be necessary until the satisfactory drug combination is found.

12. Early failure pattern, on the whole, in the medical group, but later failures can occur.

13. Side-effects and compliance can be a problem with medical treatment, although the majority of patients appear to have no major difficulty with their treatment.

Thus can the role of laser, medicine and surgery be considered in the primary therapy of open-angle glaucoma, and the advantages and disadvantages of each treatment weighed against each other.

Still relevant today is the following quotation from A Treatise on Glaucoma:

> "There are so many questions in connection with glaucoma which are still unanswered, and there is still so very much work to be done ..."
>
> Robert Henry Elliot, 1922

REFERENCES : SECTION II

1 Grant WM, Burke JF Jr : Why do some people go blind from glaucoma? Ophthalmology, 1982, 89, 991

2 Hollows FC, Graham PA : Intraocular pressure, glaucoma & glaucoma suspects in a defined population. Br. J. Ophthalmol., 1966, 50, 570

3 Banks JLK, Perkins ES, Tsolakis et al. : Bedford Glaucoma Survey. Br. Med. J., 1968, 1, 791

4 Drance SM : Studies in the susceptibility of the eye to raised IOP. Arch. Ophthalmol., 1962, 68, 478

5 Jaeger EA, Weeks SD : Perimetric & visual acuity changes during ophthalmodynamometry. Arch. Ophthalmol., 1964, 71, 484

6 Scott AB, Morris A : Visual field changes produced by artificially elevated IOP. Am. J. Ophthalmol., 1967, 63, 308

7 Berggren L : Critical flicker frequency (CFF) in man during induced ocular hypertension. Acta. Ophthalmol., 1973, 51, 562

8 Geijer C, Bill A : Effects of raised IOP on retinal prelaminar, laminar and retrolaminar optic nerve blood flow in monkeys. Invest. Ophthalmol., 1979, 8, 10/30

9 Kolker AE : Visual prognosis in advanced glaucoma. A comparison of medical and surgical therapy for retention of vision in 101 eyes with advanced glaucoma. Trans. Am. Ophthalmol. Soc., 1977, 75, 539

10 Quigley HA & Maumenee E : Long-term follow-up of treated open-angle glaucoma. Am. J. Ophthalmol., 1979, 87, 519

11 Werner EB, Drance SM, Schulzer M : Trabeculectomy & the progression of glaucomatous visual field loss. Arch. Ophthalmol., 1977, 95, 1374

12 Hart WM, Becker B : The onset and evolution of glaucomatous visual field defects. Ophthalmology, 1982, 89, 268

13 Chandler PA : Long-term results in glaucoma therapy. Am. J. Ophthalmol., 1960, 49, 221

14 Crick RP : Chronic glaucoma : a preventable cause of blindness. Lancet, 1974, 1, 205

15 Lee PF : Importance of status of visual field and optic disc in management of open-angle glaucoma. Am. J. Ophthalmol., 1962, 53,

16 Jerndal T, Lundstrom M : 330 trabeculectomies. A long-time study (3 - 5 1/2 years). Acta Ophthalmol., 1980, 58, 947

17 Henkind P, Leitman M, Weitzman E : The diurnal curve in man. New observations. Invest. Ophthalmol., 1973, 12, 750

18 Kitazawa Y, Horie T : Diurnal variation of IOP in primary open-angle glaucoma. Am. J. Ophthlamol., 1975, 79, 557

19 Worthen DM : Effect of pilocarpine drops on the diurnal IOP variation in patients with glaucoma. Invest Ophthalmol., 1976, 15, 784

20 Suda K, Furushima M, Kihara K et al. : Influence of antiglaucomatous surgery on the diurnal variation of the ocular tension in simple glaucoma. Acta. Soc. Ophthalmol. Jpn., 1961, 65, 1711

21 Greenidge KC, Spaeth GL, Fiol-Silva Z : The effect of ALT on the glaucomatous diurnal curve. Ophthalmology, 1983, 90, 800

22 Phelps CD, Woolson RF, Kolker AE, Becker B : Diurnal variation in IOP. Am. J. Ophthalmol., 1974, 77, 367

23 Armaly MF : The visual vield defect and ocular pressure level in open-angle glaucoma. Invest. Ophthalmol., 1969, 8, 105

24 Drance SM : Doyne Memorial Lecture 1975 : correlation of optic nerve and visual field defects in simple glaucoma. Trans. Ophthalmol. Soc. UK, 1975, 95, 288

25 Bebie H, Fankhauser F, Spahr J : Static perimetry : Accuracy of fluctuations. Acta. Ophthalmol., 1976, 54, 339

26 Heijl A, Drance SM : Changes in differential thresholds in patients with glaucoma during prolonged perimetry. Br. J. Ophthalmol., 1983, 67, 512

27 Flammer J, Drance SM, Zulauf M : Differential light threshold : fluctuations in patients with glaucoma, normal controls and suspected glaucoma. Arch. Ophthalmol., 1984, 102, 704

28 Wilensky JT, Joondelph BC : Variation in visual field measurements with an automated perimeter. Am. J. Ophthalmol., 1984, 97, 328

29 Niesel P, Flammer J : Correlations between IOP, visual field and visual acuity, based on 11 years of observations of treated chronic glaucomas. Int. Ophthalmol., 1980, 3, 331

30 Wise JB, Witter SL : Argon laser therapy for open angle glaucoma. A

pilot study. Arch. Ophthalmol., 1979, 97, 319

31 Forbes M : Influence of miotics on visual fields in glaucoma. Invest. Ophthalmol., 1966, 5, 139

32 McCluskey DJ, Douglas JP, O'Connor P, Story K, Ivy LM, Harvey JS : The effect of pilocarpine on the visual fields in normals. Ophthalmology, 1986, 93, 843

33 Greve EL, Furuno F, Verduin WM : The clinical significance of reversibility of glaucomatous visual field defects. Doc. Ophthalmol. Proc. Series, 1978, 19, 197

34 Schultz JS, Werner EB, Krupin T, Bishop KI, Kolke J : Intraocular pressure and visual field defects after argon laser trabeculoplasty in chronic open-angle glaucoma. Ophthalmology, 1987, 94, 553

35 Crick RP, Vogel R, Newson R et al. : Relationship between IOP and visual field progress in chronic simple glaucoma and ocular hypertension. Glaucoma 1985, 7, 208

36 Holmin C, Storr-Paulsen A L The visual field after trabeculecotmy : a follow-up study using computerised perimetry. Acta. Ophthalmol., 1984, 62, 230

37 Holmin C, Krakau CET : The visual field before and after laser trabeculoplasty : regression analysis based on computerised perimetry. Doc. Ophthalmol. Proc. Ser., 1985, 42, 371

38 Spaeth GL : The effect of change in intraocular pressure on the natural history of glaucoma : lowering intraocular pressure in glaucoma can result in improvement of visual fields. Trans. Ophthalmol Soc. U.K., 1985, 104, 256

39 Heijl A, Bengtsson B : The short-term effect of laser trabeculoplasty on the glaucomatous visual field. A prospective study using computerized perimetry. Acta. Ophthalmol., 1984, 62, 705

40 Holmin C, Bauer B : Laser trabeculoplasty in open-angle glaucoma. a short-term study using computerised perimetry. Acta. Ophthalmol., 1984, 62, 337

41 Holmin C, Krakau CET : Regression analysis of the central visual field in chronic glaucoma cases : a follow-up study using automated perimetry. Acta. Ophthalmol., 1982, 60, 267

42 Mikelberg FS, Drance SM : The mode of progression of visual field defects in glaucoma. Am. J. Ophthalmol., 1984, 98, 443

43 Sugar HS : Postoperative cataracts in successfully filtering glaucomatous eyes. Am. J. Ophthalmol., 1970, 69, 740

44 Watson PG, Grierson I : The place of trabeculectomy in the treatment of glaucoma. Ophthalmology, 1981, 88, 175

45 Spaeth GL : A prospective controlled study to compare the Scheie procedure with Watson's trabeculectomy. Ophthalmic Surg., 1980, 11, 688

46 Jerndal T, Lundstrom M : 330 trabeculectomies - follow-up study through 1/2 - 3 years. Acta Ophthalmol., 1977, 55, 52

47 Mills KB : Trabeculectomy : A retrospective long-term follow-up of 444 cases. Br. J. Ophthalmol., 1981, 65, 790

48 Watson PG, Barnett F : Effectiveness of trabeculectomy in glaucoma. Am. J. Ophthalmol., 1975, 79, 831

49 Aggarwal SP, Hendeles S : Risk of sudden visual loss following trabeculectomy in advanced primary open-angle glaucoma. Br. J. Ophthalmol., 1986, 70, 97

50 Lichter PR, Ravin JG : Risks of sudden visual loss after glaucoma surgery. Am. J. Ophthalmol, 1974, 78, 1009

51 Lichter PR : Variability of expert observers in evaluating the optic disc. Trans. Am. Ophthalmol. Soc., 1977, 74, 537

52 Pederson JE, Anderson DR : The mode of progressive disc cupping in ocular hypertension and glaucoma. Arch. Opthalmol., 1980, 98, 490

53 Sommer A, Pollack I, Maumenee AE : Optic disc parameters and onset of glaucomatous field loss. I. Methods and progressive changes in disc morphology. Arch. Opthalmol., 1979, 97, 1444

54 Drance SM : Correlation of optic nerve and visual field defects in simple glaucoma. Trans. Opthalmol. Soc. UK, 1975, 95, 288

55 Nagin P, Schwartz B, Takamoto T : Three-dimensional computer graphic display and correlation of optic disc pallor with cupping. Invest. Ophthalmol. Vis. Sci., 1985, 26 (suppl.), 223

56 Pollack IP, Robin AL, Sax H : The effect of argon laser trabeculoplasty on the medical control of primary open-angle glaucoma. Ophthalmology, 1983, 90, 785

57 Wise JB : Ten year results of laser trabeculoplasty. Does the laser avoid glaucoma surgery or merely defer it? Eye, 1987, 1, 45

58 Hitchings R, Grierson I, Sherwood M, Migdal C : Chronic glaucoma therapy : does it affect the conjunctiva? Poster Presentation : American Academy of Ophthalmology, 1988.

59 Inaba Z : Long-term results of trabeculectomy in the Japanese. An analysis of life table method. Jpn. J. Ophthalmol., 1982, 26, 361

60 Freedman J, Sher E, Ahrens M : Trabeculectomy in a Black American population. Br. J. Ophthalmol., 1976, 60, 573

61 Watkins PH Jr, Brubaker RF : Comparison of partial-thickness and full-thickness filtration procedures in open-angle glaucoma. Am. J. Ophthalmol., 1978, 86, 756

62 Shields MB : Trabeculectomy vs. full-thickness filtering operation for control of glaucoma. Ophthalmic Surg., 1980, 11, 498

63 Blondeau P, Phelps CD : Trabeculectomy vs. thermosclerostomy. A randomised prospective clinical trial. Arch. Ophthalmol., 1981, 99, 810

64 Lewis RA, Phelps CD : Trabeculectomy vs. thermosclerotomy. A 5-year follow-up. Arch. Ophthalmol., 1984, 102, 533

65 Lamping KA, Bellows R, Hutchinson BT, Afran SI : Long-term evaluation of initial filtration surgery. Ophthalmology, 1986, 93, 91

66 Migdal C, Hitchings R : Morbidity following prolonged hypotony after trabeculectomy. Ophthalmic Surgery, 1988, 19, 865

67 Krakau LET : Intraocular elevation - cause or effect in chronic glaucoma? Acta Ophthalmol., 1981, 182, 141

PLATE 1
Adolf Weber
(1829 - 1915)

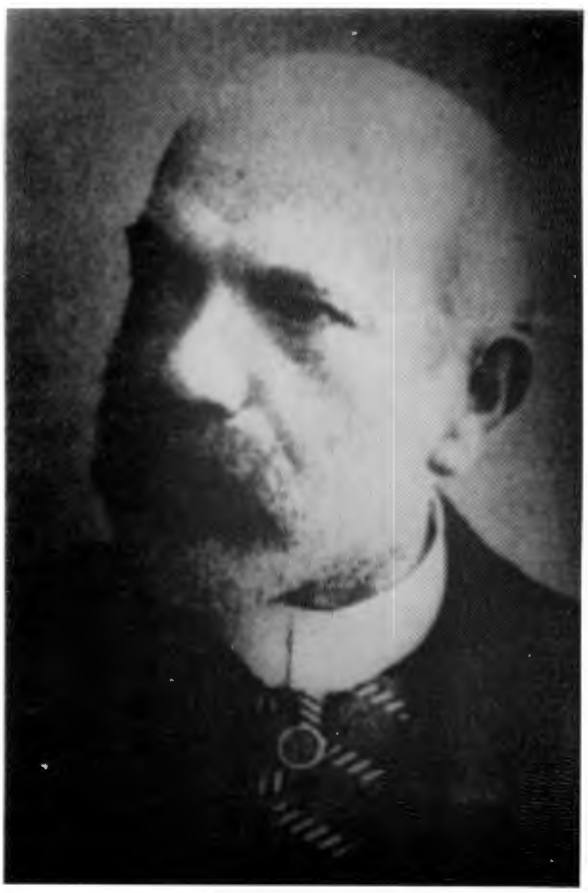


PLATE 2
Ludwig Lacqueur
(1839 - 1909)

PLATE 3
Robert Henry Elliot
(1864 - 1936)

PLATE 4
John Cairns
(1925 - 1985)

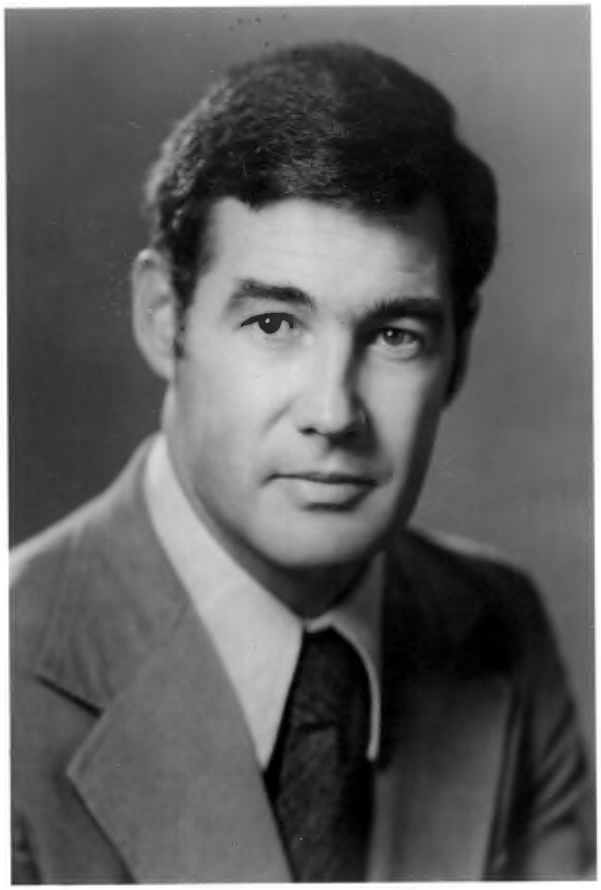
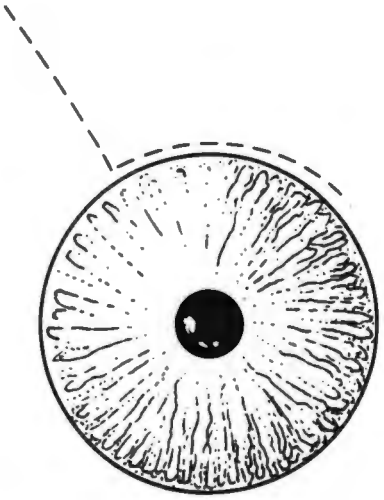


PLATE 5
James Wise

TRABECULECTOMY PROCEDURE



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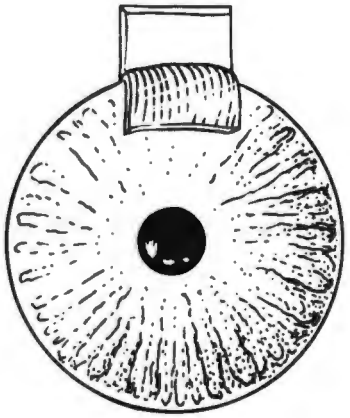

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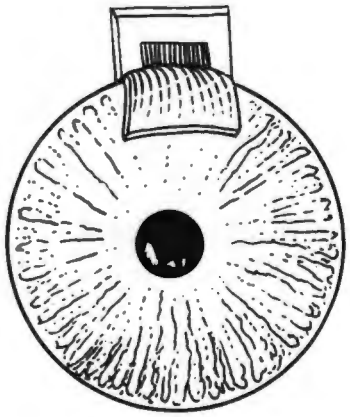

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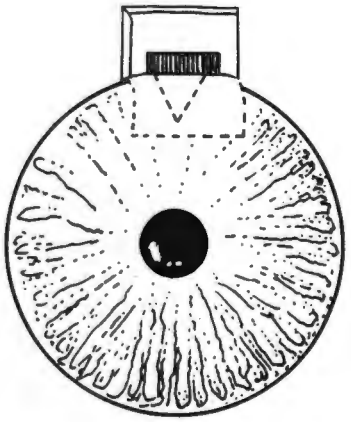

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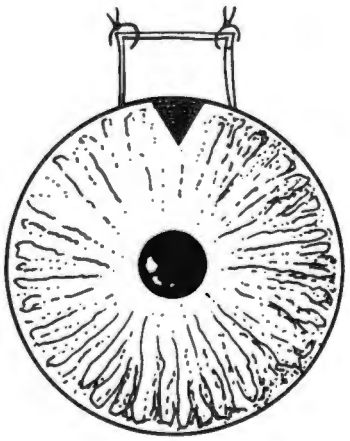

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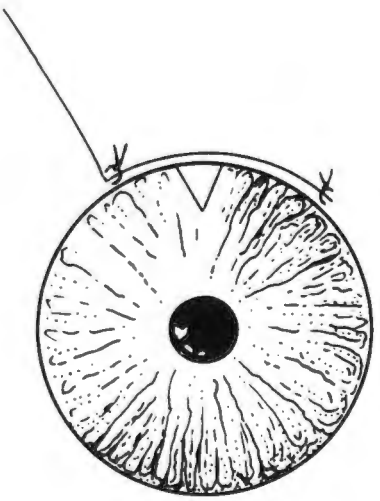

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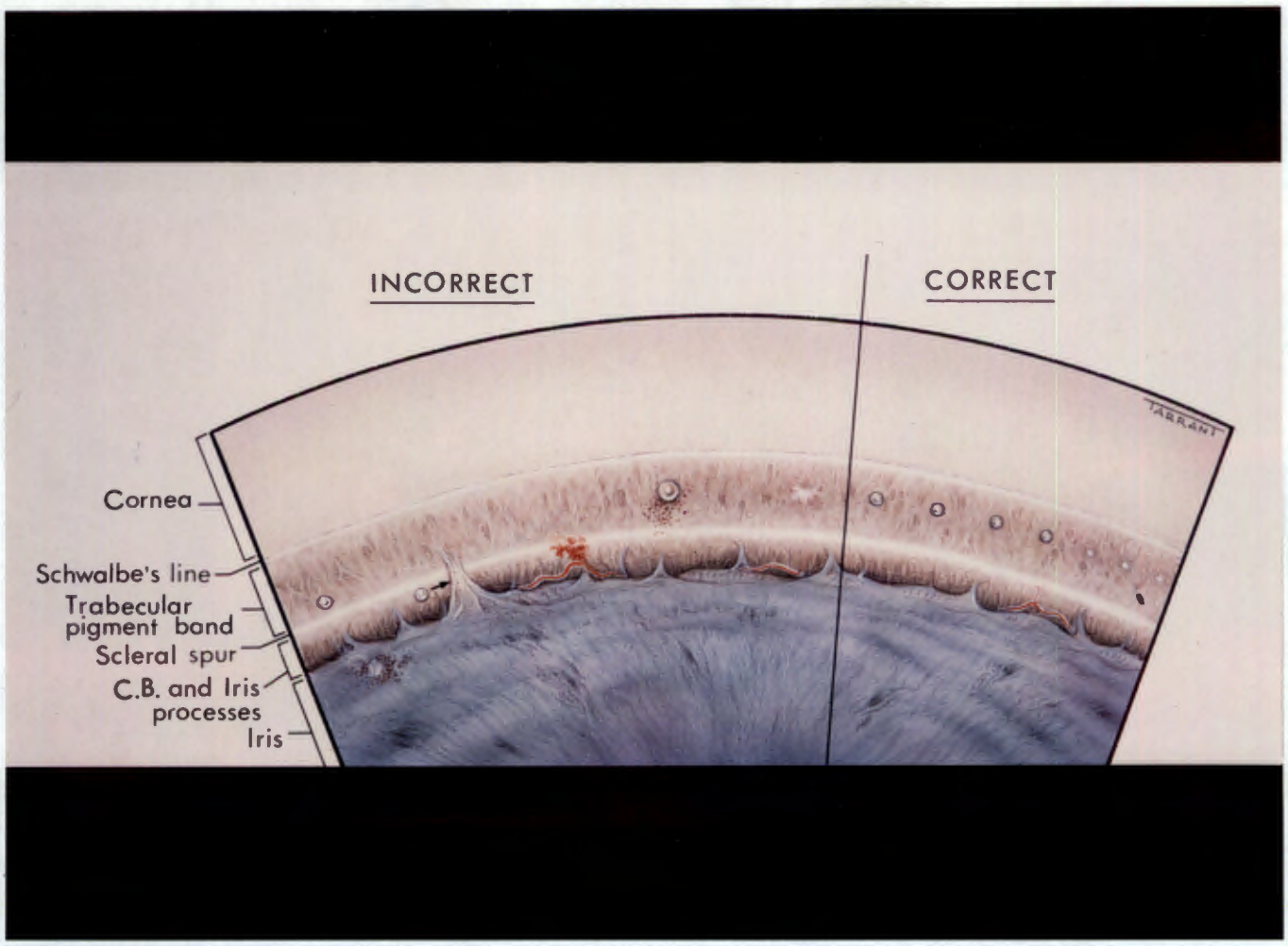


PLATE 7: LASER TRABECULOPLASTY: DO'S AND DON'TS

From left to right illustrating:

A. INCORRECT
   1. Burn too posterior, catching iris
   2. Peripheral anterior synechiae secondary to a posteriorly placed burn
   3. Posterior burn hitting a blood vessel in the angle
   4. Too heavy a burn resulting in pigment release and
   5. Scarring.

B. CORRECT
   1. Minute gas bubble formation
   2. Transient blanching of the trabecular meshwork.

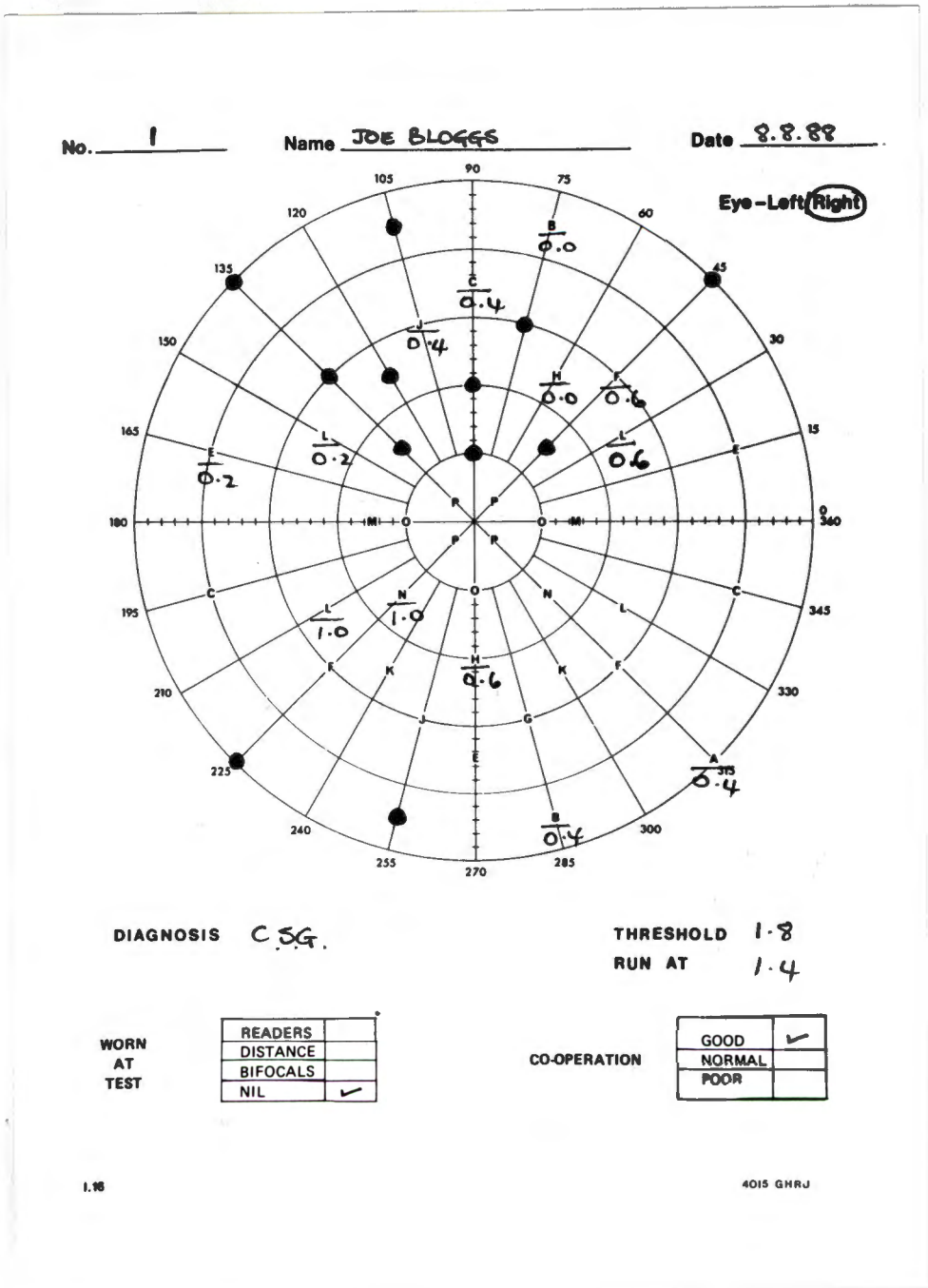
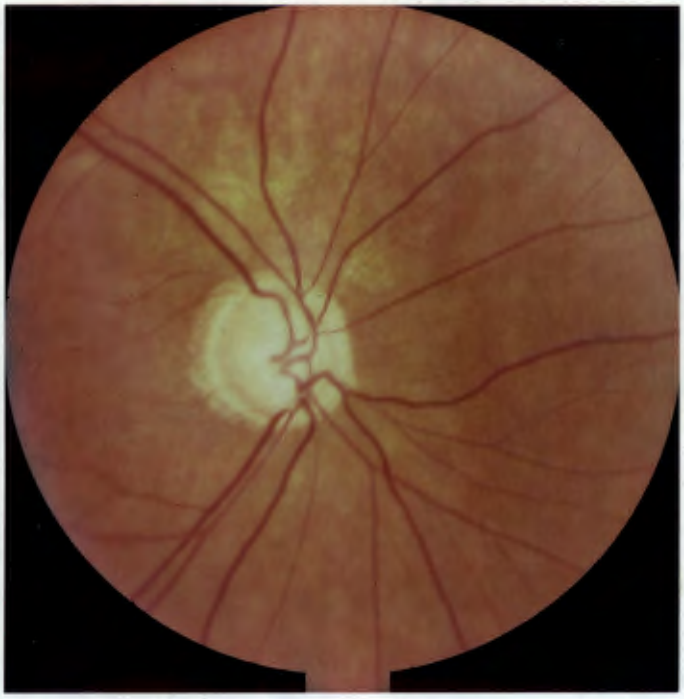


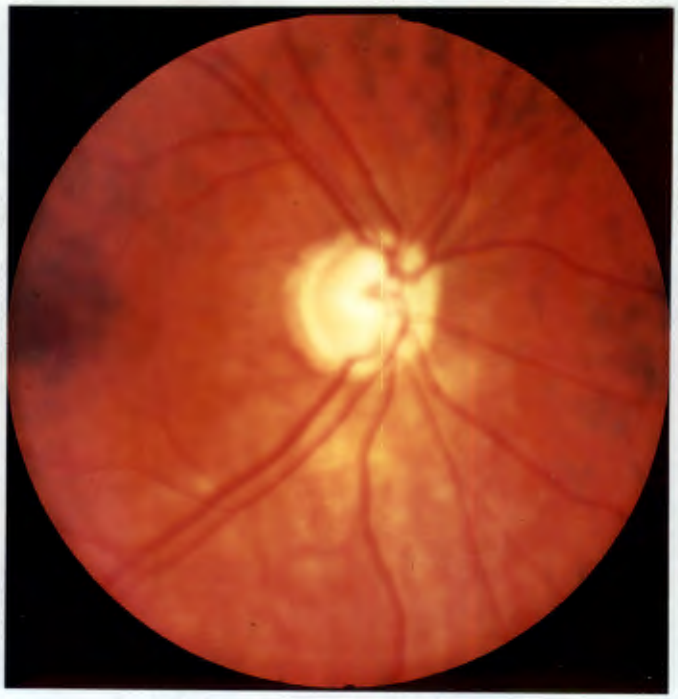
PLATE 8

FRIEDMANN FIELD SCORING EXAMPLE

	FIELD SCORE	ADJUSTED SCORE (Minus 8 most peripheral spots)
RELATIVE DEFECTS		
(No. of spots missed at intensities 0.4 log units > threshold to maximum intensity)	25	17
ABSOLUTE DEFECTS		
(No of spots missed at maximum intensity)	12	7



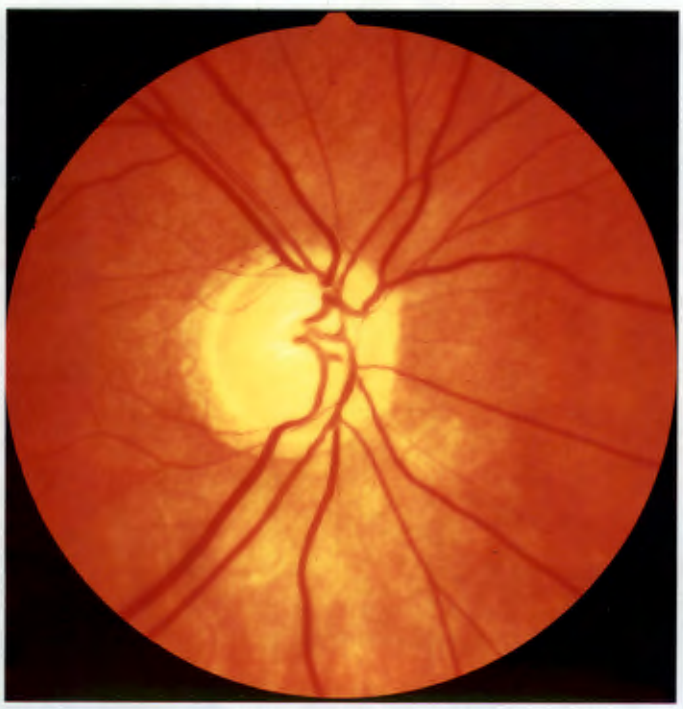
1984



1985

PLATE 9
SERIAL OPTIC DISC PHOTOS

1986



1987

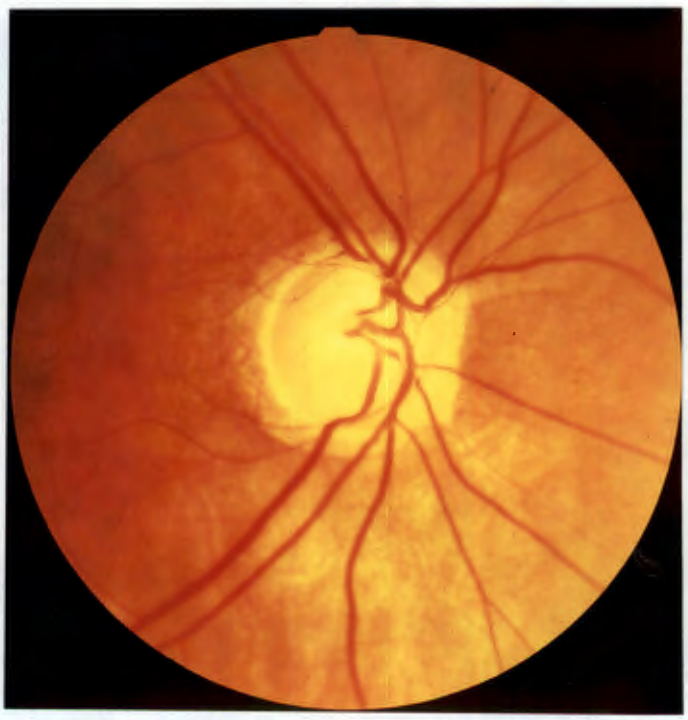
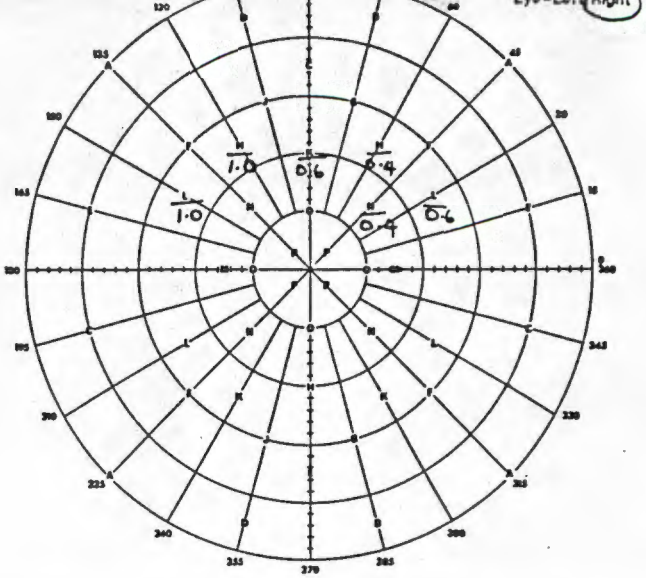
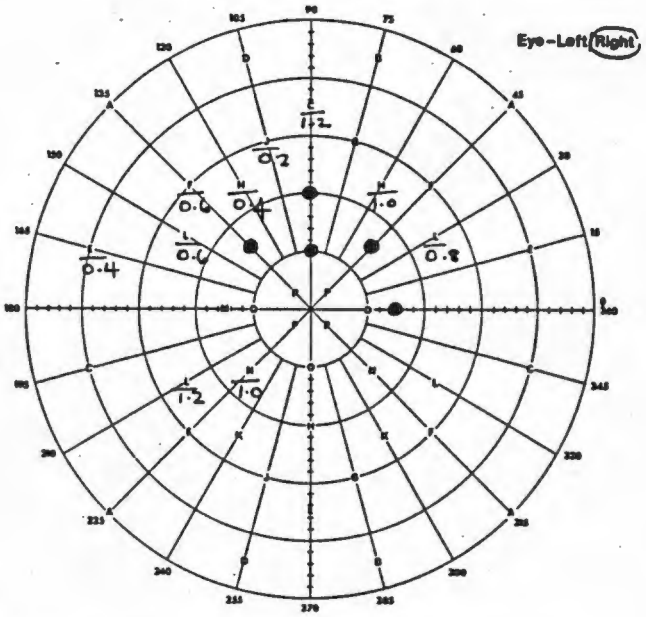


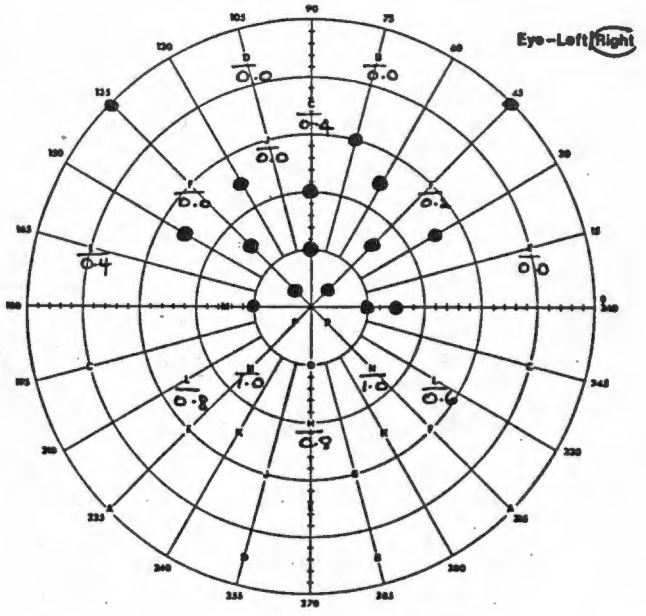
PLATE 10



DIAGNOSIS C.S.G. EARLY THRESHOLD 1·8
RUN AT 1·4



DIAGNOSIS C.S.G MODERATE THRESHOLD 1·8
RUN AT 1·4



DIAGNOSIS C.S.G ADVANCED THRESHOLD 1·8
RUN AT 1·4

PLATE II

CYSTIC DRAINAGE BLEB

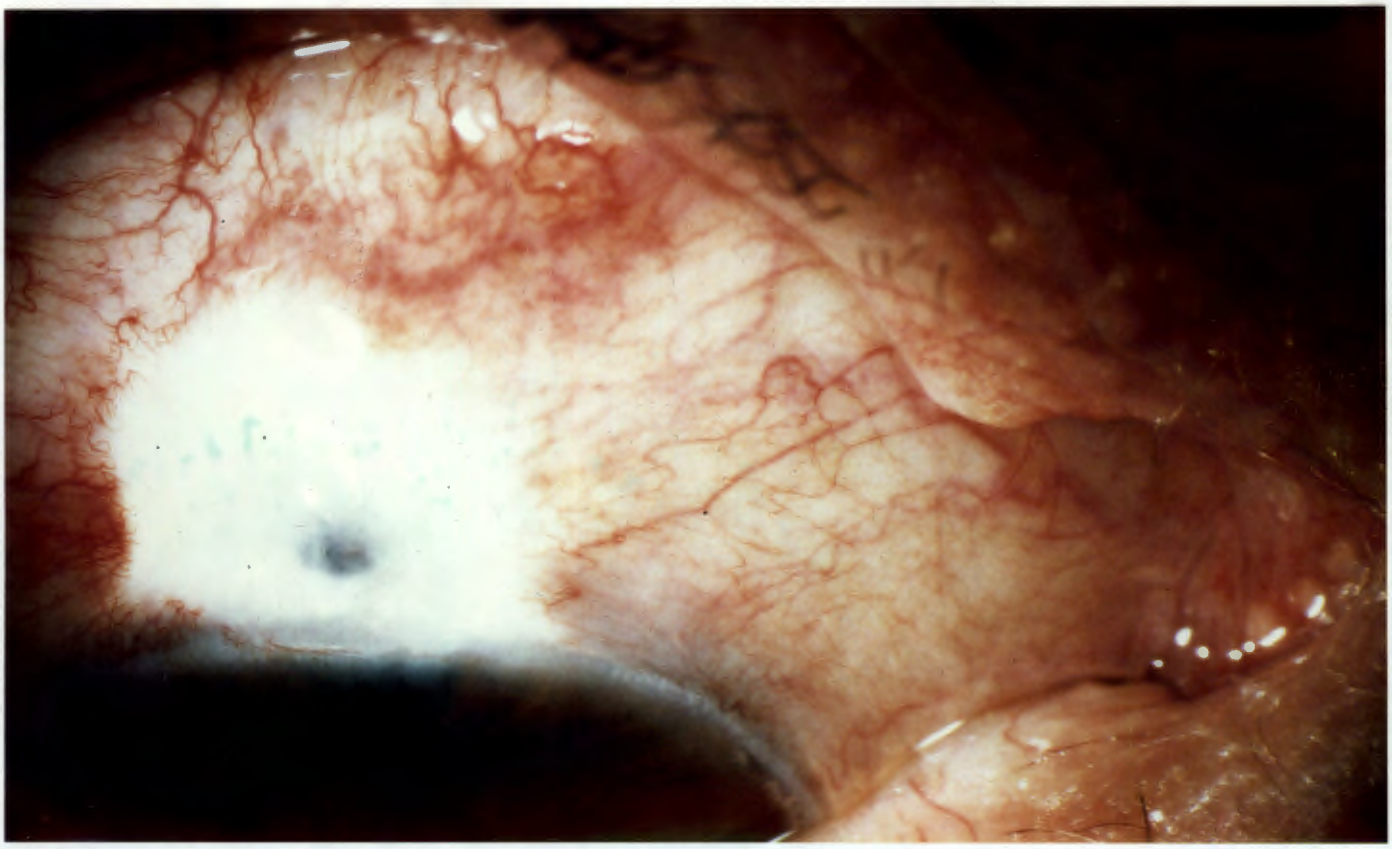
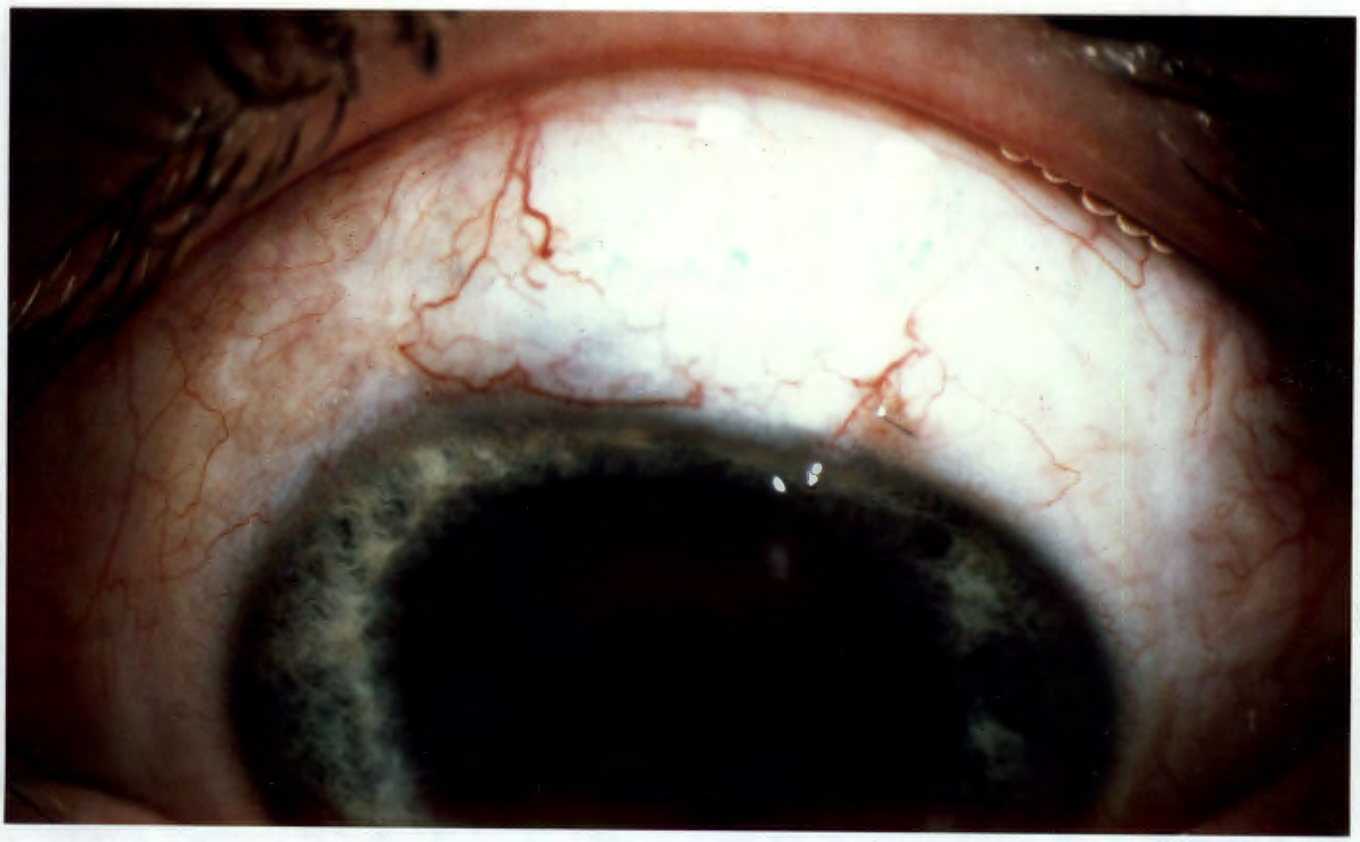


PLATE 12

DIFFUSE DRAINAGE BLEB



EXPLANATION OF GRAPHS

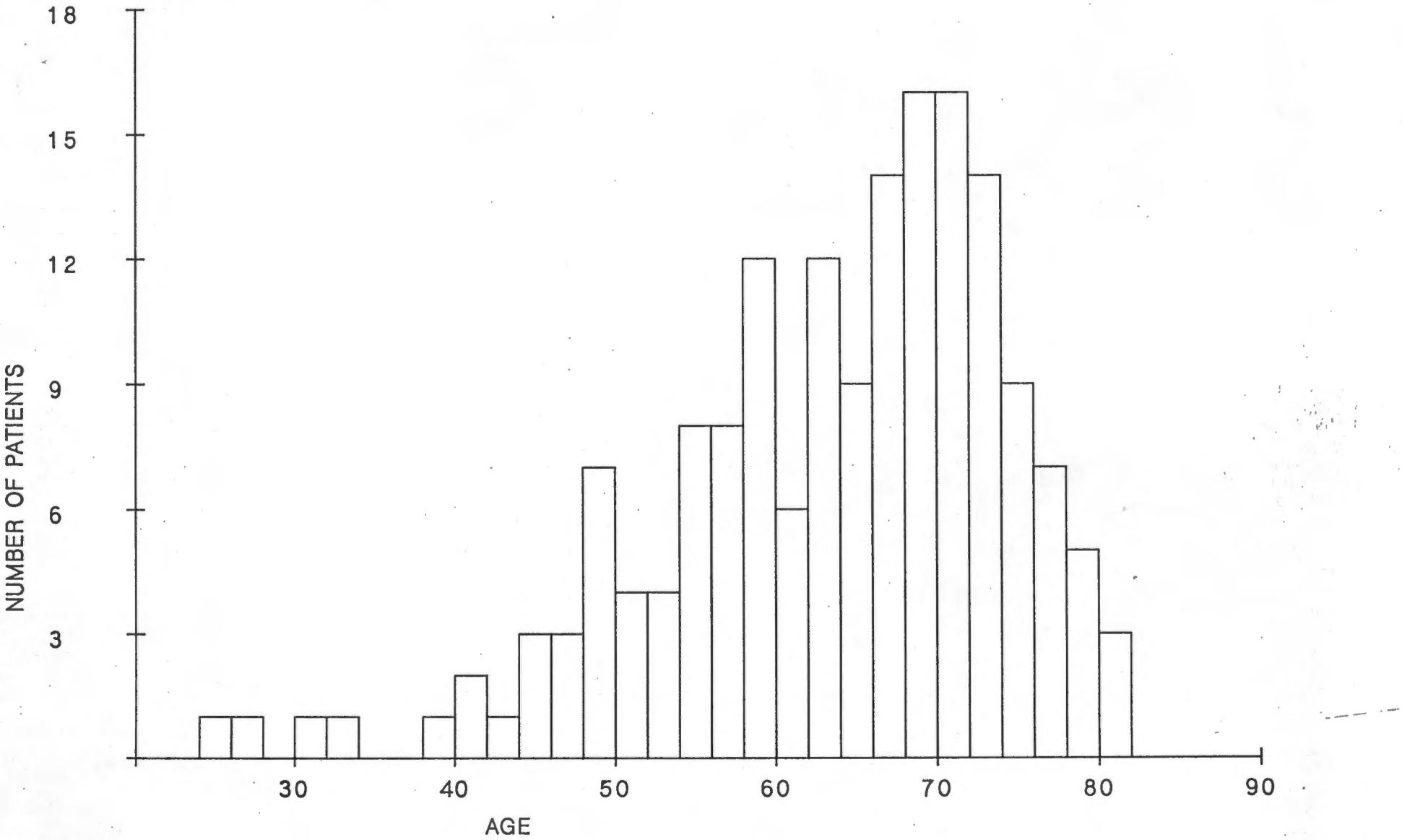
1. In Figs : 7, 11, 11-ABC, 12, 12-ABC, 13, 14, 15, 18
   The bars = 1 standard error.

2. In Fig 7-A and 15-A, the smoothed curves = normal distribution spread (using mean and standard deviation).

3. In the survival analysis graphs, vertical lines refer to death/last follow-up. The drops refer to failures.

AGE DISTRIBUTION – ALL PATIENTS

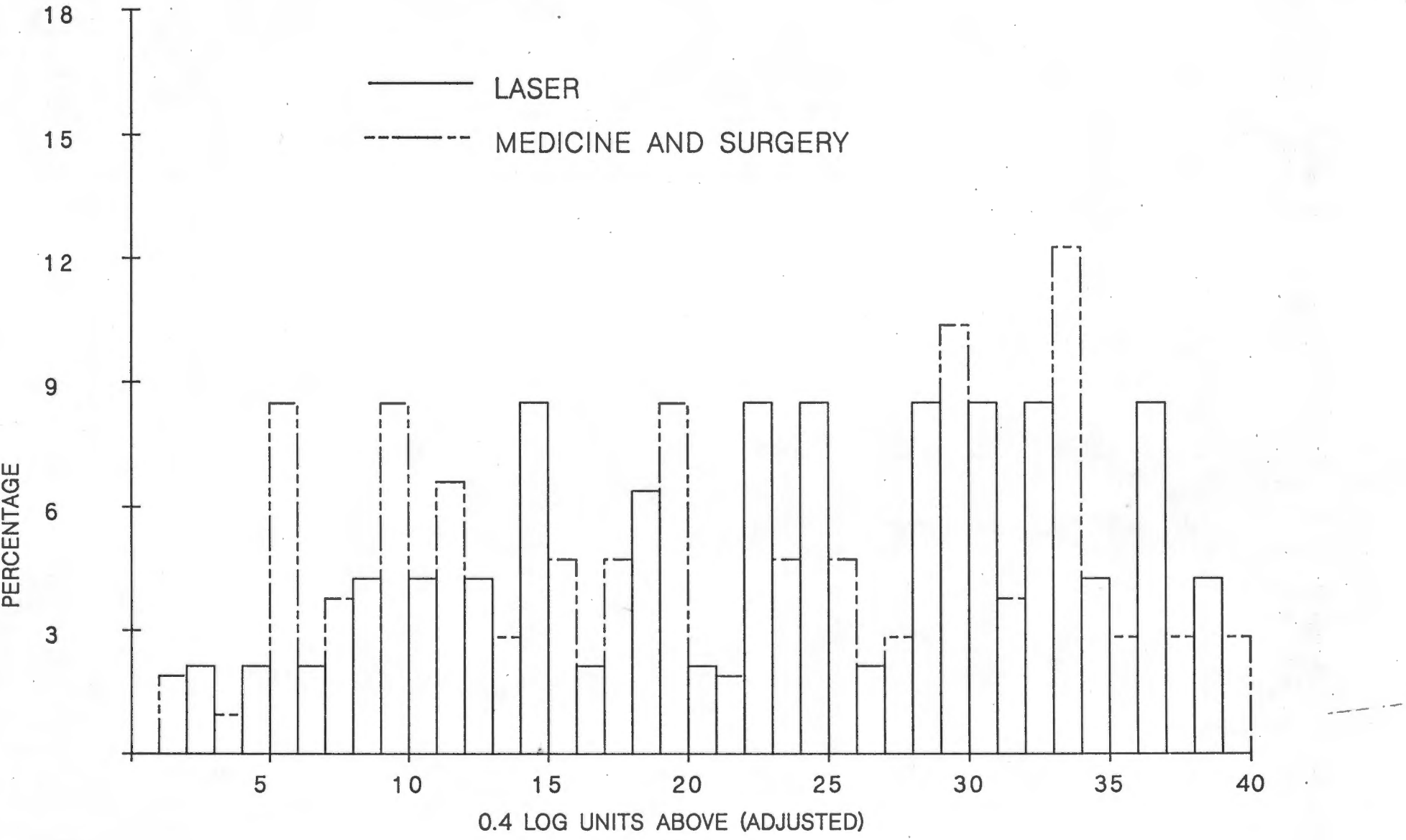
FIGURE 1



VISUAL FIELD SCORES ON ENTRY

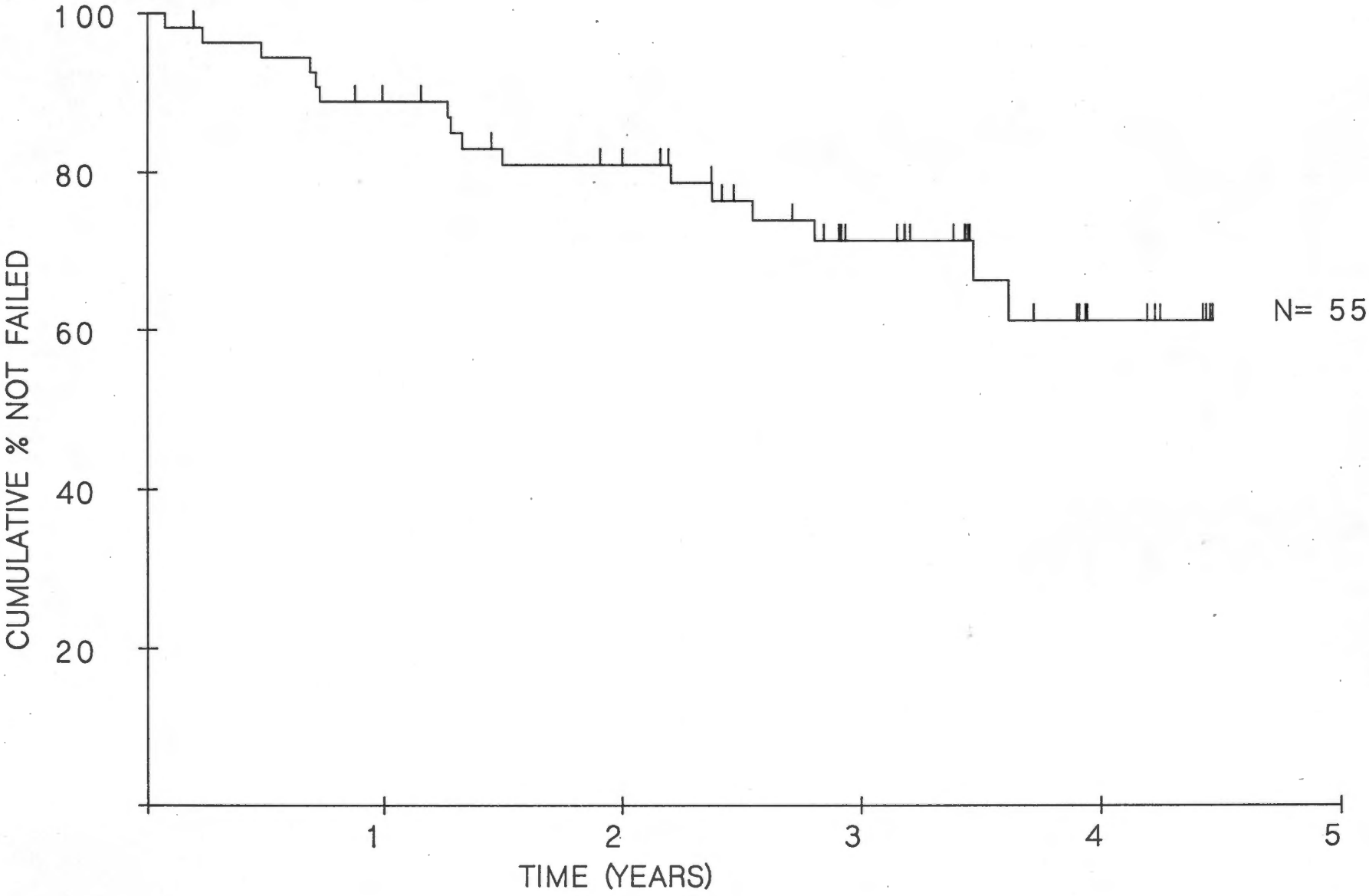
LASER v MEDICINE AND SURGERY

FIGURE 2



LASER GROUP: TIME FROM TREATMENT TO FAILURE

FIGURE 3



LASER: TIME TO FAILURE BY STAGE

FIGURE 4

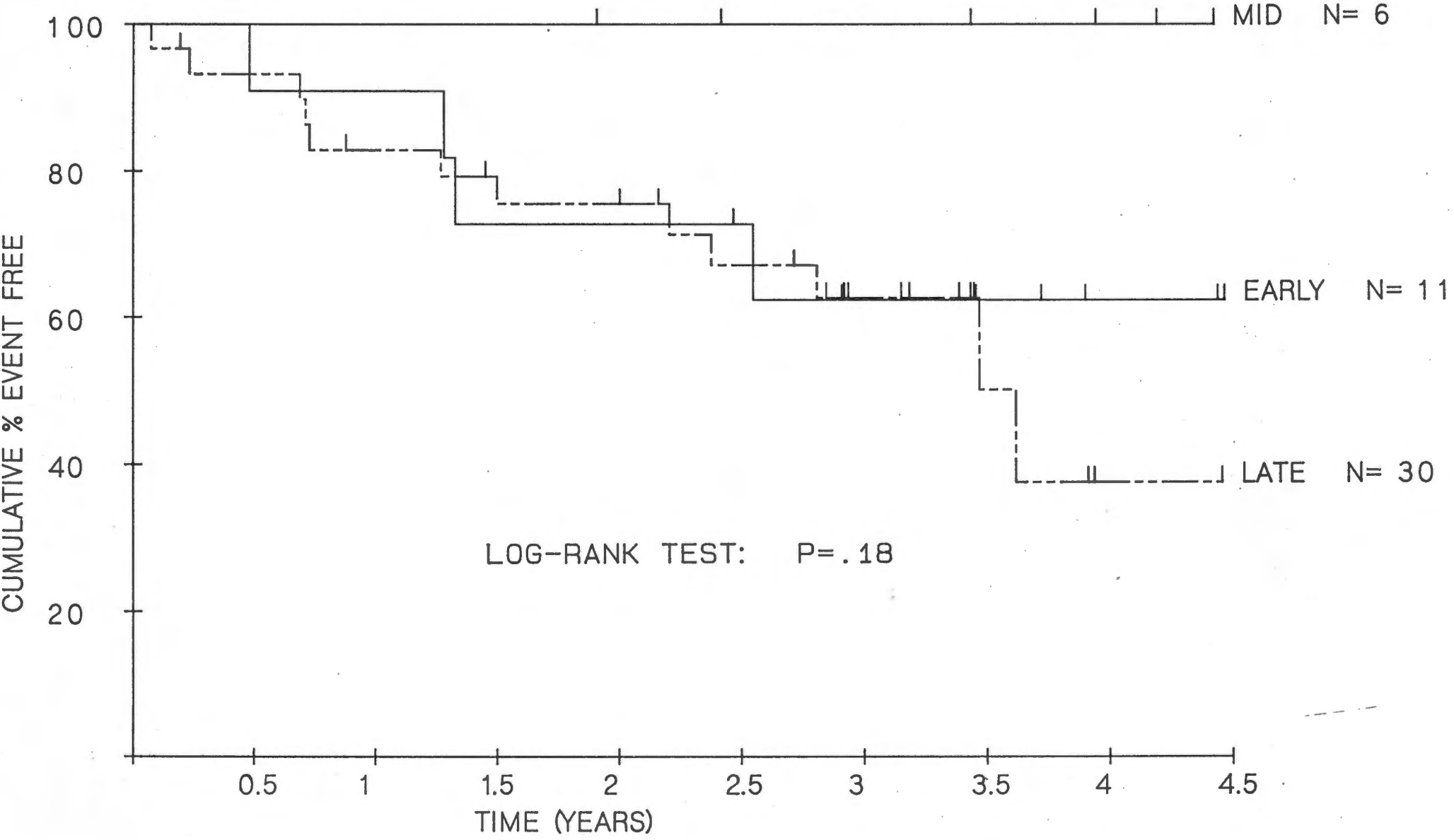
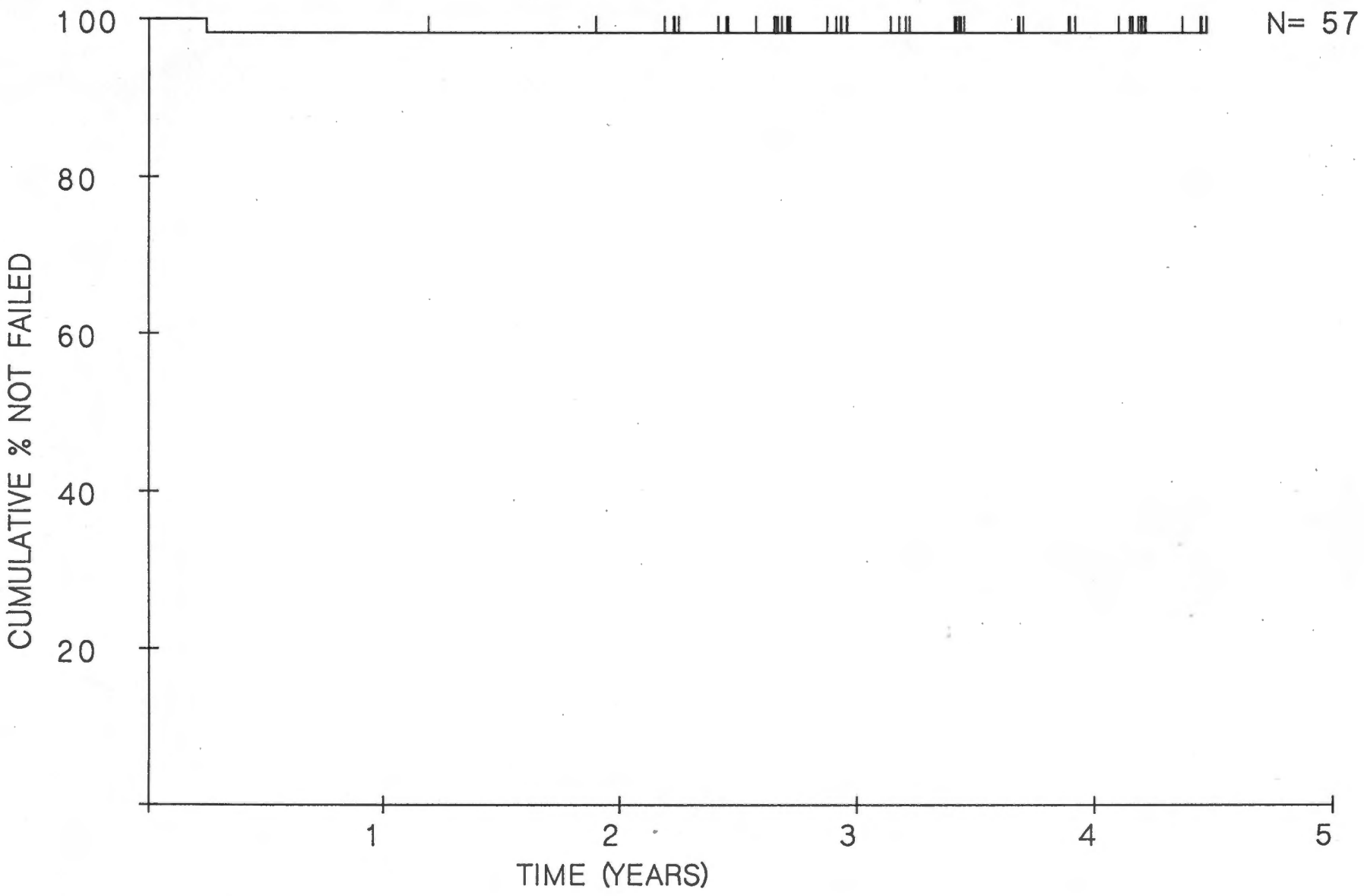
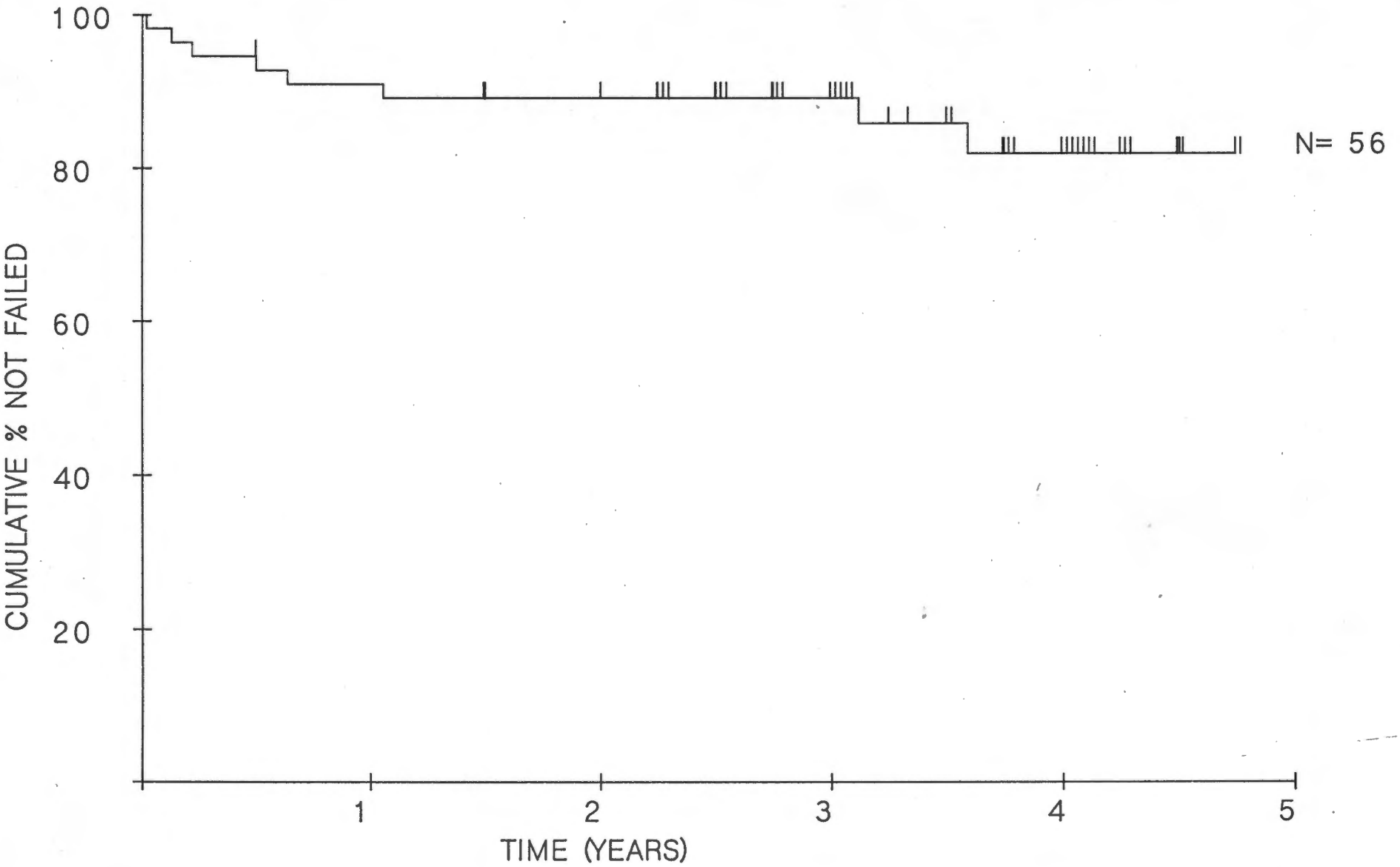


FIGURE 5


SURGERY GROUP: TIME FROM TREATMENT TO FAILURE
N= 57
100
80
60
40
20
CUMULATIVE % NOT FAILED
1
2
3
4
5
TIME (YEARS)

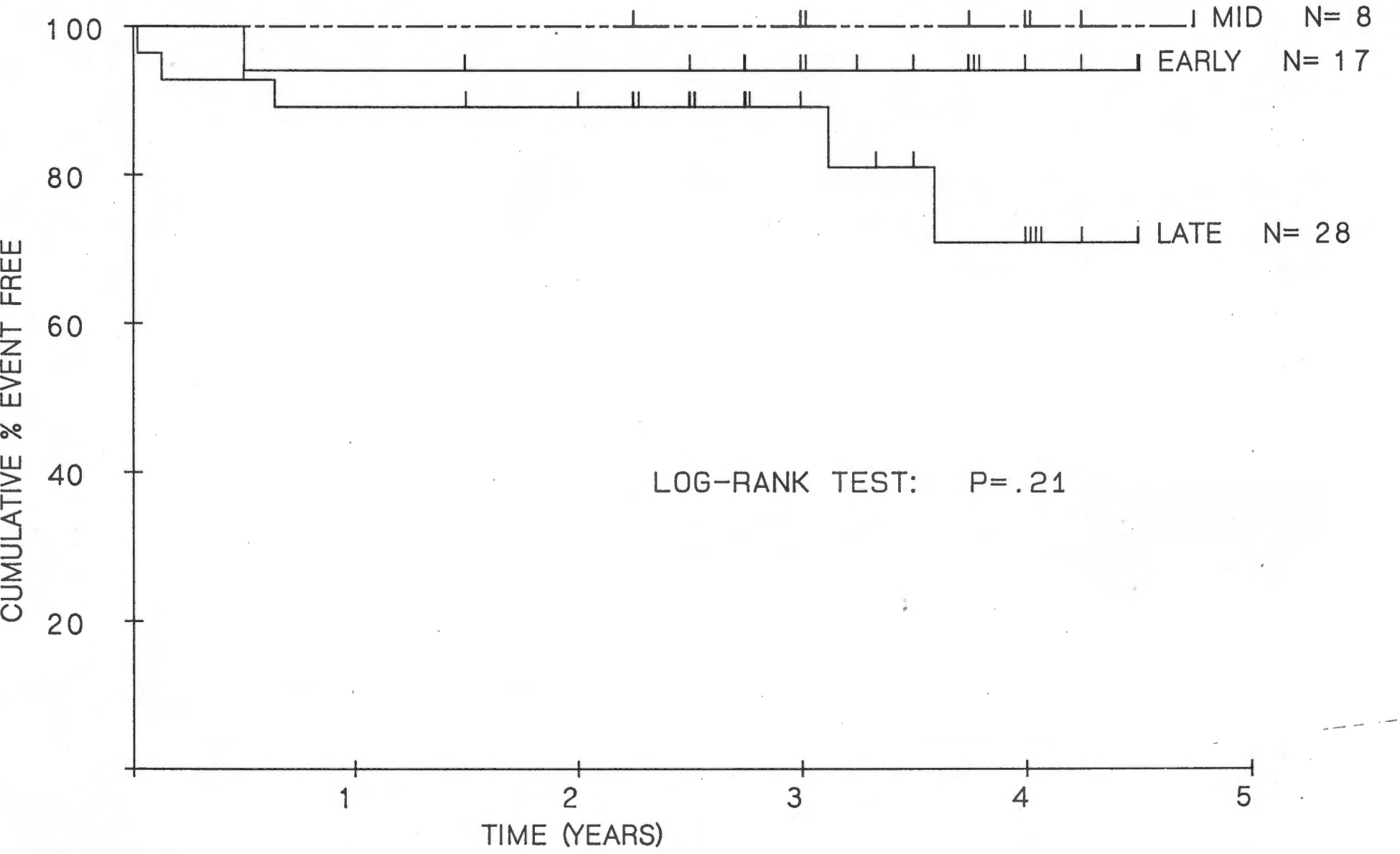
MEDICINE GROUP: TIME FROM TREATMENT TO FAILURE

FIGURE 6



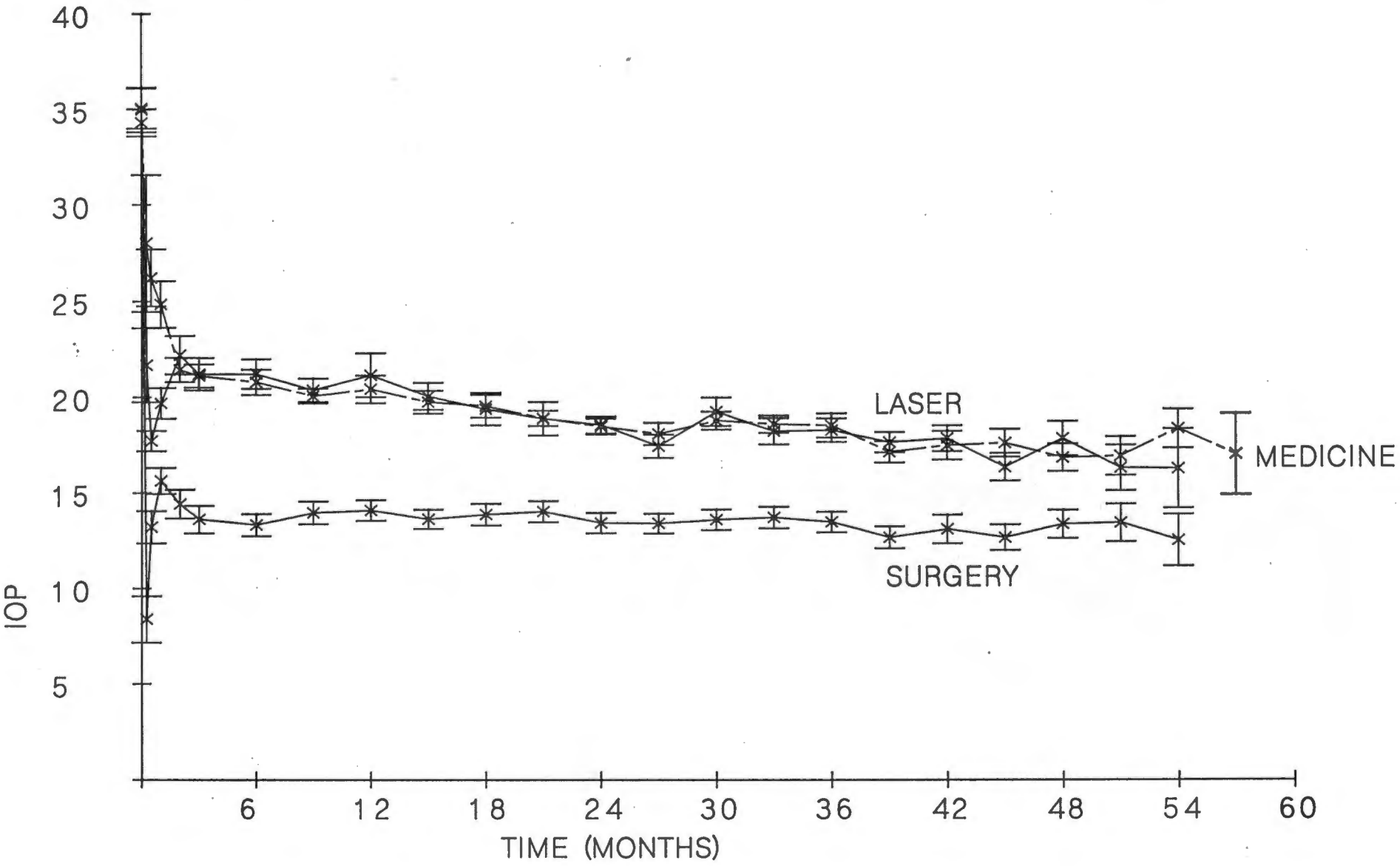
MEDICINE: TIME TO FAILURE BY STAGE

FIGURE 6-A



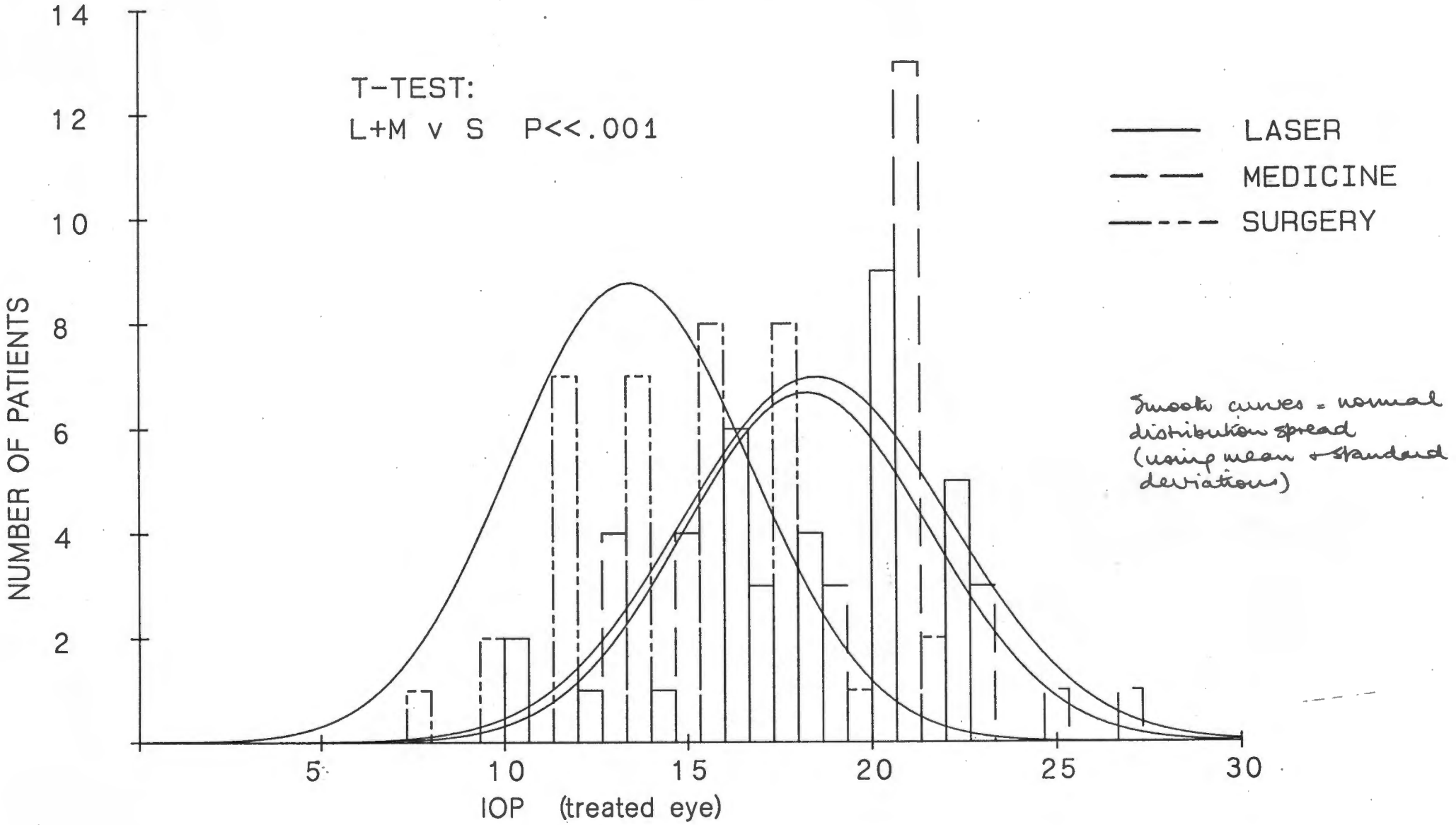
MEAN IOP : LASER v MEDICINE v SURGERY
(FAILURES EXCLUDED AT TIME OF FAILURE)

FIGURE 7



IOP LEVELS AT 3 YEARS: LASER v MEDICINE v SURGERY

FIGURE 7-A



IOP v IOP REDUCTION AT 1 YEAR: LASER

FIGURE 8

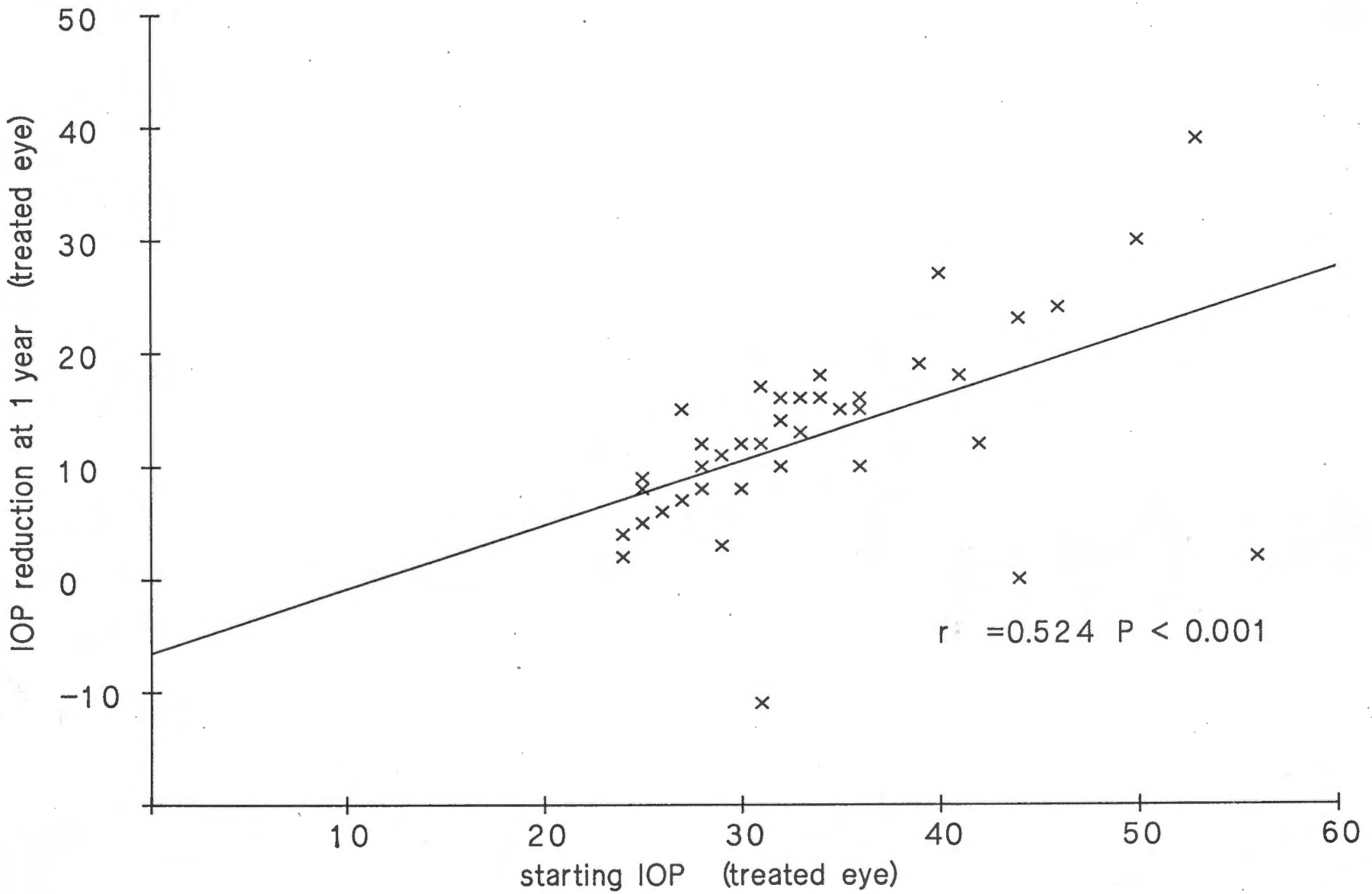
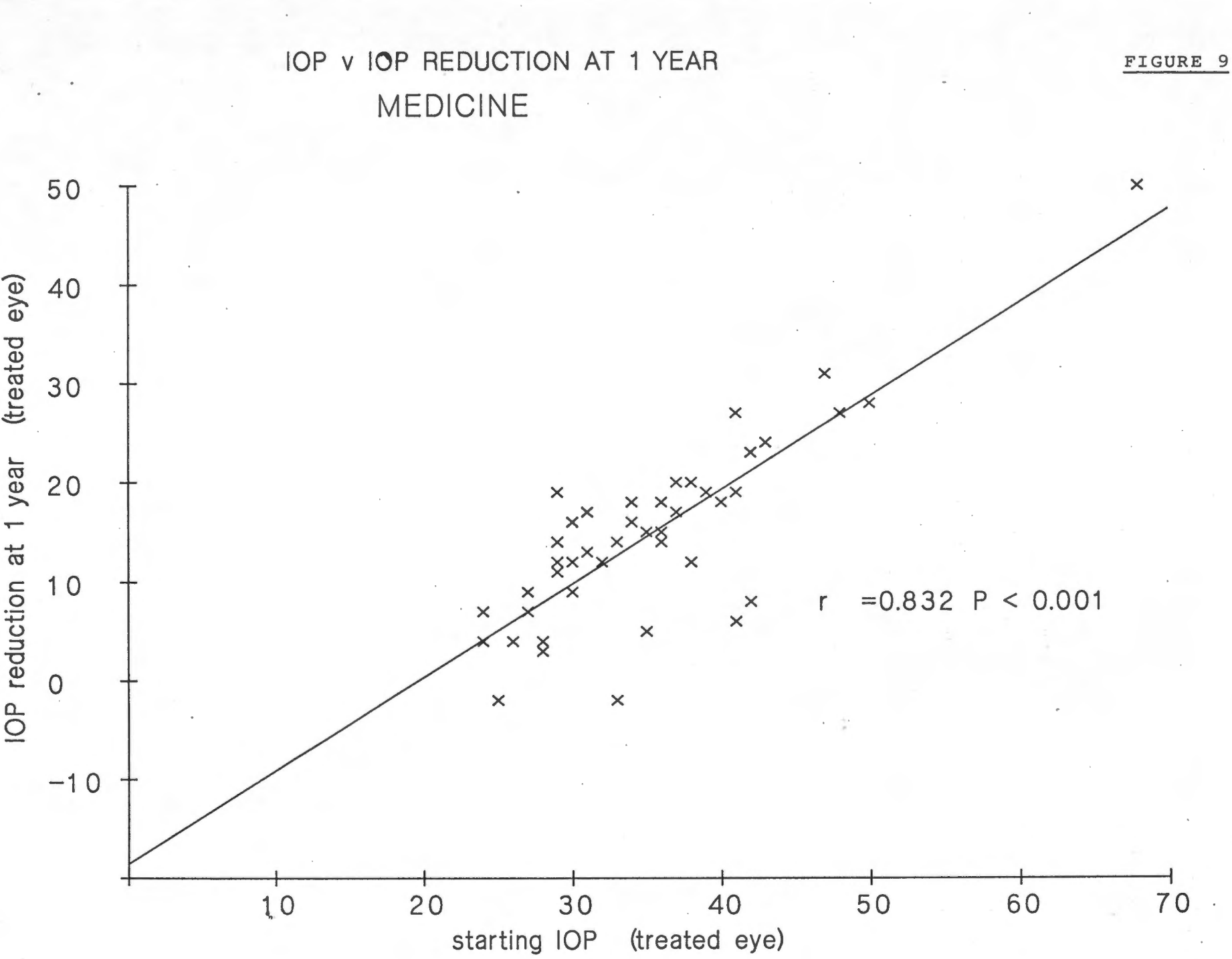
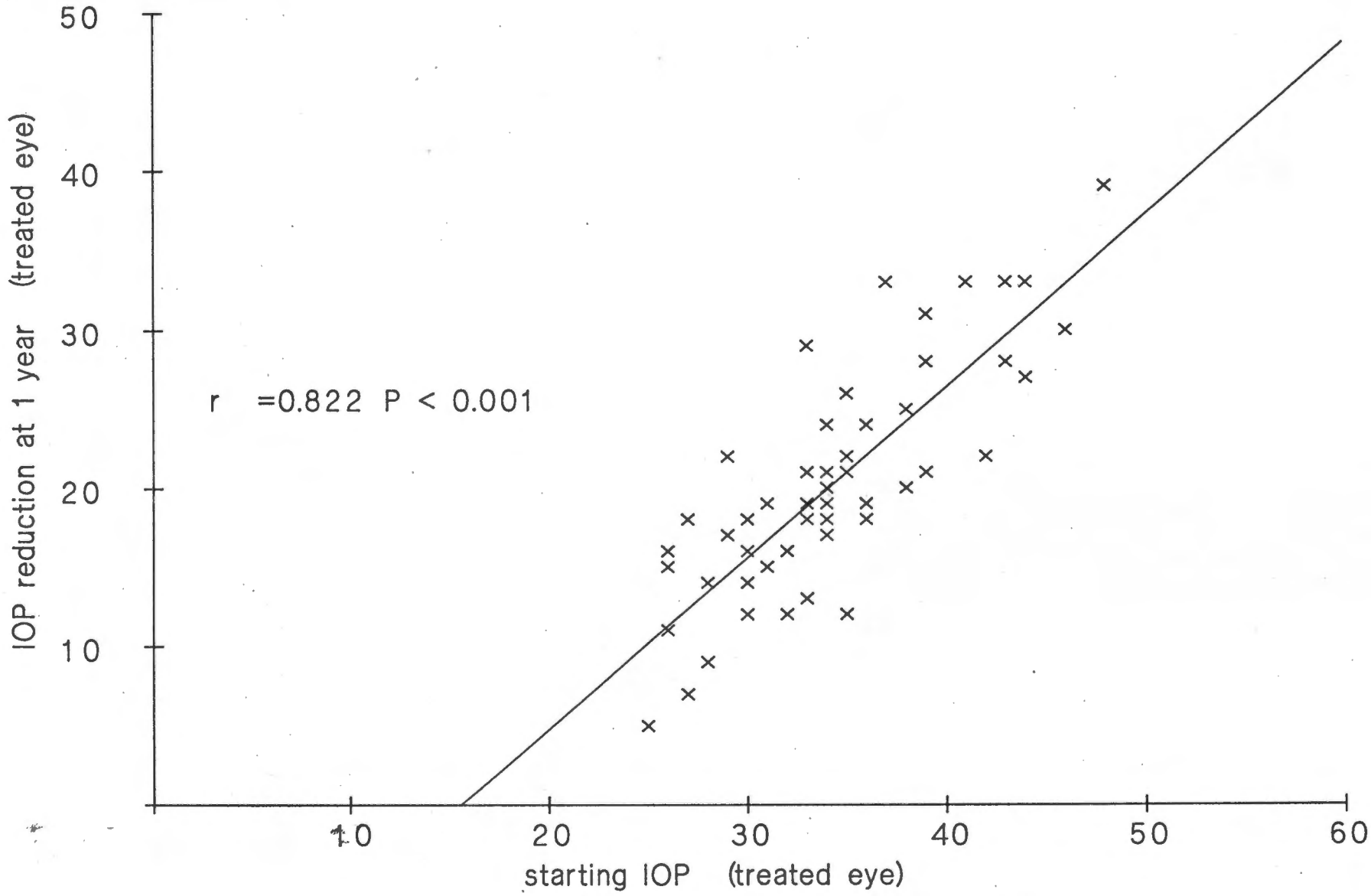


FIGURE 9


IOP v IOP REDUCTION AT 1 YEAR
MEDICINE
IOP reduction at 1 year (treated eye)
50
40
30
20
10
0
-10
10
20
30
40
50
60
70
starting IOP (treated eye)
r =0.832 P < 0.001

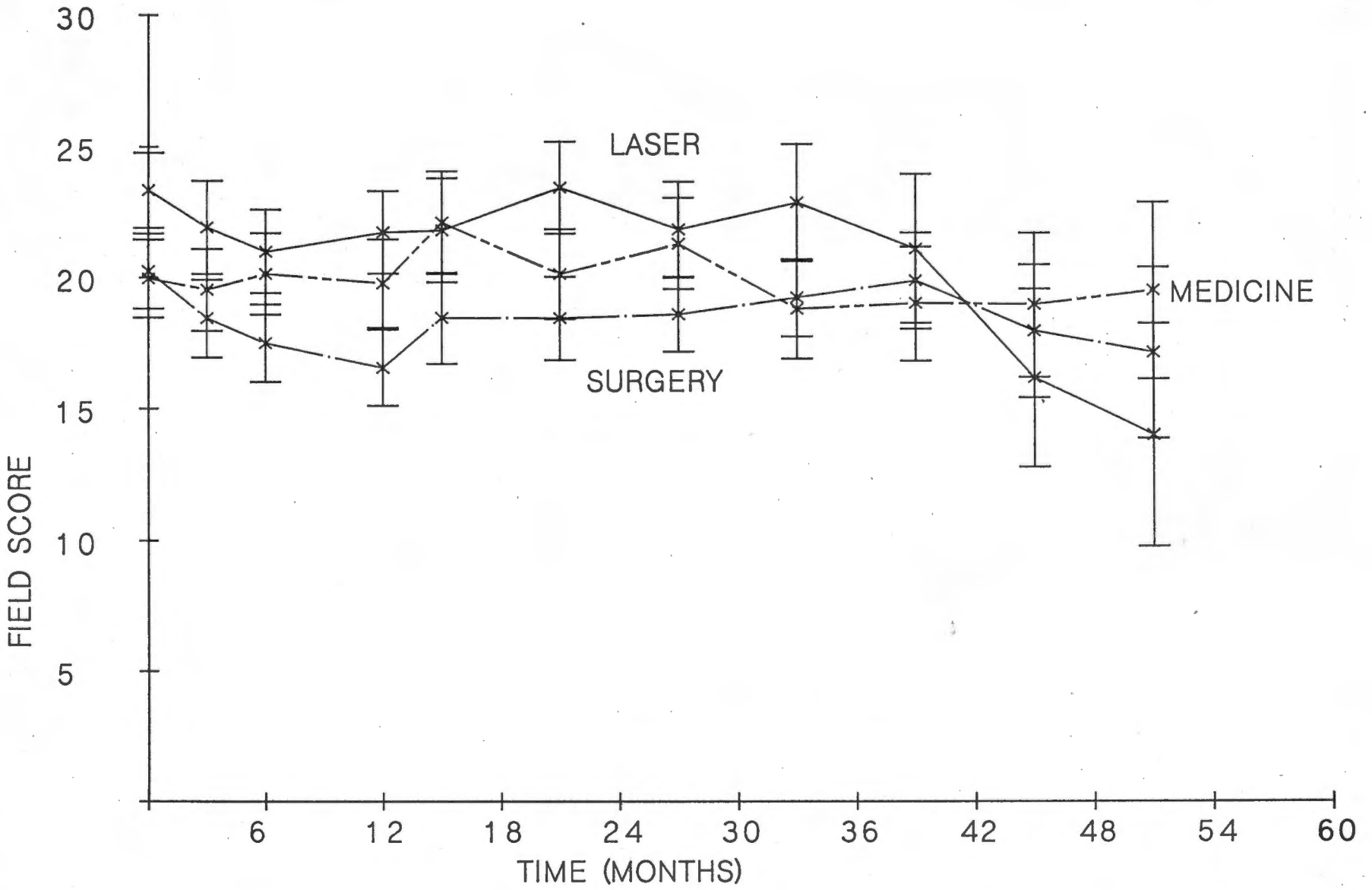
IOP v IOP REDUCTION AT 1 YEAR: SURGERY

FIGURE 10



FIELD SCORES – RELATIVE DEFECTS
(FAILURES EXCLUDED AT TIME OF FAILURE)

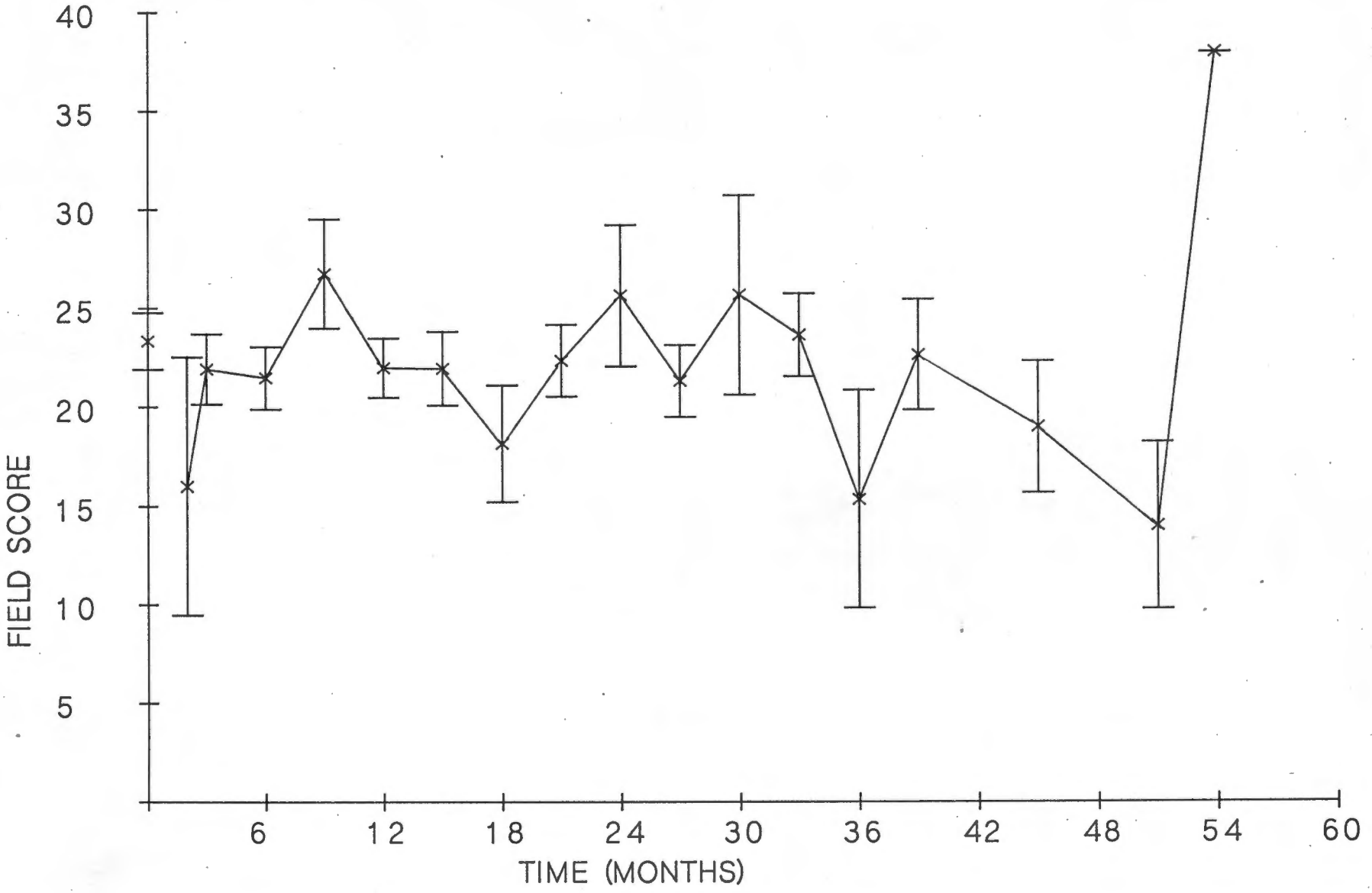
FIGURE 11



FIELD SCORE – NUMBER OF RELATIVE DEFECTS

LASER GROUP ALONE (FAILURES INCLUDED)

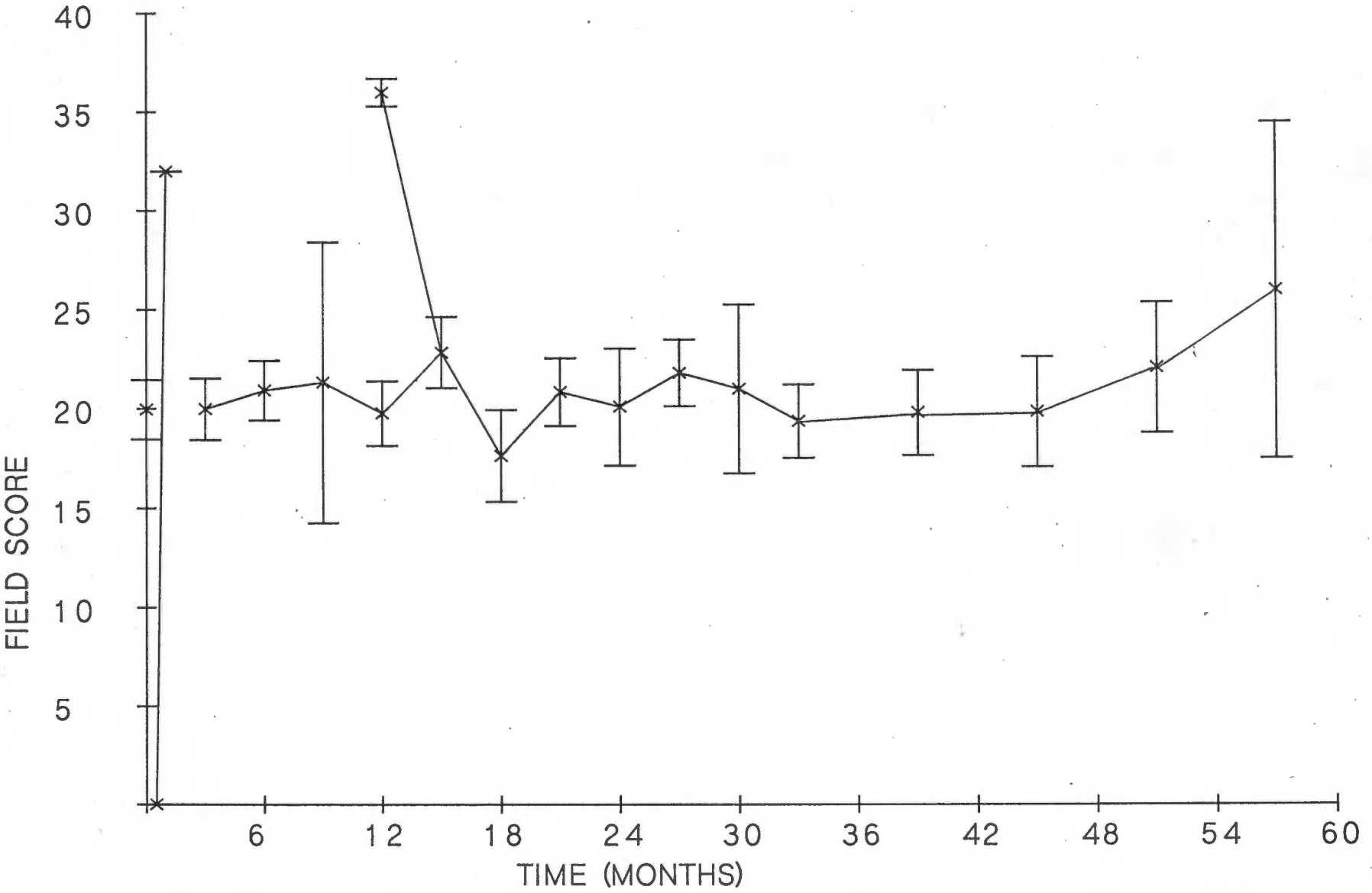
FIGURE 11-A



FIELD SCORE – NUMBER OF RELATIVE DEFECTS

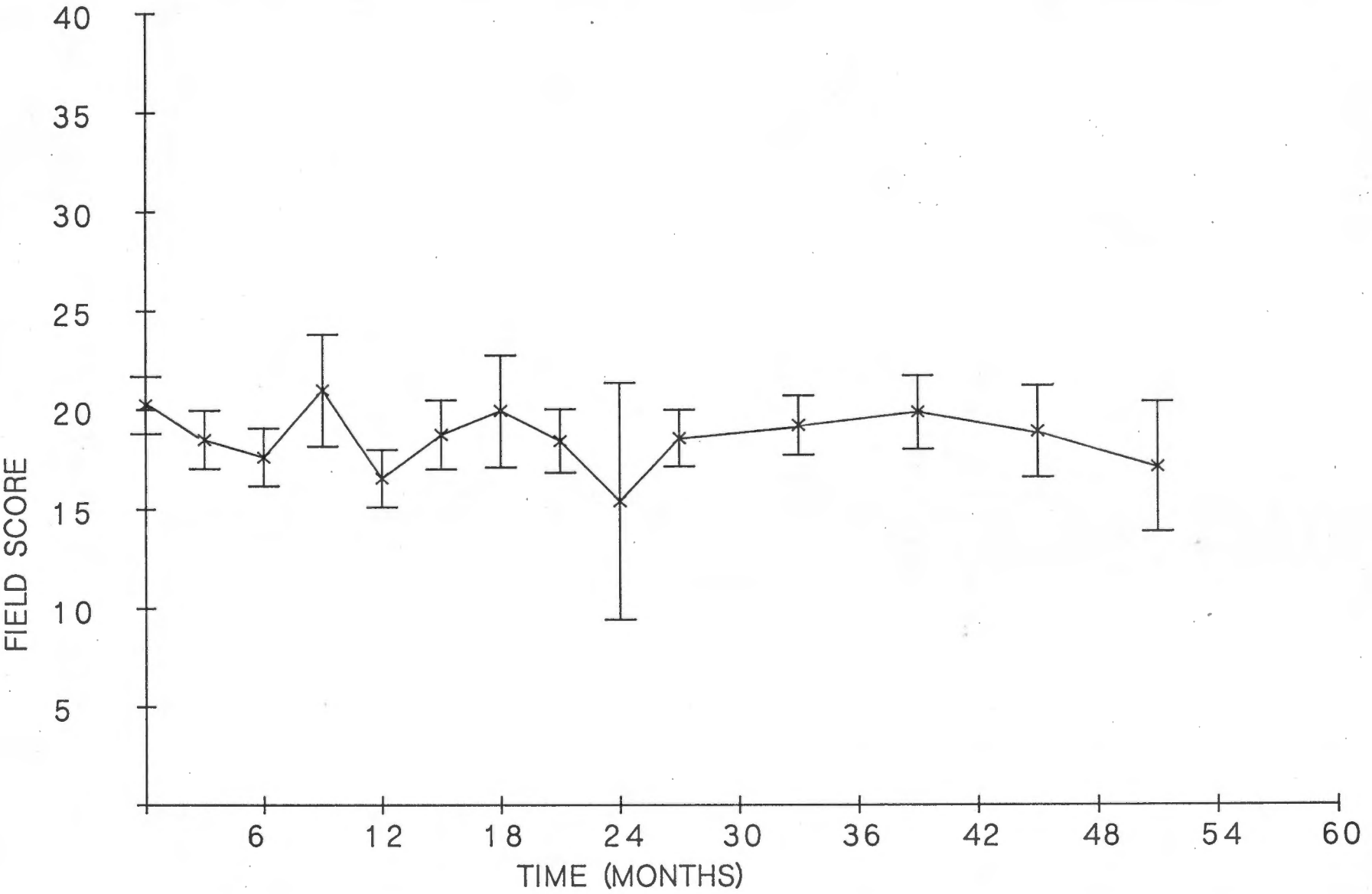
MEDICINE GROUP ALONE (FAILURES INCLUDED)

FIGURE 11-B



FIELD SCORE – NUMBER OF RELATIVE DEFECTS
SURGERY GROUP ALONE (FAILURES INCLUDED)

FIGURE 11-C



FIELD SCORES – ABSOLUTE DEFECTS
(FAILURES EXCLUDED AT TIME OF FAILURE)

FIGURE 12

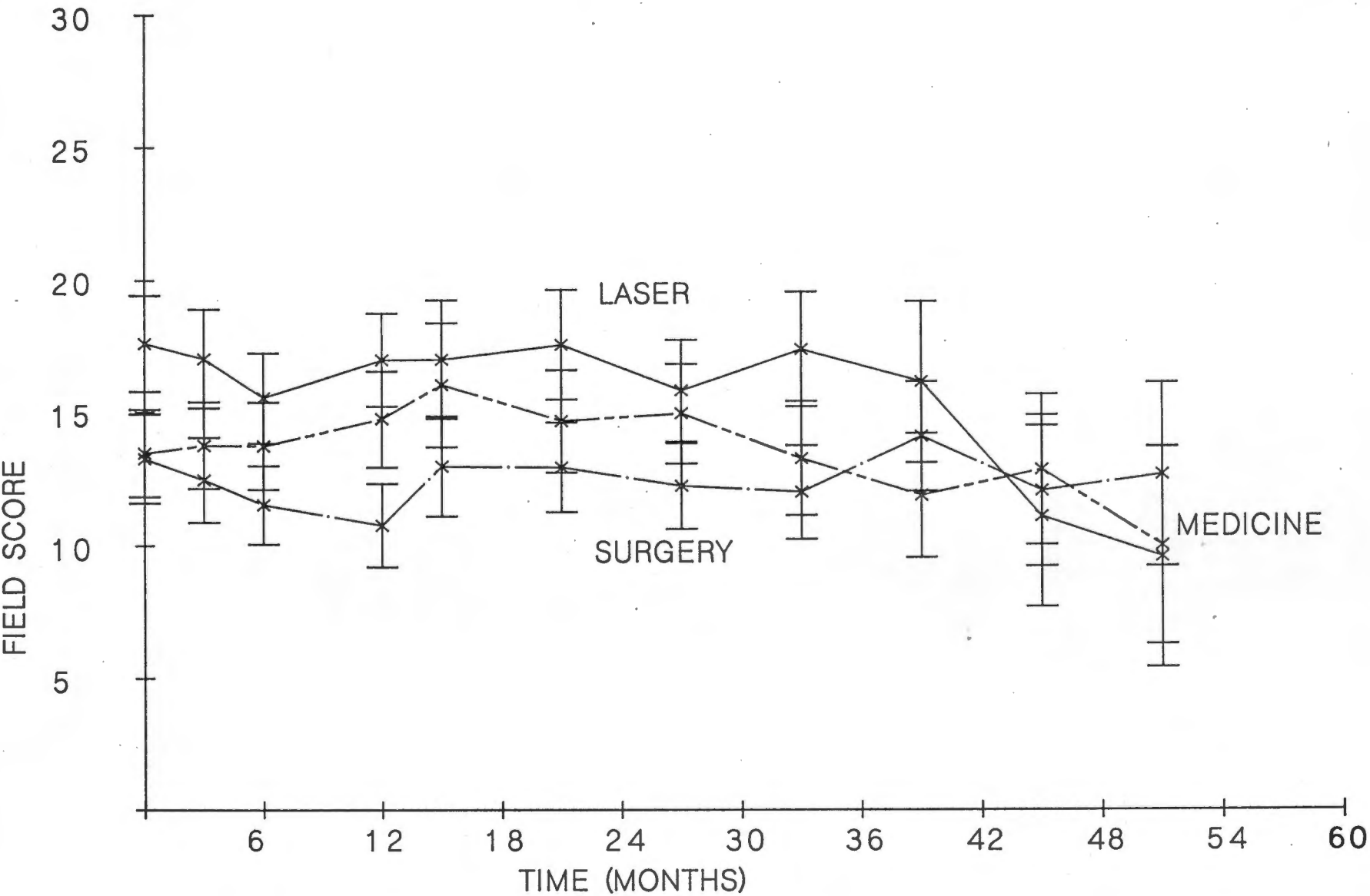


FIGURE 12-A

FIELD SCORE – NUMBER OF ABSOLUTE DEFECTS
LASER GROUP ALONE (FAILURES INCLUDED)

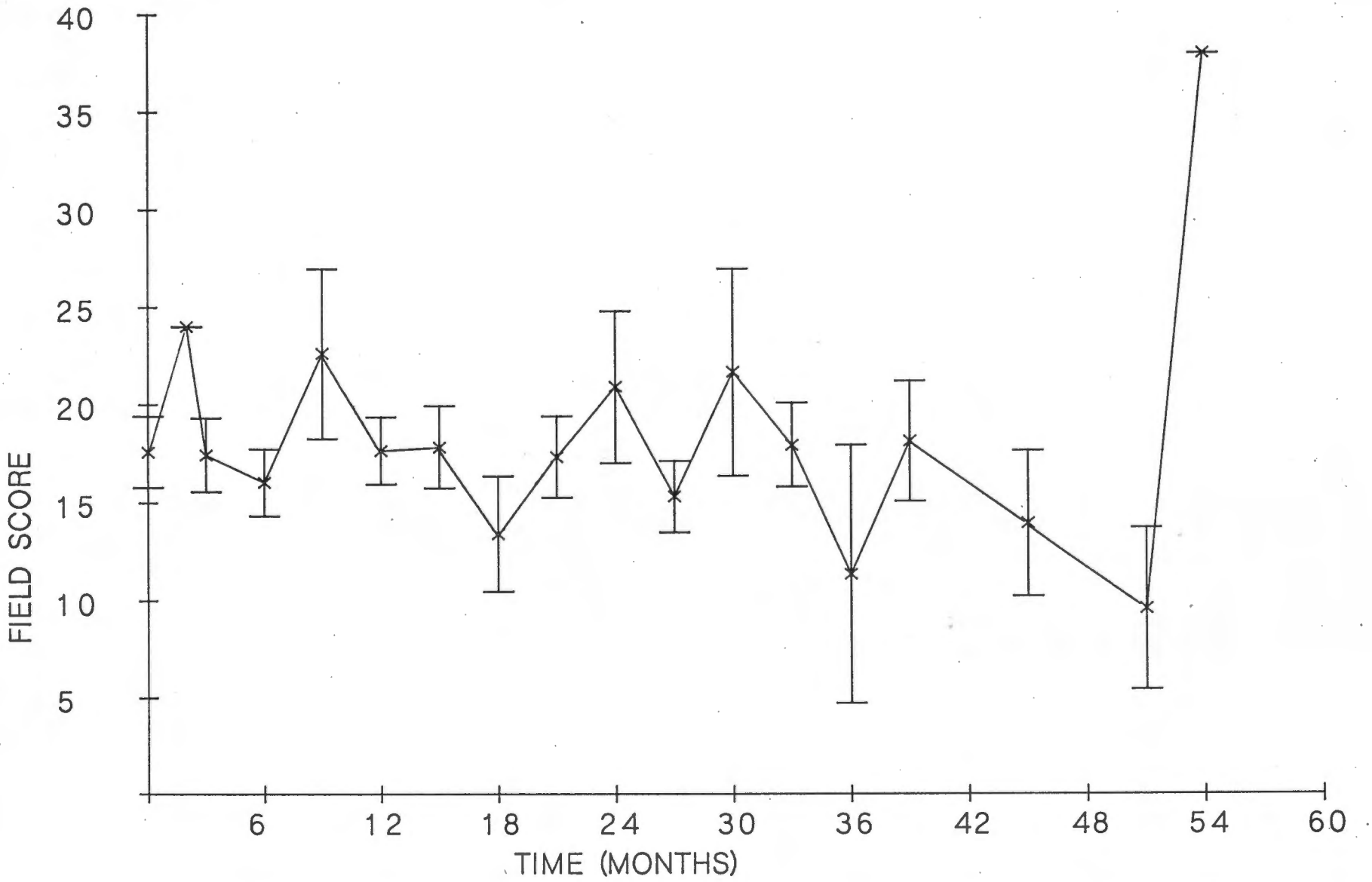
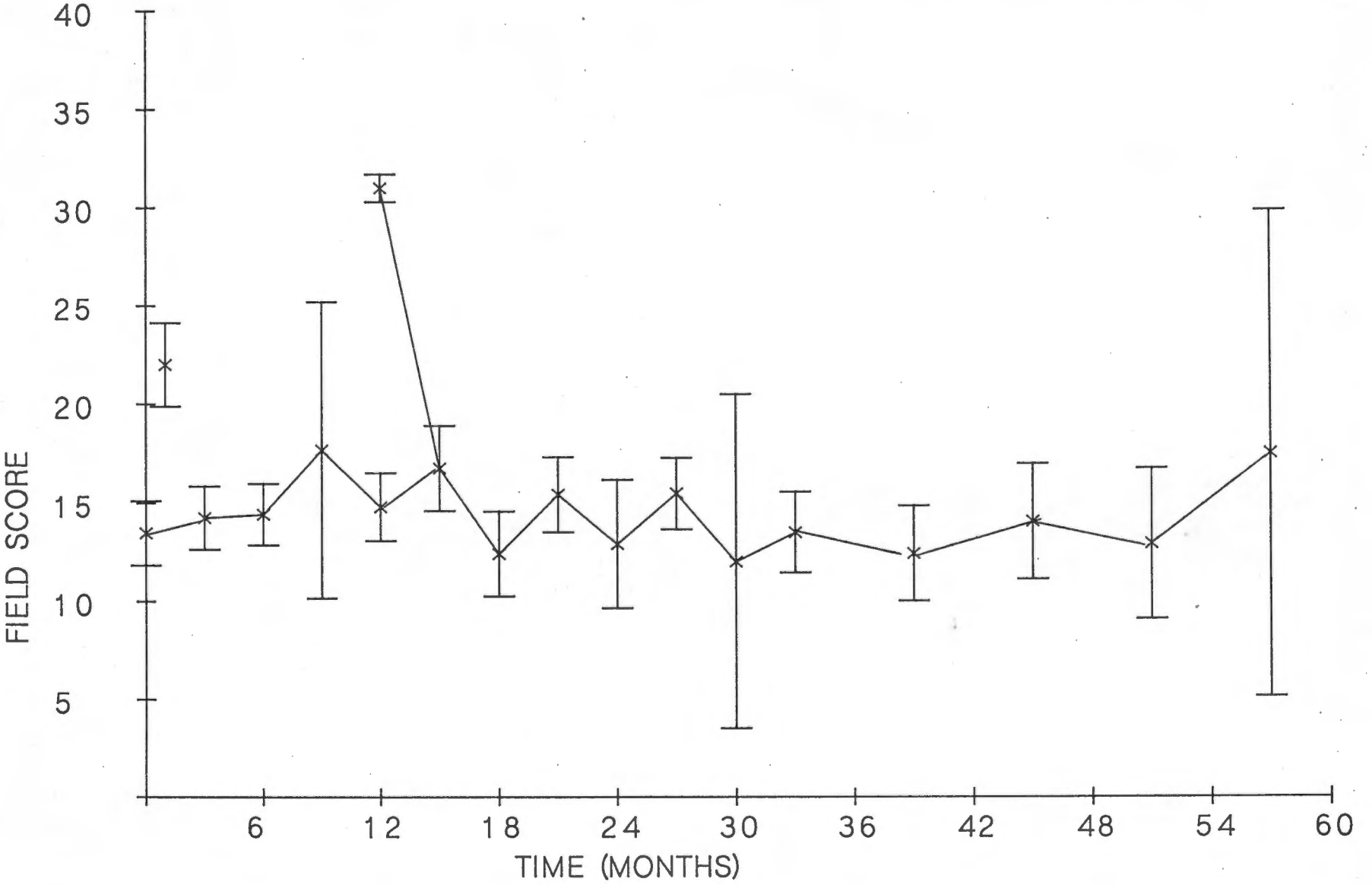


FIGURE 12-B

FIELD SCORE – NUMBER OF ABSOLUTE DEFECTS

MEDICINE GROUP ALONE (FAILURES INCLUDED)



FIELD SCORE – NUMBER OF ABSOLUTE DEFECTS
SURGERY GROUP ALONE (FAILURES INCLUDED)

FIGURE 12-C

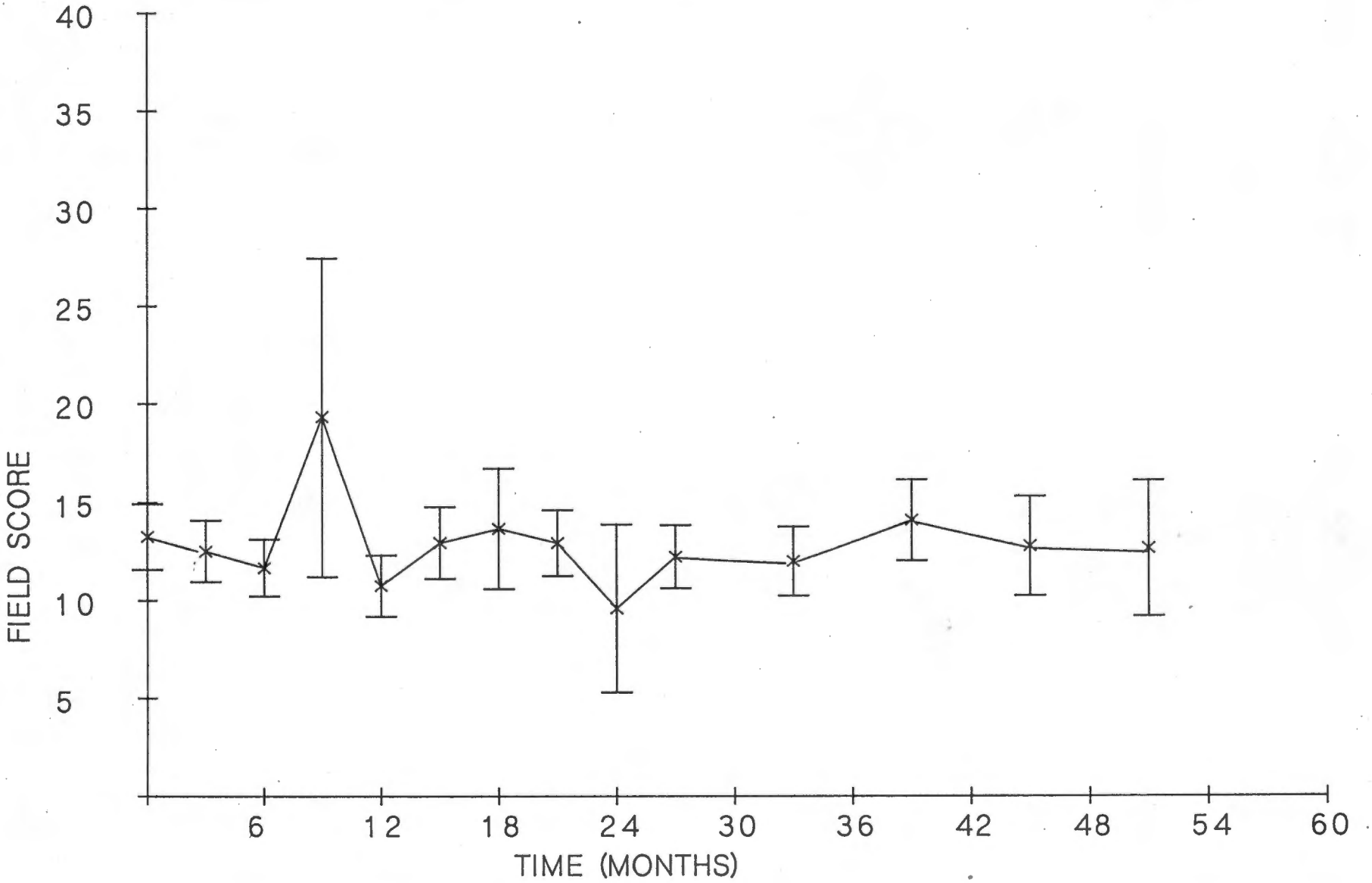
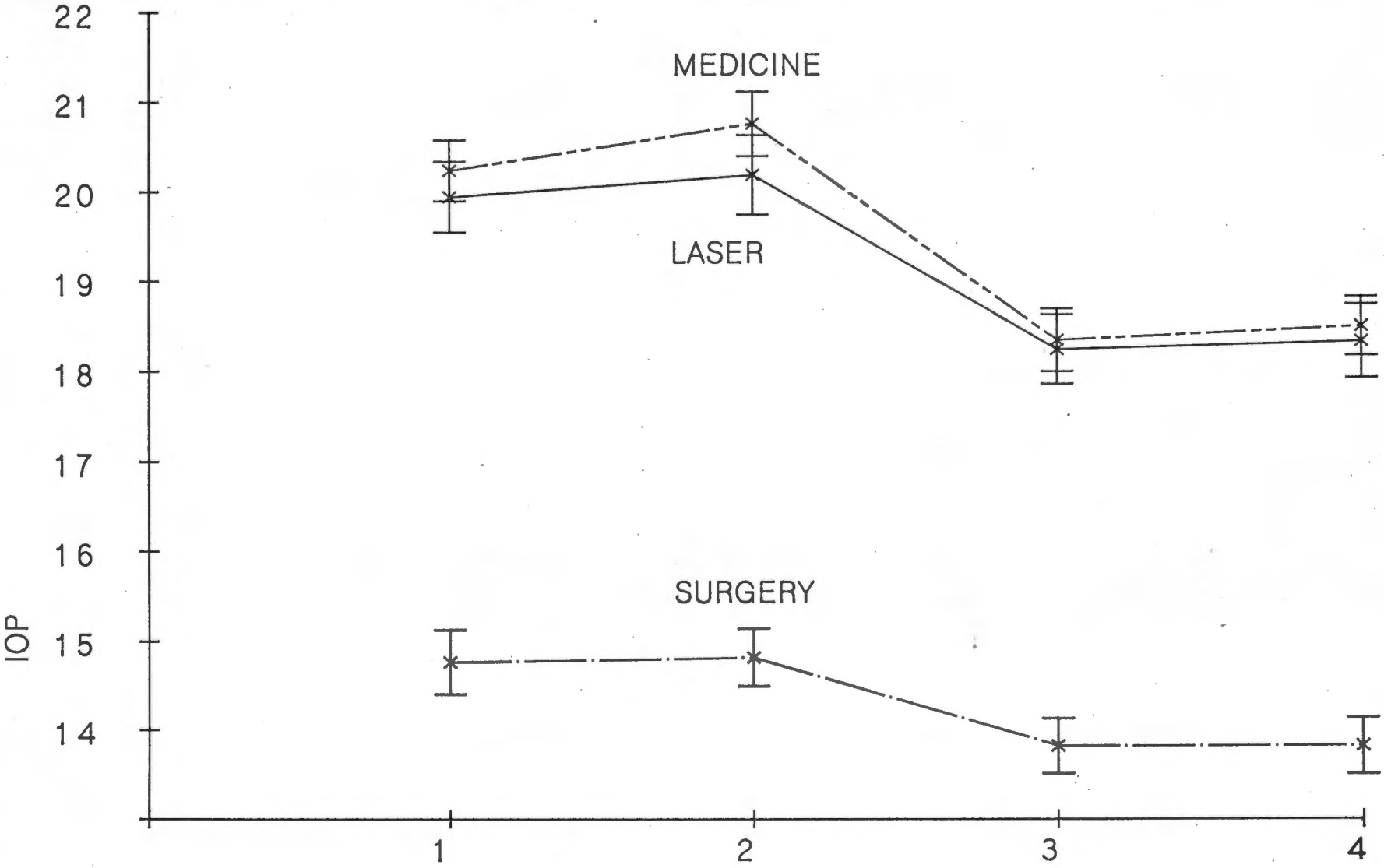


FIGURE 13

MEAN DIURNAL CURVES: LASER v MEDICINE v SURGERY

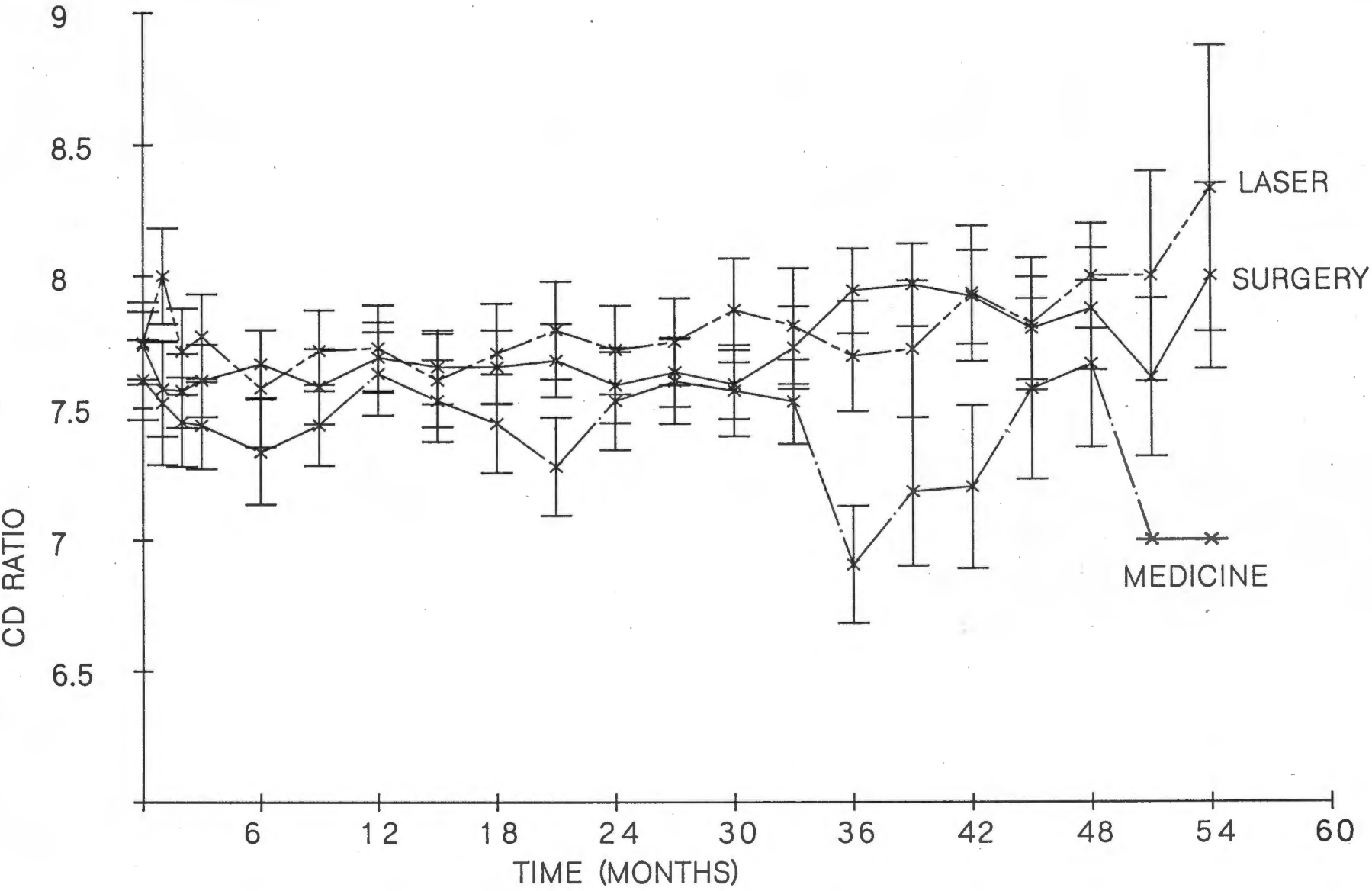
(DATA FOR ALL YEARS POOLED)

(1 =9:30, 2=11:30, 3=1:30, 4=3:30)



CD RATIO : LASER v MEDICINE v SURGERY

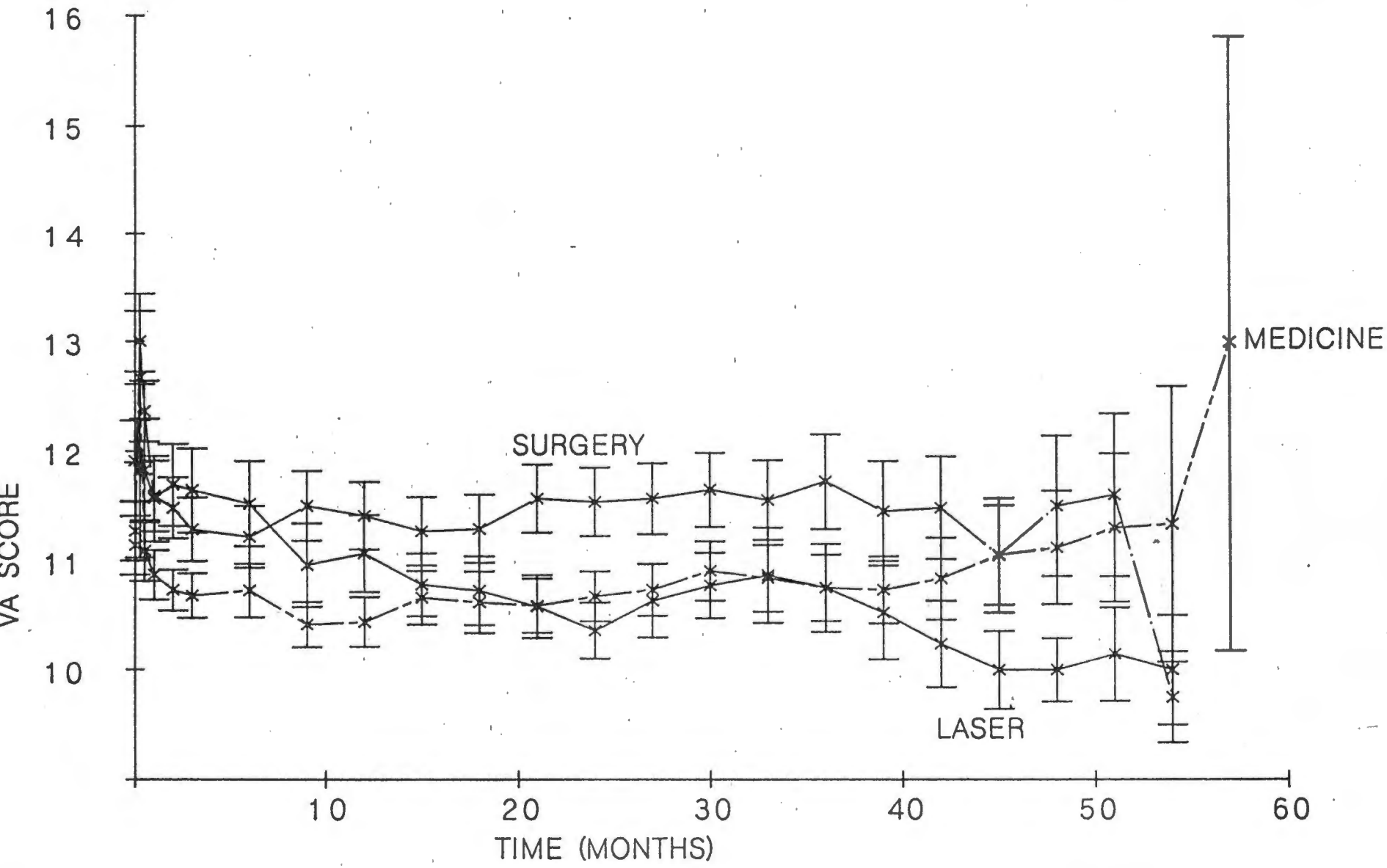
FIGURE 14



VA SCORES: LASER v MEDICINE v SURGERY

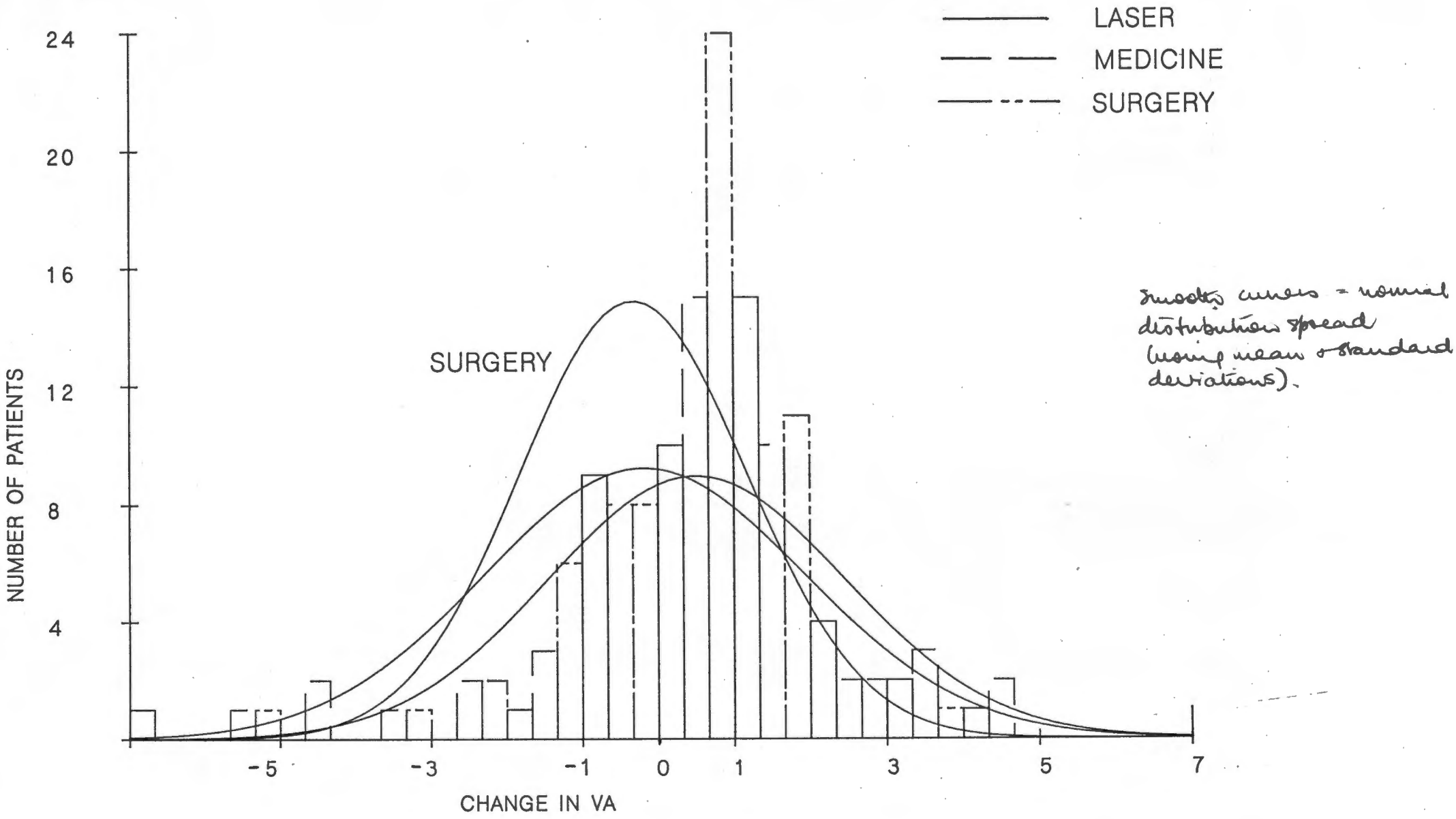
FIGURE 15

(VA SCORES IN RANGE 1-20, PATIENTS EXCLUDED AT TIME OF FAILURE)



CHANGE IN VA SCORE: INITIAL – FINAL VA: BY TREATMENT

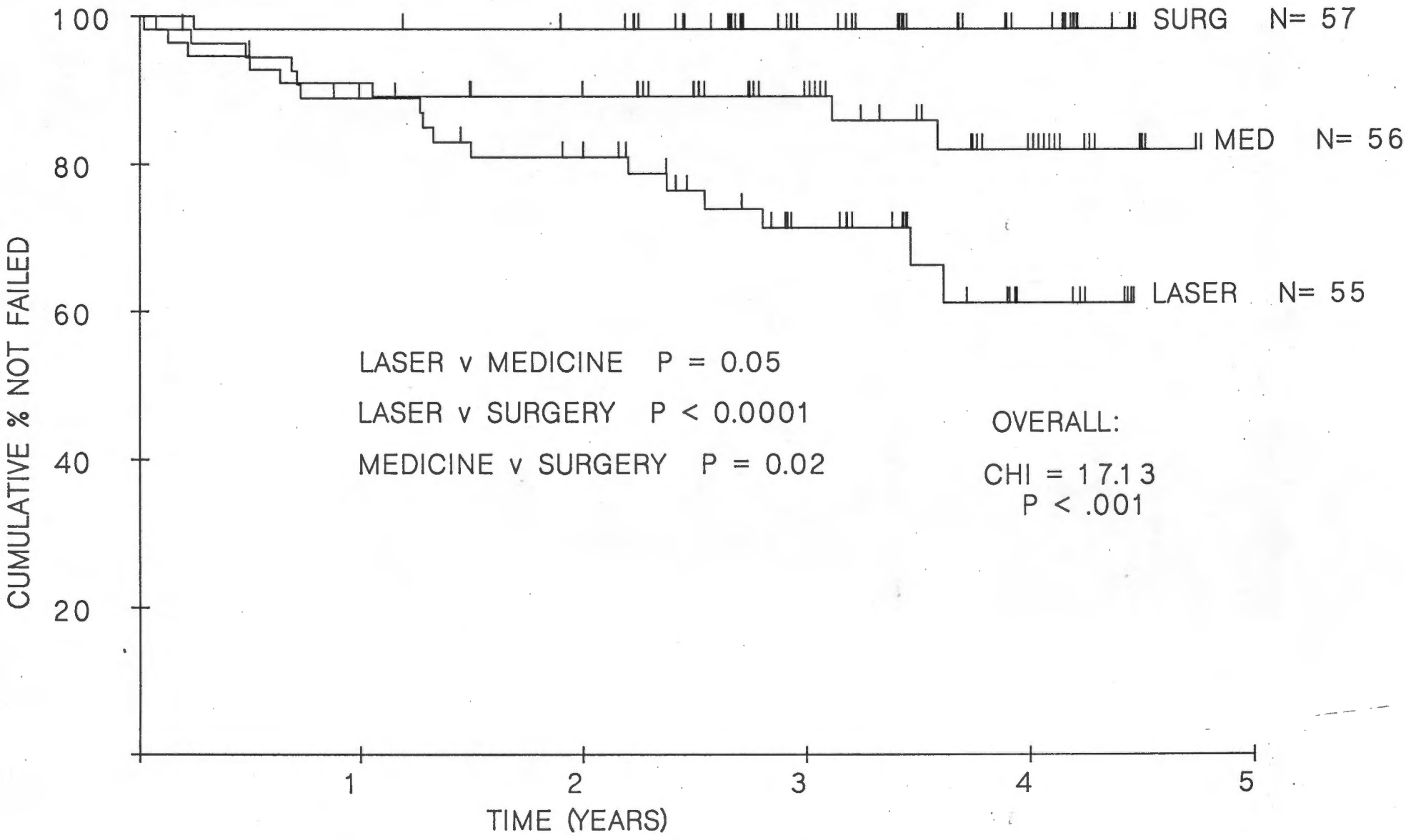
FIGURE 15-A



smooth curves = normal distribution spread (using mean + standard deviations).

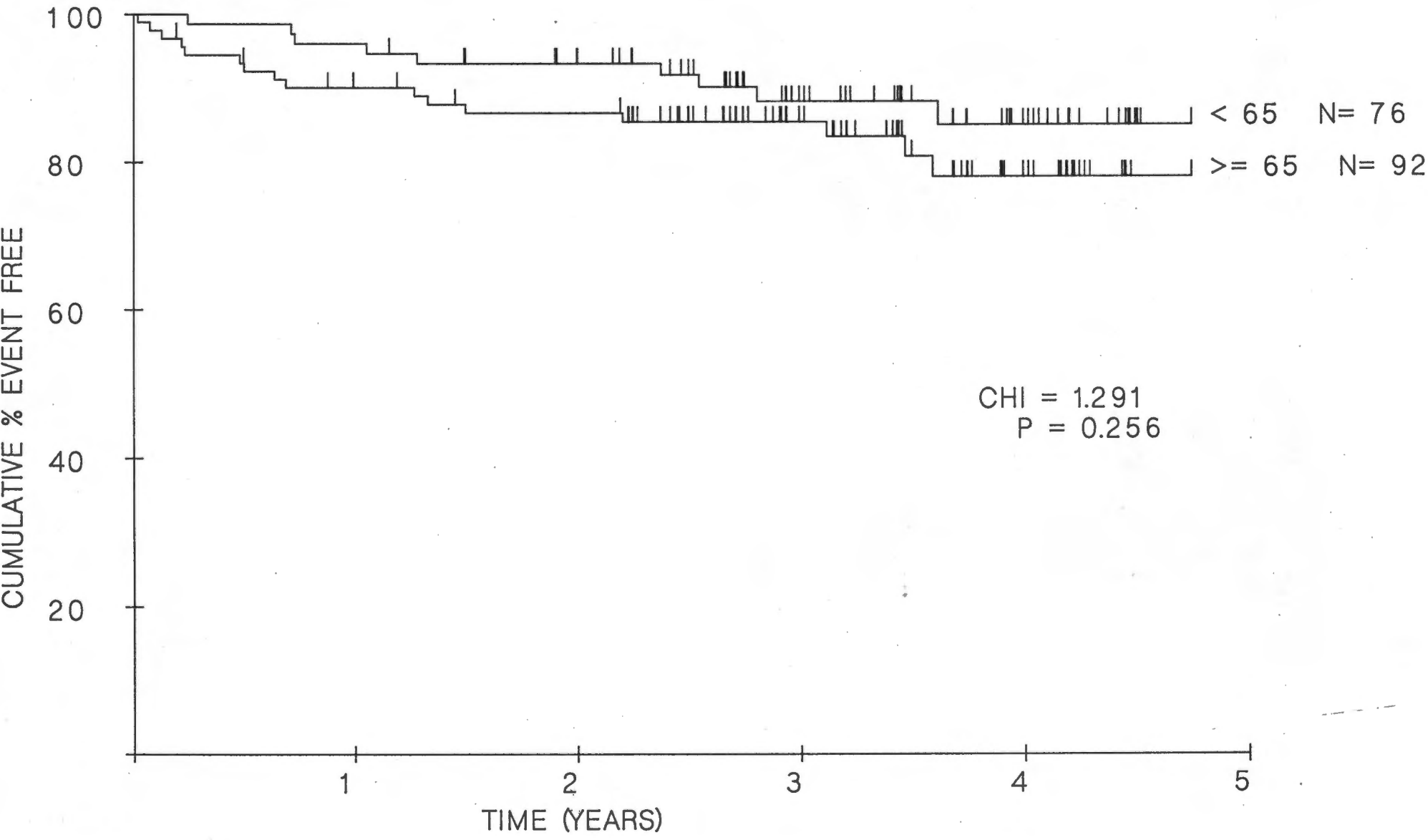
TIME FROM TREATMENT TO FAILURE BY TREATMENT GROUP

FIGURE 16



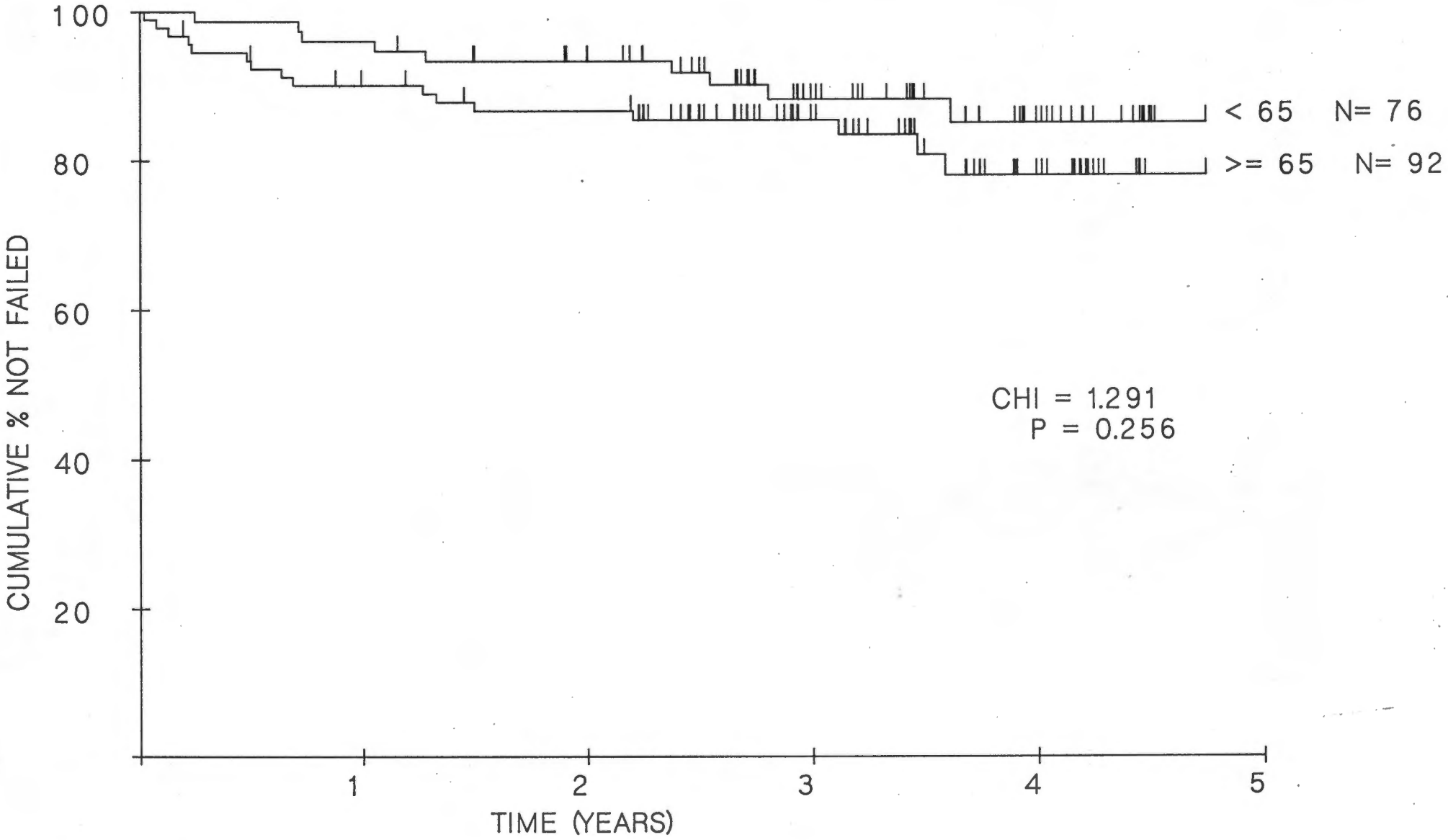
TIME TO FAILURE BY AGE

FIGURE 17



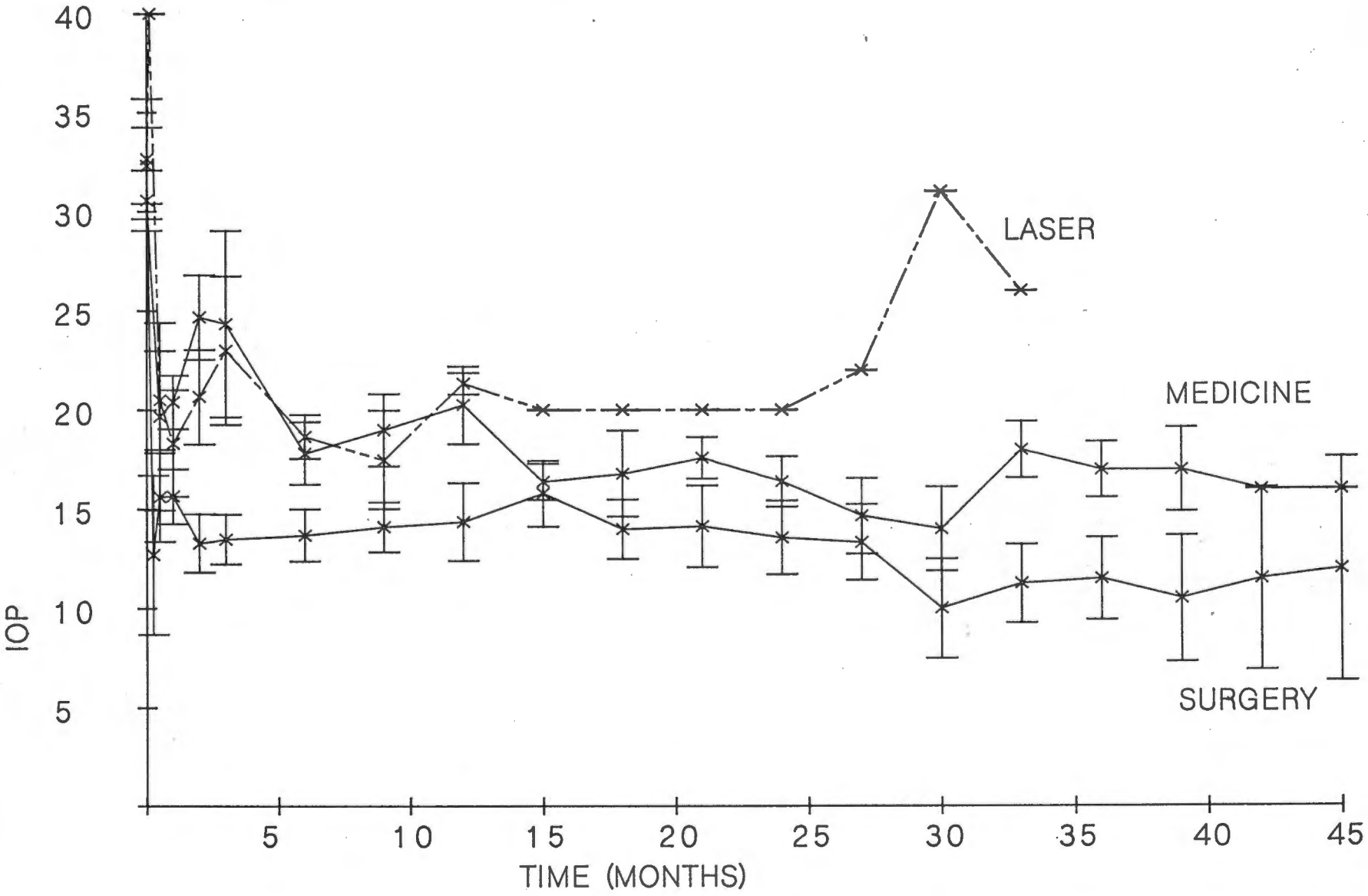
TIME FROM TREATMENT TO FAILURE BY AGE

FIGURE 17-A



MEAN IOP'S FOR 2ND TREATMENT - BY TREATMENT GROUP

FIGURE 18



APPENDIX 1 - IOP'S FOR THE LASER TREATED PATIENTS

TIME (MONTHS)	LOWER LIMIT	MEAN	UPPER LIMIT	NUMBER OF PATIENTS
0	33.81	34.98	36.15	55
0.25	19.74	21.67	23.59	12
0.50	17.17	17.70	18.23	40
1	18.88	19.68	20.48	53
2	21.20	22.19	23.19	52
3	20.37	21.21	22.05	53
6	20.44	21.21	21.98	52
9	19.76	20.37	20.98	49
12	20.01	21.15	22.29	46
15	19.34	20.04	20.74	45
18	18.53	19.38	20.22	40
21	17.99	18.87	19.75	38
24	18.09	18.54	18.98	39
27	16.81	17.42	18.03	38
30	18.48	19.23	19.98	35
33	17.51	18.20	18.89	30
36	17.63	18.25	18.87	28
39	17.09	17.62	18.15	21
42	17.15	17.82	18.50	17
45	15.61	16.33	17.05	12
48	16.92	17.82	18.72	11
51	15.10	16.29	17.48	7
54	14.18	16.25	18.32	4

APPENDIX 2 - FIELD SCORES

2A) LASER GROUP: MEAN NUMBER OF RELATIVE DEFECTS

TIME (MONTHS)	LOWER LIMIT	MEAN	UPPER LIMIT	NUMBER OF PATIENTS
0	21.91	23.34	24.77	47
3	20.14	21.92	23.69	48
6	19.40	21.00	22.60	48
12	20.16	21.73	23.31	45
15	19.82	21.81	23.81	32
21	21.69	23.44	25.19	34
27	20.02	21.84	23.66	38
33	20.63	22.86	25.10	29
39	18.25	21.10	23.95	20
45	12.78	16.17	19.55	12
51	9.77	14.00	18.23	7

2B) LASER GROUP: MEAN NUMBER OF ABSOLUTE DEFECTS

TIME (MONTHS)	LOWER LIMIT	MEAN	UPPER LIMIT	NUMBER OF PATIENTS
0	15.78	17.60	19.41	47
3	15.15	17.02	18.89	48
6	13.84	15.54	17.24	48
12	15.22	16.98	18.74	45
15	14.76	17.00	19.24	32
21	15.48	17.56	19.64	34
27	13.90	15.82	17.73	38
33	15.21	17.38	19.55	29
39	13.11	16.15	19.19	20
45	7.67	11.08	14.50	12
51	5.42	9.57	13.72	7

APPENDIX 3 - PHASINGS:

LASER GROUP:

YEAR	TIME OF DAY	LOWER LIMIT	MEAN	UPPER LIMIT	NUMBER OF PATIENTS
1	9:30	17.13	21.33	25.53	45
1	11:30	16.97	21.76	26.55	46
1	13:30	15.21	19.67	24.14	46
1	15:30	14.81	19.57	24.32	46
2	9:30	15.57	19.61	23.65	36
2	11:30	15.04	20.11	25.18	36
2	13:30	13.49	17.17	20.84	36
2	15:30	13.54	17.71	21.89	35
3	9:30	14.31	18.20	22.09	20
3	11:30	15.16	17.90	20.65	21
3	13:30	14.51	17.48	20.45	21
3	15:30	14.09	16.90	19.71	21
4	9:30	15.36	17.33	19.31	6
4	11:30	14.11	16.86	19.61	7
4	13:30	12.16	16.14	20.12	7
4	15:30	13.13	17.14	21.16	7

APPENDIX 4 - IOP'S FOR THE SURGERY TREATED PATIENTS

TIME (MONTHS)	LOWER LIMIT	MEAN	UPPER LIMIT	NUMBER OF PATIENTS
0	33.58	34.30	35.02	57
0.25	7.16	8.37	9.58	46
0.50	12.36	13.20	14.04	55
1	14.95	15.63	16.30	56
2	13.65	14.41	15.17	56
3	12.89	13.61	14.33	56
6	12.74	13.31	13.88	55
9	13.35	13.95	14.55	56
12	13.53	14.07	14.62	56
15	13.10	13.61	14.11	56
18	13.28	13.85	14.43	55
21	13.44	14.00	14.56	53
24	12.88	13.41	13.93	54
27	12.86	13.38	13.89	53
30	13.03	13.57	14.11	51
33	13.11	13.68	14.25	47
36	12.91	13.44	13.98	36
39	12.07	12.65	13.22	31
42	12.33	13.07	13.81	27
45	11.97	12.64	13.30	22
48	12.60	13.33	14.07	18
51	12.41	13.40	14.39	15
54	11.15	12.50	13.85	4

APPENDIX 5 - FIELD SCORES

5A) SURGERY GROUP: MEAN NUMBER OF RELATIVE DEFECTS

TIME (MONTHS)	LOWER LIMIT	MEAN	UPPER LIMIT	NUMBER OF PATIENTS
0	18.80	20.25	21.69	53
3	16.96	18.44	19.92	55
6	16.02	17.49	18.96	55
12	15.11	16.56	18.01	52
15	16.71	18.45	20.19	40
21	16.85	18.44	20.03	50
27	17.16	18.58	19.99	52
33	17.73	19.22	20.70	46
39	18.02	19.87	21.72	31
45	15.41	17.95	20.49	20
51	13.87	17.13	20.40	15

5B) SURGERY GROUP: MEAN NUMBER OF ABSOLUTE DEFECTS

TIME (MONTHS)	LOWER LIMIT	MEAN	UPPER LIMIT	NUMBER OF PATIENTS
0	11.60	13.26	14.93	53
3	10.87	12.46	14.06	56
6	10.05	11.53	13.00	55
12	9.18	10.75	12.32	53
15	11.10	12.98	14.85	40
21	11.26	12.94	14.62	50
27	10.62	12.23	13.84	52
33	10.23	12.00	13.77	46
39	12.04	14.10	16.16	31
45	9.21	12.05	14.89	20
51	9.21	12.67	16.12	15

APPENDIX 6 - PHASINGS:

SURGERY GROUP:

YEAR	TIME OF DAY	LOWER LIMIT	MEAN	UPPER LIMIT	NUMBER OF PATIENTS
1	9:30	9.86	15.31	20.77	54
1	11:30	10.89	15.00	19.11	55
1	13:30	10.56	14.69	18.82	55
1	15:30	9.89	14.07	18.25	54
2	9:30	10.30	14.46	18.62	52
2	11:30	9.79	14.15	18.50	54
2	13:30	9.49	13.24	16.99	54
2	15:30	9.47	13.26	17.06	53
3	9:30	10.66	14.26	17.86	31
3	11:30	11.66	15.52	19.38	31
3	13:30	9.58	13.13	16.67	31
3	15:30	10.67	14.26	17.85	31
4	9:30	10.49	14.33	18.17	15
4	11:30	10.25	14.20	18.15	15
4	13:30	10.51	13.80	17.09	15
4	15:30	9.90	13.15	16.41	13

APPENDIX 7 - IOP'S FOR THE MEDICINE TREATED PATIENTS

TIME (MONTHS)	LOWER LIMIT	MEAN	UPPER LIMIT	NUMBER OF PATIENTS
0	34.00	35.05	36.11	56
0.25	24.44	28.00	31.56	6
0.50	24.74	26.21	27.68	33
1	23.61	24.83	26.06	54
2	20.79	21.42	22.05	52
3	20.51	21.11	21.72	53
6	20.12	20.78	21.44	51
9	19.68	20.07	20.45	46
12	19.69	20.42	21.14	48
15	19.15	19.74	20.34	47
18	18.93	19.53	20.13	47
21	18.49	18.89	19.29	46
24	18.04	18.46	18.87	46
27	17.48	18.07	18.65	45
30	18.29	18.76	19.24	42
33	18.11	18.57	19.02	37
36	17.86	18.50	19.14	32
39	16.56	17.12	17.67	26
42	16.71	17.46	18.21	24
45	16.85	17.58	18.31	19
48	16.11	16.82	17.54	17
51	15.90	16.90	17.90	10
54	17.31	18.33	19.35	6
57	14.88	17.00	19.12	2

APPENDIX 8 - FIELD SCORES

8A) MEDICINE GROUP: MEAN NUMBER OF RELATIVE DEFECTS

TIME (MONTHS)	LOWER LIMIT	MEAN	UPPER LIMIT	NUMBER OF PATIENTS
0	18.47	19.96	21.46	53
3	17.96	19.53	21.10	51
6	18.58	20.14	21.70	50
12	18.07	19.77	21.47	44
15	20.14	22.11	24.08	28
21	18.41	20.14	21.86	37
27	19.55	21.30	23.04	44
33	16.90	18.78	20.67	37
39	16.82	19.00	21.18	24
45	16.19	18.95	21.71	20
51	16.13	19.50	22.87	10
57	17.51	26.00	34.49	2

8B) MEDICINE GROUP: MEAN NUMBER OF ABSOLUTE DEFECTS

TIME (MONTHS)	LOWER LIMIT	MEAN	UPPER LIMIT	NUMBER OF PATIENTS
0	11.84	13.47	15.10	53
3	12.15	13.76	15.38	51
6	12.11	13.74	15.37	50
12	12.95	14.75	16.55	44
15	13.70	16.04	18.37	28
21	12.75	14.68	16.60	37
27	13.08	14.95	16.83	44
33	11.13	13.27	15.41	37
39	9.54	11.88	14.21	24
45	10.03	12.85	15.67	20
51	6.29	10.00	13.71	10
57	5.13	17.50	29.87	2

APPENDIX 9 - PHASINGS:

MEDICINE GROUP:

YEAR	TIME OF DAY	LOWER LIMIT	MEAN	UPPER LIMIT	NUMBER OF PATIENTS
1	9:30	18.08	21.05	24.01	44
1	11:30	18.16	22.09	26.01	45
1	13:30	15.53	19.58	23.62	45
1	15:30	16.77	19.36	21.94	45
2	9:30	15.96	20.45	24.95	42
2	11:30	15.85	20.34	24.83	44
2	13:30	13.88	17.44	21.01	43
2	15:30	13.47	17.52	21.58	40
3	9:30	15.47	19.00	22.53	25
3	11:30	15.60	20.04	24.48	25
3	13:30	14.52	18.92	23.32	25
3	15:30	16.09	20.00	23.91	24
4	9:30	18.45	20.88	23.30	8
4	11:30	17.06	19.56	22.05	9
4	13:30	12.82	15.88	18.93	8
4	15:30	12.39	16.33	20.28	9

APPENDIX 9A - VISUAL ACUITY SCORES

VISUAL ACUITY SCORES: LASER, MEDICINE AND SURGERY

(VA MEASURED ON A SCALE OF 1 TO 20)

(Nl, Nm, Ns = NUMBERS IN EACH GROUP)

TIME	L	M	S	Nl	Nm	Ns
0.00	11.91	11.27	11.14	55	55	57
0.25	11.82	12.67	13.00	11	6	46
0.50	11.82	11.09	12.36	40	33	55
1.00	11.57	10.87	11.59	53	54	56
2.00	11.69	10.73	11.48	52	52	56
3.00	11.64	10.68	11.29	53	53	56
6.00	11.52	10.73	11.22	52	51	55
9.00	10.96	10.41	11.50	49	46	56
12.00	11.07	10.44	11.41	46	48	56
15.00	10.78	10.66	11.27	45	47	56
18.00	10.73	10.62	11.29	40	47	55
21.00	10.58	10.59	11.57	38	46	53
24.00	10.36	10.67	11.54	39	46	54
27.00	10.63	10.73	11.57	38	45	53
30.00	10.77	10.90	11.65	35	42	51
33.00	10.87	10.84	11.55	30	37	47
36.00	10.75	10.75	11.72	28	32	36
39.00	10.52	10.73	11.45	21	26	31
42.00	10.24	10.83	11.48	17	24	27
45.00	10.00	11.05	11.05	12	20	22
48.00	10.00	11.12	11.50	11	17	18
51.00	10.14	11.30	11.60	7	10	15
54.00	10.00	11.33	9.75	4	6	4
57.00	-1.00	13.00	-1.00	0	2	0

VA scores: p-values:

	Time				
Comparison	Preop	1	2	3	4
Laser v Medicine	0.17	0.14	0.37	1.00	0.13
Laser v Surgery	0.10	0.46	0.008	0.12	0.10
Medicine v Surgery	0.73	0.02	0.03	0.08	0.66

APPENDIX 10

VISUAL ACUITY SCORES: LASER GROUP

(VA MEASURED ON A SCALE OF 1 TO 20)

TIME (MONTHS)	LOWER LIMIT	MEAN	UPPER LIMIT	NUMBER OF PATIENTS
0	11.54	11.91	12.28	55
0.25	11.03	11.82	12.61	11
0.50	11.35	11.82	12.30	40
1	11.18	11.57	11.96	53
2	11.32	11.69	12.07	52
3	11.26	11.64	12.03	53
6	11.13	11.52	11.91	52
9	10.58	10.96	11.34	49
12	10.71	11.07	11.42	46
15	10.49	10.78	11.07	45
18	10.41	10.73	11.04	40
21	10.29	10.58	10.87	38
24	10.10	10.36	10.62	39
27	10.30	10.63	10.97	38
30	10.47	10.77	11.07	35
33	10.43	10.87	11.30	30
36	10.35	10.75	11.15	28
39	10.09	10.52	10.95	21
42	9.84	10.24	10.63	17
45	9.65	10.00	10.35	12
48	9.71	10.00	10.29	11
51	9.72	10.14	10.57	7
54	9.50	10.00	10.50	4

APPENDIX 11

VISUAL ACUITY SCORES: SURGERY GROUP

(VA MEASURED ON A SCALE OF 1 TO 20)

TIME (MONTHS)	LOWER LIMIT	MEAN	UPPER LIMIT	NUMBER OF PATIENTS
0	10.87	11.14	11.41	57
0	12.72	13.00	13.28	46
0	12.09	12.36	12.64	55
1	11.27	11.59	11.91	56
2	11.21	11.48	11.76	56
3	11.00	11.29	11.58	56
6	10.94	11.22	11.50	55
9	11.18	11.50	11.82	56
12	11.10	11.41	11.72	56
15	10.96	11.27	11.58	56
18	10.98	11.29	11.60	55
21	11.26	11.57	11.87	53
24	11.23	11.54	11.85	54
27	11.24	11.57	11.89	53
30	11.31	11.65	11.98	51
33	11.19	11.55	11.92	47
36	11.29	11.72	12.16	36
39	11.00	11.45	11.91	31
42	11.01	11.48	11.95	27
45	10.52	11.05	11.57	22
48	10.86	11.50	12.14	18
51	10.85	11.60	12.35	15
54	9.34	9.75	10.16	4

APPENDIX 12

VISUAL ACUITY SCORES: MEDICINE GROUP

(VA MEASURED ON A SCALE OF 1 TO 20)

TIME (MONTHS)	LOWER LIMIT	MEAN	UPPER LIMIT	NUMBER OF PATIENTS
0	11.00	11.27	11.54	55
0.25	11.90	12.67	13.44	6
0.50	10.81	11.09	11.37	33
1	10.64	10.87	11.10	54
2	10.54	10.73	10.92	52
3	10.47	10.68	10.88	53
6	10.48	10.73	10.97	51
9	10.21	10.41	10.62	46
12	10.21	10.44	10.67	48
15	10.41	10.66	10.90	47
18	10.34	10.62	10.90	47
21	10.34	10.59	10.83	46
24	10.45	10.67	10.90	46
27	10.50	10.73	10.97	45
30	10.63	10.90	11.18	42
33	10.53	10.84	11.14	37
36	10.45	10.75	11.05	32
39	10.43	10.73	11.04	26
42	10.46	10.83	11.21	24
45	10.59	11.05	11.51	20
48	10.60	11.12	11.64	17
51	10.62	11.30	11.98	10
54	10.07	11.33	12.60	6
57	10.17	13.00	15.83	2

STATEMENT TO THE PATIENT

The tests on your eyes which we have just completed show that you suffer from Chronic Simple Glaucoma. This is a disease where the sight is slowly lost from a long standing increase in your eye pressure. To prevent further loss the eye pressure needs to be reduced to a safe level. There are three ways in which this can be done; medical treatment by drops and tablets, an operation, or a much newer type of treatment - laser treatment. At the present time we have yet to decide which of these three treatments is most effective. Medical treatment is easiest but may cause many unwanted symptoms and, in the long run, may be the lease effective. No one wants to have an operaiton but, glaucoma surgery to-day is very safe and in over 90% of cases effective in controlling your intraocular pressures. Once the operation is over little long term treatment is required. Finally, laser treatment is extremely simple, it may be carried out as an out-patient procedure and may be the most effective method of treatment available. However, it is quite new and has not been shown to be successful in controlling the eye pressure in the long term.

Because of doubt as to which of these methods of treatment is the most effective we are conducting a study comparing all three. If you would like to join the study you will be given one of these three types of treatment, the type will be decided by chance. You will then be followed in the normal fashion for all glaucoma patients at this hospital. If, during follow-up, it should be considered that the first treatment is insufficient then you would be given one of the other two types of treatment - and again this will be decided by chance.

Should you not wish to participate in this study then you will be treated in the standard pattern for this hospital which is medical treatment initially and then laser or surgical treatment should medical treatment fail.

I have read the above and wish to participate in the study.

SIGNED Signed DATE 12.7.83

WITNESSED BY [signature] DATE 12.7.83

Appendix 14

IMPLANT (SETON) PROCEDURES FOR OPEN-ANGLE GLAUCOMA

In an attempt to maintain patency of the drainage fistula in either full-thickness or partial thickness filtering operations (usually in refractory cases of glaucoma and therefore not primary glaucoma surgery), a wide variety of foreign materials have been placed in the fistula. Despite earlier lack of success, research with newer designs is showing promise.

Tubes

The success of newer implant operations appears to be due, at least in part, to the concept of aqueous drainage through patent translimbal tubes. Devices successfully used in humans include a strip of hydrogel with parallel capillary channels [1], and Silicone [2] and Teflon [3] tubes. In some techniques, tubes are run from the anterior chamber to an acrylic plate on the sclera [4,5,6,7], on to an encircling band [8,9], both of which are supposed to maintain reservoirs into which the aqueous can drain.

Valves

An example of a valve which allows one-way flow from the anterior chamber and which opens at a predetermined IOP level is the Krupin valve [10]. The valve may also be directed into a reservoir [11].

References

1 Krejci L : Hydrogel capillary drainage for glaucoma : Nine years' clinical experience. Glaucoma, 1980, 2, 259

2 Honrubia IM, Gomez ML, Hernandez A, Grijalbo MP : Long-term results of silicone tube in filtering surgery for eyes with neovascular glaucoma. Am. J. Ophthalmol., 1984, 97, 501

3 Kuljaca Z, Ljubojevic V, Momiror D : Draining implant for neovascular glaucoma. Am. J. Ophthalmol., 1983, 96, 372

4 Molteno ACB: New implant for drainage in glaucoma. Clinical trial. Br. J. Ophthalmol., 1969, 53, 606

5 Anker E, Molteno ACB : Surgical treatment of chronic aphakic glaucoma with the Molteno plastic implant. Klin. Monatsbl. Augenheilkd., 1980, 177, 365

6 Cairns JE : The Molteno long-tube implant. Trans. Ophthalmol. Soc. UK, 1983, 103, 39

7 Anker E, Molteno ACB : Molteno drainage implant for neovascular

glaucoma. Trans. Ophthalmol. Soc. UK, 1982, 102, 122

8 Schocket SS, Lakhanpal V, Richards RD : Anterior chamber tube shunt to an encircling band in the treatment of neovascular glaucoma. Ophthalmology, 1982, 89, 1188

9 Schocket SS, Nirankari VS, Lakhanpal V et al. : Anterior chamber tube shunt to an encircling band in the treatment of neovascular glaucoma and other refractory glaucomas. A long-term study. Ophthalmology, 1985, 92, 553

10 Krupin T, Podos SM, Becker B, Newkirk JB : Valve implants in filtering surgery. Am. J. Ophthalmol., 1976, 81, 232

11 Haas JS, Peyman GA, Lim J : Experimental evaluation of a posterior drainage system. Ophthalmic Surg., 1983, 14, 494

Appendix 15

DEFINITIONS OF OCULAR HYPERTENSION & LOW-TENSION GLAUCOMA

Ocular Hypertension

Defined as an IOP above 21 mmHg for which there is no apparent cause, but where the patient has normal optic nerve heads and visual fields [1-4].

Low-tension Glaucoma

Defined as patients who have typical glaucomatous damage of the visual fields and/or optic nerve heads despite IOP's that are consistently 21 mmHg or less [5-10].

Drance and co-workers [6-7] describe two forms of low-tension glaucoma: [1] a non-progressive form, which is usually associated with a transient episode of vascular shock; [2] a progressive form, which is believed to result from chronic vascular insufficiency of the optic nerve head.

References

1 Chandler PA, Grant WM : 'Ocular hypertension' vs open-angle glaucoma. Arch. Ophthalmol., 1977, 95, 585

2 Kolker AE, Becker B : 'Ocular hypertension' vs open-angle glaucoma: A different view. Arch Opthalmol., 1977, 95, 586

3 Shaffer R : 'Glaucoma suspect' or 'ocular hypertension'? Arch. Ophthalmol., 1977, 95, 588

4 Phelps ED : Ocular hypertension : to treat or not to treat? Arch. Ophthalmol., 1977, 95, 588

5 Drance SM : Some factors in the production of low tension glaucoma. Br. J. Ophthalmol., 1972, 56, 229

6 Drance SM, Sweeney VP, Morgan RW, Feldman F : STudies of factors involved in the production of low tension glaucoma. Arch. Ophthalmol., 1973, 89, 457

7 Drance SM, Morgan RW, Sweeney VP : Shock-induced optic neuropathy. A cause of nonprogressive glaucoma. N. Engl. J. Med., 1973, 288, 392

8 Lewis RA, Hayreh SS, Phelps CD : Optic disc and visual field correlations in primary open-angle and low tension glaucoma. Am. J. Ophthalmol., 1983, 96, 148

9 Clumbley LA, Brubaker RF : Low-tension glaucoma. Am. J.

Ophthalmol., 1976, 81, 761

10 Caprioli SJ, Spaeth GL : Comparison of visual field defects in low-tension glaucomas with those in the high tension glaucomas. Am. J. Ophthalmol., 1984, 97, 730

Appendix 16

VISUAL ACUITY SCORING

The visual acuities were initially measured using an extended system of scoring on a scale of 1-20. Subsequently, this was refined, translating the standard Snellen acuities as follows:

6/5 = 9

6/6 = 10

6/9 = 11

6/12 = 12

6/18 = 13

6/24 = 14

6/36 = 15

6/60 = 16

CF = 17

HM = 18

PL = 19

NPL = 20

ADDITIONAL COMMENTS

1. Definition of success.
2. Removal of failures from analysis of each group.
3. Explanation of visual changes.
4. Comparison of efficacy of one form therapy over another.
5. Compliance and side effects.
6. Patients' attitude and response.
7. Statistics explanation.
8. The major issue.

1. DEFINITION OF 'SUCCESS'

The definition of 'successful' outcome of therapy used in this study, although simplistic, was the only practical option available. In setting up a prospective study, one needs to set an end point, above which it is unfair to expose the patient to possible increased risk of further glaucoma damage. At the time the trial was initiated, laser trabeculoplasty was relatively new and primary surgery was not in general use. Ethical considerations required definitive and absolute guidelines to protect the patient. As field loss may take a while to be demonstrated, given that individual patients may show considerable short-term fluctuations and therefore a series of fields is necessary to document progression, (and that the same is applicable to optic disc changes), IOP levels were considered the most practical method of evaluation and the upper level of 22 mmHg chosen (the concept of 'normal' pressure range is dealt with in the discussion).

The percentage drop in pressure in the different groups is documented in the results (viz. laser alone : 38.1%; laser + pilocarpine 55.9%; surgery 60.3%; medicine 46.3%.).

2. REMOVAL OF FAILURES FROM ANALYSIS OF EACH GROUP

When any case 'failed', (i.e. if the selected treatment did not control the IOP at <22 mmHg), a second treatment was randomly allocated, again by computer selection. To include these cases which were being treated with other forms of therapy would defeat the objective of the study, namely to assess the outcome of 3 different forms of primary therapy in glaucoma. The method of statistical analysis of Kaplan & Meier used in this study, takes into account the removal of failed cases, deaths and dropouts.

3. EXPLANATION OF THE VISUAL FIELD CHANGES

While it might be expected that, in the less well controlled medical group with its higher IOP's and greater diurnal fluctuations, that a number of patients would have lost visual field, two factors make the differentiation of a significant statistical difference between this and the other groups difficult, namely that we are looking at the mean field loss in the group and that there were some large fluctuations in individual patients' field scores which could have affected this mean.

Another factor to be taken into account is that relatively gross changes were picked up using the definition of 'significant field loss'; smaller areas of field loss may have been missed over the short term. With the Friedmann fields being less accurate than the newer Humphrey fields, it will be interesting to see if a significant difference between the groups can be detected by the latter apparatus when a long-enough follow-up period has been achieved (a Humphrey Field analyser was only obtained part-way through the study).

The references quoted by the examiner [1,2] both refer to field loss in advanced glaucoma and use kinetic (Goldmann) as opposed to static perimetry. Kolker himself [2] states in the first paragraph that "once the defect approaches fixation, therefore, the value of visual fields in following the progression of the disease is greatly compromised."

References

1 Odberg T : Visual field prognosis in advanced glaucoma. Acta Ophthalmol., 65 (suppl), 1987, 182, 17-25

2 Kolker AE : Visual prognosis in advanced glaucoma : a comparison of medical and surgical therapy for retention of vision in 101 eyes with advanced glaucoma. Trans. Am. Ophthalmol. Soc., 1977, 75, 539-555

Note that of the 43 patients who showed field deterioration by far the majority consisted of laser (17 patients) and medically treated (20 patients) cases. Only 6 surgical cases showed a deterioration according to this definition (cf Chap.9, pg. 5)

Cf also references 11, 36 and 42 (Section II).

4. COMPARISON OF THE EFFICACY OF ONE FORM OF TREATMENT OVER ANOTHER DURING THE COURSE OF THE STUDY

Chronic open-angle glaucoma is a long-term disease requiring a prolonged period of follow-up before any relevant statistical conclusions can be drawn regarding disease progress. It is difficult to assess visual fields over the short-term due to the fluctuations that occur, while optic disc changes in the majority of cases take time to develop. The results of IOP control and phasing over the course of this study clearly show the relation between the levels reached by each group for each year of the study.

5. COMPLIANCE AND SIDE EFFECTS IN THE MEDICAL GROUP

To provide hard data about compliance with eyedrops would require computerised dropper bottles (ref. no. 102, section I) for any degree of accuracy. These were not available for this study.

The common side-effects encountered with the various topical drugs used have been enumerated. The protocol did not require questioning or documentation of every possible side-effect of each drug, therefore a more detailed analysis of this common problem is not possible in this study.

6. PATIENTS' ATTITUDE & RESPONSE TO THE FORM OF TREATMENT GIVEN

All patients were primed with a detailed informed consent (see appendix) and explanation of the three forms of therapy and their possible advantages and disadvantages. Any uncertainties were cleared up before the patient was entered into the trial. For this reason patients appeared to accept whatever treatment was allocated, without exception.

Because the second eye in cases of bilateral glaucoma in this study was treated medically, it was possible to assess the reaction of patients to surgery or laser as opposed to medicine. Several surgical patients actually requested an operation in the second eye, preferring this course to the use of eyedrops. However, ethical considerations when drawing up the protocol, dictated that the second eye should be treated in the standard fashion (namely medical treatment).

The same occurred with several of the laser patients. No one volunteered at any time that they would have preferred, in retrospect, not to have undergone surgery or laser. (This applied to both primary and secondary treatments.)

While it may be possible to ask patients specifically which treatment they preferred when the trial is brought to its conclusion, such a question at an earlier stage may only confuse and complicate the issue.

7. STATISTICS EXPLANATION

1. Deaths and dropouts in the survival analysis were censored by the method of Kaplan & Meier (see Chapter 7 pg. 7).
2. In the graphs showing the survival analysis, the upright lines represent death or last follow-up. The drops represent failures.

3. The bars on Figs. 7, 11, 11-ABC, 12, 12-ABC, 13-15, 18 represent 1 standard error.

4. The patient with the infected bleb and complications was not regarded as a failure. The intraocular pressure remained well controlled and the cause of visual loss, even after cataract removal, could not be directly related to the filtering surgery. (The V.A. initially improved to the preoperative level following cataract extraction, but was subsequently reduced following a vein occlusion).

5. The graphs including 'failed' cases are shown for relative and absolute field defects in Figs. 11-ABC, 12-ABC. The failures are excluded from the IOP graphs as they are not relevant - we wished to show the IOP levels with each primary treatment alone.

6. The smoothed curves in Fig. 7-A and 15-A equal normal distribution spread (using mean and standard deviation).

7. Correlation co-efficient is a measure in this case of how the IOP values at 1 year are related to the starting values, e.g. correlation coefficient of 0 shows no correlation i.e. random; correlation coefficient of 1.0 = highly predictable.

8. THE 'MAJOR ISSUE' IN GLAUCOMA

Whether primary medical, surgery or laser is the best initial approach to the management of a case of primary open angle glaucoma will only be answered with time, as emphasised in the conclusions of this study.

There is no doubt that an individual with early glaucoma whose IOP is reduced to the mid-teens with a twice daily eyedrop can do very well but compliance is necessary and the long-term effects of eyedrops on the conjunctiva [1], which might effect the results of later surgery, should glaucoma control be lost with eyedrops, must be considered. Problems of compliance and side effects can only be multiplied when more than one topical medicine becomes necessary.

Surgery has been shown to lower IOP effectively, and to maintain this control, perhaps at the expense, in some cases, of a slight reduction of vision. As modern surgical instrumentation and techniques continue to improve, perhaps this complication will be lessened.

Laser trabeculoplasty does appear to lower IOP effectively in many cases, but, because of the questionable length of efficacy, it may be best reserved for elderly patients with a relatively shorter life expectancy.

This study has shown the possibility of using surgery as a primary form of therapy for open-angle glaucoma and may radically change the conventional order of treatment for this disease.

References

1 Lavin M, Migdal C, Hitchings R : The influence of previous medical therapy on the outcome of trabeculectomy. (In Press)