Cataract surgery in patients with diabetes

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1. ABSTRACT

Patients with diabetes account for one eighth of all patients undergoing cataract surgery. Despite this, there is uncertainty over the best operative technique, and although postoperative visual acuity may be poor as a result of macular oedema, the optimal management of this entity is undefined, and natural history data on which to base management are lacking.

In this thesis a prospective randomised paired-eye controlled trial comparing phakoemulsification with extracapsular cataract surgery in diabetes identified a lower incidence of capsular opacification and postoperative inflammation, and slightly better visual acuity, in eyes undergoing phakoemulsification. There was no difference in retinopathy progression or incidence of macular oedema. The principal determinants of postoperative visual acuity in each surgical group were the presence of macular oedema at the time of surgery, and to a lesser extent, the severity of retinopathy.

A study directed at defining the natural history of postoperative macular oedema attempted to identify predictors of likely spontaneous resolution. Angiographic findings, in particular postoperative optic disc hyperfluorescence, were not predictive. By contrast, clinical examination was a useful predictor, since macular oedema present at the time of surgery showed no tendency to spontaneous resolution, whereas that arising after surgery resolved in three-quarters of eyes by one year. The presence of macular oedema at the time of surgery was the principal determinant of postoperative visual acuity.

These findings suggest that macular oedema should be managed expectantly if it arises after surgery, and treated with laser if present at the time of surgery. Phakoemulsification appears to be the preferred surgical approach, but the choice of surgical technique may be less critical to outcome than operating early enough to ensure that cataract does not prevent identification of macular oedema, the presence of which at the time of surgery is associated with poor postoperative visual acuity.

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2 INTRODUCTION

2.1 INTRODUCTION

The global prevalence of diabetes is undergoing a marked increase. Estimated in 1994 at 110 million, it is projected to reach 221 million by 2010 (Amos, McCarty et. al., 1997). In Western countries, diabetes is the commonest risk factor for cataract. Data from the Framingham Eye Study and the Health and Nutrition Examination Survey indicate a three to fourfold excess prevalence of cataract in diabetic patients under 65, and up to twofold excess prevalence in older patients (Ederer, Hiller et. al., 1981). Cataract is also an important cause of visual loss in patients with diabetes; in the Wisconsin Epidemiologial Study of Diabetic Retinopathy (WESDR), cataract was the principal cause of legal blindness in older onset diabetics, and the second commonest cause after proliferative diabetic retinopathy in younger onset diabetics (Klein, Klein et. al., 1984). Cataract occurs at an earlier age in diabetic than non-diabetic patients, and thus the visual loss consequent upon it has a significant impact on the working population (Klein, Klein et. al., 1995c). The incidence of cataract surgery in diabetic patients is also high. The Wisconsin study identified a ten-year cumulative incidence of cataract surgery of more than 27% in younger onset diabetics ≥45 years of age, and of more than 44% in older onset diabetics ≥75 years of age (Klein, Klein et. al., 1995b). These figures may even be an underestimate - mortality rates are increased in patients with diabetes if cataract is present, and in this study the ten-year mortality was 55% in the older onset cohort, and 15% in the younger onset cohort. In the UK, although only 2% of the population are diabetics, approximately 11% of cataract extractions are performed on diabetic patients (Harding, Egerton et. al., 1993).

In earlier reports, cataract surgery in diabetics, particularly in eyes with retinopathy, was associated with a high incidence of postoperative complications, including fibrinous uveitis (Hykin, Gregson et. al., 1993), posterior capsule opacification (Ionides, Dowler et. al., 1994), anterior segment neovascularisation (Ulbig, Hykin et. al., 1993), accelerated progression of retinopathy (Jaffe, Burton et. al., 1992) , and macular oedema (Pollack, Leiba et. al., 1992b). Visual acuity was frequently poor (Pollack, Leiba et. al., 1992b; Schatz, Atienza et. al., 1994). By contrast, recent studies (Henricsson, Heijl et. al., 1996; Antcliff, Poulson et. al., 1996) have tended to report a lower incidence of complications and much improved visual outcome. This improvement may be due to better management of retinopathy prior to surgery, with recognition of the findings of the Diabetic Retinopathy Study (DRS) and the Early Treatment Diabetic Retinopathy Study (ETDRS) (Diabetic Retinopathy Study Research Group., 1981; Early Treatment Diabetic Retinopathy Study Research Group, 1985), altered indications for cataract surgery in diabetes, evolution of operative technique, and appreciation of the importance of systemic factors such as glycaemic and hypertensive control in retinopathy progression as a result of the Diabetes Control and Complications Study (DCCT) , and the UK Prospective Diabetes Study (UKPDS) (Diabetes Control and Complications Trial Research Group, 1993; UK Prospective Diabetes Study Group, 1998a; UK Prospective Diabetes Study Group, 1998b). Much still remains uncertain, however, including appropriate timing of surgery, the precise effect of surgical technique on outcome, and the natural history and optimal management of postoperative macular oedema.

In this thesis, the background to current research into diabetic cataract surgery, and the results of clinical and angiographic studies into the anterior and posterior segment complications of surgery are presented. It is hoped that through a clearer understanding of the effect of diabetes on cataract surgery, the visual outcome of surgery may be improved.

2.2 CATARACT SURGERY IN DIABETES

2.2.1 Preoperative management

Data from the DCCT and UKPDS provide good evidence linking the progression of retinopathy to the quality of glycaemic control in both type 1 and type 2 diabetes (Diabetes Control and Complications Trial Research Group, 1993; UK Prospective Diabetes Study Group, 1998a; UK Prospective Diabetes Study Group, 1998b). Since there are several reports associating cataract surgery with accelerated progression of retinopathy (Hykin, Gregson et. al., 1993; Jaffe, Burton et. al., 1992; Benson, Brown et. al., 1993), it seems logical to attempt to improve glycaemic control prior to undertaking cataract surgery. Although no study has specifically addressed this issue, two studies have identified a correlation between glycaemic control and the visual outcome of cataract surgery (Tsujikawa, Otani et. al., 1995; Henricsson, Heijl et. al., 1996). Some care may, however, be required in extending such findings to the inference that improvement in glycaemic control prior to cataract surgery is desirable, because of possible synergy between the phenomenon of transient worsening of retinopathy with improvement in glycaemic control, and the progression of retinopathy associated with cataract surgery. A similar synergy might be inferred in the Diabetes in Early Pregnancy Study (Chew, Mills et. al., 1995), which rapid improvement in glycaemic control during the first trimester was found to be a particular risk factor for accelerated retinopathy progression during pregnancy (Chew, Mills et. al., 1995). Other systemic factors which may impact on postoperative progression of retinopathy include hypertension, shown in the UKPDS to be a potent influence on visual acuity and retinopathy progression in type 2 diabetics (UK Prospective Diabetes Study Group, 1998b), and renal impairment, which may be associated with worsening of maculopathy.

Cataract surgery in eyes with sight-threatening diabetic retinopathy appears to be associated with poor postoperative visual acuity (Hykin, Gregson et. al., 1992). It therefore seems desirable that laser therapy for clinically significant macular oedema or high-risk proliferative retinopathy be applied before surgery. This may be problematic, however, since even minor cataract may impede clinical recognition of retinal thickening or neovascularisation, and degrade angiographic images. Furthermore, even if sight-threatening retinopathy can be diagnosed, lens opacity may obstruct laser therapy. In eyes with proliferative retinopathy, the use of longer wavelengths, eg dye yellow (577nm), or diode infrared (810nm), better suited to penetrating nuclear cataract than argon green (514nm) has been advocated (Dowler, Hykin et. al., 1995a). Panretinal photocoagulation may also be easier to apply with the indirect ophthalmoscope or trans-scleral diode probe (Dowler, Hykin et. al., 1995a). In eyes with proliferative retinopathy and cataract sufficiently dense to completely prevent preoperative laser, B-Scan ultrasound may be valuable to determine whether vitreous haemorrhage or traction macular detachment is present. If so, a combination of cataract extraction, vitrectomy and endolaser may be considered (Hutton, Pesicka et. al., 1987). If not, indirect laser panretinal photocoagulation applied during cataract surgery may reduce the incidence and severity of surgical complications (West, Dowler, et. al., 1995). This appears preferable to unsighted panretinal cryotherapy, in which the risk of precipitating traction retinal detachment appears significant (Vernon and Cheng, 1988). In eyes with macular oedema, however, treatment may be complicated by difficulties in identifying microvascular landmarks, and regulating laser power according to local variations in cataract density and retinal thickness. This represents a particular problem, since macular oedema appears to be a major cause of poor visual acuity after cataract surgery (Pollack, Leiba et. al., 1992b; Dowler, Hykin et. al., 1995b).

2.2.2 Indications and timing

Some authors have advocated a markedly conservative approach to the management of cataract in patients with diabetes. Pollack, on the basis of a study in the UK literature, in which only 31% of patients achieved a postoperative visual acuity ≥ 6/12, advocates that "cataract extraction should not be recommended for eyes with diabetic retinopathy until vision has deteriorated to 6/30-6/60" (Pollack, Leiba et. al., 1992b). Likewise Schatz, on the basis of a study in the US literature, in which only 9% of patients achieved a postoperative visual acuity ≥ 6/12 suggests that "A patient who has diabetes and cataract might wish to postpone surgery or elect not to have it all, given the chance of a markedly poor result, especially if any retinopathy is present preoperatively" (Schatz, Atienza et. al., 1994).

Such a conservative approach is not universally accepted, however. Data from UK studies (Courtney, 1992) indicate that some 4% of cataract procedures are undertaken in patients with diabetic retinopathy. In the WESDR, the incidence of cataract surgery was two to five fold higher in patients with diabetes than in a comparable non-diabetic population from the Beaver Dam Study (Klein, Klein et. al., 1995a). In addition, recent studies have indicated a reduced incidence of complications and improved visual outcome compared to earlier work on which the conservative rationale was based. Henriccson, for example, reports that 89% of her diabetic patients undergoing cataract surgery achieved a postoperative visual acuity ≥6/12 (Henricsson, Heijl et. al., 1996). Furthermore, since the visual outcome of cataract surgery tends to be poorer (Dowler, Hykin et. al., 1995b) and the incidence of complications higher (Hykin, Gregson et. al., 1993; Ionides, Dowler et. al., 1994) in eyes with more severe retinopathy, one might expect that that if a conservative approach were adopted, the incidence of cataract surgery might decline with increasing severity of retinopathy. However in the WESDR, the opposite trend was observed patients in with juvenile onset diabetes (Klein, Klein et. al., 1995b). It appears, therefore, that there is some

discrepancy between common practice and the recommendations of authors in favour of more conservative management.

2.2.3 Surgical technique

Many studies of cataract surgery in diabetes have adopted operative techniques identical to those used in age-related cataract, on the assumption that the principal determinant of outcome is the modification by diabetes of the tissue response to surgery, rather than the nature of the surgical injury. Differences exist, however, between surgery for age-related cataract and cataract surgery in diabetic patients in the pattern of complications and determinants of outcome, and it would therefore be surprising if the optimal surgical technique was identical in the two cases, particularly given evidence that attributes of the surgical technique and intraocular lens used may modify the incidence of specific complications of surgery for age-related cataract. Such considerations are particularly relevant in the context of the recent shift towards the use of small incision techniques and new intraocular lens designs and materials. Despite this, there is little modern prospective data regarding the effect of operative technique on the diabetic eye.

Posterior segment complications are a frequent cause of poor visual acuity following cataract extraction in diabetes. The ideal surgical technique would thus be associated with a low incidence of such complications, and a clear and uninterrupted fundus view after surgery to permit their early recognition, and, where appropriate, treatment. The type of intraocular lens implanted may influence the attainment of these objectives. The rigid, large optic diameter polymethylmethacrylate (PMMA) lens, by virtue of its stability, permits fashioning of a wide posterior capsulotomy early in the postoperative course. This is important, since eyes with more severe retinopathy at the time of surgery have a greater risk both of deterioration of retinopathy (Hykin, Gregson et. al., 1993) and capsular opacification (Ionides, Dowler et. al., 1994), and a clear view

of peripheral retina may valuable if panretinal photocoagulation or vitrectomy surgery becomes necessary (McCuen and Klombers, 1990). Such eyes are prone to massive cellular proliferation at posterior capsulotomy margins (Jones, McLeod et. al., 1995), and in this context PMMA lenses have the additional advantage that if vitrectomy is required this material may be safely cleared and the capsulotomy enlarged without fear of posterior dislocation of the lens. PMMA lenses, however, have a tendency to accumulate surface deposits (Borgioli, Coster et. al., 1992), and require a relatively large incision, which may delay refractive stabilisation and exacerbate postoperative inflammation. In addition, posterior synechiae to the posterior lens capsule may develop behind the intraocular lens optic ("optic capture"), restricting fundus visualisation.

Foldable silicone lenses combine some of the advantages of large optic diameter with those of a small incision, and to date more implanted foldable intraocular lenses have been made of silicone than any other material. However, plate-haptic variants are associated with certain complications which may be important in patients with diabetes. Although newer designs have incorporated larger dialling holes in order to improve capsular fixation, there appears some risk of posterior dislocation following posterior capsulotomy (Gonzalez and Irvine, 1996). This is of concern in patients with proliferative diabetic retinopathy, in which the requirement for posterior capsulotomy may be high (Ionides, Dowler et. al., 1994). Anterior dislocation has also been described (Tuft and Talks, 1998). Postoperative contraction of the anterior capsular aperture in non-diabetic eyes appears particularly marked following implantation of plate-haptic silicone lenses (Gonvers, Sickenberg et. al., 1997), potentially compromising visualisation of the peripheral retina. This complication appears to occur more frequently in diabetic eyes, particularly those with retinopathy (Hayashi, Hayashi et. al., 1998). All silicone lenses have the additional disadvantage that if vitrectomy is required, adherence of fluid droplets to the lens may impair fundus visualisation temporarily during fluid gas exchange (Francese, Christ et. al., 1995), or more permanently in eyes undergoing silicone

oil injection and subsequent oil removal and posterior capsulotomy (Apple, Federman et. al., 1996). Acrylic lenses, which may also be implanted through a small incision, appear stable, show less adherence of silicone oil (Apple, Isaacs et. al., 1997), and may be associated with a reduced incidence of posterior capsule opacification in non-diabetic eyes (Ursell, Spalton et. al., 1998). Designs with PMMA haptics also appear relatively resistant to postoperative contraction of the anterior capsule aperture (Sickenberg, Gonvers et. al., 1998). Little information is however available about the use of such lenses in diabetics, and further study is necessary to determine their role.

The use of an extracapsular technique may be of benefit in diabetic cataract surgery in that it permits insertion of a large optic PMMA lens with the advantages discussed above. In addition, if a can-opener capsulotomy is employed, the risk of postoperative contraction of the anterior capsular aperture is eliminated. In extracapsular surgery, however, the additional tissue damage associated with a larger incision and the iris trauma attendant on nuclear expression has the potential to produce more severe postoperative inflammation than occurs after phakoemulsification, particularly in the presence of abnormalities of iris vasculature due to diabetes (Taniguchi, Nakao et. al., 1968; Moriarty, Spalton et. al., 1994) or poor mydriasis. In addition, implantation of the intraocular lens in the ciliary sulcus may result in greater compromise of the blood-aqueous barrier than in-the-bag fixation (Miyake, Asakura et. al., 1984). In patients with diabetes, who have, in any case, a tendency to severe postoperative inflammation (Krupsky, Zalish et. al., 1991), this may be relevant because of the need to maintain fundus view, and because of the possibility that anterior segment inflammation may potentiate such posterior segment complications as macular oedema and retinopathy progression. Furthermore, the more rapid refractive stabilisation afforded by phakoemulsification surgery permits detailed fundus assessment and laser treatment earlier in the postoperative course than is possible with extracapsular techniques. This may allow recognition and treatment of sight-threatening retinopathy present at the

time of surgery but unrecognised or untreated because of cataract, and the evaluation of baseline retinopathy severity. Such considerations, however, remain theoretical until prospective studies comparing the two techniques are published.

2.2.4 Complications of surgery

2.2.4.1 Macular oedema

2.2.4.1.1 Incidence

Macular oedema is a common complication of cataract surgery in patients without diabetes, detectable angiographically in 50-70%, and clinically manifest in 5-15% (Gass and Norton, 1966; Hitchings, Chisholm et. al., 1975). It is also an important cause of poor visual acuity following cataract surgery in diabetes, in which it may be considered as a complex of several potential components; diabetic macular oedema, present at the time of surgery but unrecognised or untreated because of the presence of cataract, diabetic macular oedema arising after cataract surgery (Jaffe and Burton, 1988), or Irvine-Gass macular oedema (Gass and Norton, 1966). Although the natural history of these components is likely to differ, discrimination of the various elements may be problematical. Diabetic macular oedema may be difficult to identify before surgery, since even mild lens opacity may impede recognition of retinal thickening. Any visual loss consequent on it may be ascribed to cataract, particularly if, as some advocate (Schatz, Atienza et. al., 1994; Pollack, Leiba et. al., 1992b), surgery is not undertaken until the cataract is dense, marked visual loss occurs, and fundus visualization is by inference severely compromised. Equally, in the early postoperative period recognition of macular oedema may be impeded by photophobia, postoperative uveitis, capsular opacity, and, following large incision surgery, refractive instability. If recognised later in the postoperative course, it may be difficult to distinguish from macular oedema arising after surgery, since the postoperative interval during which it is reasonable to infer

the presence of macular oedema at the time of surgery on the basis of its subsequent identification is uncertain.

It may also be difficult to distinguish Irvine-Gass macular oedema from diabetic macular oedema arising de novo after surgery. It has been suggested that the presence of optic disc hyperfluorescence in postoperative angiograms indicates likely resolution of macular oedema; this, however, awaits confirmation (Royal College of Ophthalmologists, 1997). Although Irvine-Gass macular oedema tends to resolve, and diabetic macular oedema to progress, the absence of prospective natural history studies indicating a likely time scale for these events may prevent early differentiation of the two entities, and expectant management of macular oedema may not be considered justified in eyes with retinopathy. Furthermore, an absolute distinction may not be possible, some cases labelled as diabetic macular oedema possibly representing Irvine-Gass syndrome which because of existing diabetic vascular damage demonstrate incomplete or absent resolution.

The fact that early postoperative macular assessment is not invariably performed, the difficulty in excluding the presence of macular oedema at the time of surgery, the absence of reliable means of differentiating Irvine-Gass macular oedema from diabetic macular oedema, the retrospective nature of many studies, the varying postoperative intervals at which assessments are made, and differences in the definition of macular oedema make estimation of the incidence of macular oedema arising de novo after diabetic cataract surgery problematical. Published figures are shown in Table 2.1, arranged according to retinopathy severity. Most data relate to extracapsular extraction, and figures should therefore be interpreted with caution, both because refractive instability in the early postoperative period may result in an underestimation of the incidence of self-limiting Irvine-Gass forms of macular oedema, and because it may not be valid to assume comparable incidences of macular oedema after small incision surgery. Nonetheless, there is a considerable body of evidence

suggesting a significant incidence of macular oedema following cataract surgery in patients with diabetes.

Table 2-1: Reported incidences of macular oedema after cataract surgery in diabetes

Retinopathy	Author	Design	Year	n	Surgery	CMO	AMO	Interval
None	Menchini	Prospective	91	24	ECCE		60%	at 6 weeks
	Menchini	Prospective	91	24	ECCE		25%	at 1 year
	Cunliffe	Retrospective	91	33	ECCE	3%		fu ~18 months
	Cheng	Retrospective	88	21	ECCE	11%		fu > 6 months
	Pollack	Prospective	92	28	ECCE	11%	32%	in first yr
	Antcliff	Retrospective	96	24	Phako	12%		fu ~30 months
NPDR	Antcliff	Retrospective	96	23	Phako	43%		fu ~30 months
	Cunliffe	Retrospective	91	23	ECCE	52%		fu ~18 months
	Benson	Retrospective	93	49	ECCE	71%		fu ~30 months
	Cheng	Retrospective	88	13	ECCE	61%		fu > 6 months
PDR	Antcliff	Retrospective	96	27	Phako	7%		fu ~30 months
	Ruiz	Retrospective	91	19	ECCE	8%		fu > 6months
	Hykin	Retrospective	93	40	ECCE	13%		6 months
	Benson	Retrospective	93	58	ECCE	48%		fu ~30 months
	Cunliffe	Retrospective	91	10	ECCE	60%		fu ~18 months

CMO: clinical macular oedema, AMO: angiographic macular oedema, fu: follow up, No DR: no diabetic retinopathy, NPDR: nonproliferative diabetic retinopathy, PDR: proliferative diabetic retinopathy, Phako: phakoemulsification, ECCE: extracapsular cataract extraction.

2.2.4.1.2 Pathogenesis

Irvine-Gass macular oedema represents one potential component of postoperative macular oedema in diabetic eyes. A large number of potential aetiological factors for the Irvine-Gass syndrome have been suggested, including inflammation and prostaglandin release (Kraff, Sanders et. al., 1982; Flach, Stegman et. al., 1990), vitreomacular traction (Jaffe, 1967), surgical technique (Miami Study Group, 1979), topical adrenergic compounds (Michels and Maumenee, 1975), hyaluronidase in local anaesthetic (Roper and Nisbet, 1978), operating microscope phototoxicity (McDonald and Irvine, 1983), and hypotony (Duke Elder, 1971). The presence of posterior vitreous cells and disc swelling on clinical examination, fluorescein angiographic evidence of leakage from disc retinal and perifoveal vessels (Gass and Norton, 1966), response to treatment with steroids and nonsteroidal anti-inflammatory agents (Flach, Stegman et. al., 1990), and histological evidence of iritis and retinal periphlebitis (Martin, Green et. al., 1977), support an inflammatory aetiology. In patients with diabetes the greater severity of postoperative inflammation might augment the tendency to macular oedema due to such a mechanism, and increased retinal vascular permeability due to diabetes add to any similar effect of inflammatory mediators. The relatively infrequent occurrence of macular oedema following surgical procedures producing comparable postoperative inflammation to cataract surgery (Miyake, Miyake et. al., 1983) suggests, however, that other processes may also be involved. Early reports in non-diabetic eyes indicating that rupture of the anterior hyaloid face and vitreous incarceration in the wound were common associations of Irvine-Gass macular oedema (Gass and Norton, 1966) seemed to implicate vitreomacular traction in its pathogenesis, and improved acuity following vitrectomy in patients with vitreous incarceration in the cataract wound seems to support this (Fung, 1985). Vitreous attachment to the macula cannot, however, usually be demonstrated (Fung, 1985). In diabetic eyes, the vitreous appears to have some role in macular oedema, since the incidence of macular oedema is lower in eyes with posterior vitreous

detachment (Nasrallah, Jalkh et. al., 1988; Nasrallah, Van et. al., 1989), and there is some evidence to suggest that vitrectomy may ameliorate diffuse diabetic macular oedema (Tachi and Ogino, 1996). The precise nature of this role, and how it relates to post-cataract macular oedema is unclear. It is possible that alterations to vitreous configuration as a result of the reduced lens volume may influence the pharmacokinetics of retinal growth factors which modulate retinal vascular permeability. Finally, in non-diabetic eyes, a component of Irvine-Gass macular oedema fluid may derive from trans pigment epithelial flow as suggested by fluorescein leakage from the retinal pigment epithelium in Irvine-Gass syndrome, and resolution of chronic oedema with acetozolamide treatment (Cox, Hay et. al., 1988). Operating microscope photic injury and perioperative variation in intraocular (Schulte, Wolf et. al., 1996) and hence choroidal perfusion pressure may contribute to this injury to the outer blood retinal barrier.

Diabetic macular oedema represents the other potential component of postoperative macular oedema. Early histological features of diabetic retinopathy include pericyte loss and endothelial basement membrane thickening. These changes may be associated with evidence of increased capillary permeability and intra-retinal leakage of plasma elements. Fluorescein angiography indicates that leakage arises from microaneurysms in focal oedema, and the whole length of capillaries in diffuse oedema (Bresnick, 1986). Molecular biology studies suggest that loss of the normally anti-thrombogenic surface of endothelial cells, coupled with the hyper-aggregability of platelets in diabetes (Collier, Tymkewycz et. al., 1986), may result in intra-vascular fibrin deposition (Forrester, 1987). It is possible that this may result in cytoskeletal changes within the endothelial cell, with retraction of cell-cell contacts, as has been demonstrated in vitro (Olander, Bremer et. al., 1985). Ultrastructural studies of endothelial cells from diabetic patients also suggest a possible transcellular mechanism for breakdown of the inner blood retinal barrier

(Ishibashi and Inomata, 1993). Such mechanisms appear exquisitely sensitive to the action of growth factors such as vasoactive endothelial growth factor.

The effect of cataract surgery on these processes is uncertain, but several possibilities exist. Postoperative changes in vitreous configuration, and alteration of aqueous humour dynamics may modify the pharmacodynamics of retina-derived growth factors in such a way as to increase vascular permeability. Other potential influences include the posterior diffusion of vasoactive agents released in the anterior segment as a result of inflammation, and the effects of peribulbar anaesthetic agent, intracameral adrenaline (Chiou, Girgis et. al., 1988), and perioperative alterations in intraocular pressure (Schulte, Wolf et. al., 1996).

2.2.4.1.3 Management

The optimal management of macular oedema identified after cataract surgery in diabetes is undefined. It might be anticipated that diabetic macular oedema present at the time of cataract surgery would prove refractory to laser treatment because of delay in treatment occasioned by the presence of cataract, worsening of oedema due to surgery, and further delay in treatment due to expectant postoperative management based on a mistaken diagnosis of Irvine-Gass syndrome. Macular oedema arising after surgery is likely to progress if the principal component is due to diabetes, and resolve if due to the Irvine-Gass syndrome, but these entities may be difficult to differentiate. There has been a tendency, therefore, to adopt an empirical approach (Benson, 1992), in which laser for macular oedema is deferred until six months after surgery to permit resolution of Irvine-Gass elements, but this may result in unnecessary treatment of eyes in which Irvine-Gass macular edema resolves slowly, or delay treatment of diabetic macular oedema, which can deteriorate significantly within six months of surgery (Jaffe and Burton, 1988). Ideally, the decision to apply laser therapy for postoperative macular edema would be based on the likelihood of its spontaneous resolution, but relevant natural history data are not available,

except for eyes without retinopathy, in which laser therapy is unlikely to be contemplated (Menchini, Bandello et. al., 1993). There is therefore a need for natural history studies on which to base strategies for the management of macular oedema after cataract surgery in diabetes.

2.2.4.2 Progression of retinopathy

2.2.4.2.1 Incidence

There is considerable variation between studies in the criteria used to determine progression of retinopathy after cataract surgery in diabetes, and in the postoperative interval during which progression of retinopathy is attributed to surgery. It may not be possible to establish that postoperative deterioration of retinopathy has been accelerated by surgery; even in those paired eye studies in which retinopathy progressed more in the operated than unoperated fellow eye (Jaffe, Burton et. al., 1992), the observation that cataract surgery is commoner in eyes with more severe retinopathy raises the possibility that an asymmetry in retinopathy existed before surgery. It is notable that some studies have failed to demonstrate significantly greater progression of retinopathy in operated than in fellow unoperated eyes (Schatz, Atienza et. al., 1994; Wagner, Knaflic et. al., 1996).

It may also be difficult to determine in detail the extent of postoperative progression of retinopathy, since cataract may prevent accurate definition of preoperative retinopathy severity, obscuring postoperative progression of retinopathy, or attributing to it lesions unrecognised prior to surgery. For these reasons, incidences of postoperative retinopathy progression, shown in Table 2.2, should be interpreted with some care. It is widely perceived, however, that cataract surgery is associated with accelerated progression of diabetic retinopathy, although this cannot be considered to be proven beyond doubt.

Table 2-2: Reported incidences of retinopathy progression after cataract surgery in patients with diabetes

Retinopathy	Author	Design	Year	Surgery	n	Prog	Interval
None	Cheng	Retrospective	88	ECCE	21	7%	fu > 6 months
	Antcliff	Retrospective	96	Phako	24	8%	fu ~30 months
	Kodama	Retrospective	93	ECCE	25	12%	6 months
	Cunliffe	Retrospective	91	ECCE	33	15%	fu ~18 months
	Wagner	Prospective	96	Phako	158	18%	at 6 months
	Pollack	Prospective	92	ECCE	28	25%	in first yr
NPDR	Hykin	Retrospective	93	ECCE	64	3%	6 months
	Kodama	Retrospective	93	ECCE	20	12%	6 months
	Antcliff	Retrospective	96	Phako	23	13%	fu ~30 months
	Cheng	Retrospective	88	ECCE	13	15%	fu > 6 months
	Cunliffe	Retrospective	91	ECCE	23	26%	fu ~18 months
	Benson	Retrospective	93	ECCE	49	29%	fu ~30 months
	Wagner	Prospective	96	Phako	45	31%	at 6 months
	Pollack	Prospective	92	ECCE	16	70%	in first yr
	Jaffe	Prospective	92	ECCE	19	74%	fu ~18 months
PDR	Hykin	Retrospective	93	ECCE	40	10%	6 months
	Fung	Retrospective	87	Phako	10	10%	fu>1 year
	Antcliff	Retrospective	96	Phako	27	19%	fu ~30 months
	Ruiz	Retrospective	91	ECCE	19	20%	fu > 6 months
	Wagner	Prospective	96	Phako	20	21%	at 6 months
	Benson	Retrospective	93	ECCE	58	33%	fu ~30 months
	Cunliffe	Retrospective	91	ECCE	10	50%	fu ~18 months

Prog: retinopathy progression, fu: follow up, No DR: no diabetic retinopathy, NPDR: nonproliferative diabetic retinopathy, PDR: proliferative diabetic retinopathy, Phako: phakoemulsification, ECCE: extracapsular cataract extraction.

2.2.4.2.2 Pathogenesis

The early pathological features of diabetic retinopathy include pericyte loss, a reduction in total capillary density, vessel wall changes including microaneurysm formation and endothelial basement membrane thickening with abnormal vascular permeability, and intravascular microthrombi with areas of focal retinal ischaemia leading ultimately to neovascularisation. The first cells to escape growth control appear to be endothelial cells (Forrester, Shafiee et. al., 1993). The angiogenic response is controlled by the interaction of matrix cues, provided by eg laminin, collagen and fibronectin, and growth factors, such as vascular endothelial growth factor, fibroblast growth factor, transforming growth factor, plasminogen activator, insulin-like growth factor and platelet derived growth factor (Forrester, Shafiee et. al., 1993; Glaser, 1988). The angiogenic balance is normally weighted towards growth inhibition; although endothelial cells have considerable capacity to divide, turnover is low in mature vasculature (Archer, 1983). In diabetic retinopathy, mechanisms such as polyol accumulation, glyco-oxidation, or NADH consumption may cause endothelial cells to lose the normally anti-thrombogenic nature of their surface (Forrester, 1987). This, combined with diabetic platelet hyperaggregability (Tindall, Paton et. al., 1981), may result in microthrombus formation, capillary closure, and the release of platelet-derived growth factors which promote angiogenesis. In addition, systemic activation of leukocytes, particularly monocytes, may lead to capillary occlusion through increased adhesiveness of leukocytes to the damaged endothelial cell surface. Activated macrophages, probably derived both from diapedesis of circulating cells, and from the resident microglial population, may release growth factors in a more sustained fashion than platelets, to overcome natural inhibitory mechanisms and stimulate endothelial cell proliferation (Tindall, Paton et. al., 1981; Forrester, 1987).

Cataract extraction may influence these processes in several ways. Postoperative inflammation, which tends to be more severe and prolonged in diabetic patients (Hykin, Gregson et. al., 1992; Ferguson and Spalton, 1992), may reduce clearance

of retina-derived growth factors as a result of elevated aqueous protein levels (Zaczek and Zetterstrom, 1998) and altered aqueous dynamics. Inflammatory mediators released in the anterior segment may enhance the effect of retina-derived factors by posterior diffusion. Retinal injury as a result of perioperative fluctuations in intraocular pressure (Schulte, Wolf et. al., 1996), operating microscope phototoxicity, anterior segment inflammation, and the pharmacological effects of anaesthetic agents and intracameral catecholamines (Chiou, Girgis et. al., 1988), may activate repair mechanisms which may serve to increase the metabolic load on the inner retina. This, in the context of supra-normal impairment of retinal autoregulation by perioperative variations in blood glucose (Kohner, 1993), may result in further decompensation of the retinal circulation with increased growth factor release. The configuration of the vitreous and posterior lens capsule may also be important, some authors (Alpar, 1984; Alpar, 1987; Levin, Kincaid et. al., 1988) reporting a lower incidence of retinopathy progression after extracapsular extraction than with intracapsular surgery. This may be due to effects on growth factor pharmacokinetics, although the lens itself may play some part, since human lens extracts have been shown to inhibit vascular endothelial cell proliferation in vitro (Williams, Eisenstein et. al., 1984).

2.2.4.2.3 Management

Given that diabetic retinopathy may progress after cataract extraction, close postoperative surveillance is desirable, and assessment soon after surgery necessary to establish a baseline for any subsequent progression, and to note any indicators of likely progression of retinopathy, such as venous beading, intraretinal microvascular abnormalities, haemorrhages, microaneurysms and cotton wool spots in nonproliferative retinopathy, or the presence of non high-risk proliferative retinopathy (Early Treatment Diabetic Retinopathy Study Research Group., 1991). In eyes in which control of neovascularisation is not achieved prior to cataract surgery, or in which proliferative disease is diagnosed at or after surgery, laser treatment may be attempted in the early postoperative

period in accordance with the recommendations of the DRS (Diabetic Retinopathy Study Research Group., 1981). Photophobia, therapeutic contact lens intolerance, poor mydriasis, posterior synechiae, fibrinous postoperative uveitis, intraocular lens deposits, lens edge effects and capsular opacification may however obstruct such treatment. In addition, evidence that the outcome of cataract surgery may be related to glycaemic control (Tsujikawa, Otani et. al., 1995; Henricsson, Heijl et. al., 1996) raises the possibility that systemic measures may also be of value in postoperative management.

2.2.4.3 Anterior segment neovascularisation

2.2.4.3.1 Incidence

Anterior segment neovascularisation, a complication of cataract surgery occurring almost exclsusively in patients with diabetes, occurs in three forms. Vessels derived from the anterior segment may give rise to neovascularisation of the iris as in phakic eyes (Benson, Brown et. al., 1993), or may extend over the anterior surface of the posterior lens capsule - rubeosis capsulare (Eifrig, Hermsen et. al., 1990). Both these processes may result in synechial angle closure and neovascular glaucoma. Alternatively, vessels derived from anterior retina may pass along the anterior hyaloid face to the posterior surface of the crystalline lens - anterior hyaloidal fibrovascular proliferation (Ulbig, Hykin et. al., 1993). This may result in posterior capsule opacification with loss of fundus visualisation. Anterior hyaloidal fibrovascular proliferation and rubeosis capsulare are uncommon, but the incidence of iris neovascularisation is better defined (Table 2.3).

Table 2-3: Incidence of iris neovascularisation and neovascular glaucoma after cataract surgery in patients with diabetes

Retinopathy	NVI	NVG	Surgery	Author
NPDR	8%	1.5%	ECCE	Benson
	8%	-	ECCE	Alpar
	-	1.5%	ECCE	Cheng
QPDR	5%	2.0%	ECCE	Hykin
	10%		ECCE	Benson
	13%		ECCE	Ruiz
APDR	40%		ICCE	Aiello

NVI: iris neovascularisation, NVG: neovascular glaucoma, NPDR: nonproliferative diabetic retinopathy, QPDR: quiescent proliferative diabetic retinopathy, APDR: active proliferative diabetic retinopathy, ECCE: extracapsular cataract extraction, ICCE: intracapsular cataract extraction

Case reports of rapidly progressive iris neovascularisation developing in the early postoperative course of typically arteriopathic patients with nonproliferative retinopathy may reflect a patient subgroup at particular risk (Beasley, 1970; Pavese and Insler, 1987; Prasad, Setna et. al., 1990), perhaps due to widespread capillary nonperfusion (Verdaguer, le Clercq et. al., 1987). In general, however, the incidence of postoperative iris neovascularisation appears to be related to the severity of retinopathy.

2.2.4.3.2 Pathogenesis

The risk of neovascular glaucoma is greater in eyes undergoing intracapsular surgery, or extracapsular surgery with primary capsulotomy, than in eyes going extracapsular surgery without primary capsulotomy (Poliner, Christianson et. al., 1985). Similarly, aphakic vitrectomized eyes have a higher incidence of iris neovascularisation than phakic vitrectomized eyes (Aaberg, 1979; Aaberg, 1981;

Blankenship, 1980; Blankenship, Cortez et. al., 1979; Blankenship and Machemer, 1985; Rice, Michels et. al., 1983; Schachat, Oyakawa et. al., 1983; Tolentino, Freeman et. al., 1980) . These observations support the concept that the forward diffusion of growth factors from ischaemic retina may be responsible for iris neovascularisation, and that an intact lens capsule may act as a partial barrier to this diffusion (Moffat, Blumenkranz et. al., 1984; Ohrloff, Schalnus et. al., 1990; Ozaki, 1984). High levels of vascular endothelial growth factor, a potent stimulator of angiogenesis, have been observed in eyes with proliferative retinopathy and iris neovascularisation (Aiello, Avery et. al., 1994), and it is possible that postoperative inflammation may enhance the local effect of such growth factors, or impede their clearance through the trabecular meshwork. Accumulation of growth factors on the lens capsule may similarly account for anterior hyaloidal fibrovascular proliferation and rubeosis capsulare.

2.2.4.3.3 Management

Iris neovascularisation after cataract surgery in diabetic eyes is managed in much the same way as iris neovascularisation in the phakic eye. Key factors include the visual potential of the eye, the activity and extent of the neovascularisation, and the intraocular pressure. If the eye has good visual potential, and neovascularisation involves the drainage angle of the eye, shows evidence of progression, or is associated with diabetic retinopathy study high-risk characteristics, panretinal photocoagulation (Little, Rosenthal et. al., 1976; Pavan, Folk et. al., 1983; Wand, Dueker et. al., 1978), or cryotherapy (Vernon and Cheng, 1988; May, Bergstrom et. al., 1980; Brodell, Olk et. al., 1987) may cause rubeosis to regress. If raised intraocular pressure persists despite regression of neovascularisation, trabeculectomy with (Tsai, Feuer et. al., 1995) or without (Flanagan and Blach, 1983) antimetabolites, tube drainage surgery (Molteno, Van et. al., 1977), cycloablation with Nd:YAG (Klapper, Wandel et. al., 1988) or diode (Hawkins and Stewart, 1993) laser, or even iris ablation (Stirpe, Bucci et. al., 1994) may allow normalisation of intraocular pressure and preservation of

vision. In eyes with nonprogressive iris neovascularisation, which does not involve the anterior chamber drainage angle, and which is not associated with high-risk proliferative retinopathy, fluorescein angiography may be valuable to quantify capillary nonperfusion and plan review (Verdaguer, le Clercq et. al., 1987). In painful eyes with poor visual potential, cycloablation, anti-inflammatory medications, retrobulbar alcohol injection or enucleation may be justified (Brooks and Gillies, 1990).

2.2.4.4 Uveitis

2.2.4.4.1 Incidence

In a study of postoperative inflammation, the incidence of pigment dispersion was 13%, fibrin deposition 6%, and posterior synechia formation 14% in patients without diabetes, and at least twice as frequent in patients with diabetes (Krupsky, Zalish et. al., 1991). Fibrin deposition, which appears to be a particularly prominent in diabetic eyes, may promote the formation of posterior synechiae (Krupsky, Zalish et. al., 1991; Baltatzis, Georgopoulos et. al., 1993) either to the posterior lens capsule ("optic capture") or to the capsulorrhexis edge, with the risk of pseudophakic pupil block glaucoma (Weinreb, Wasserstrom et. al., 1986). Fundus visualisation may be compromised if fibrin membranes form over the pupil or posterior lens capsule, or if significant intraocular lens deposits accumulate as a result of severe postoperative inflammation or pigment dispersion (Krupsky, Zalish et. al., 1991). This may be important, since it appears that there is some correlation between the severity of diabetic retinopathy, and both the tendency to postoperative progression of retinopathy, and the severity of postoperative inflammation (Hykin, Gregson et. al., 1993; Cunliffe, Flanagan et. al., 1991). Thus as the likelihood of laser therapy being required increases, so also does the severity of postoperative inflammation tending to obstruct its application.

2.2.4.4.2 Pathogenesis

Inflammation after cataract surgery probably represents a combination of the response to anterior uveal injury and a foreign body reaction to the intraocular lens. In the patient without diabetes, the severity of anterior uveal injury and the reaction to it appear to relate significantly to incision size (Pande, Spalton et. al., 1996). The reaction to intraocular lens biomaterials is less defined. Whereas intraocular lenses can activate complement by the alternate pathway (Mondino, Nagata et. al., 1985), contact between intraocular lens biomaterials and lens epithelial cells may induce metaplasia and cytokine synthesis (Nishi, Nishi et. al., 1992b). Parameters such as hydrophilicity of intraocular lens biomaterials appear to correlate with postoperative flare intensity in animal models (Miyake, Ota et. al., 1996), and the nature of cellular deposition on intraocular lenses is also linked to biomaterial (Ravalico, Baccara et. al., 1997; Borgioli, Coster et. al., 1992).

In patients with diabetes, structural abnormalities of iris vasculature similar to those of retinal vasculature may be identified, including endothelial basement membrane thickening, endothelial cell proliferation, and acellular capillaries (Taniguchi, Nakao et. al., 1968). These changes are associated with an elevation in aqueous protein concentration (Moriarty, Spalton et. al., 1994) which appears to be related to the severity of diabetic retinopathy. If cataract surgery is performed, aqueous fluorophotometry studies indicate a breakdown of the blood-aqueous barrier more marked and more prolonged in diabetic than in non-diabetic eyes (Ferguson and Spalton, 1992). Similarly there appears to be some correlation between the severity of retinopathy and postoperative laser flare intensity (Zaczek and Zetterstrom, 1998). Retina-derived growth factors such as vasoactive endothelial growth factor increase vascular permeability as well as induce endothelial proliferation, and since the aqueous concentration of VEGF at the time of cataract surgery is related to the severity of retinopathy (Aiello, Avery et. al., 1994), such growth factors may act as mediators of the increased vascular permeability which characterises inflammation after cataract

surgery in patients with diabetes. Some effect on lens epithelial cytokine synthesis is also possible (Nishi, Nishi et. al., 1992b).

Glycogen accumulation in iris pigment epithelium may contribute to the tendency to anterior segment pigment dispersion (Krupsky, Zalish et. al., 1991). This may be exacerbated by iris trauma during nucleus expression or rigid intraocular lens implantation due to poor preoperative mydriasis (Huber, Smith et. al., 1985), and poorly maintained intra-operative mydriasis (Zaczek and Zetterstrom, 1997) as a result of diabetic pupillomotor autonomic neuropathy. Further pigment may be released as a consequence of pseudophakic iris chafing if the intraocular lens is implanted into the ciliary sulcus (Masket, 1986).

2.2.4.4.3 Management

Phakoemulsification may offer some theoretical advantages over extracapsular techniques in reducing inflammation after cataract surgery in diabetes. These include a smaller incision (Pande, Spalton et. al., 1996; Laurell, Zetterstrom et. al., 1997), less iris trauma, and in-the-bag fixation of the intraocular lens (Miyake, Asakura et. al., 1984). These issues are discussed further in section 2.2.3.

In patients without diabetes, heparin surface modification of PMMA lenses appears to be associated with a reduction in anterior segment inflammation (Umezawa and Shimizu, 1993), fibrin deposition (Laurell, Zetterstrom et. al., 1997), posterior synechia formation (Borgioli, Coster et. al., 1992), and intraocular lens deposits (Ygge, Wenzel et. al., 1990). These attributes have prompted suggestions that they be used in patients with diabetes (Lin, Wang et. al., 1994). Beneficial effects of surface modification of PMMA lenses may, however, not be specific to heparin, since the incidence of fibrinous postoperative uveitis may also be reduced by surface coating with hydroxy-propyl-methyl cellulose (Rose, 1992). The trend towards small incision surgery has, however, shifted interest away from surface modification of rigid PMMA

lenses to the biocompatibility of folding lens materials. One in vivo study in non-diabetic patients identified no postoperative epithelioid cell deposition on polyethylmethacrylate, hydrogel or polydimethyl diphen siloxane silicone lenses, whereas cellular deposits did occur on surface-passivated, surface-modified, and plain PMMA lenses (Ravalico, Baccara et. al., 1997). The authors concluded that lens materials which were markedly hydrophobic (silicone) or hydrophilic (hydrogel) tended to repel cellular deposition. By contrast studies examining the relationship between postoperative aqueous flare and the physical attributes of three foldable lens materials - acrylic, silicone and memory (PMMA/hydrogel) (Miyake, Ota et. al., 1996) - suggest that the severity of blood-aqueous barrier breakdown is related to the hydrophobicity of the lens. A similar relationship was observed between lens hydrophobicity and anterior capsule opacification, an indication of lens epithelial cell metaplasia. The disparity between indices of biocompatibility makes generalisation about optimal lens materials difficult.

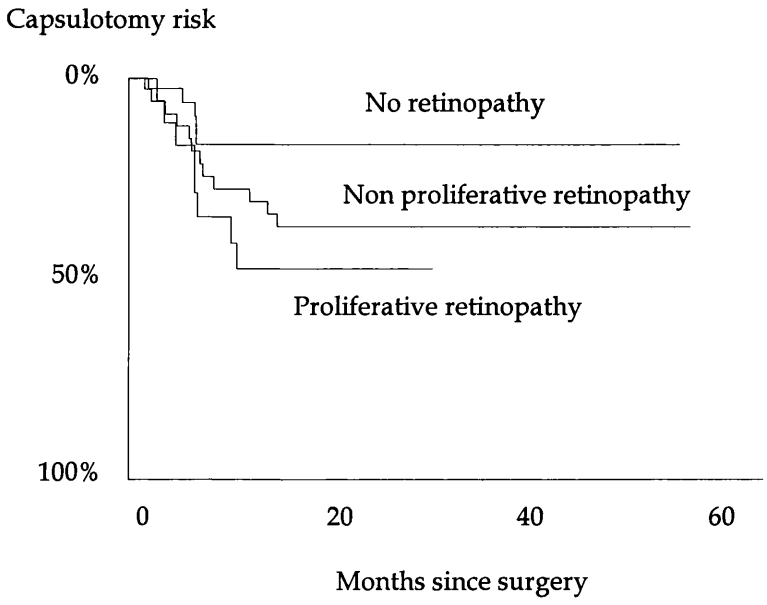
Topical (Krupsky, Zalish et. al., 1991) and repository steroid (Corbett, Hingorani et. al., 1995) appear effective in the management of postoperative uveitis in patients with diabetes. Fibrin membrane formation may be effectively treated in the acute phase with 25μg of intraocular tissue plasminogen activator (tPA) (Heiligenhaus, Schilling et. al., 1996). The incidence of complications of tPA therapy appears low (Moon, Chung et. al., 1992), and in particular, intraocular haemorrhage appears to occur less frequently than when tPA is used after diabetic vitrectomy (Dabbs, Aaberg et. al., 1990). Topical tPA therapy appears less effective. If fibrin membranes become established, Nd:YAG laser lysis (Lin, Jin et. al., 1995) may be required, or iridotomy if pseudophakic pupil block glaucoma develops (Weinreb, Wasserstrom et. al., 1986).

2.2.4.5 Capsular opacification

2.2.4.5.1 Incidence

There is conflicting evidence regarding the incidence of posterior capsule opacification (PCO) following diabetic cataract extraction. Two studies have suggested a lower incidence of PCO in patients with diabetes than in those without. A large scale retrospective study of extracapsular surgery identified an incidence of capsulotomy, taken as an index of PCO, of 22% in patients with diabetes, and 28% in those without (Knorz, Soltau et. al., 1991). No correction was made for age, or for length of follow up in different groups, which varied between 1 and 53 months. Some eyes were treated with surgical irrigation aspiration rather than Nd:YAG capsulotomy, which may have modified the threshold for intervention. The relationship of capsulotomy rate to retinopathy severity was not examined. A more recent prospective study examined the incidence of PCO, evaluated by computerised scoring of retroillumination images, after phakoemulsification surgery with implantation of a heparin surface modified PMMA lens (Zaczek and Zetterstrom, 1999). The patient population consisted of 26 normal patients and 26 with diabetes, of whom 13 had retinopathy. There was no difference in PCO scores between patients with diabetes and those without at one year, but at two years scores in diabetic patients were significantly lower. A third study retrospectively examined capsulotomy rates after extracapsular cataract extraction in 263 normal patients and 90 with diabetes, and using life table analysis to correct for inequality of follow up, identified a relationship between retinopathy severity and capsulotomy rate (Ionides, Dowler et. al., 1994) (Fig 2.1). The divergence in findings between different studies is perhaps unsurprising given the range of factors, discussed below, which appear to affect PCO.

Figure 2-1: Relationship between capsulotomy risk over time and retinopathy severity in patients with diabetes undergoing extracapsular cataract surgery



2.2.4.5.2 Pathogenesis

PCO appears to occur as a result of proliferation, metaplasia and migration of lens epithelial cells (LEC) derived from the lens equator and anterior lens capsule. A variety of influences appear to affect PCO; capsulorrhexis apertures smaller than the diameter of the intraocular lens optic (Ravalico, Tognetto et. al., 1996), effective clearance of lens cortex (Apple, Solomon et. al., 1992), placement of the intraocular lens inside the capsular bag (Martin, Sanders et. al., 1992), smaller lens size (Mamalis, Crandall et. al., 1995), posteriorly convex optic configuration (Pearlstein, Lane et. al., 1988), sharp edged optic (Nagata and Watanabe, 1996), plate haptic rather than three piece silicone lens design (Cumming, 1993) and acrylic rather than silicone or PMMA optic (Ursell, Spalton et. al., 1998) have all been stated to reduce its incidence.

Some authors link postoperative inflammation and PCO, hypothesizing that LEC-intraocular lens contact stimulates LEC fibrous metaplasia and disruption of the blood-aqueous barrier (Nishi and Nishi, 1992a), resulting in capsular fibrosis and intensified inflammation. This is supported by in vitro studies demonstrating cytokine release from LECs (Nishi, Nishi et. al., 1992b), and the observation that LEC proliferation and migration appear more marked in high protein environments (Wormstone, Liu et. al., 1997). However, in animal studies, whereas indomethacin coated intraocular lenses were associated with less PCO (Nishi, Nishi et. al., 1995), intraocular sustained release indomethacin reduced postoperative inflammation without reducing PCO (Nishi, Nishi et. al., 1996). In addition, clinical studies in patients with uveitis have demonstrated no increase in the incidence of PCO other than felt to be explainable on the basis of age (Dana, Chatzistefanou et. al., 1997). The link between PCO and postoperative inflammation appears unproven.

A higher incidence of PCO in the eyes of patients with diabetes might be anticipated on a number of grounds. Soluble retina-derived growth factors cleared through the anterior segment might encourage LEC proliferation. This would account for the relationship between capsulotomy risk and retinopathy severity observed in one study (Ionides, Dowler et. al., 1994), and perhaps also the tendency to massive LEC proliferation at the margins of posterior capsulotomy apertures in eyes which have undergone vitrectomy for advanced diabetic retinopathy (Jones, McLeod et. al., 1995). In addition, breakdown of the blood-aqueous barrier present before surgery, and enhanced by it, provide a relatively protein rich environment which encourages lens epithelial cell proliferation (Wormstone, Liu et. al., 1997). Finally, poor mydriasis as a result of diabetes (Zaczek and Zetterstrom, 1997) may impair operative clearance of lens cortex, leaving a larger population of viable LECs at the end of the procedure.

A lower incidence of PCO in the eyes of patients with diabetes is more difficult to explain, but one possibility is that exposure to high glucose concentrations

may result in accumulation of sorbitol within the lens (Kinoshita, 1974). LECs, at the interface between lens and aqueous, may be particularly vulnerable to the consequent osmotic stress (Jedziniak, Chylack et. al., 1981), and free radical damage may also occur (Hothersall, Taylaur et. al., 1988). This may account for reports that LEC density is lower in patients with diabetes (Saitoh, Nishi et. al., 1990), which might result in a reduced tendency to postoperative proliferation, metaplasia and migration.

2.2.4.5.3 Management

Management of PCO in developed countries centres around Nd:YAG laser capsulotomy. Surgical intervention is only adopted when Nd:YAG lasers are not available, as may be the case in the developing world, when membranes are very dense (Weidle, Lisch et. al., 1986) or when pearl formation represents the prominent source of opacification (Baller, 1977).

However, given that the incidence of capsular opacification in all patients approaches 30% at three years, interest has focussed on means of prevention as much as treatment. Surgical measures include atraumatic approach (Apple, Solomon et. al., 1992), capsulorrhexis diameter such as to overlie the lens optic (Ravalico, Tognetto et. al., 1996), meticulous clearance of lens cortex (Apple, Solomon et. al., 1992), and in-the-bag fixation of the intraocular lens (Martin, Sanders et. al., 1992). Suggested features of the intraocular lens have included smaller size (Mamalis, Crandall et. al., 1995), posteriorly convex optic configuration (Pearlstein, Lane et. al., 1988), sharp edged optic (Nagata and Watanabe, 1996) and particular lens materials (Ursell, Spalton et. al., 1998). In addition, the use of specific agents in retarding capsular opacification has been examined largely in the context of in vivo rabbit models. These include antimitotic agents such as methtrexate (Hansen, Tyndall et. al., 1987), daunomycin (Hartmann, Wiedemann et. al., 1990), 5 fluorouracil and mitomycin C (Ismail, Alio et. al., 1996), inhibitors of cell migration such as integrin blockers (Nishi, Nishi et. al., 1997) and colchicine (Legler, Apple et. al., 1993), and a

miscellany of other agents including thapsigargin, a mitochondrial ATP-ase inhibitor (Duncan, Wormstone et. al., 1997), heparin (Mastropasqua, Lobefalo et. al., 1997), and indomethacin (Nishi, Nishi et. al., 1996). Although providing insights into the mechanisms of PCO, none of these approaches has yet reached widespread clinical applicability.

2.2.5 Postoperative visual acuity

Although typically some 90% of all patients undergoing cataract extraction achieve 6/12 visual acuity in the operated eye after surgery (Sarkies N, Everson J et. al., 1995), there are numerous reports suggesting postoperative visual acuity may be poorer in patients with diabetes, and may be influenced by the severity of diabetic retinopathy and maculopathy at the time of surgery (Benson, Brown et. al., 1993; Cheng and Franklin, 1988; Cunliffe, Flanagan et. al., 1991; Fung, 1987; Hykin, Gregson et. al., 1993; Jaffe, Burton et. al., 1992; Levin, Kincaid et. al., 1988; Pollack, Dotan et. al., 1991a; Pollack, Dotan et. al., 1991b; Pollack, Leiba et. al., 1992a; Pollack, Leiba et. al., 1992b; Ruiz and Saatci, 1991; Kennedy, Lim et. al., 1984). However, because most studies examined small populations of patients with a preponderance of particular categories of retinopathy, the precise effect of preoperative severity of retinopathy and maculopathy on postoperative visual acuity is unclear. A meta-analysis was therefore undertaken to examine this issue (Dowler, Hykin et. al., 1995b). Studies of extracapsular cataract extraction in patients with diabetes were included if the severity of retinopathy and status of the macula prior to surgery, and the proportions of patients in each subgroup achieving a postoperative visual acuity $\geq$ 6/12 were explicitly stated. Ten studies (Cunliffe, Flanagan et. al., 1991; Benson, Brown et. al., 1993; Hykin, Gregson et. al., 1993; Pollack, Dotan et. al., 1991b; Pollack, Leiba et. al., 1992b; Sebestyen, 1986; Menchini, Bandello et. al., 1993; Kennedy, Lim et. al., 1984; Straatsma, Pettit et. al., 1983; Cheng and Franklin, 1988) satisfied these criteria, giving an aggregate sample size of 546. The weighted mean percentage of eyes in all retinopathy subgroups achieving a

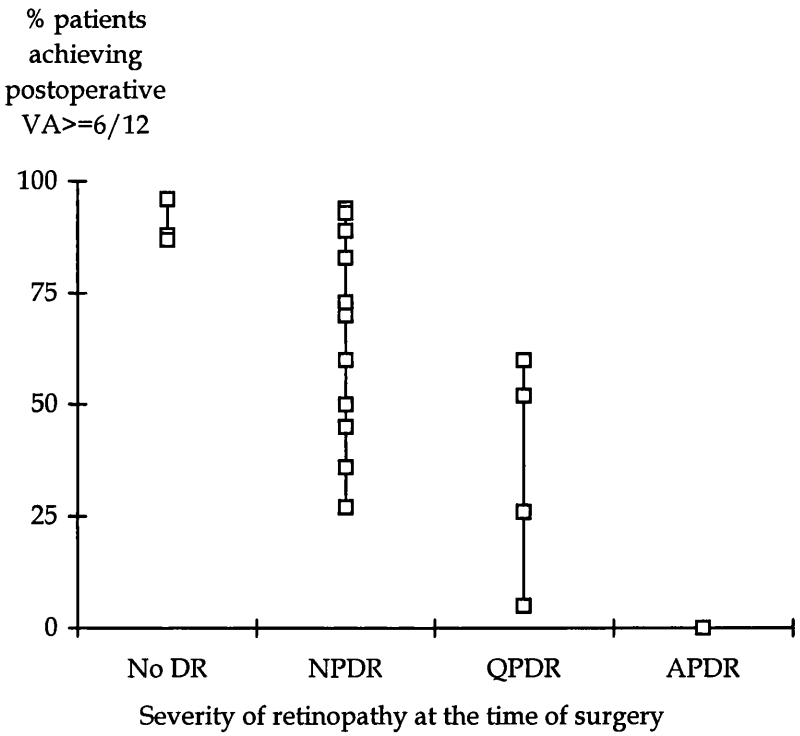
postoperative visual acuity ≥ 6/12 was 46%. The weighted mean percentage of eyes achieving a postoperative vision ≥ 6/12 was also calculated for each retinopathy subgroup (Table 2.4).

Table 2.4 Meta - analysis of visual acuity following extracapsular cataract extraction in patients with diabetes: Weighted mean percentages of patients in each subgroup of preoperative diabetic retinopathy and maculopathy severity achieving visual acuity ≥6/12 after cataract surgery

Retinopathy severity	Maculopathy	% VA ≥6/12
None		87%
Non proliferative	-	80%
Quiescent proliferative	-	57%
Non proliferative	+	41%
Quiescent proliferative	+	11%
Active proliferative		0%

A natural hierarchy of visual outcome across retinopathy groups was apparent, such that the more severe the preoperative retinopathy, the lower the proportion of eyes achieving a postoperative visual acuity ≥ 6/12. (Fig 2.2). There was a significant difference between groups, ($p<0.0005$) mostly attributable to a trend across groups ($p<0.0005$).

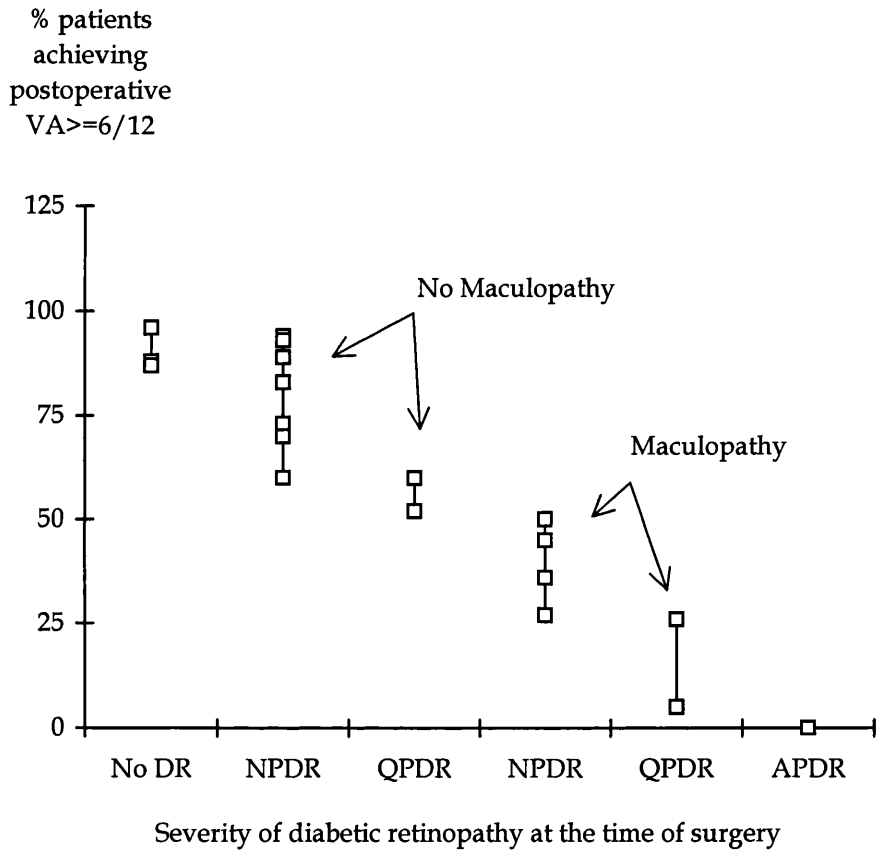
Figure 2-2: Meta - analysis of visual acuity following extracapsular cataract extraction in patients with diabetes: relationship between preoperative severity of retinopathy and proportion of patients achieving a postoperative visual acuity >=6/12.



No DR = No diabetic retinopathy. NPDR = non proliferative diabetic retinopathy. QPDR = quiescent proliferative retinopathy. APDR = active proliferative retinopathy.

If the nonproliferative and quiescent proliferative retinopathy groups were further subdivided according to the presence or absence of maculopathy, the hierarchy was preserved, a lower proportion of eyes with maculopathy achieving a postoperative visual acuity ≥ 6/12 compared to eyes without maculopathy (Fig 2.3). The difference between groups was significant, ($p<0.0005$) mostly attributable to a trend across the groups ($p<0.0005$).

Figure 2-3: Meta - analysis of visual acuity following extracapsular cataract extraction in patients with diabetes: effect of maculopathy on relationship between preoperative severity of retinopathy and proportion of patients achieving a postoperative visual acuity >=6/12.



No DR = No diabetic retinopathy. NPDR = non proliferative diabetic retinopathy. QPDR = quiescent proliferative retinopathy. APDR = active proliferative retinopathy.

Logistic regression indicated that maculopathy was a more potent predictor of visual acuity ≤ 6/12 (odds ratio 6.4, $p<0.0005$) than retinopathy severity (odds ratio 3.33, $p<0.0005$). The presence of active proliferative retinopathy was invariably associated with a postoperative visual acuity ≤ 6/12.

Some caution is appropriate in interpreting these results. Definitions of retinopathy and maculopathy may have varied between studies, and there are difficulties in grading retinopathy in eyes with cataract. Some variation in surgical technique between centres is inevitable, and indications for laser therapy may also have been non-uniform, since some studies began recruitment prior to publication of the findings of the ETDRS (Early Treatment Diabetic Retinopathy Study Research Group, 1987). Some discrepancy may have occurred within and between studies in the interval between surgery and visual acuity measurement. Most studies were retrospective, and some acknowledged the presence of intercurrent ocular pathology in a proportion of eyes studied. Finally, as with all meta-analysis, there is the potential for bias due to the inclusion only of data from published studies (publication bias).

This meta-analysis was published in 1995, and several studies have since been published which have examined the visual outcome of cataract surgery in patients with diabetes (Kodama, Hayasaka et. al., 1993; Wagner, Knaflic et. al., 1996; Henricsson, Heijl et. al., 1996; Antcliff, Poulson et. al., 1996; Raskauskas PA, Walker JP et. al., 1999). It might be anticipated that wider acceptance of the indications for laser therapy (Aaberg, 1979; Diabetic Retinopathy Study Research Group., 1981; Early Treatment Diabetic Retinopathy Study Research Group, 1985), appreciation of the importance of glycaemic control in retinopathy progression (Diabetes Control and Complications Trial Research Group, 1993), and the shift to small incision surgery might result in an improvement in postoperative visual acuity. However, results have been mixed. Whereas Henriccson reports postoperative visual acuity $\geq 6/12$ in 89% of her patients, and Antcliff in 74%, Raskauskas reports only 51%, little better than the 46% calculated from meta-analysis (Henricsson, Heijl et. al., 1996; Antcliff, Poulson et. al., 1996; Raskauskas PA, Walker JP et. al., 1999; Dowler, Hykin et. al., 1995b).

2.3 UNRESOLVED ISSUES

Diabetes is one of the most-studied diseases in medicine. Paradoxically, however, cataract extraction in patients with diabetes is a relatively poorly examined area.

Although the influences of glycaemic and hypertensive control on retinopathy progression are well documented (Diabetes Control and Complications Trial Research Group, 1993; UK Prospective Diabetes Study Group, 1998a; UK Prospective Diabetes Study Group, 1998b), their effects on the outcome of cataract surgery are unknown. The optimal timing of surgery is uncertain, opinion being polarised between the extremes of conservatism and early intervention. The most appropriate surgical technique is not known. Encouraging early reports of phakoemulsification surgery in patients with diabetes (Fung, 1987; Antcliff, Poulson et. al., 1996; Henricsson, Heijl et. al., 1996; Wagner, Knaflic et. al., 1996) have been tempered by recent less sanguine accounts (Raskauskas PA, Walker JP et. al., 1999), and no randomised controlled comparison with extracapsular surgery has been published. The related issue of the preferred intraocular lens for use in eyes of patients with diabetes is undecided, the use of large optic diameter rigid lenses as advocated by some (McCuen BW II and Klombers, 1990) substantially neutralising any benefits accruing from small incision surgery, whereas the ideal foldable intraocular lens design and material continues to be the focus of intense research activity and debate.

The optimal management of macular oedema occurring after cataract surgery in patients with diabetes is undefined, and indeed there are no natural history data on which to base management, other than in eyes with no retinopathy, in which laser therapy is unlikely to be considered (Menchini, Bandello et. al., 1993). It has been stated that the presence of postoperative hyperfluorescence of the optic

disc is an indicator of likely spontaneous resolution of postoperative macular oedema (Royal College of Ophthalmologists, 1997), but this awaits confirmation. Accelerated postoperative progression of diabetic retinopathy, as manifested by greater severity of retinopathy in operated than unoperated fellow eyes, has been found by some (Jaffe, Burton et. al., 1992) but not all (Schatz, Atienza et. al., 1994; Wagner, Knaflic et. al., 1996) investigators, and cannot be said to be proven beyond doubt. The factors predisposing to severe postoperative uveitis have not been fully elucidated, and the relationship between postoperative inflammation and posterior capsule opacification is undetermined. The effect of diabetes on posterior capsule opacification is unclear, some studies suggesting a reduced incidence (Knorz, Soltau et. al., 1991; Zaczek and Zetterstrom, 1999), others an increased incidence related to the severity of retinopathy (Ionides, Dowler et. al., 1994). The mechanisms of postoperative complications such as macular oedema, retinopathy progression, severe uveitis and capsular opacification are undetermined. Finally, the factors which influence visual acuity after cataract surgery in patients with diabetes remain incompletely understood.

2.4 AIMS

1. To compare extracapsular cataract surgery with phakoemulsification in patients with diabetes in regard to postoperative inflammation, capsular opacification, macular oedema, progression of retinopathy, and visual acuity.

2. To examine the ocular factors affecting postoperative visual acuity for each surgical technique.

3. To make recommendations regarding the optimal surgical technique for cataract extraction in patients with diabetes.

4. To determine the practicality of intra-operative fluorescein angiography as a means of determining the state of the macula at the time of cataract surgery.

5. To estimate the postoperative interval, if any, during which macular angiographic appearances remain unaltered, in order to determine how soon after surgery baseline assessment must be made to exclude postoperative change.

6. To define the natural history of macular oedema after cataract surgery in patients with diabetes in angiographic and clinical terms.

7. To identify clinical and angiographic predictors of likely spontaneous resolution of macular oedema, and in particular the predictive value of postoperative optic disc hyperfluorescence.

8. To formulate a strategy for the management of postoperative macular oedema based on natural history data.

3 PATIENTS AND METHODS

3.1 PHAKOEMULSIFICATION VS. EXTRACAPSULAR SURGERY

3.1.1 Patients

3.1.1.1 Inclusion criteria

Existing or new patients attending diabetic retinopathy clinics at Moorfields Eye Hospital who met the following criteria were invited to participate in the trial:

1. Patients with diabetes mellitus diagnosed according to the 1985 WHO standard, operative at the start of the study, of a fasting venous blood glucose ≥ 7.8 mmol, or ≥ 11.1 mmol 2 hours after a 75g oral glucose load (World Health Organisation, 1985). All patients would meet more recent criteria for the diagnosis of diabetes according to the World Health Organisation (Alberti, Zimmet et. al., 1998) and American Diabetic Association (Expert committee on the diagnosis and classification of diabetes mellitus, 1997). Patients with insulin-dependent or non-insulin dependent diabetes were considered eligible.

2. Patients with bilateral cataract sufficient in each eye to either cause visual symptoms such as reduced visual acuity, glare, material index myopia, or monocular polyopia, or sufficient to impair fundus visualisation, in particular appreciation of the presence or absence of retinal thickening at the macula.

3.1.1.2 Exclusion criteria

Patients were excluded from the study if suffering from the following:

1. Clinically significant macular edema (CSME) as defined by the Early Treatment Diabetic Retinopathy Study (ETDRS) (Early Treatment Diabetic Retinopathy Study Research Group, 1985). Patients in whom CSME had regressed following appropriate laser treatment were considered eligible.

2. High-risk proliferative retinopathy as defined by the Diabetic Retinopathy Study (DRS) (Diabetic Retinopathy Study Research Group., 1981). Patients in whom high-risk proliferative retinopathy had regressed following appropriate laser treatment were considered eligible.

3. Diabetes associated with specific genetic syndromes (type A insulin resistance); induced by drugs, chemicals, or endocrinopathies; or secondary to pancreatic tumour or pancreatectomy.

4. Coexistent ocular disease likely to modify visual acuity, for example age-related macular degeneration, amblyopia, retinal venous occlusion.

5. Coexistent disease likely to significantly affect retinopathy progression, for example severe carotid occlusive disease, high myopia, glaucoma. Patients with renal dysfunction were however, included in the study, as dictated by the need to recruit sufficient patients with more severe retinopathy, in whom some renal impairment was common.

6. Prior intraocular surgery to either eye.

3.1.1.3 Withdrawal criteria

Patients who met any of the following criteria were withdrawn from the study once entered:

1. Surgery to both eyes not performed within the space of one year.

2. Less than one year's follow up available for either eye.

3. Immediate postoperative retinal assessment was not performed.

4. Operative complication occurred which might modify visual acuity or influence the retina or its assessment, for example vitreous loss, corneal decompensation, or endophthalmitis.

5. Postoperative development of disease likely to modify visual acuity or influence the retina or its assessment, for example infective keratitis.

6. Postoperative development of macular traction retinal detachment, or other indication for vitrectomy.

7. Patients elected to withdraw from randomization schedule and undergo the same surgical technique to both eyes.

3.1.2 Intervention

3.1.2.1 Randomization

Surgery was undertaken first to left or right eye according to patient preference. The nature of the surgical procedure undergone by this eye was determined by using a pseudorandom number generator in statistical software (Stata, Stata Corporation, Texas 77840, USA) to generate a number between 1 and 2 on a laptop computer. If the first digit after the decimal point was even, the first operated eye underwent phakoemulsification, if odd, extracapsular surgery.

3.1.2.2 Preoperative regimen

Mydriasis was achieved in eyes due surgery by administration of G. Phenylephrine 5% and G. Cyclopentolate 1% six times in the 90 minutes prior to operation. No preoperative or intra-operative systemic or topical anti-inflammatory agents were used.

3.1.2.3 Anaesthetic technique

All patients fasted for six hours prior to surgery. Anaesthesia in all procedures consisted of two peribulbar injections through a 15/16" 25 gauge needle of a 50:50 mix of bupivacaine 0.5% and lignocaine 2% without adrenaline with 300 units of hyaluronidase, one of 5mls administered through the inferior conjunctival fornix, and one of 2mls along the medial aspect of the globe.

3.1.2.4 Surgical technique

3.1.2.4.1 Extracapsular surgery

Extracapsular cataract extraction was carried out through a corneal incision, using a can-opener capsulotomy, nucleus expression, manual aspiration of cortex using balanced salt solution containing 1ml of 1:1000 adrenaline per

500ml, implantation of a one piece, no dialling hole, biconvex, 7-mm polymethylmethacrylate intraocular lens (Iolab 6840U), and wound closure with five interrupted 10/0 nylon sutures.

3.1.2.4.2 Phakoemulsification

Phakoemulsification surgery was carried out through a 3.2-mm self sealing scleral pocket incision, using continuous curvilinear capsulorrhexis, hydrodissection, phakoemulsification, manual aspiration of cortex using balanced salt solution containing 1ml of 1:1000 adrenaline per 500ml, and implantation of a foldable intraocular lens with a 6-mm silicone optic and polypropylene haptics (Iolab L141U).

3.1.2.5 Postoperative regimen

At the conclusion of each procedure, a subconjunctival injection of betamethasone 4mg and cefuroxime 125mg was administered. No non-steroidal anti-inflammatory agent was employed. After surgery, patients were treated with G. Dexamethasone 0.1% four times daily for two weeks then twice daily for two weeks.

3.1.2.6 Management of postoperative complications

3.1.2.6.1 Postoperative uveitis

If ≥ 3+ of cells or flare (see below for definitions) were present at any postoperative visit, clinically significant postoperative inflammation was deemed present, and intensive topical medication and additional review instituted. If ≥ 2+ of cells and flare occurred after the first postoperative month, late postoperative inflammation was deemed to be present and appropriate topical medication and additional review instituted.

3.1.2.6.2 Capsular opacification

At any postoperative visit after 6 weeks, if capsular opacity was present which was sufficient to cause visual symptoms such as glare or visual loss, or compromise retinal visualisation, Nd:YAG capsulotomy was undertaken to permit continued surveillance of retinopathy and to optimize visual acuity. G. Dexamethasone 0.1% four times daily was then applied to the eye for one week, and additional clinical review arranged.

3.1.2.6.3 Macular oedema

No macular laser treatment was undertaken within six months of surgery in eyes in which CSME was identified after surgery, but if CSME was present six or more months after surgery, macular laser treatment was applied in accordance with the recommendations of the ETDRS (Early Treatment Diabetic Retinopathy Study Research Group, 1987).

3.1.2.6.4 Proliferative retinopathy

If high-risk proliferative retinopathy were identified at any point after surgery, panretinal photocoagulation was performed in accordance with the recommendations of the DRS (Diabetic Retinopathy Study Research Group., 1981).

3.1.2.6.5 Iris neovascularisation

In eyes in which iris neovascularisation involved the drainage angle, showed evidence of progression, or was associated with diabetic retinopathy study high-risk characteristics, panretinal photocoagulation was applied. If raised intraocular pressure persisted following regression of the rubeosis, the patient was withdrawn from the study and referred for management of glaucoma.

3.1.3 Outcome parameters

3.1.3.1 Visual acuity

Best-corrected visual acuity was recorded using a back lit ETDRS logMAR acuity chart at a distance of six metres (Ferris, Podgor et. al., 1987). Autorefraction was performed, and logMAR acuity recorded with this correction. A subjective refraction was then performed and logMAR acuity recorded with this correction. The better of the two acuities was taken as the best-corrected visual acuity.

3.1.3.2 Retinopathy progression

Retinopathy was recorded clinically using a clinical modification (Aiello LM, 1994) of the ETDRS final retinopathy severity scale (Early Treatment Diabetic Retinopathy Study Research Group., 1991).

Table 3-1: Scale for clinical grading of retinopathy severity

Level	Definition
No DR	No retinopathy
Mild NPDR	At least one microaneurysm
Moderate NPDR	H/Ma > ETDRS standard photograph 2A or cotton wool spot/VB/IRMA definitely present
Severe NPDR	H/Ma > ETDRS standard photograph 2A in 4 quadrants or VB in 2 or more quadrants or IRMA > ETDRS standard photograph 8A in 1 quadrant
Very Severe NPDR	Any two or more of severe NPDR
PDR without HRC	New vessels
PDR with HRC	NVD > one half to one third disc area or NVD & vitreous or pre-retinal haemorrhage or NVE ≥ one half disc area & vitreous or pre-retinal haemorrhage

DR: diabetic retinopathy, NPDR: nonproliferative diabetic retinopathy, PDR: proliferative diabetic retinopathy, HRC: high-risk characteristics, ETDRS: Early Treatment Diabetic Retinopathy Study, H/Ma: hemorrhages/microaneurysms, VB: venous beading, IRMA: intra-retinal microvascular abnormalities, NVD: new vessels disc, NVE: new vessels elsewhere.

3.1.3.3 Iris neovascularisation

Iris neovascularisation was graded clinically according to the classification of Tauber (Tauber, Lahav et. al., 1987). The location of most severe involvement (in descending order D>C>B>A) was characterised first, then the quadrantic extent, and then perfusion.

Table 3-2: Scale for clinical grading of iris neovascularisation

Grade	Location	Quadrants	Perfusion
A 1-4	Pupil margin	1 - 4	+ / -
B 1-4	Iris stroma	1 - 4	+ / -
C 1-4	Drainage angle	1 - 4	+ / -
D 1-4	Synechial closure	1 - 4	+ / -

3.1.3.4 Macular oedema

Clinically significant macular edema (CSME) as defined by the Early Treatment diabetic Retinopathy Study (Early Treatment Diabetic Retinopathy Study Research Group, 1987) was graded as follows:

Table 3-3: Scale for clinical grading of macular oedema:

Grade	Description
0.	No clinically significant macular oedema; criteria not met for 1,2,3.
1.	A zone of retinal thickening 1 disc area or larger in size within 1 disc diameter of the centre of the macula but not within 500μ of it.
2.	Thickening of the retina located ≤ 500μ from the centre of the macula but not involving it, or hard exudates with thickening of adjacent retina located ≤ 500μ from the centre of the macula but not involving it
3	Thickening of the retina involving the centre of the macula or hard exudates with thickening of adjacent retina involving the centre of the macula.

3.1.3.5 Postoperative inflammation

Anterior chamber cells and flare were graded clinically as follows, based on standard clinical measures (Hogan, Kimura et. al., 1959):

Table 3-4: Scale for grading anterior chamber cells

Grade	Cells
0	no cells
+	5-10 cells per field
2+	10-20 cells per field
3+	20-50 cells per field
4+	>50 cells per field
5+	hypopyon

Table 3-5: Scale for grading anterior chamber flare

Grade	Flare
0	no flare
+	faint flare
2+	moderate flare; iris details clear
3+	marked flare; iris details hazy
4+	fibrin present

Similar schemes were used to grade posterior synechiae and intraocular lens deposits:

Table 3-6: Scale for grading posterior synechiae

Grade	Posterior synechiae
0	none
+	one quadrant
2+	two quadrants
3+	three quadrants
4+	four quadrants

Table 3-7: Scale for grading intraocular lens deposits

Grade	Intraocular lens (IOL) deposits
0	no deposits
+	1-10 deposits on IOL
2+	11-50 deposits on IOL
3+	11-50 deposits on IOL
4+	IOL covered by deposits

3.1.3.6 Capsular opacification

Posterior capsule opacification was graded as follows:

Table 3-8: Scale for grading posterior capsule opacification

Grade	Posterior Capsule Opacification (PCO)
0	no PCO
+	PCO off visual axis only
2+	central PCO, no symptoms, retinal visualisation unimpaired
3+	capsulotomy indicated: symptoms, or retinal visualisation impaired
4+	Nd:YAG capsulotomy performed

3.1.4 Review schedule

Eyes were examined before surgery, immediately afterwards and up to 48 hours after surgery until it was possible to assess presence or absence of CSME, and retinopathy severity. These findings were taken to represent retinal status at the time of surgery. Further examinations were carried out at one week, six weeks, three, nine and twelve months after surgery, and at least six monthly thereafter. At each visit CSME, retinopathy severity, iris neovascularisation, anterior chamber cells and flare, intraocular lens deposits, posterior synechiae, and severity of capsular opacification were assessed. Best-corrected logMAR visual acuity was recorded before surgery, and six and twelve months after surgery.

3.2 INTRA-OPERATIVE FLUORESCEIN ANGIOGRAPHY STUDIES

3.2.1 Description of Studies

3.2.1.1 Pilot Study

A small pilot study on patients without diabetes was performed to assess the practicality of intra-operative fluorescein angiography.

3.2.1.2 Early Postoperative study

A study was performed in patients with diabetes to compare fluorescein angiograms performed at various points in the early postoperative period with the intra-operative angiogram, with the object of determining the postoperative interval, if any, during which the angiographic status of the macula approximates to its status at the time of surgery.

3.2.1.3 Natural History study

A study was performed in which the natural history of macular oedema after cataract surgery in diabetes was traced angiographically with reference to the intra-operative angiogram, and clinically with reference to the condition of the macula evaluated within 48 hours of surgery.

3.2.2 Patients

3.2.2.1 Inclusion criteria

3.2.2.1.1 Pilot study

Patients with cataract sufficient to either cause visual symptoms such as reduced visual acuity, glare, material index myopia, or monocular polyopia.

3.2.2.1.2 Early Postoperative Study & Natural History Study

1. Patients with diabetes mellitus as defined above (World Health Organisation, 1985).

2. Patients with cataract sufficient to either cause visual symptoms such as reduced visual acuity, glare, material index myopia, or monocular polyopia, or sufficient to impair fundus visualisation, in particular appreciation of the presence or absence of retinal thickening at the macula.

3.2.2.2 Exclusion criteria

Patients were excluded from the study if suffering from the following:

1. A history of adverse reaction to fluorescein angiography, or other serious adverse drug reaction.

2. Systemic conditions which would render fluorescein angiography potentially unsafe, eg uncontrolled hypertension.

3. Clinically significant macular edema (CSME) as defined by the Early Treatment Diabetic Retinopathy Study (ETDRS) (Early Treatment Diabetic Retinopathy Study Research Group, 1985) in the eye scheduled for surgery. Patients in whom CSME had regressed following appropriate laser treatment were considered eligible.

4. High-risk proliferative retinopathy as defined by the Diabetic Retinopathy Study (DRS) (Diabetic Retinopathy Study Research Group., 1981) in the eye scheduled for surgery. Patients in whom high-risk proliferative retinopathy had regressed following appropriate laser treatment were considered eligible.

5. Diabetes associated with specific genetic syndromes (type A insulin resistance); induced by drugs, chemicals, or endocrinopathies; or secondary to pancreatic tumour or pancreatectomy.

6. Coexistent ocular disease likely to modify visual acuity, for example age-related macular degeneration, amblyopia, retinal venous occlusion in the eye scheduled for surgery.

7. Coexistent disease likely to significantly affect retinopathy progression, for example severe carotid occlusive disease, high myopia, glaucoma. Patients with renal dysfunction were however, included in the study, as dictated by the need to recruit sufficient patients with more severe retinopathy, in whom some renal impairment was common.

8. Prior intraocular surgery to the eye to be operated upon.

3.2.2.3 Withdrawal criteria

Patients who met any of the following criteria were withdrawn from the study once entered.

1. Adverse reaction to fluorescein angiography.

2. Intra-operative angiogram of insufficient quality to grade.

3. Patients declined further fluorescein angiography after the intra-operative angiogram.

4. Immediate postoperative retinal assessment not performed.

5. Operative complication occurred which might modify visual acuity or influence the retina or its assessment, for example vitreous loss, corneal decompensation, endophthalmitis.

6. Postoperative development of disease likely to modify visual acuity or influence the retina or its assessment, for example infective keratitis.

7. Postoperative development of macular traction retinal detachment or other indication for vitrectomy.

8. Less than one year's follow up available, or defaulting on two or more review appointments.

3.2.3 Intervention

3.2.3.1 Preoperative management

Preoperative mydriasis was achieved by administration of G. Phenylephrine 5% and G. Cyclopentolate 1% six times in the 90 minutes prior to operation. No preoperative or intra-operative systemic or topical anti-inflammatory agents were used.

3.2.3.2 Anaesthetic technique

All patients fasted for six hours prior to surgery. In all cases an intravenous cannula was placed prior to anaesthesia. Anaesthesia in all but two procedures consisted of two peribulbar injections through a 15/16" 25 gauge needle of a 50:50 mix of bupivacaine 0.5% and lignocaine 2% without adrenaline with 300 units of hyaluronidase, one of 5mls administered through the inferior conjunctival fornix, and one of 2mls along the medial aspect of the globe. A compression bag was not employed, in order to minimize the stress to ocular

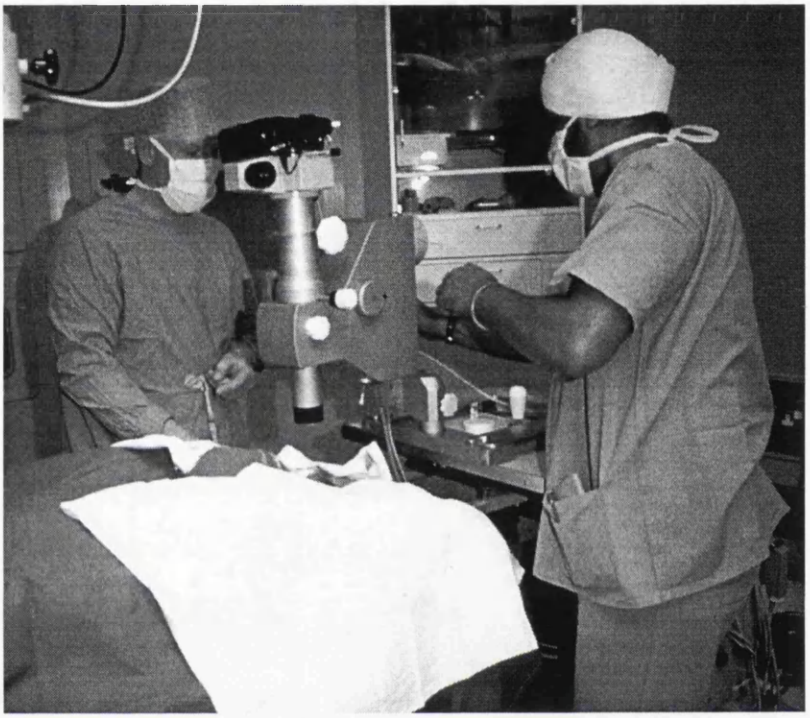
haemodynamics prior to surgery. In two procedures topical anaesthesia of 3 drops of amethocaine 1% only was employed.

During the procedure continuous cardiovascular and respiratory monitoring was undertaken by an anaesthetist or operating department technician. In addition pharyngeal suction apparatus was activated by an operating department technician immediately before injection of fluorescein so that in the event of retching, the airway could be cleared with the patient in the supine position.

3.2.3.3 Surgical technique

All patients underwent phakoemulsification surgery through a sutureless 3.2mm scleral tunnel. Miosis necessitated the use of iris retractors in 2 patients. Continuous curvilinear capsulorrhexis, hydrodissection with balanced salt solution, preceded nuclear phakoemulsification using balanced salt solution containing 1ml of 1:1000 adrenaline per 500mls. Cortical lens matter was aspirated and a foldable silicone intraocular lens, with a 6mm silicone optic and polypropylene haptics (Iolab L141U) was inserted. The anterior chamber was inflated with a viscous agent (2% hydroxy-propyl-methyl-cellulose). Topical chloramphenicol and a second layer of surgical drapes were applied. Following intravenous injection of 5mls of 20% sodium fluorescein, fundus fluorescein angiography was carried out using Zeiss fundus camera adapted with a vertical mount for use on supine patients (Fig 3.1). Forceps were used to move the eye in cases in which peribulbar anaesthesia had been used. Following angiography, the second layer of surgical drapes was removed, viscous agent was aspirated from the eye, and subconjunctival betamethasone 4mg and cefuroxime 125mg administered.

Figure 3-1: Vertically mounted fundus camera prepared for intra-operative fluorescein angiography



3.2.3.4 Postoperative regimen

After surgery, patients were treated with G Dexamethasone 0.1% four times daily for two weeks then twice daily for two weeks. No non-steroidal anti-inflammatory agent was employed.

3.2.3.5 Postoperative angiography

Postoperative fluorescein angiography was performed using standard techniques (Novotny HR and Alvis DL, 1961) and a horizontally mounted fundus camera of similar specification to that employed for intra-operative fluorescein angiography.

3.2.3.6 Management of postoperative complications

3.2.3.6.1 Postoperative uveitis

Postoperative uveitis was managed as in section 3.1.2.6.1

3.2.3.6.2 Capsular opacification

Capsular opacification was managed as in section 3.1.2.6.2

3.2.3.6.3 Macular oedema

In patients with diabetes no laser therapy for macular oedema was applied within one year of surgery. Eyes with clinically significant macular oedema at the time of surgery, and eyes developing macular oedema during the first postoperative year were observed without treatment. Eyes with macular oedema one year after surgery underwent macular laser according to the guidelines of the ETDRS (Early Treatment Diabetic Retinopathy Study Research Group, 1987).

3.2.3.6.4 Proliferative retinopathy

Proliferative retinopathy was managed as in section 3.1.2.6.4

3.2.3.6.5 Iris neovascularisation

Iris neovascularisation was managed as in section 3.1.2.6.5

3.2.4 Outcome parameters

3.2.4.1 Postoperative optic disc hyperfluorescence

Angiograms were graded by consensus of two ETDRS-accredited graders at a national retinopathy grading centre. They were masked to the identity of patients and the sequence of postoperative angiograms. The mid venous phase of the intra-operative angiogram of each patient was used as a reference with which to compare optic disc fluorescence in the mid venous phase of postoperative angiograms (Table 3.9). Graders also specified the postoperative angiogram showing the greatest optic disc hyperfluorescence relative to the intra-operative angiogram.

Table 3-9: Scale for grading postoperative fluorescence

Level	Description
-2	Fluorescence markedly less than intra-operative angiogram
-1	Fluorescence less than intra-operative angiogram
0	Fluorescence same as intra-operative angiogram
+1	Fluorescence more than intra-operative angiogram
+2	Fluorescence markedly more than intra-operative angiogram
9	Cannot grade

3.2.4.2 Postoperative macular hyperfluorescence

Macular hyperfluorescence was graded with reference to the intra-operative angiogram in the same way as optic disc fluorescence, and the postoperative angiogram showing the greatest macular hyperfluorescence relative to the intra-operative angiogram identified.

3.2.4.3 Angiographic definition

Graders also characterised the definition of angiograms according to the following scale:

Table 3-10: Scale for grading resolution of angiograms

Level	Description
0	No photograph
10	Photo off field by more than one disc diameter
20-40	Only major vessels visible
50-80	Major and minor vessels visible
90-110	Microaneurysms can be counted
120-160	Microaneurysms can be counted and FAZ assessed

3.2.4.4 Postoperative visual acuity

Visual acuity was assessed as in section 3.1.3.1.1

3.2.4.5 Macular oedema

Postoperative macular oedema was assessed clinically as described in section 3.1.3.1.4

3.2.4.6 Retinopathy progression

Retinopathy progression was assessed clinically as described in section 3.1.3.1.2

3.2.5 Review schedule

3.2.5.1 Pilot study

Patients were examined before surgery and at six weeks, three months, six months and twelve months after surgery. At each postoperative visit, the presence or absence of clinical macular oedema was assessed, and fluorescein angiography performed. Best-corrected logMAR visual acuity was recorded before surgery, and six and twelve months after surgery.

3.2.5.2 Early Postoperative Angiography Study

Patients underwent fluorescein angiography during surgery, and on one occasion in the first six weeks after surgery. Patients were examined before surgery, and both immediately after and up to 48 hours after surgery, until it was possible to grade CSME, and retinopathy severity.

3.2.5.3 Natural History study

Patients were examined before surgery, and both immediately after and up to 48 hours after surgery, until it was possible to grade CSME and retinopathy severity. These findings were taken to represent retinal status at the time of surgery. Further examinations were carried out at six weeks, three, nine and twelve months after surgery, and at least six monthly thereafter. At each visit CSME, retinopathy severity, iris neovacularisation, anterior chamber cells and flare, and severity of capsular opacification were assessed, and fluorescein angiography performed. Best-corrected logMAR visual acuity was recorded before surgery, and six and twelve months after surgery.

3.3 ETHICAL ISSUES

All studies were assessed and approved by the institutional ethics committee. Patients gave informed consent to participation in the studies, and the requirements of the Helsinki declaration were met. Patients declining involvement in studies, or withdrawing from them were advised that in no way would their decision affect the quality of their management.

3.4 STATISTICAL METHODS

Wilcoxon's signrank and ranksum tests were used to assess equality of distributions and medians, and Cuzick's non-parametric test to detect trend across ordered groups (Cuzick, 1985). Fisher's exact test was used to compare proportions in unmatched, and McNemar's chi-squared test, in matched data. A two-sided significance level of 5% (α=0.05) was adopted throughout. Bonferroni correction for multiple comparisons was not employed; rather, hypotheses formed in univariate analysis were subjected to multivariate analysis where possible. Independent variables were tested for collinearity. Sample size and power calculations were performed using techniques due to Fleiss (Fleiss JL, 1981). A default power value of 90% (β=0.9) was used in calculating sample size. All statistical analysis was performed on an IBM compatible personal computer using Stata statistical analysis software (Stata Corporation, 702 University Drive East, College Station, Texas 77840, USA). Statistical support was provided by Miss Bianca di Stavolo, Statistics Laboratory, Imperial Cancer Research Fund.

4 RESULTS

4.1 PHAKOEMULSIFICATION VS. EXTRACAPSULAR SURGERY

4.1.1 Patient characteristics

Recruitment was undertaken over an eighteen-month period, and follow up lasted for a median of 2 years. Forty six patients met inclusion criteria and were retained in the study. All patients were diagnosed as diabetic after the age of thirty years, and approximately one third required insulin (Table 4.1). Retinopathy severity ranged from no retinopathy to non high-risk proliferative retinopathy (Fig. 4.1). Glycaemic control was generally good with some exceptions. Anti-hypertensive medication was taken by 20/46 (43%) of patients.

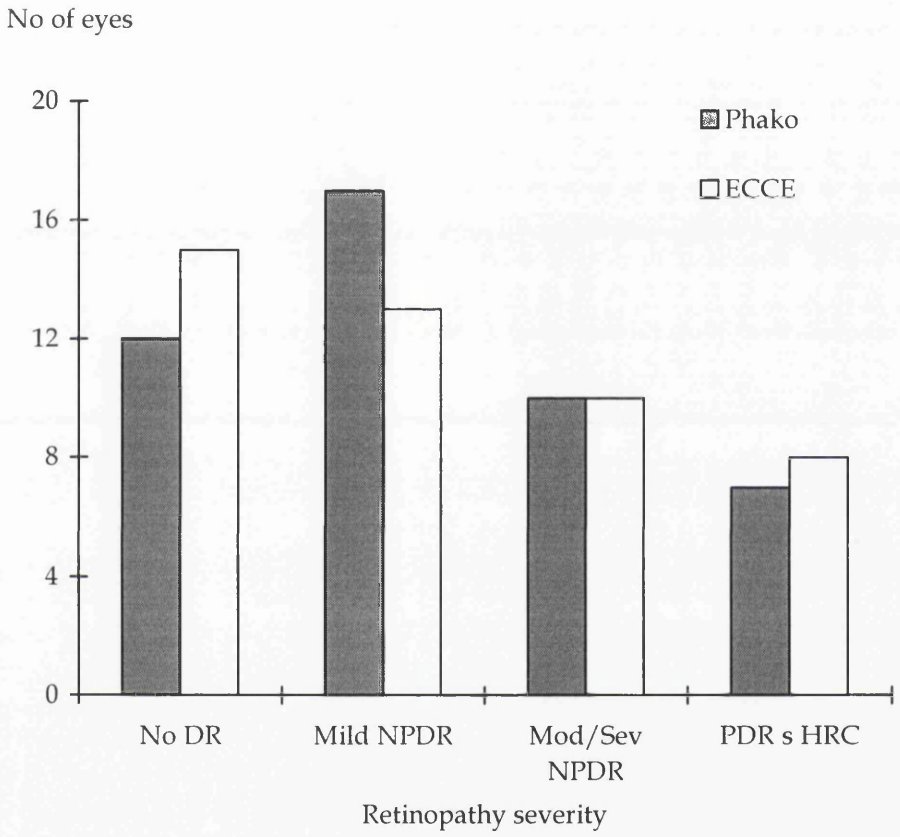
There was no difference between surgical groups in severity of retinopathy at the time of surgery (median mild NPDR in both groups, p=0.8), or presence of CSME at the time of surgery (4 eyes (9%) undergoing phakoemulsification, 6 eyes (13%) undergoing extracapsular surgery, p=0.3). Phakoemulsification was carried out in 21 right eyes and 25 left eyes (p=1), endorsing the validity of randomization.

Table 4-1: Phakoemulsification vs. Extracapsular Surgery: Patient characteristics.

Age (years)	66 (45-81)
Male : Female	25M : 21F
White : Asiatic : Afro-Caribbean	24 : 13 : 9
NIDDM:ITDM	31 : 15
Diabetes duration (years)	11 (0-33)
Follow up (years)	2.2 (1.3-3.1)

NIDDM: non insulin dependent diabetes mellitus; ITD: insulin treated diabetes mellitus (NIDDM subsequently converted to insulin)

Figure 4-1: Phakoemulsification vs. Extracapsular Surgery: Retinopathy severity at the time of Surgery.



Phako: phakoemulsification, ECCE: extracapsular cataract extraction, No DR: no diabetic retinopathy, Mild NPDR: mild nonproliferative diabetic retinopathy, Mod/Sev NPDR: moderate to severe nonproliferative diabetic retinopathy, PDR s HRC: proliferative diabetic retinopathy without high-risk characteristics.

4.1.2 Comparison between techniques

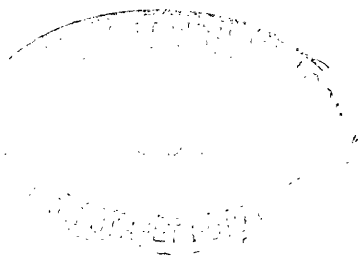
4.1.2.1 Visual acuity

A high proportion of eyes in both surgical groups achieved visual acuity ≥ 6/12 one year after surgery (96% vs. 83% respectively), but LogMAR visual acuity one year after surgery was significantly greater in eyes undergoing phakoemulsification than in eyes undergoing extracapsular surgery (0.06 vs. 0.08, 6/6 vs. 6/7.5, p=0.02). This difference was greater in eyes with retinopathy (0.08 vs. 0.14, 6/7.5 vs. 6/9 respectively; p=0.01), and absent in eyes without (0.00 vs. 0.06, 6/6 vs. 6/6 respectively, p=0.5) (Table 4.2).

Table 4-2: Phakoemulsification vs. Extracapsular Surgery: Postoperative Visual Acuity

	Phako	ECCE	p
Median 1 year logMAR (Snellen) VA:	0.06 (6/6)	0.08 (6/7.5)	0.02 *
- Retinopathy at surgery	0.08 (6/7.5)	0.14 (6/9)	0.01*
- No retinopathy at surgery	0.00 (6/6)	0.06 (6/6)	0.5
- CSME at surgery	0.09 (6/7.5)	0.66 (6/24)	0.1
- No CSME at surgery	0.05 (6/6)	0.08 (6/7.5)	0.02*
≥ 6/12 Snellen at 1 year	44 (96%)	38 (83%)	0.1

Phako: phakoemulsification, ECCE: extracapsular cataract extraction, VA: visual acuity, CSME: clinically significant macular oedema



4.1.2.2 Postoperative uveitis

By comparison with eyes undergoing phakoemulsification, eyes managed with extracapsular surgery had significantly more anterior chamber cells and flare one week after surgery, and a higher incidence of posterior synechiae and intraocular lens deposits in the first postoperative year (Table 4.3). There was no difference between techniques in the incidence of late or severe postoperative uveitis.

Table 4-3: Phakoemulsification vs. Extracapsular Surgery: Anterior Segment Findings.

	Phako	ECCE	P
Median AC cells at 1 week	0 to +	+	0.0004 *
Median AC flare at 1 week	0	0 to +	0.007 *
Eyes with posterior synechiae in 1st year	1/46 (2%)	7/46 (15%)	0.04 *
Eyes with IOL deposits in 1st year	10/46 (22%)	38/46 (83%)	<0.0005 *
Eyes with late or severe uveitis	6 (13%)	10/46 (22%)	0.2
Eyes requiring capsulotomy in 1st year	5/46 (11%)	16/46 (35%)	0.01 *

Phako: phakoemulsification, ECCE: extracapsular cataract extraction, AC: anterior chamber, IOL: intraocular lens.

4.1.2.3 Capsular opacification

Nd:YAG posterior capsulotomy was more commonly required in the first postoperative year after extracapsular surgery than after phakoemulsification (16/46 (35%) vs. 5/46 (11%), p=0.01) (Table 4.3). Retinopathy was more severe in eyes undergoing capsulotomy than in those not (p=0.02), but there was no difference in the level of cells and flare at one week, the incidence of severe or

delayed postoperative inflammation, posterior synechiae formation or intraocular lens deposits (p=0.3, 0.8, 0.8, 0.4, 0.9 respectively).

4.1.2.4 Macular oedema

No difference was identified between eyes undergoing phakoemulsification and those managed with extracapsular surgery in respect of postoperative incidence of pseudophakic macular oedema, CSME arising within six months of surgery and resolving within six months of surgery, and CSME arising within six months of surgery and still present six months after surgery (Table 4.4).

Table 4-4: Phakoemulsification vs. Extracapsular Cataract Surgery: Incidence of postoperative macular oedema.

	Phako	ECCE	p
Eyes with no retinopathy:			
Pseudophakic macular oedema	4/7 (57%)	6/8 (75%)	0.3
Eyes with retinopathy:			
CSME absent at surgery Occurring within 6 months of surgery Resolving spontaneously	10/39 (26%)	12/38 (32%)	1.0
CSME absent at surgery Occurring within 6 months of surgery Still present at 6 months	6/39 (15%)	6/38 (16%)	1.0
CSME present at surgery In all cases present at 6 months	4/39 (10%)	6/38 (16%)	0.3

Phako: phakoemulsification, ECCE: extracapsular cataract extraction, CSME: clinically significant macular oedema.

Macular oedema meeting criteria for CSME, arose de novo after surgery in approximately half the eyes with retinopathy (18/32 (56%) of eyes managed with extracapsular surgery, and 16/35 (46%) of eyes undergoing phakoemulsification), and resolved spontaneously within 6 months in the majority (12/18 (56%), and 10/16 (62%) respectively).

Despite preoperative examination suggesting its absence, CSME was found to be present within 48 hours of surgery in 4 eyes undergoing phakoemulsification and 6 eyes undergoing extracapsular surgery (p=0.5). In contrast to CSME arising after surgery, CSME present at the time of surgery showed no tendency to resolve spontaneously, being in all cases present at six months in both surgical groups.

Within one year of surgery, 22 eyes required macular laser therapy for CSME, 1 also requiring panretinal photocoagulation.

The power of the study to detect differences in the postoperative incidence of CSME at a significance level of 0.05, and the required sample size to detect the observed difference with 90% power were calculated. For CSME occurring within six months of surgery and resolving spontaneously, the study power was 5%, and the sample size required for 90% power 1248 per arm. For CSME occurring within six months of surgery and persistent at six months, the power was 4.5% and the sample size required for 90% power 164,955 per arm.

4.1.2.5 Progression of retinopathy

No significant difference was identified between eyes undergoing phakoemulsification and those managed with extracapsular surgery in respect of postoperative incidence of one-step progression of retinopathy or development of high-risk proliferative retinopathy (Table 4.5). Retinopathy progressed during the first postoperative year in approximately one third of eyes in each surgical group (Fig 4.2). Panretinal photocoagulation for high-risk proliferative retinopathy was required in 4 eyes and fundus visualization was adequate for laser therapy in all.

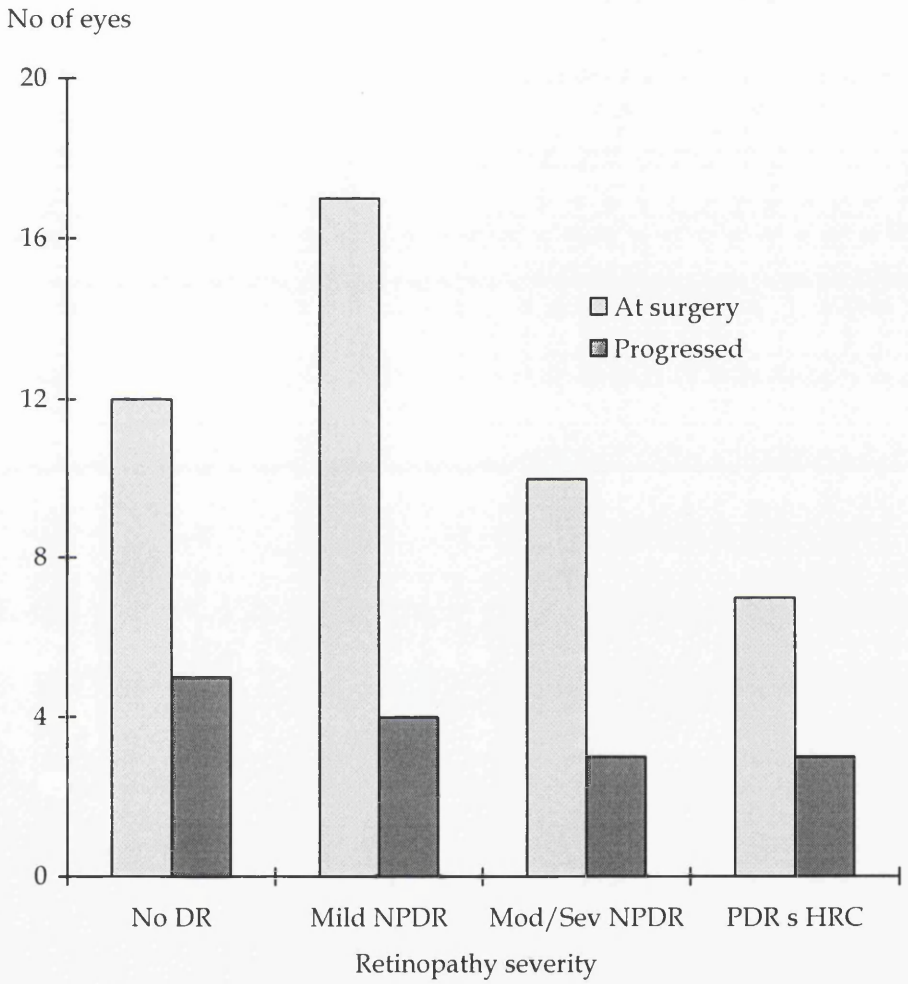
Table 4-5: Phakoemulsification vs. Extracapsular Cataract Surgery: Retinopathy progression

	Phako	ECCE	p
Median retinopathy severity at operation	Mild NPDR	Mild NPDR	0.8
Eyes with progression of DR in 1st year	15 (33%)	14 (30%)	0.8
Eyes with retinopathy in 1st year	39/46	38/46	0.2
Eyes with high-risk PDR in 1st year	1 (2%)	3 (7%)	0.2

Phako: phakoemulsification, ECCE: extracapsular cataract extraction, DR: diabetic retinopathy, PDR: proliferative diabetic retinopathy, NPDR: non-proliferative diabetic retinopathy

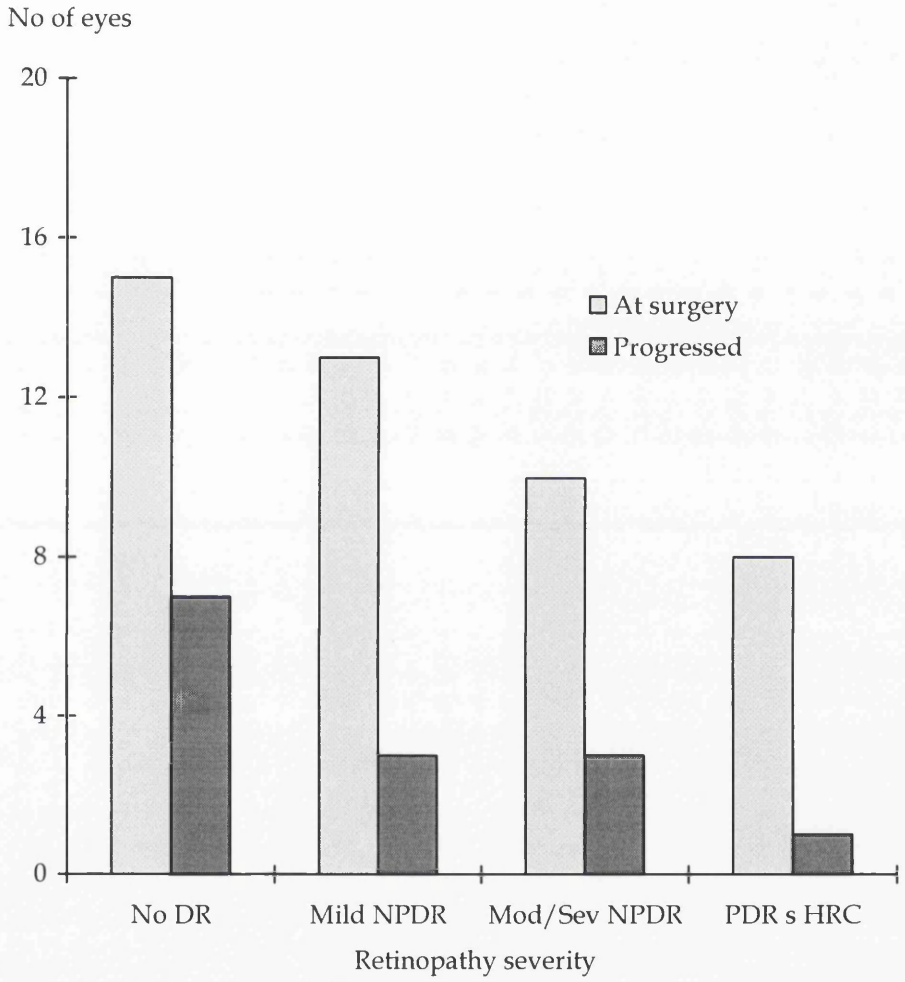
The power of the study to detect differences in postoperative retinopathy progression at a significance level of 0.05, and the required sample size to detect the observed difference with 90% power, were calculated. For one-step progression of retinopathy, the study power was 2.5%, and the sample size required for 90% power was 9635 per arm. For development of high-risk retinopathy, the power was 7.5% and the sample size required for 90% power 401 per arm.

Figure 4-2: Retinopathy severity at the time of surgery, and numbers of eyes with retinopathy progression one year after phakoemulsification surgery:



No DR: no diabetic retinopathy, Mild NPDR: mild nonproliferative diabetic retinopathy, Mod/Sev NPDR: moderate to severe nonproliferative diabetic retinopathy, PDR s HRC: proliferative diabetic retinopathy without high-risk characteristics.

Figure 4-3: Retinopathy severity at the time of surgery, and numbers of eyes with retinopathy progression one year after extracapsular surgery:



No DR: no diabetic retinopathy, Mild NPDR: mild nonproliferative diabetic retinopathy, Mod/Sev NPDR: moderate to severe nonproliferative diabetic retinopathy, PDR s HRC: proliferative diabetic retinopathy without high-risk characteristics.

4.1.3 Predictors of visual outcome for each technique

4.1.3.1 Phakoemulsification

Stepwise multiple regression analysis was carried out with one year logMAR visual acuity as the dependent variable, and the following independent variables: severity of retinopathy at the time of surgery, presence or absence of CSME at the time of surgery, diabetes duration, diabetes type, race, and sex. For phakoemulsification, presence or absence of CSME at the time of surgery ($p=0.001$, ($\beta=0.21$ (0.10-0.33)) and retinopathy severity at the time of surgery ($p<0.0005$, ($\beta=0.04$ (0.02-0.06)) were the only significant independent variables retained in the model ($p<0.00005$, $R^2=0.46$).

The independence of presence of CSME at the time of surgery from retinopathy severity was checked by univariate analysis, no significant association being identified ($p=0.6$). In eyes with CSME 6 months after surgery, one year logMAR visual acuity was significantly worse in those with CSME at the time of surgery than in those without (0.2 vs. 0.1, $p=0.05$).

4.1.3.2 Extracapsular surgery

Stepwise regression using the same variables as for phakoemulsification was applied to data from eyes undergoing extracapsular surgery. The presence or absence of CSME at the time of surgery ($p=0.008$, $\beta=0.37$ (0.10-0.65)) and retinopathy severity at the time of surgery ($p=0.03$, $\beta=0.05$ (0.01-0.11)) were the only significant independent variables retained in the model ($p=0.0004$, $R^2=0.45$).

The independence of presence of CSME at the time of surgery from retinopathy severity was checked by univariate analysis, no significant association being identified ($p=0.1$). In eyes with CSME 6 months after surgery, one year log MAR visual acuity was significantly worse in those with CSME at the time of surgery than in those without (0.66 vs. 0.19, $p=0.01$).

4.2 INTRA-OPERATIVE FLUORESCEIN ANGIOGRAPHY STUDIES

4.2.1 Patient characteristics

Recruitment was undertaken over a two-year period. Follow up, which varied according to study, is detailed below.

4.2.1.1 Pilot study: Normal patients

Eight patients without diabetes, ranging from early middle-aged to elderly, scheduled for routine cataract surgery, were recruited into a pilot study to assess the practicality of intra-operative fluorescein angiography.

Table 4-6: Patient characteristics: Pilot Study

Age (years)	73 (40-86)
Male : Female	5M : 3F
Caucasian : Asiatic : Afro-Caribbean	6 : 1 : 1
Hypertension	2/8 (25%)
Follow up (years)	1 (1-1.5)

4.2.1.2 Early Postoperative Angiography Study

Thirty two patients with diabetes recruited into and retained in the early postoperative angiography study. Most were middle-aged to elderly, a quarter were hypertensive, and seven-eighths suffered from maturity-onset diabetes. There was considerable variation in duration of diabetes and quality of diabetic control (Table 4.7).

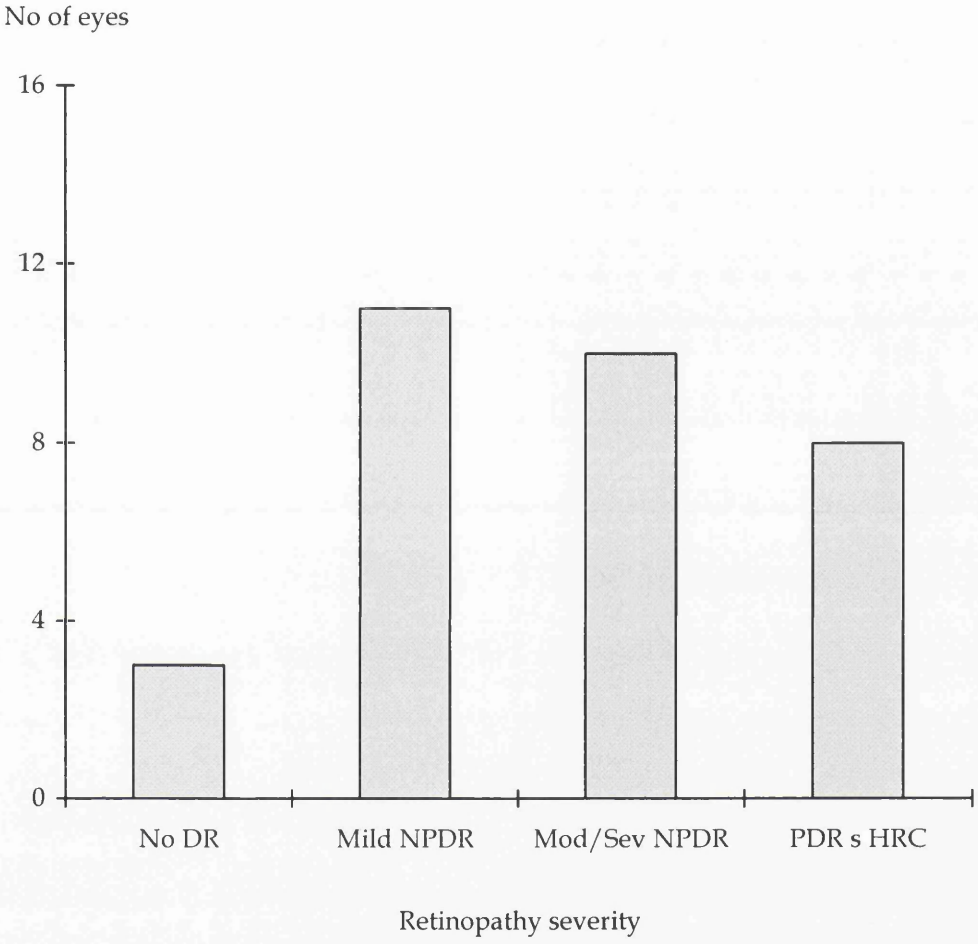
Table 4-7: Patient characteristics: Early Postoperative Angiography Study

Age (years)	65 (51-81)
Male : Female	17M : 15F
Caucasian : Asiatic : Afro-Caribbean	20 : 7 : 5
Hypertension	8/32 (25%)
Diabetes type - IDDM : NIDDM : ITDM	5 : 13 : 14
Diabetes duration (years)	13 (1-53)
Follow up (years)	1 (0.25-2)

IDDM: insulin dependent diabetes mellitus NIDDM: non insulin dependent diabetes mellitus; ITDM: insulin treated diabetes mellitus (NIDDM subsequently converted to insulin).

Retinopathy severity in operated eyes of these patients was distributed as shown in Fig 4.4. Macular laser therapy had been undertaken at the time of surgery in 6 eyes, panretinal photocoagulation in 4, and both treatments in 4.

Figure 4-4: Distribution of retinopathy severity in the early postoperative angiography study



No DR: no diabetic retinopathy, Mild NPDR: mild nonproliferative diabetic retinopathy, Mod/Sev NPDR: moderate to severe nonproliferative diabetic retinopathy, PDR s HRC: proliferative diabetic retinopathy without high-risk characteristics.

4.2.1.3 Natural History Study

Thirty-two patients with diabetes were recruited into and retained in the natural history study. Most were middle-aged to elderly, more than a third were derived from ethnic minority groups (Table 4.8), and a quarter were hypertensive. The majority of patients suffered from maturity-onset diabetes. The duration of diabetes was highly variable. Glycaemic control was generally good.

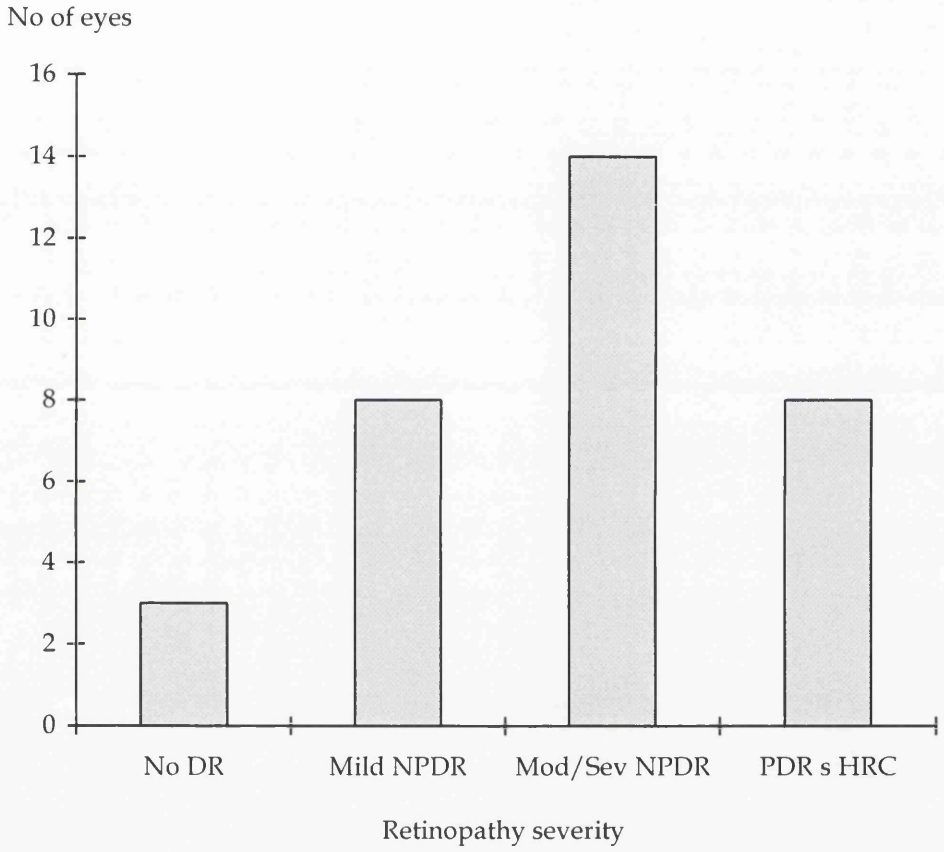
Table 4-8: Patient characteristics: Natural History Study

Age (years)	65 (51-90)
Male : Female	20M : 12F
Caucasian : Asiatic : Afro-Caribbean	20 : 9 : 3
Hypertension	8/32 (25%)
Diabetes type - IDDM : NIDDM : ITD	3 : 17 : 12
Diabetes duration (years)	13 (1-53)
Follow up (years)	1.5 (1-2)

IDDM: insulin dependent diabetes mellitus NIDDM: non insulin dependent diabetes mellitus; ITDM: insulin treated diabetes mellitus (NIDDM subsequently converted to insulin)

Retinopathy in operated eyes of these patients at the time of surgery tended towards the more severe grades (Fig 4.5). Macular laser therapy had been undertaken at the time of surgery in 6 eyes, panretinal photocoagulation in 4, and both treatments in 3.

Figure 4-5: Distribution of retinopathy severity in the natural history study



No DR: no diabetic retinopathy, Mild NPDR: mild nonproliferative diabetic retinopathy, Mod/Sev NPDR: moderate to severe nonproliferative diabetic retinopathy, PDR s HRC: proliferative diabetic retinopathy without high-risk characteristics.

4.2.2 Technique

4.2.2.1 Angiographic quality

Intra-operative angiograms were of good definition, a median quality score of 100 (70-130) indicating that major and minor vessels were resolvable and microaneurysms could be counted (Fig 4.6). Postoperative angiograms were of excellent definition, a median quality score of 120 (70-160) indicating that the foveal avascular zone was resolvable (Fig 4.7). The difference in resolution between Intra-operative and postoperative angiograms, though small, was significant (p=0.0002)

Figure 4-6: Grading frame of specimen Intra-operative angiogram

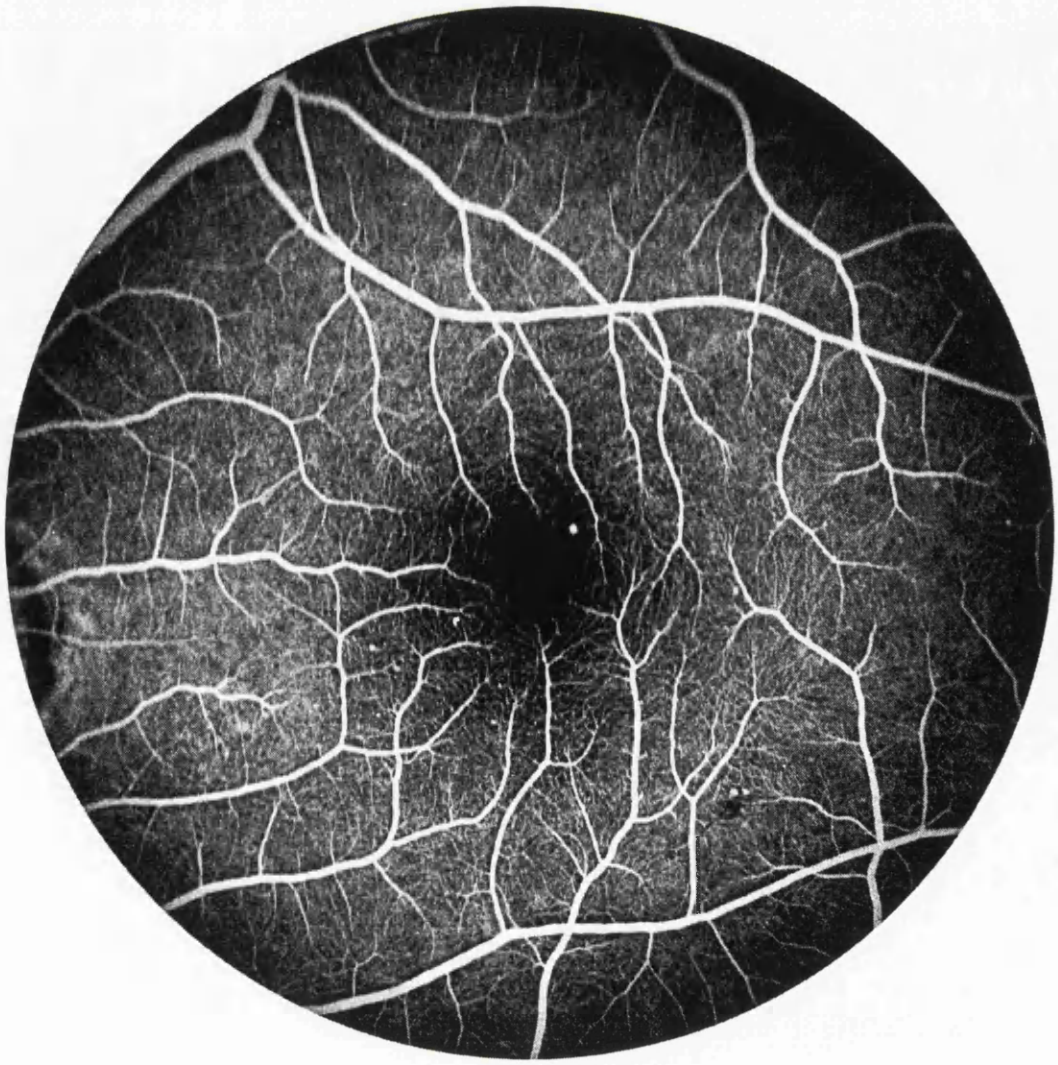
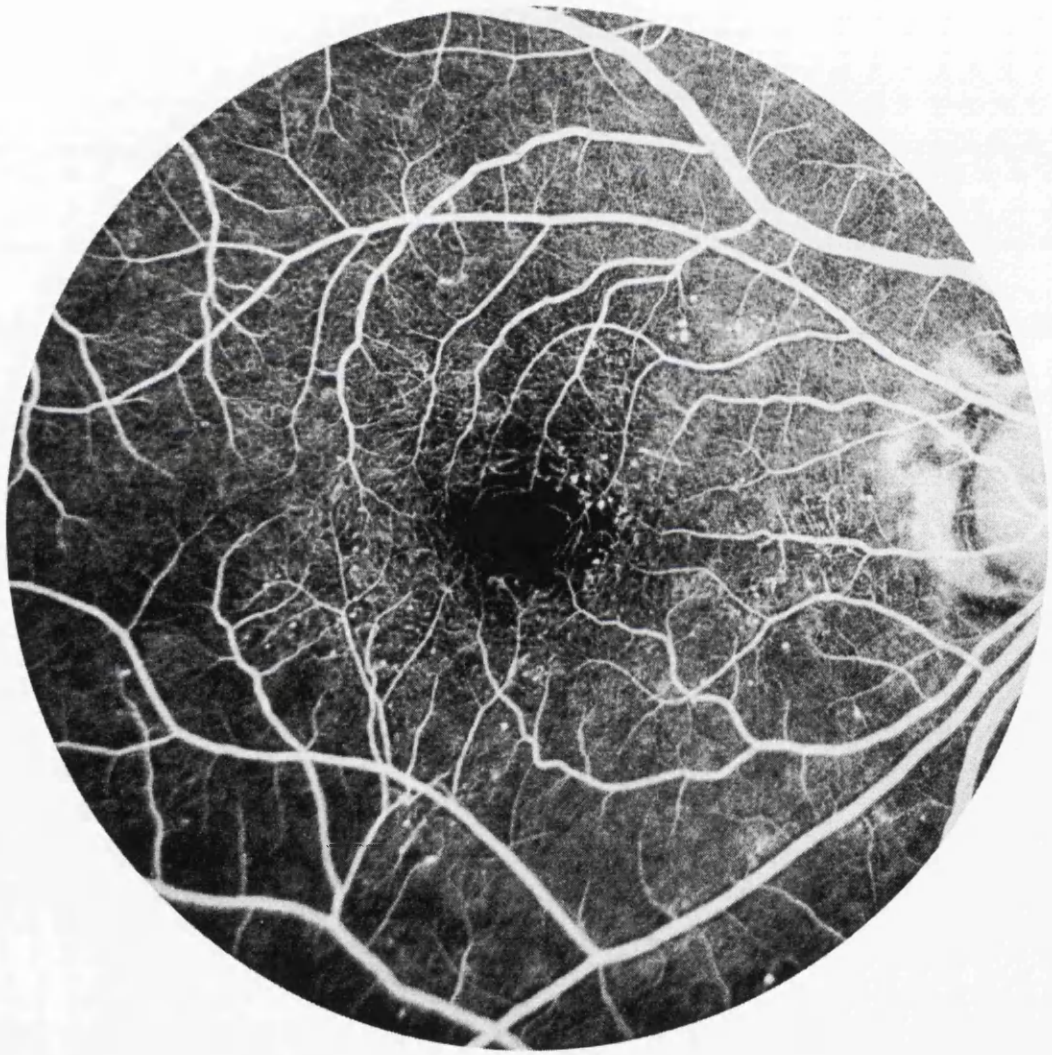


Figure 4-7: Grading frame of specimen postoperative angiogram



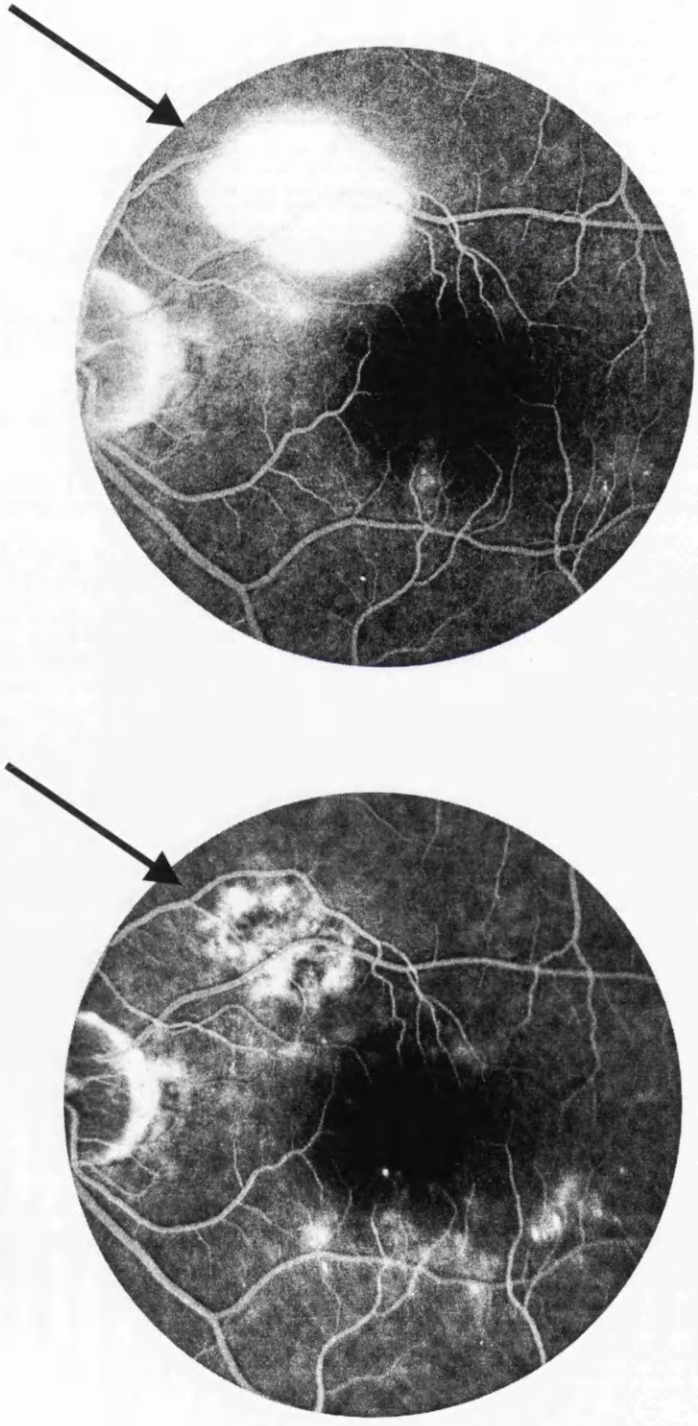
4.2.2.2 Safety issues

Phakoemulsification surgery combined with intra-operative fluorescein angiography took a median of 45 minutes (35-75 minutes). Four patients (8%) experienced transient nausea following intravenous injection of fluorescein, in two cases accompanied by retching. No other adverse systemic reactions occurred. No intra-operative surgical complications such as vitreous loss or suprachoroidal haemorrhage occurred. Two patients (4%) required more frequent topical steroid administration than the standard regimen for postoperative uveitis. No case of endophthalmitis occurred. One patient declined postoperative angiography after developing phlebitis proximal to the site of intra-operative injection of fluorescein.

4.2.2.3 Incidental findings

A circumscribed area of hyperfluorescence, identified in the intra-operative angiograms, and subsequently showing angiographic and clinical evolution typical of an operating microscope phototoxic lesion (Michels, 1995) was encountered in four eyes (8%) (Fig 4.8).

Figure 4-8: Operating microscope burn evolution: Intra-operative and six week angiograms



4.2.3 Pilot Study

Macular cystoid spaces, and a postoperative increase in macular and optic disc fluorescence relative to the intra-operative angiogram were identified in 4/8 (50%) of normal eyes. Both macular and optic disc fluorescence reached a postoperative peak a median of six weeks after surgery. Macular fluorescence returned to its intra-operative level within six months in all eyes in which it had increased after surgery, and optic disc fluorescence returned to its intra-operative level within six months of surgery in 3/4 (75%) eyes. Four eyes showed no postoperative increase in macular or optic disc fluorescence. Median logMAR acuity score at one year was minus 0.02 (minus 0.08 to plus 0.18) (6/5 - 6/9).

4.2.4 Early Postoperative Angiography Study

A postoperative increase in macular fluorescence relative to the intra-operative angiogram was found in 14/22 patients in whom angiography was performed 7-30 (median 9) days after surgery, but in none of ten patients in whom angiography was performed 2-6 (median 3) days after surgery (Fisher exact p=0.001). There was no difference between these two groups in regard to retinopathy severity, the proportion showing subsequent angiographic deterioration of macular edema, or the proportion subsequently developing CSME (p=0.85, 0.62, 0.37 respectively).

4.2.5 Natural History Study

4.2.5.1 Postoperative macular hyperfluorescence

In the first postoperative year, macular fluorescence remained at its intra-operative level in 2/32 (6%) eyes, and increased in 30/32 (94%), returning to its intra-operative level within a year in 13/30 (43%) (total resolution), falling to a

level intermediate between peak postoperative and intra-operative level in 7/30 (23%) (partial resolution), and never falling below peak postoperative level in 10/30 (33%) (no resolution). Peak postoperative macular fluorescence occurred a median of six weeks after surgery (range six weeks to one year), occurring later in the postoperative course in eyes with less complete resolution of postoperative macular hyperfluorescence ($p=0.005$). After reaching its maximum, macular fluorescence declined within six months of surgery in 16/20 (80%) of eyes showing total or partial resolution of postoperative macular hyperfluorescence. (Fig 4.9). Instances of spontaneous resolution of postoperative macular hyperfluorescence derived from diabetic microvascular abnormalities were observed (Fig 4.10).

Figure 4-9: Natural history of postoperative macular hyperfluorescence

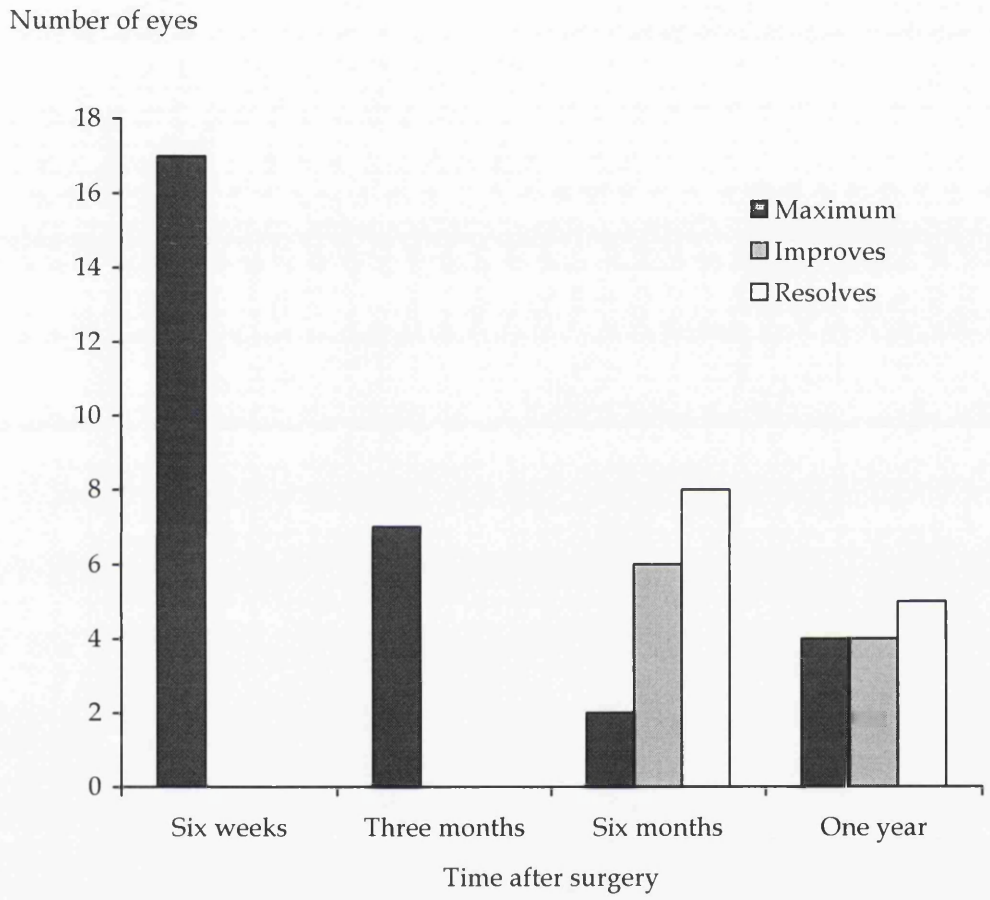
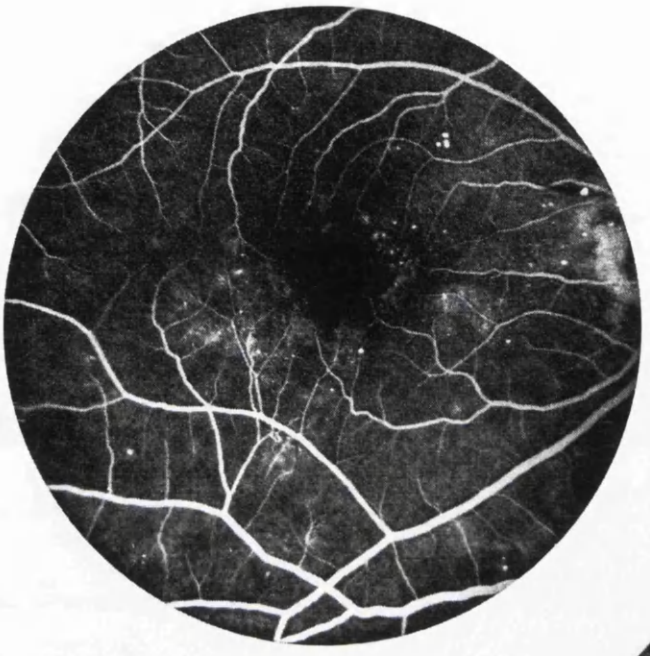
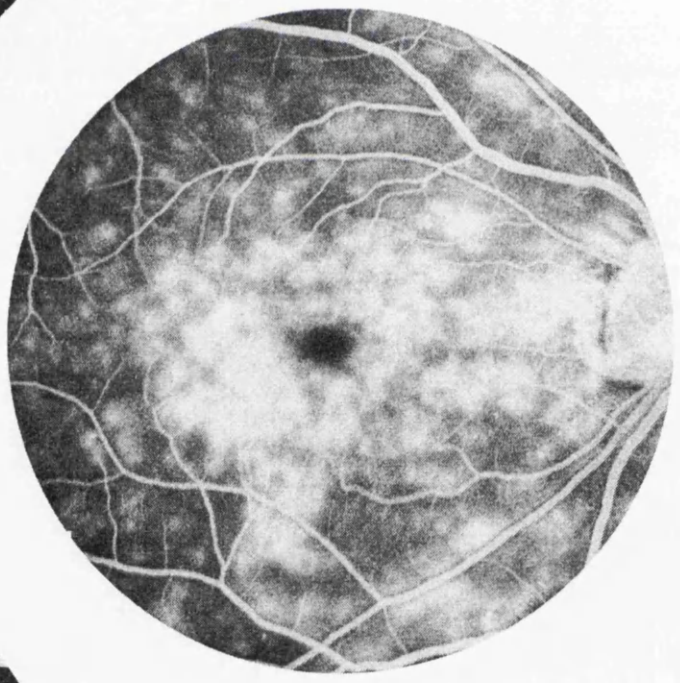


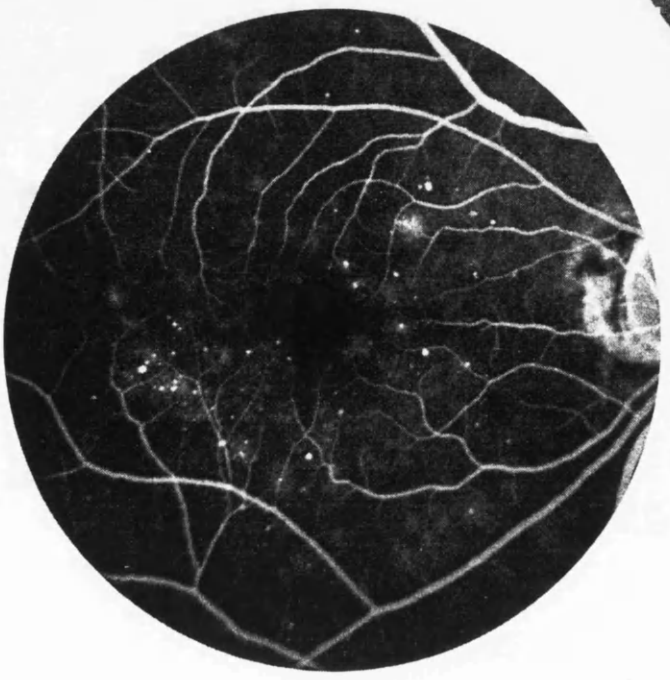
Figure 4-10: Spontaneous resolution of postoperative hyperfluorescence derived from diabetic microvascular abnormalities



Intra-operative



Three month angiogram

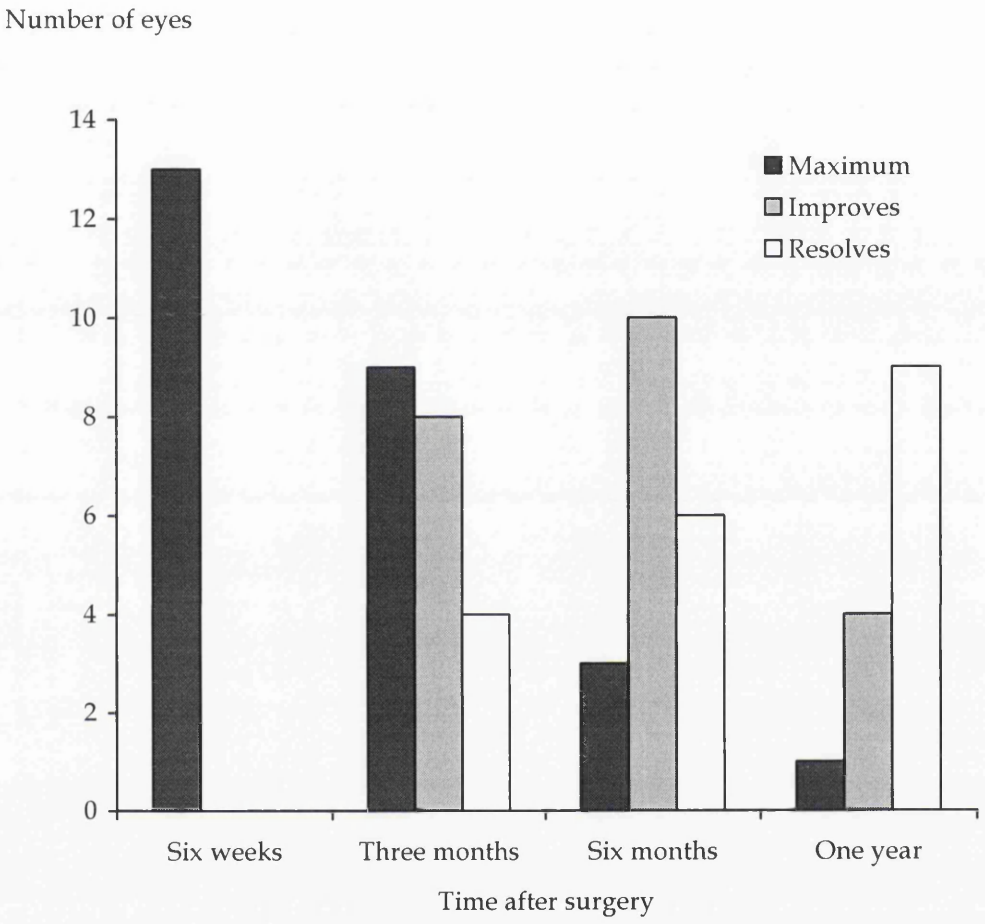


One year angiogram

4.2.5.2 Postoperative optic disc hyperfluorescence

In the first postoperative year, optic disc fluorescence remained at its intra-operative level in 2/32 (6%) eyes, was not graded in 3/32 (9%) eyes because of optic disc fibrous proliferation (2 eyes) or absent optic disc intra-operative angiogram (1 eye), and increased in 27/32 (84%) of eyes, returning to its intra-operative level in 19/27 (70%) eyes (total resolution), falling to a level intermediate between intra-operative and peak postoperative level in 3/27 (11%) (partial resolution), and never falling below peak postoperative level in 5/27 (19%) (no resolution). Peak postoperative optic disc fluorescence occurred a median of three months after surgery (range six weeks to one year) occurring later in the postoperative course in eyes with less complete resolution of postoperative optic disc hyperfluorescence ($p=0.01$) (Fig. 4.11). After reaching its maximum, optic disc fluorescence declined within six months of surgery in 18/22 (82%) of eyes showing total or partial resolution of postoperative macular hyperfluorescence.

Figure 4-11: Natural history of postoperative optic disc hyperfluorescence



Postoperative optic disc hyperfluorescence occurred in all 27 eyes showing postoperative macular hyperfluorescence in which the optic disc was graded, irrespective of whether total, partial or no resolution of macular hyperfluorescence occurred. Total resolution of postoperative optic disc hyperfluorescence occurred in all 11 eyes in which total resolution of postoperative macular hyperfluorescence occurred, and 8/16 eyes in which it did not (p=0.005). It was thus not possible to differentiate pseudophakic from diabetic macular edema on the basis of optic disc hyperfluorescence.

Table 4-9: Resolution of postoperative hyperfluorescence: optic disc vs. macula

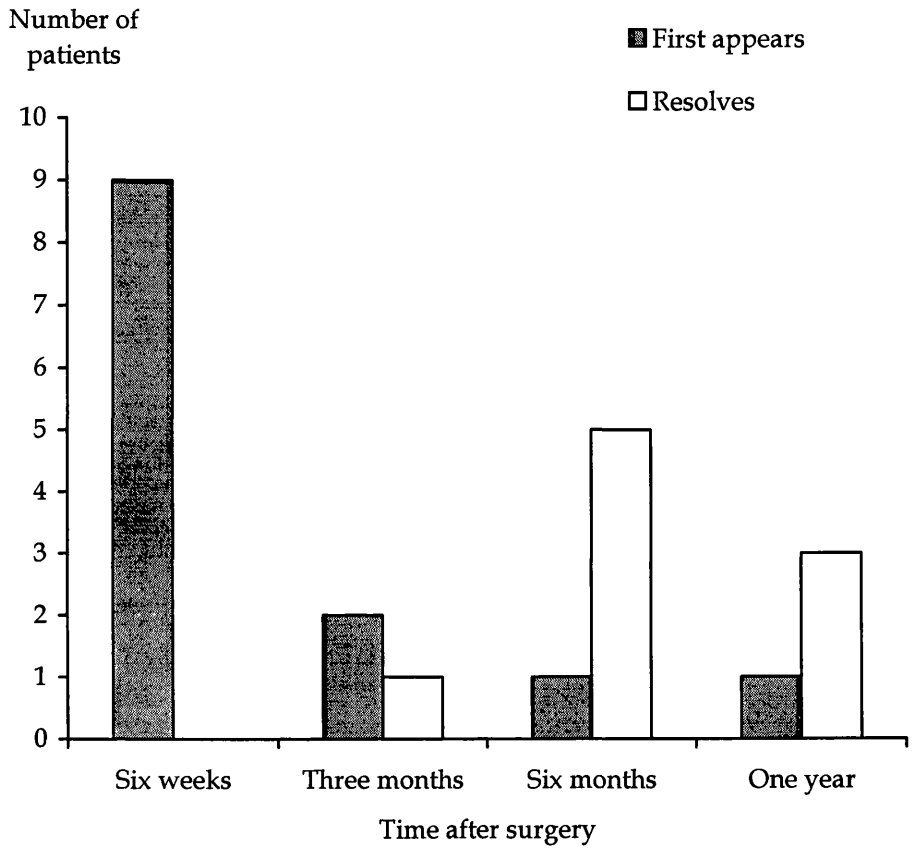
		Optic disc resolution		
		Total	Partial	None
Macular resolution	Total	11	0	0
	Partial	6	1	0
	None	2	2	5

4.2.5.3 Macular oedema

CSME was identified at some point in the first postoperative year in 18/32 (56%) patients. In five eyes (16%), all of which had undergone preoperative macular laser, CSME was present within 2 days of surgery, despite preoperative evaluation suggesting its absence. In these eyes, CSME was present at all examinations in the first year. No association between presence of CSME at the time of surgery and retinopathy severity was identified (p=0.1). CSME appeared for the first time within a year of surgery in 13 (48%) eyes, in twelve by six months, and in one at a year; two had undergone macular laser before surgery. CSME arose a median of six weeks after surgery, and of those arising within six months of surgery, 6 (50%) resolved by six months, and 9 (75%) by one year (Fig 4.11). CSME was present one year after surgery in all five eyes with CSME at the time of surgery, but in only 4/13 in which it arose after surgery (p=0.05).

All eyes with CSME at any point in the first year after surgery showed a postoperative increase in macular and optic disc fluorescence. Total or partial resolution of postoperative macular hyperfluorescence occurred in 1/5 eyes with CSME at the time of surgery, and in 9/12 eyes in which CSME developed within six months of surgery (p=0.2). Resolution of postoperative macular hyperfluorescence was associated with an increased likelihood of resolution within one year of CSME arising within six months of surgery (p=0.005). By contrast, resolution of postoperative optic disc hyperfluorescence was not associated with an increased likelihood of resolution within one year of CSME arising within six months of surgery (p=0.4). In addition, total or partial resolution of optic disc hyperfluorescence occurred in all 12 eyes developing CSME within 6 months of surgery, irrespective of whether CSME persisted at one year.

Figure 4-12: Natural history of CSME arising after surgery

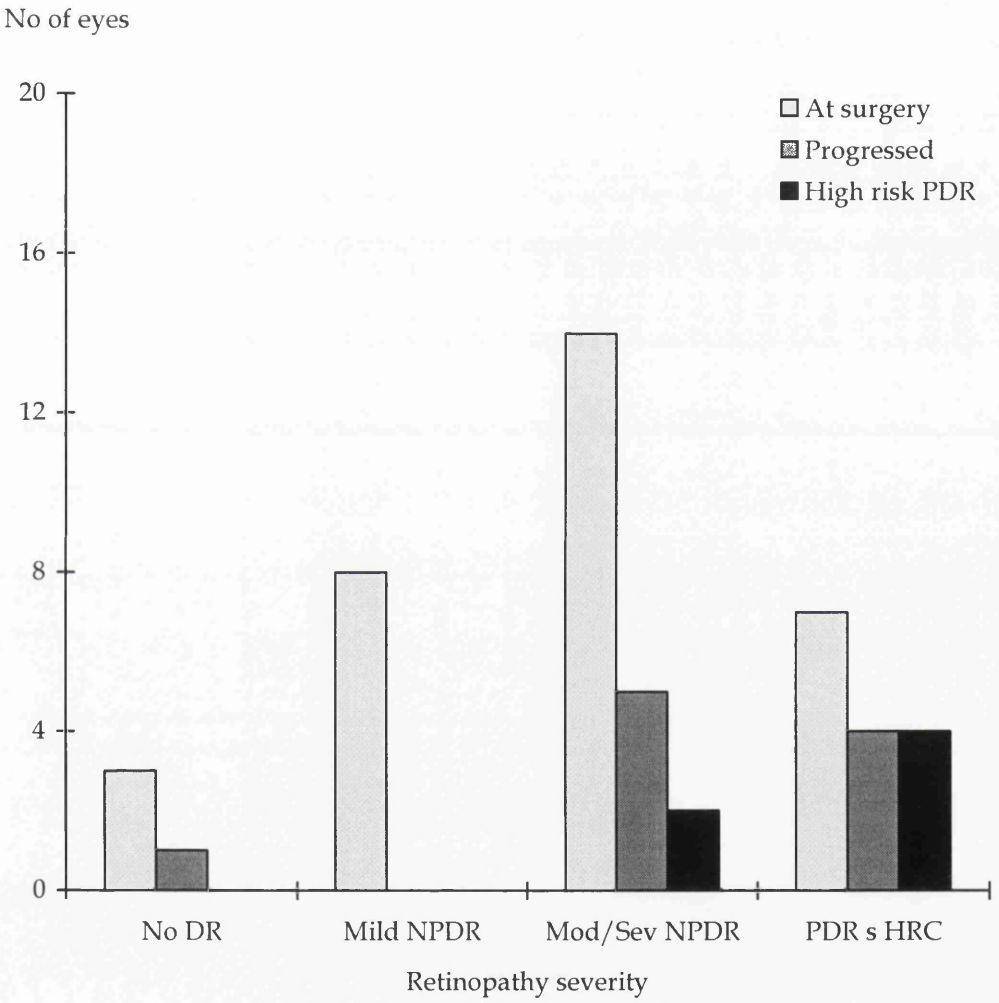


4.2.5.4 Retinopathy progression and laser therapy

Within a year of surgery, progression of retinopathy by at least one level occurred in 10/32 (31%) of eyes (Fig 4.13). Retinopathy was more severe at the time of surgery in eyes showing progression of retinopathy than in those not ($p=0.02$). High-risk proliferative retinopathy developed in six eyes (19%), in one, three months, and in five, one year after surgery. Retinopathy was more severe (median severe NPDR) in eyes in which CSME arising within six months of surgery failed to resolve within one year than in eyes in which it resolved (median mild NPDR) ($p=0.005$). More severe retinopathy was also associated with a reduced tendency to resolution of postoperative optic disc hyperfluorescence, ($p=0.04$), and resolution of postoperative macular hyperfluorescence ($p=0.03$).

Eyes showing total resolution of postoperative macular hyperfluorescence were found to have a bimodal distribution of retinopathy severity, eight having no or only mild nonproliferative retinopathy, and five having severe nonproliferative to non high-risk proliferative retinopathy. This prompted unmasked review of angiograms in the latter group, which revealed one eye with very severe NPDR, and two eyes with non high-risk proliferative retinopathy, in which resolution of postoperative macular hyperfluorescence was associated with progressive macular capillary nonperfusion. All three eyes developed high-risk proliferative retinopathy within one year of surgery.

Figure 4-13: Natural history study: Progression of retinopathy

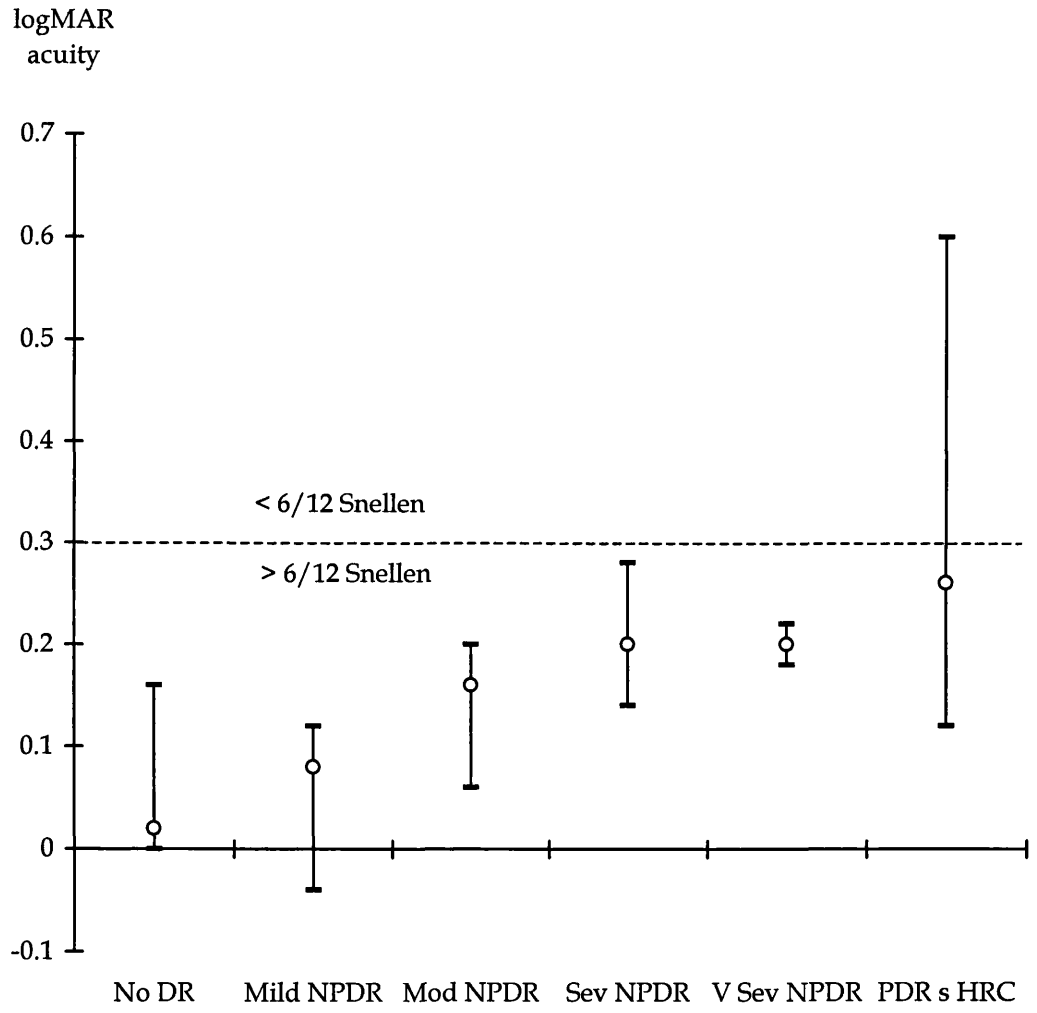


No DR: no diabetic retinopathy, Mild NPDR: mild nonproliferative diabetic retinopathy, Mod/Sev NPDR: moderate to severe nonproliferative diabetic retinopathy, PDR s HRC: proliferative diabetic retinopathy without high-risk characteristics.

4.2.6 Postoperative visual acuity

One year after surgery 27/32 (84%) of patients achieved LogMAR visual acuity ≤0.3 (≥ 6/12). Acuity below this level was encountered in two eyes with macular ischaemia and three eyes with macular oedema. Overall, median LogMAR visual acuity at one year was 0.15 (6/9), ranging from minus 0.08 to plus 0.78 (6/5 - 6/36). Surgery produced a halving of the visual angle in 24 (75%) eyes, and no visual acuity improvement in 2 (6%). Visual acuity at one year was poorer in eyes with CSME at the time of surgery (LogMAR median 0.6, range 0.12 to 0.78) than in eyes without (LogMAR median 0.14, range minus 0.08 to plus 0.6) (p=0.02), and poorer in eyes in which CSME arising within six months of surgery persisted (logMAR median 0.24, range 0.1 to 0.78) than in eyes in which it resolved within a year (LogMAR median 0.08, range 0 to 0.26) (p=0.01). Visual acuity at one year declined with increasing retinopathy severity (Fig 4.14), and lesser degrees of angiographic macular or optic disc resolution, but although these univariate associations were significant (p=0.01, 0.02, 0.004) they were small. A stepwise multiple regression model with one year logMAR visual acuity as the dependent variable, and as independent variables, retinopathy severity, presence of CSME at the time of surgery, resolution of optic disc hyperfluorescence and resolution of macular hyperfluorescence retained, as the only significant independent variable, the presence of CSME at the time of surgery (R^2=0.5, p=0.005).

Figure 4-14: Relationship between visual acuity and retinopathy severity in the natural history study



No DR: no diabetic retinopathy, Mild NPDR: mild nonproliferative diabetic retinopathy, Mod NPDR: moderate nonproliferative diabetic retinopathy, Sev NPDR: severe nonproliferative diabetic retinopathy, V Sev NPDR: very severe nonproliferative diabetic retinopathy, PDR s HRC: proliferative diabetic retinopathy without high-risk characteristics.

5 DISCUSSION

5.1 TECHNIQUE OF INTRA-OPERATIVE FLUORESCEIN ANGIOGRAPHY

5.1.1 Safety

In studies employing it, the technique of intra-operative fluorescein angiography was associated with a low incidence of adverse effects. Prolongation of the surgical procedure, albeit slight, and the additional ocular manipulation involved, might be thought to increase the risk of severe postoperative inflammation and endophthalmitis. The incidence of marked postoperative uveitis, however, proved to be lower than reported in diabetics undergoing extracapsular cataract surgery without intra-operative fluorescein angiography (Krupsky, Zalish et. al., 1991), and comparable to eyes in the phakoemulsification vs. extracapsular study undergoing phakoemulsification alone. No instance of endophthalmitis occurred, although the incidence of this entity is so low that this finding must be interpreted with caution in the light of the limited sample size of the studies. Nausea and attendant retching, which may occur after injection of fluorescein, might be expected to increase the risk of vitreous loss or suprachoroidal haemorrhage, but these complications did not occur, possibly because the self-sealing nature of the incision protected against ocular decompression. Clearly, however, such complications represent a significant risk were any attempt made to employ intra-operative fluorescein angiography in large incision or extracapsular surgery. The use of a standard external flash unit avoided risks of retinal photic injury associated with endo-illuminated fluorescein angiography during vitrectomy surgery (Krueger, Morales et. al., 1994), and the only phototoxic lesions encountered were typical of those induced by the operating microscope (Michels, 1995).

5.1.2 Validity

In the pilot study, early postoperative angiography study and natural history study, intra-operative fluorescein angiography was used to determine the state of the macula at the time of operation. However, fluorescein angiography is subject to a number of influences during cataract surgery which do not routinely affect it, and which might modify angiographic findings. These include the effect of perioperative blood glucose fluctuations on retinal autoregulation (Kohner, 1993), the effects of peribulbar anaesthetic agent and intracameral adrenaline (Chiou, Girgis et. al., 1988), the influence of peroperative variations in intraocular pressure (Schulte, Wolf et. al., 1996) and the effect of posture (Kothe and Lovasik, 1988). If, however, substantial artefact in intra-operative angiograms occurred as a result of the immediate effect of these influences during surgery, a difference in the level of macular fluorescence between intra-operative and early postoperative angiograms might be expected. Although the grading system employed was relatively simple, such a difference was not identified. Furthermore, in a number of both normal and diabetic eyes, macular fluorescence underwent no change from its intra-operative level at any point in the first year after surgery, an observation not consistent with the presence of significant error in the intra-operative angiogram. Finally, in normal eyes with angiographic Irvine-Gass syndrome, a postoperative return of macular fluorescence to the level of the intra-operative angiogram was invariably associated with the restoration of normal angiographic macular appearances. On these grounds it seems reasonable to infer that intra-operative fluorescein angiography provides an acceptable representation of the state of the macula at the time of surgery, within the parameters of the grading system employed.

5.1.3 Definition of intra-operative angiograms

As a result of the refractive stability of small incision surgery, typical definition of intra-operative fluorescein angiograms was sufficient to resolve microaneurysms, and more than adequate for the grading system employed in these studies. In addition, the use of topical anaesthesia in more recent work has been associated with improved quality of intra-operative angiograms (Fig. 4.6), since the patient is able to align his eye as requested by the photographer, without the distortion produced by peribulbar anaesthetic agent and traction from the surgeon's forceps. The quality of postoperative angiograms was nonetheless found to be slightly greater than intra-operative angiograms, and given that those performed soon after surgery appear be an acceptable reflection of macular status at the time of surgery, and are more conveniently obtained, they will tend to be preferred in most instances.

5.1.4 Future roles

There are circumstances in which conventional angiography may not be possible, for example in the mentally handicapped, and in children, and in which intra-operative fluorescein angiography under general anaesthesia allows derivation of good quality images. In addition, intra-operative angiography may be used to provide insight into operative events, as in recent studies at our institution into vitrectomy surgery for idiopathic macular hole. Other potential applications include assessment of the macula during vitrectomy surgery for complications of diabetes or for excision of choroidal neovascular membranes.

5.2 NATURAL HISTORY OF POSTOPERATIVE MACULAR OEDEMA

5.2.1 Timing of postoperative retinal examination

It is widely considered that neither the Irvine-Gass syndrome nor diabetic macular oedema occurring as a complication of cataract surgery arise immediately after surgery (Gass and Norton, 1966; Schatz, Atienza et. al., 1994; Pollack, Leiba et. al., 1992b; Jaffe and Burton, 1988; Benson, Brown et. al., 1993; Hykin, Gregson et. al., 1993; Jaffe, Burton et. al., 1992; Ruiz and Saatci, 1991; Menchini, Bandello et. al., 1993), and that there is an interval after surgery during which macular appearances remain relatively unaltered. This contention is supported by the finding in that no eye showed any change in macular fluorescence from its intra-operative level in the first six days after surgery. Since it is unlikely that clinically detectable retinal thickening would develop without an increase in macular fluorescence, this finding also suggests that the identification of CSME in the immediate postoperative period indicates the presence of CSME at the time of surgery.

On the basis of these findings, it seems reasonable to recommend clinical and angiographic examination of patients with diabetic retinopathy undergoing cataract surgery within six days of surgery. This would serve to establish a baseline for any future change, and to determine the presence or absence of CSME at the time of surgery, which as described below can be used as a means of determining subsequent management of macular oedema.

5.2.2 CSME at the time of surgery: treatment implications

In the natural history study, and in both surgical groups of the phakoemulsification vs. extracapsular surgery study, CSME present at the time of surgery showed no tendency to spontaneous postoperative resolution. Furthermore, the natural history study demonstrated in these eyes a tendency to progressive postoperative increase in macular fluorescence, and by implication worsening of oedema. It therefore seems inappropriate to withhold laser therapy in the expectation of spontaneous resolution in eyes with CSME at the time of surgery.

The likely response to such early macular laser treatment is uncertain, however. Provided that the reported association between diabetic maculopathy and poor visual acuity following cataract surgery in patients with diabetes (Pollack, Leiba et. al., 1992b; Dowler, Hykin et. al., 1995b) is appreciated by the surgeon, the presence of CSME at the time of surgery implies that it was unrecognised, and presumably therefore untreated, prior to that point. One might expect that such deferral of treatment would render CSME relatively refractory to laser treatment. Consideration of eyes with CSME six months after surgery in the phakoemulsification vs. extracapsular surgery study, all of which underwent macular laser at that point, provides some support for this view. One year logMAR visual acuity - six months after macular laser therapy - was worse in eyes in which CSME had been present at the time of surgery than in those in which it had not. However, in the natural history study, eyes with CSME six months after surgery did not undergo macular laser therapy at that point, and spontaneous resolution of CSME occurred in none of those with CSME at the time of surgery, and half of those without. That is, some of those diagnosed as having CSME six months after surgery demonstrated behaviour more typical of pseudophakic than diabetic macular oedema. By contrast, those with CSME at the time of surgery may be considered to have purely diabetic macular oedema. The difference in visual outcome with laser treatment between those with CSME

at the time of surgery and those without may thus be due to admixture of eyes with pseudophakic oedema in the second group rather than a poor response to laser in the first.

The deferral of laser treatment for CSME present at the time of surgery inherent in the failure to recognise it before surgery, any additional postoperative deferral of treatment in the hope of spontaneous resolution, and the tendency to postoperative worsening of such oedema as evidenced by the increasing macular hyperfluorescence observed in such eyes in the natural history study, creates the potential for the occurrence of particularly marked oedema. It is possible that accounts of particularly severe macular oedema after cataract surgery in patients with diabetes (Jaffe and Burton, 1988) describe postoperative progression of CSME present but unrecognised at the time of surgery. CSME may not have been identified early in the postoperative course in such patients because at that time the importance of such examination may not have been appreciated, the definition of CSME and its importance had yet to be widely disseminated, and the refractive instability of extracapsular wounds in the early postoperative period may have hindered examination.

5.2.3 CSME arising after surgery : treatment implications

In the natural history study, CSME arising de novo in the first 6 months after surgery was characterised by relatively benign natural history. It occurred in half the eyes in which CSME was absent at the time of surgery, its peak incidence was at six weeks, and it resolved spontaneously by six months in half the eyes affected, and by a year in three quarters. Angiographic findings reflected this. Postoperative macular hyperfluorescence relative to the intra-operative angiogram was found in all eyes with CSME arising after surgery, and some spontaneous resolution occurred in 77%, the time course paralleling that of CSME. These findings suggest that CSME arising after surgery in eyes in

which it was not present at the time of surgery might be managed conservatively in anticipation of spontaneous resolution, rather than be subjected to early macular laser, as has been proposed.

The postoperative interval, proposed by Benson (Benson, 1992), during which macular laser therapy for CSME should be withheld to allow spontaneous resolution of pseudophakic components of macular oedema, was six months. In the natural history study, and in both arms of the phakoemulsification vs. extracapsular surgery study, approximately half the eyes with CSME developing within six months of surgery showed spontaneous resolution six months after surgery. In these eyes, unnecessary macular laser therapy, with its potential for complications, was avoided. However, in the natural history study, it was observed that of those eyes in which CSME developed within six months of surgery and in which spontaneous resolution of CSME had not occurred six months after surgery, half showed spontaneous resolution within the next six months. This suggests that an even longer postoperative interval might be permitted to allow spontaneous resolution of pseudophakic components of macular oedema.

In the natural history study, macular laser therapy was undertaken one year after surgery for CSME present at that point. The natural history of CSME arising within six months of surgery, present one year after surgery and left untreated at that point, is not defined by this study. It becomes possible, however, to estimate the likely effect of deferral of laser treatment beyond the first postoperative year if it is assumed that the likelihood of spontaneous resolution of CSME occurring in the first six months after surgery is constant within a given period. The assumption is tenable within a year of surgery, since CSME developing within six months of surgery resolved in half the eyes affected in the first six months after surgery, and in half of the remainder within the next six months. Extrapolating on the basis of this assumption beyond the first postoperative year, the likelihood of spontaneous resolution of CSME

occurring within six months of surgery by the end of each six month period after surgery would be successively 87.5% by eighteen months and 93.75% by two years. This would appear to support a markedly conservative approach to CSME arising de novo after surgery. However, the finding that retinopathy severity was significantly greater in eyes which CSME arising within six months of surgery failed to resolve by one year casts doubt on the assumption that the likelihood of spontaneous resolution remains constant in successive periods. If the absence of spontaneous resolution results from pre-existing decompensation of retinal vasculature rather than chance alone, one would expect that the likelihood of resolution within a given cohort would progressively decline with time, since the patients in which resolution had not occurred would increasingly represent those in which resolution was unlikely to occur because of the severity of pre-existing retinal vascular decompensation. For this reason, it may not be appropriate to defer beyond a year laser therapy for persistent CSME arising within six months of surgery.

5.2.4 Predictive value of optic disc hyperfluorescence

The original description of aphakic macular oedema by Gass was entitled "Cystoid macular edema and papilledema following cataract extraction" (Gass and Norton, 1966) and the association between optic disc and macular changes in this condition appears strong. As a consequence, the occurrence of postoperative optic disc hyperfluorescence in a patient with cystoid macular oedema following cataract surgery has been considered to imply that Irvine-Gass syndrome is present, and provided surgery is uncomplicated, that spontaneous resolution of macular oedema is likely. This seems reasonable in patients without diabetes or other intercurrent ocular pathology, but some have extended this argument to patients with diabetes (Royal College of Ophthalmologists, 1997).

In the natural history study, postoperative optic disc hyperfluorescence was invariable in eyes with increased postoperative macular fluorescence. Neither optic disc hyperfluorescence, nor its resolution, were predictive of resolution of postoperative macular hyperfluorescence or CSME. Based on these findings it is clearly inappropriate to use the presence of postoperative optic disc hyperfluorescence as an indicator of likely resolution of macular oedema. This is not surprising, given evidence to suggest that the natural history of pseudophakic macular oedema is different in patients with diabetes even in the absence of retinopathy (Menchini, Bandello et. al., 1993). The presence of disc hyperfluorescence may indicate that Irvine-Gass syndrome is present, but the likelihood of spontaneous resolution may depend on other influences, as discussed below.

Given the observation that the presence of angiographic features typical of pseudophakic macular oedema does not necessarily connote spontaneous resolution of macular oedema, it is interesting also that the natural history study provides evidence that the converse observation may also be true, that postoperative leakage from diabetic macular microvascular abnormalities may resolve spontaneously without treatment (Fig. 4.10). In pseudophakic macular oedema in patients without diabetes, fluorescein leakage from the perifoveal capillary bed presumably implies some particular susceptibility of this vasculature to the injury produced by cataract surgery. It does not seem unreasonable to assume that the presence of pre-existing diabetic damage to vascular endothelium may represent a similar, alternative susceptibility, and provided pre-existing damage is not severe, that spontaneous recovery may occur.

5.2.5 Predictive value of retinopathy severity

In the natural history study, it was observed that of patients with CSME which arose within 6 months of surgery, spontaneous resolution of CSME occurred within a year of surgery in 75%. Retinopathy severity was greater in patients in which spontaneous resolution did not occur than in those in which it did. Likewise, the tendency to resolution of postoperative hyperfluorescence of optic disc and macula was significantly reduced in eyes with more severe retinopathy. If pseudophakic macular oedema represents evidence of the ocular injury produced by cataract surgery, one might expect that in eyes with more severe retinopathy, in which by inference there is more impairment of retinal vascular autoregulation, more extensive capillary non-perfusion, and higher concentrations of growth factors promoting increased vascular permeability, the likelihood of spontaneous resolution of macular oedema would be reduced. An exception to this was noted in the few eyes in which resolution of postoperative macular hyperfluorescence was associated with progressive capillary non-perfusion. If capillary non-perfusion is sufficiently extensive, the additional insult of cataract surgery may be sufficient to accelerate its progression to the point where an overall reduction in macular fluorescence is observed.

5.3 INFLUENCE OF SURGICAL TECHNIQUE ON COMPLICATIONS

5.3.1 Postoperative inflammation

In the phakoemulsification vs. extracapsular surgery study, diabetic eyes managed with extracapsular cataract surgery showed a greater tendency to early postoperative inflammation than those undergoing phakoemulsification. Similar findings have been reported in non-diabetic eyes (Pande, Spalton et. al., 1996), and may reflect the effects of larger incision size, and greater potential for iris trauma during nucleus expression and rigid intraocular lens implantation in extracapsular surgery. Marked postoperative inflammation is commoner in diabetes, and a fibrin reaction may occur in eyes with more severe retinopathy, in which preoperative breakdown of the blood-aqueous barrier is most marked (Ferguson and Spalton, 1992; Zaczek and Zetterstrom, 1998; Hykin, Gregson et. al., 1993). Extracapsular surgery may exacerbate these tendencies, because the effects of iris trauma may be more severe in diabetes as a result of abnormalities of iris vasculature (Moriarty, Spalton et. al., 1994; Taniguchi, Nakao et. al., 1968) or poor mydriasis. The higher incidence of intraocular lens deposits following extracapsular surgery may be a reflection of increased postoperative inflammation, although biocompatibility may also be relevant, as suggested by the lower incidence of intraocular lens deposits with materials other than PMMA in non-diabetic patients (Ravalico, Tognetto et. al., 1997). Postoperative inflammation and intraocular lens deposits are of importance in diabetic eyes because they may compromise fundus visualization and management of retinopathy. That these phenomena are more marked after extracapsular surgery may be of concern in eyes with severe retinopathy, in which the tendency to postoperative inflammation (Hykin, Gregson et. al., 1993), and the need for surveillance of retinopathy is greatest.

5.3.2 Capsular opacification

A higher incidence of posterior capsule opacification was encountered in diabetic eyes undergoing extracapsular surgery than in those undergoing phakoemulsification surgery. Retinopathy was more severe in eyes undergoing capsulotomy than in those not, as in earlier studies (Ionides, Dowler et. al., 1994), but there was no difference in retinopathy severity between eyes undergoing extracapsular surgery and phakoemulsification surgery, so the disparity in capsulotomy rates between the two groups cannot be explained on this basis. Flare was more marked one week after surgery in eyes undergoing extracapsular cataract extraction, and lens epithelial cell proliferation, which is associated with posterior capsule opacification, is more marked in media with higher protein concentrations (Liu, Wormstone et. al., 1996). In addition, both the incidence of severe postoperative inflammation (Hykin, Gregson et. al., 1993), and the requirement for capsulotomy (Ionides, Dowler et. al., 1994) have been found to be greater in eyes with more severe retinopathy. However, in this study, no index of postoperative inflammation was greater in eyes undergoing capsulotomy than in those not, and it is therefore difficult to infer a direct link between posterior capsular opacification and postoperative inflammation. It seems probable that the higher capsulotomy rate in eyes undergoing extracapsular surgery was due either to the characteristics of the surgical technique or intraocular lens used, but the study design did not allow discrimination of these effects.

It is notable that in the phakoemulsification vs. extracapsular surgery study, any potential improvement of peripheral fundus visualization resulting from implantation of a rigid large-optic intraocular lens was offset by a higher incidence of posterior capsule opacification. In addition, posterior capsule opacification was commoner in eyes with more severe retinopathy, in which the need for peripheral fundus visualization is greatest (McCuen and Klombers, 1990). Although in this study retinopathy was generally less severe, and further

study is required in higher risk eyes, these findings weaken the case for the use of this form of surgery on grounds of enhanced fundus visualization.

5.3.3 Retinopathy progression and macular oedema

No difference was identified between phakoemulsification and extracapsular surgery in regard to the incidence of postoperative CSME, progression of retinopathy, or development of high-risk proliferative retinopathy. In the patients studied, therefore, the impact of operative technique on posterior segment disease was small. However, many eyes had no or only mild nonproliferative retinopathy, only four eyes required panretinal laser, and no eye required vitrectomy. It is possible that the choice of operative technique and intraocular lens may be more critical in eyes with more severe retinopathy. It has been shown, however, that phakoemulsification in eyes with proliferative retinopathy (Fung, 1987) is associated with a similar rate of retinopathy progression to that observed in eyes undergoing extracapsular surgery (Hykin, Gregson et. al., 1993) (Tables 1.1, 1.2).

It might be argued that the sample size of the phakoemulsification vs. extracapsular study was insufficient to detect differences in incidence of retinopathy progression and macular oedema, since calculations indicate the power of the study in these comparisons to be low. However, this is largely due to the similarity between incidences of retinopathy progression and macular oedema in the two surgical groups, and to achieve acceptable power in these comparisons would require a very large sample size, as the calculations indicate.

5.4 INFLUENCES ON VISUAL OUTCOME

5.4.1 CSME at time of surgery

Within each surgical group of the phakoemulsification vs. extracapsular surgery study, and in the natural history study, the effect on visual acuity of CSME at the time of surgery was significant and substantial. This finding is in accord with results of meta-analysis (Dowler, Hykin et. al., 1995b).
It may also serve to explain the variation in postoperative visual acuity in studies of cataract surgery in diabetes. In the natural history study, 84% of patients achieved a postoperative visual acuity ≥ 6/12, and in the phakoemulsification vs. extracapsular study, the respective proportions were 96% and 83%. This, whilst similar to one series (Henricsson, Heijl et. al., 1996), is in marked contrast to several earlier reports, and even one recent study (Raskauskas PA, Walker JP et. al., 1999; Jaffe and Burton, 1988; Schatz, Atienza et. al., 1994), in which postoperative visual acuity was poor. It is possible that this may have been due, in some cases, to the presence of macular oedema at the time of surgery, which remained undetected before surgery because of the presence of cataract, and after surgery because of poor mydriasis, photophobia, fibrinous postoperative uveitis, intraocular lens deposits, capsulorrhexis aperture contraction, capsular opacification, and in earlier studies, the refractive instability of extracapsular wounds.

The association of poor postoperative visual acuity with the presence of CSME at surgery has important implications for the timing of surgery. Some authors (Schatz, Atienza et. al., 1994; Pollack, Leiba et. al., 1992a; Pollack, Leiba et. al., 1992b) have recommended that cataract surgery in patients with diabetic retinopathy be deferred until visual acuity is markedly reduced, or not undertaken at all. Deferral of surgery, however, is likely to increase the risk of undetected macular oedema at the time of surgery and therefore poor postoperative visual acuity. It seems more logical to operate before cataract has

developed sufficiently to impede appreciation of retinal thickening, so that the risk of undetected macular oedema at the time of surgery is reduced. If so, retinal specialists should have a low threshold for referring patients with diabetic retinopathy for cataract surgery, and close pre- and postoperative co-operation between retinal specialist and cataract surgeon should be encouraged, to optimise management of macular oedema and visual outcome.

5.4.2 Retinopathy severity

A significant, though small, negative association between retinopathy severity and postoperative visual acuity was encountered in both surgical groups of the phakoemulsification vs. extracapsular surgery study. Univariate analysis identified a similar relationship in the natural history study, but this was not sufficiently robust to be apparent on multivariate analysis. Meta-analysis also suggests such a relationship (Dowler, Hykin et. al., 1995b).
This observation cannot be explained on the basis of an association between presence of CSME at the time of surgery and severity of retinopathy at the time of surgery, since in both arms of the phakoemulsification vs. extracapsular surgery study and in the natural history study, such an association was sought but not found. A more likely explanation may be that, as in the natural history study, more severe retinopathy was associated with a reduced tendency to spontaneous resolution of postoperative macular edema, with consequent impairment of visual acuity.

5.4.3 Operative technique

In this study, postoperative visual acuity was greater after phakoemulsification than extracapsular surgery, especially if retinopathy was present. There was no difference between techniques in the incidence of CSME, and the difference in visual acuity cannot therefore be explained on this basis. However, indices of

postoperative inflammation were greater in eyes undergoing extracapsular surgery, and it is possible that vitreous opacity or intraocular lens deposits may have degraded acuity in some eyes undergoing extracapsular surgery. The greater disparity in visual acuity between surgical groups in eyes with retinopathy accords with this, since the degree of postoperative inflammation appears to correlate with presence and severity of retinopathy (Zaczek and Zetterstrom, 1998).

5.5 FUTURE DIRECTIONS

5.5.1 Early surgery for diabetic cataract

On the basis of the data presented, it is reasonable to infer that cataract surgery undertaken in patients with diabetic retinopathy before cataract has progressed to the point at which recognition of retinal thickening is impaired, may reduce the risk of CSME at the time of surgery and a poor visual outcome. Sample sizes were however small, and the implications of proving such a hypothesis are considerable, given the numbers of patients with diabetes undergoing cataract surgery each year. There is thus a need for a large scale prospective trial to address this issue.

5.5.2 Laser treatment of postoperative macular oedema

The observation that CSME present at the time of surgery showed no tendency to resolution in the first postoperative year, and showed angiographic evidence of worsening, suggests that there is little justification for withholding macular laser therapy in such patients. However, the deferral of laser therapy due to failure to recognise CSME before surgery may render CSME refractory to treatment, and limit any visual benefit. A therapeutic trial is required to inform management and appropriately advise patients.

5.5.3 The effect of systemic factors on the outcome of cataract surgery in diabetes.

The studies described in this thesis focus largely on ocular determinants of the outcome of cataract surgery in patients with diabetes. Recent data make it clear that systemic factors, particularly hypertension (UK Prospective Diabetes Study Group, 1998b), and glycaemic control (UK Prospective Diabetes Study Group, 1998a; Diabetes Control and Complications Trial Research Group, 1993), have a major impact on retinopathy, and it seems likely that they may influence the outcome of cataract surgery in diabetes, as preliminary data suggest (Henricsson, Heijl et. al., 1996). Studies in pregnant patients with diabetes (Chew, Mills et. al., 1995) have shown that not only glycaemic control, but also changes in glycaemic status, may influence the likelihood of progression of retinopathy, and similar relationships may exist in regard to cataract surgery. Further study is required to address this issue.

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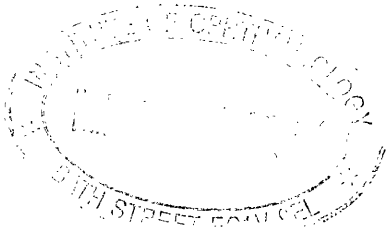

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7 PUBLICATIONS ARISING FROM THIS WORK

1. Phakoemulsification vs. extracapsular cataract extraction in diabetes Dowler JGF, Hykin PG Hamilton AM. Ophthalmology. 1999; In press.

2. The natural history of macular edema after cataract surgery in diabetes. Dowler JGF, Sehmi KS, Hykin PG, Hamilton AM. Ophthalmology 1999; 106: 663-665.

3. Panretinal photocoagulation during cataract extraction in patients with active proliferative diabetic eye disease. West JA, Dowler JGF, Hamilton AMP, Boyd SR, Hykin PG. Eye 1999; 13: 170-173.

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8 GLOSSARY

APDR	Active proliferative diabetic retinopathy
CSME	Clinically significant macular edema
DCCT	Diabetes control and complications trial
DR	Diabetic retinopathy
DRS	Diabetic retinopathy study
DRS HRC	Diabetic retinopathy study high-risk characteristics
ECCE	Extracapsular cataract extraction
ETDRS	Early treatment diabetic retinopathy study
IOL	Intraocular lens
NPDR	Nonproliferative diabetic retinopathy
PCO	Posterior capsule opacification
PDR	Proliferative diabetic retinopathy
PDR s HRC	Proliferative diabetic retinopathy without DRS HRC
Phako	Phakoemulsification surgery
PMMA	Polymethylmethacrylate
QPDR	Quiescent proliferative retinopathy
UKPDS	UK prospective diabetes study
WESDR	Wisconsin epidemiological study of diabetic retinopathy

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