

A National Research Strategy for Ophthalmology

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1 Introduction

Ophthalmic disease is common. By the time we retire 1 in 50 of us will have developed a visual disorder - and after retirement the incidence rises sharply. The diagnosis and treatment for sight threatening ocular disease may be made too late to prevent significant visual disability, and some of the more common blinding disorders currently have no useful treatment at all. Legal blindness affects mainly the elderly and respects no one. In an ageing population there is an increasing need for research into incidence, causation and treatment of blinding eye disease. Because researchers never have sufficient resources for their perceived needs a system of prioritisation is required.

Why research into eye disease? Not only is eye disease common, but also the effects can be devastating. Loss of vision comes only second to chronic pain in the league table of patient fears. Blindness dramatically increases the risk of long-term unemployment in the young and social dependency in the elderly, both resulting in huge economic impact. Any research that minimises this effect on society must be seen to have major benefit to us all. Chapter 2 provides a brief description of the epidemiology of eye disease, drawing on work funded by the NHS and the voluntary sector. It is augmented by additional information on the risk factors for disease and the burden of visual impairment on the health and well being of the population.

The Royal College of Ophthalmologists has sought the views of researchers into eye disease for the major problems affecting the specialty and asked them to prioritise research areas for the next five years. The areas covered have been retinal diseases, cataract, glaucoma, cornea and external eye disease, ocular adnexal disease, neuro-ophthalmology and the specialised area of visual rehabilitation. These are followed by chapters on paediatric ophthalmology, squint and amblyopia. Each section has included health services, clinical and laboratory research. Each has followed the principle that the problems of diagnosis, mechanism and treatment are best addressed by combining laboratory and clinical research and are dependent on free interplay between clinical and laboratory skills. The outcomes of any research endeavour need to be looked at in terms of prevention, treatment and rehabilitation, and will be dependent upon dissemination of results throughout the community in such a way as to improve public awareness and eye health. Each chapter concludes with a set of research priorities.

The contributors to this document include patient support groups, laboratory workers, clinical scientists, ophthalmologists and other health professionals. The results are a composite of their views and priorities. The original drivers for research come from population need, and this has been set out in the following section that outlines the health burden of eye disease and the economic consequences.

As with any exercise in crystal ball gazing the research priorities that have been identified may be near the mark now, but be knocked off course by new problems or unexpected solutions developing during the five-year period of the plan. However, their ideas are combined into a national view of the directions ophthalmic research can be expected to take.

Roger Hitchings Paul Hiscott John Marshall

2 Epidemiology of Eye Disease in the Older Population

2.1 Background

In general, when estimating the incidence and prevalence of disease or state of health in the population, epidemiologists draw on mortality data, registration data (cancer), data from surveillance and notification, utilisation data, and on results of large-scale population-based studies. Some of these approaches are relevant only to particular diseases. In the case of eye disease in the UK, there has been heavy reliance on registration and utilisation data to the detriment of more valid epidemiological approaches such as population based cross-sectional and cohort studies. Epidemiological studies also address the issues of causation, risk, and the effectiveness of preventive, screening and treatment programmes. The funding of epidemiological studies in eye research has been at a modest level compared with the experience in North America, where there has been substantial investment in pertinent approaches. Nevertheless, there have been a number of important studies in the last decade in the UK and Ireland that have provided useful data. These include The RNIB Survey (1991), the OPCS Causes of Blindness Study (1995), The Irish Glaucoma Survey (1992), The North London Eye Study (NLES) (1998), and The National Cataract Surgery Survey (2000). The sources of data utilised for this report and some of the most important study references are listed at the end of this section (2.4)

2.1.1 Notes on Methodology

In estimating the magnitude of visual impairment and the major eye disorders in the population, we have collated the prevalence (and incidence) data specific to subgroups defined by age, sex, and (where relevant ethnic groupings), obtained from the most germane recent studies that have investigated ‘unbiased’ samples from defined populations. These group-specific ‘rates’ from samples have been applied to the corresponding strata in the older population (60 or older) of England and Wales, to compute the magnitude estimates for the whole older population and for various age groups within it. This preferred methodological approach has not been possible for some of the less frequent eye disorders for which there are no satisfactory prevalence or incidence data. In the absence of longitudinal cohort studies, most of the incidence rates used here have been derived from age-specific prevalence data according to a widely employed statistical procedure. Thus the incidence estimates are not based on direct measures and should be interpreted with due caution. For glaucoma, we have also used predictive equations based on the collective data from several cross-sectional studies in Europe, Australia, and North America. The utility of these predictive equations are addressed in reference 3 of source 2 (2.4). For cataract, some of the findings from an epidemiological model of the population dynamics of the disorder are also reported (source 2, reference 2).

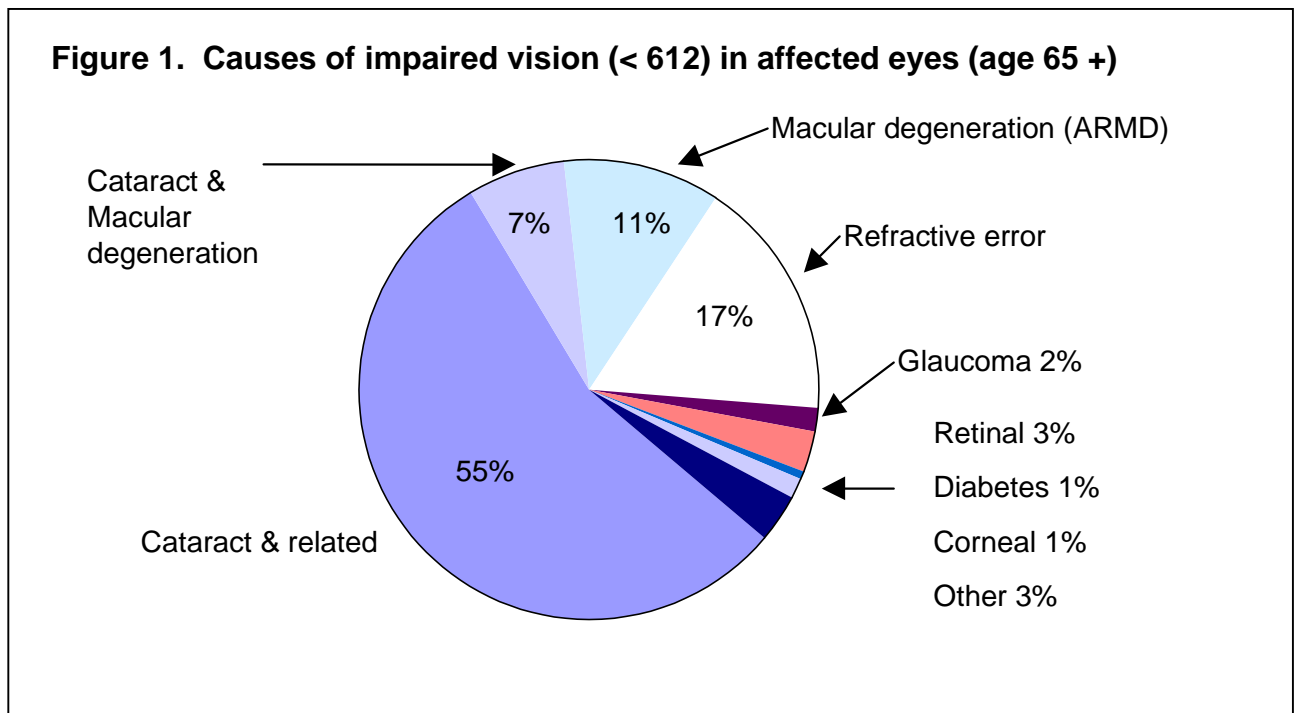
2.2 The Magnitude of the Problem and the Population Need

The following estimated figures for the older population are derived from the data sources listed in 2.4. Formally, the older population is defined as those aged 60 and older. Most of the estimates, however, refer to the population aged 65 and older, for whom robust epidemiological data were available. Visual impairment and its causes are presented first, followed by refractive errors and the impact of visual loss on health and social well being. The next topic is that of macular disease and diabetic eye disease. This is followed by data on cataract and glaucoma, including their treatment costs in the UK.

2.2.1 Visual Impairment and its causes

In the older population of 8.3 million aged 65 and above in England and Wales, 4.3 million have impaired vision (<6/12) in one or both eyes (source 1). Of these, 2.4 million have impaired vision in both eyes. It is estimated that 72% are remedial through surgery or refraction and dispensing of spectacles.

Figure 1 shows the causes of impaired vision in those aged 65 and older (source 1). The largest cause is cataract with 55%. Macular degeneration accounts for 11%, and a further 7% of cases have both cataract and macular degeneration. In 17% of cases, the impairment is attributed to refractive error.



According to the RNIB notification received from the ONS (source 5), some 168,000 are registered blind and 147,000 are registered as partially sighted in England and Wales (all ages). Although the register is useful for estimating incidence and prevalence of blindness and serious visual impairment, the degree of under-certification may be as high as 64% for blind and 77% for partially-sighted people (source 8, ref 10).

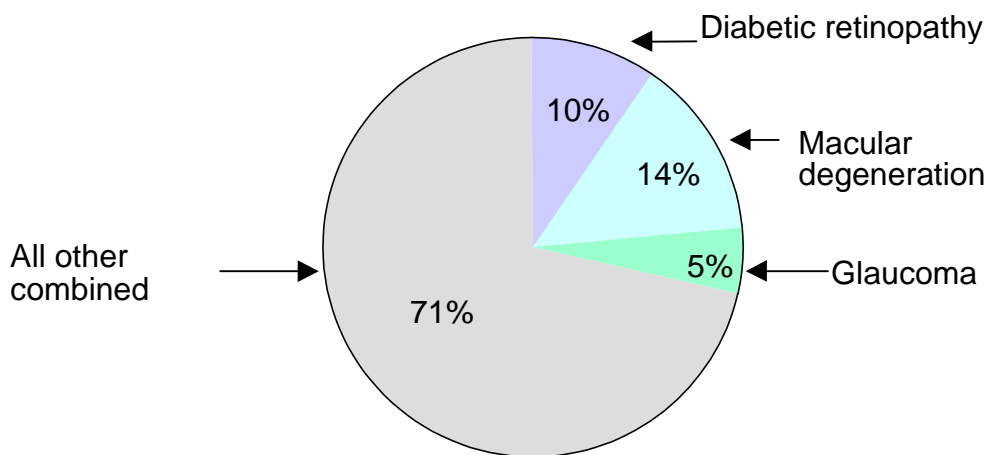
An analysis of the new blindness and partial sight certifications received by the ONS in one year (1990-91) has given an indication of the annual incidence of the largely irremediable serious visual loss (source 8, ref 11). A summary of the figures, shown in [Table 1](#), points to macular degeneration as the leading cause.

Table 1. Blindness and partial sight certification in England and Wales during one year (1990-91) for those aged 65 and older.

Cause	Blind	Partial sight (PS)	Blind+PS	Percentage of total
Macular degeneration	6,445	6,747	13,192	54%
Glaucoma	1,517	1,348	2,865	12%
Diabetic retinopathy	262	276	538	2%
All other causes	3,520	4,301	7,821	32%
Totals	11,744	12,672	24,416	

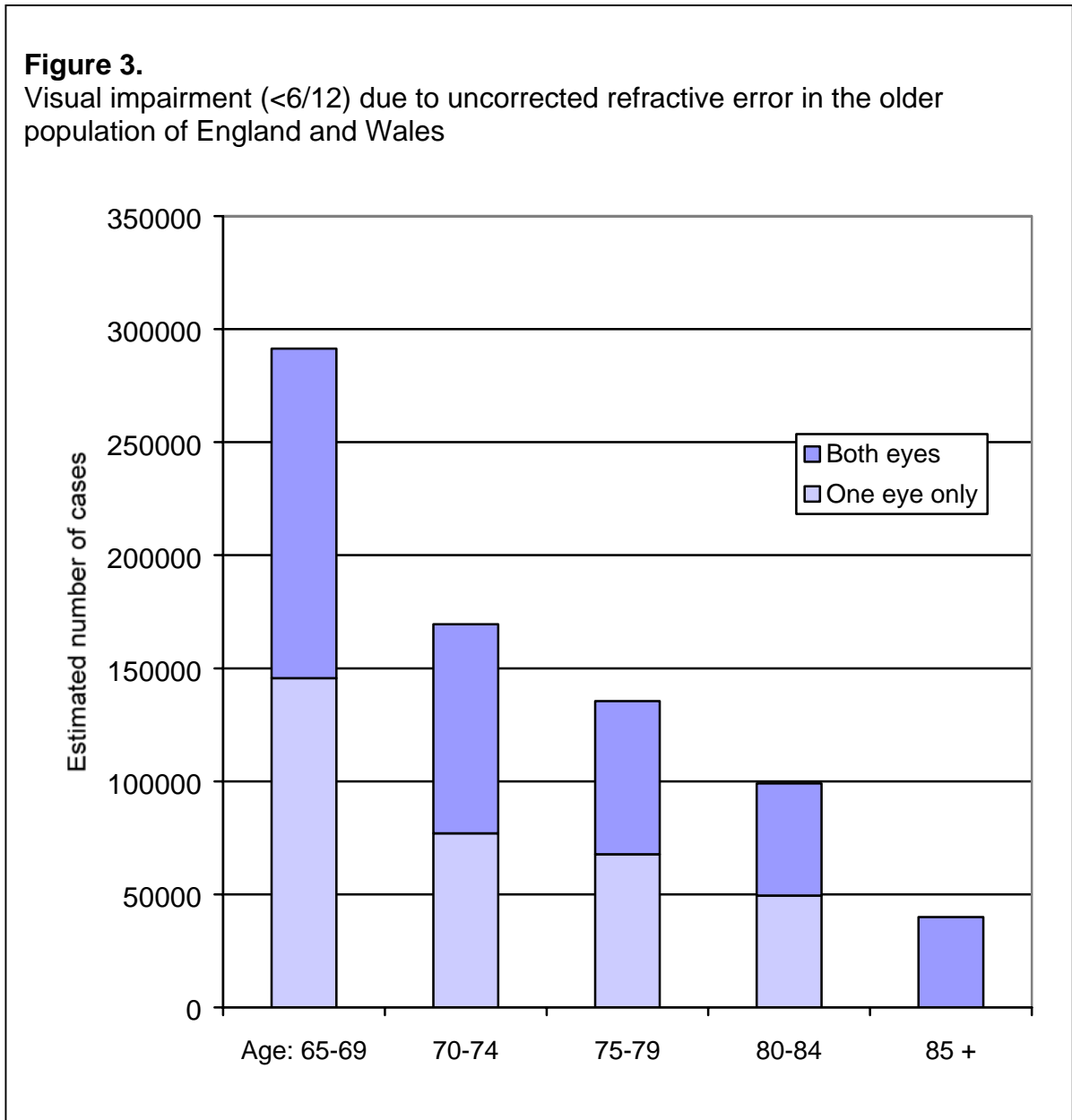
The causes of new blind and partial sight certification in England and Wales for the working population aged 16-64 are presented in [Figure 2](#) (source 8, ref 11). This shows that macular degeneration accounts for 14%, diabetic retinopathy 10%, and glaucoma 5% of the 3943 certifications received by the ONS in one year.

Figure 2. New blind and partial sight certifications in England & Wales in 1 year for the working population aged 16-64.



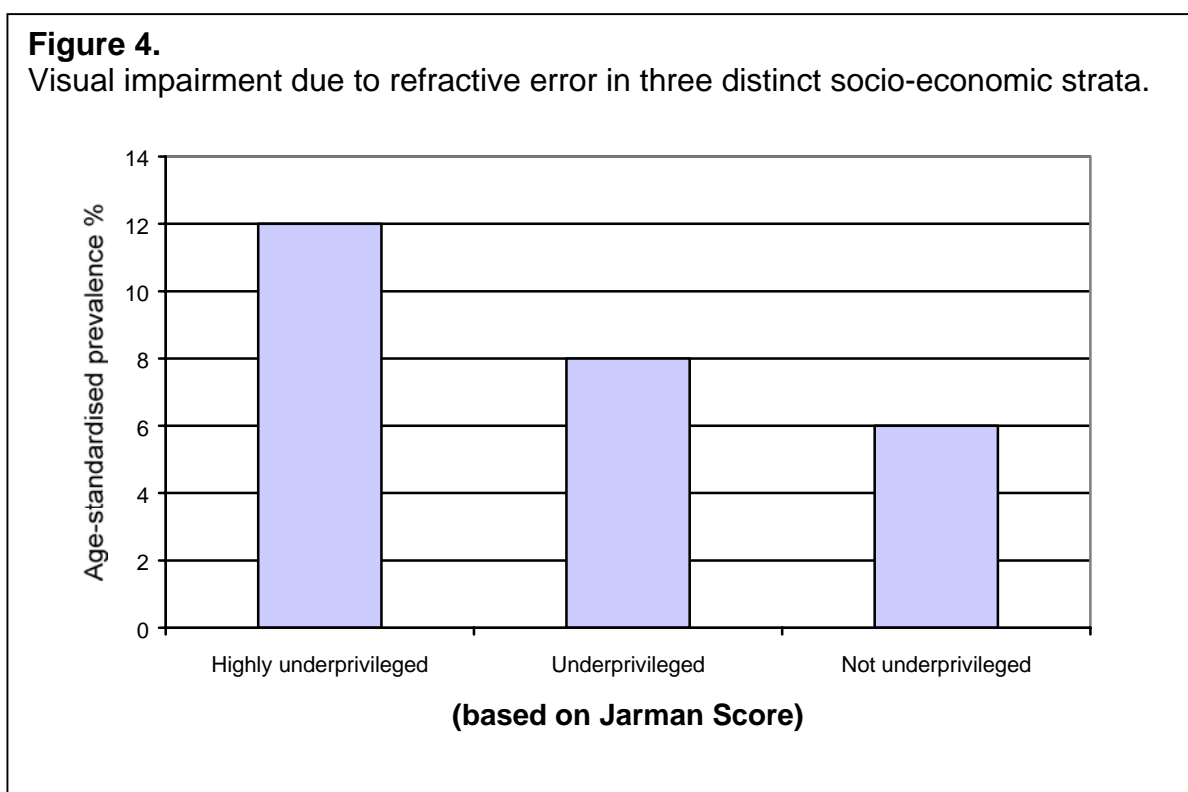
2.2.2 Refractive errors

In the older population of England and Wales (age 65 and older), a total of 735,000 have impaired vision (<6/12) in one or both eyes due to refractive error. Figure 3 shows the age distribution of the cases.



Some 395,000 have impaired vision in both eyes and need spectacles to bring their visual acuity up to the level required for driving. Prior to introduction of the free sight test in 1999, at least 2/3 had not had a recent eye test (source 1).

Visual impairment due to uncorrected refractive error is significantly more common in underprivileged areas (findings from NLES). [Figure 4](#) shows the age-standardised prevalence in three socio-economically distinct areas (grouping based on the ‘Jarman Scores’).



2.2.3 The Impact of Visual Impairment on Health and Social Wellbeing

Sub-populations of adults thought to be particularly at high risk of sight-impairing disease are:

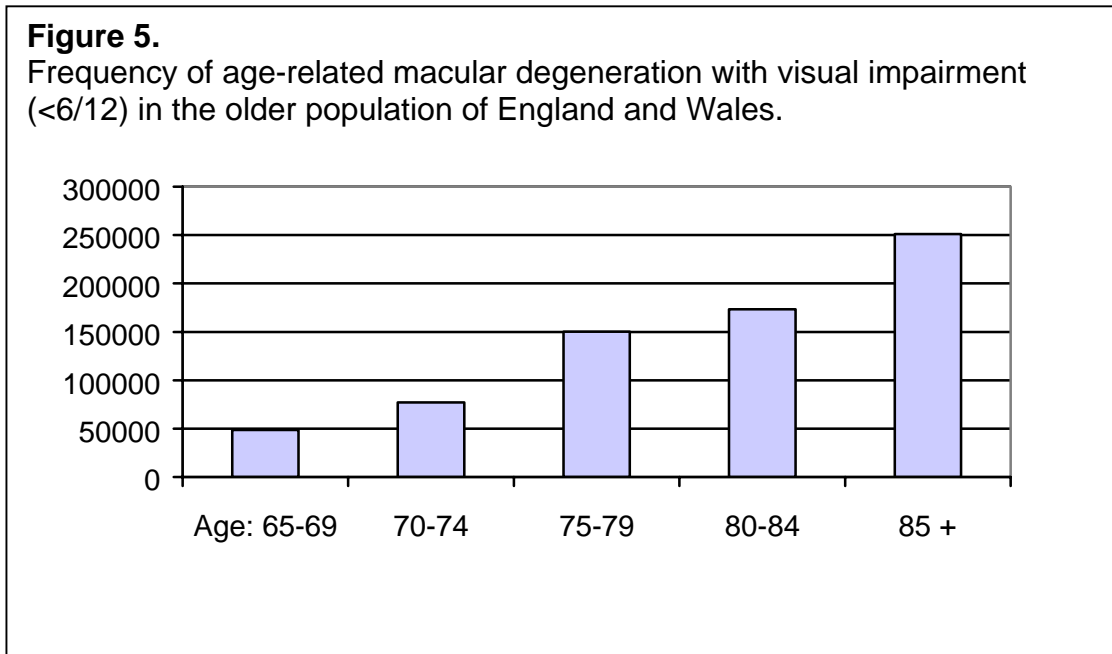
- Asian & African-Caribbean ethnic groups
- families of affected individuals

Studies have demonstrated an association between visual impairment and:

- Increased mortality
- Increased morbidity from falls and fractured neck of femur
- Increased risk of road accidents
- Increased levels of anxiety and depression
- Poorer levels of self-care and independence, and
- Higher usage of community & institutional resources
- Social isolation, & diminished leisure activities
- Loss of income

2.2.4 Macular disease

Almost 700,000 aged 65 and older have sight-impairing macular degeneration. [Figure 5](#) shows the estimated number of cases in various age groups of the population (source 1).



Macular degeneration is largely irremediable, and according to source 8 (ref 11), is the leading cause of blindness certification in those aged 65 and older, accounting for 6445 (55%) of the 11744 new certifications in one year ([Table 1](#)).

A survival analysis (source 2) of the prevalent cases (based on the age distribution shown above) indicates that in the absence of effective treatment, 5.7 million person-years of impaired vision are expected among those aged 65 years and older ([Table 2](#)).

Table 2. Person-years of impaired vision expected among prevalent cases of macular degeneration in England and Wales.

Age Group	Number of prevalent cases	Person-years (millions) of impaired vision expected.
65-69	48,558	0.8
70-74	77,042	1.0
75-79	150,005	1.5
80-84	173,339	1.2
85 +	250,929	1.2
65 and older	699,873	5.7

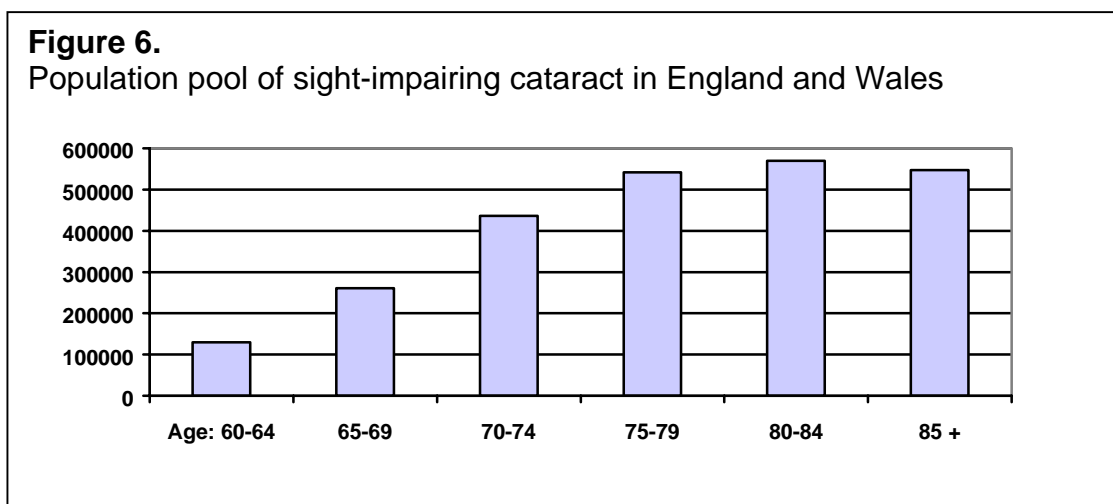
2.2.5 Diabetic eye disease

An estimated 1.4 million in the UK have diabetes. One million more are thought to have the condition, as yet undiagnosed (source 4). Prevalence of diabetic retinopathy requiring treatment among diabetics registered with GPs is estimated to be between 1% to 6% (source 2, ref 5). This amounts to between 14,000 and 84,000 persons with sight-threatening diabetic retinopathy in England & Wales. The imprecision of these estimates reflects the paucity of epidemiological data on the UK diabetic population.

Among the working population, diabetic retinopathy is the commonest single cause of certification for blindness, accounting for 201 (12%) of the total of 1695 cases (source 8, ref 11). An analysis (source 2, ref 4) suggests that a community-based screening programme encompassing detection, referral, treatment, and follow-up would save 260 new cases of blindness in diabetics under the age of 70 each year in England and Wales.

2.2.6 Cataract

Figure 6 depicts the population pool of cataract cases with impaired vision (<6/12) in one or both eyes, in England and Wales. The data (based on source 1, and 2) indicate that 2.5 million aged 60 and older have sight-impairing cataract. Most of these (2.4 million) are aged 65 and older.



An estimated 225,000 new cases are expected each year. The 5-year cumulative incidence is estimated at 1.1 million new cases among the population aged 65 and older (source 2)

A total of 188,558 cataract operations were performed in the UK in the year 1999-2000 (NHS Executive 'Reference Costs 2000'). Not all of these operations, however, would relate to the pool of cases depicted in Figure 6. Some 85 to 87% of all operations are performed on patients aged 65 and older (DoH Hospital Episodes Statistics, and source 3), and 27% of these operations are performed on eyes with visual acuity better than 6/12 (source 3). Thus at most about 64% of all cataract operations are directed at the pool of 2.4 million potential cases depicted in Figure 6, i.e. persons aged 65 and older who have visual impairment (<6/12) due to cataract.

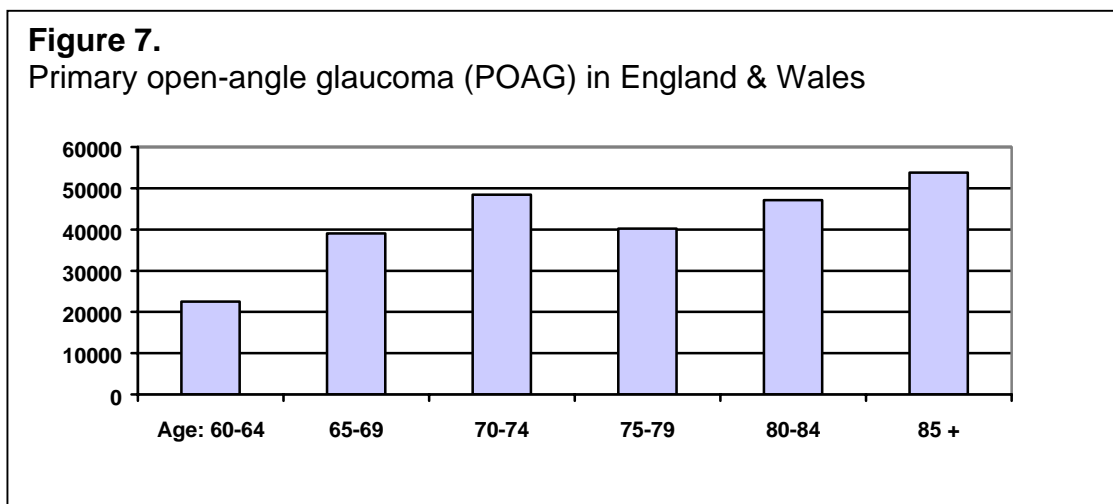
Based on the figures in ‘Reference Costs 2000’ we estimate that the current total annual cost of cataract surgery in the UK is at least **£119 million**. The portion spent on cases aged 65 and older in England and Wales is about **£103 million** (source 9, ref 13)

An epidemiological model of the population dynamics of cataract and its management (source 2, 1999) has suggested that if no changes were made in provision of cataract surgery (no targeting or prioritisation and only an expected 10,000 or so additional operations per year), the population pool of cases would increase by about 8.5% in a 5-year period. The provision of about 95,000 additional operations per year should control the population pool, with no escalation of the backlog over the 5-year period. An estimated **£60 million** would be required annually to achieve this, using the present service output and surgery thresholds. More cost-efficient strategies using prioritisation or targeting may be possible. The cost of controlling the backlog may be reduced substantially to under **£20 million** if epidemiology and economics research was employed to inform and evaluate the alternative strategies.

2.2.7 Glaucoma

Primary open-angle glaucoma (POAG) requires life-long treatment & follow-up.

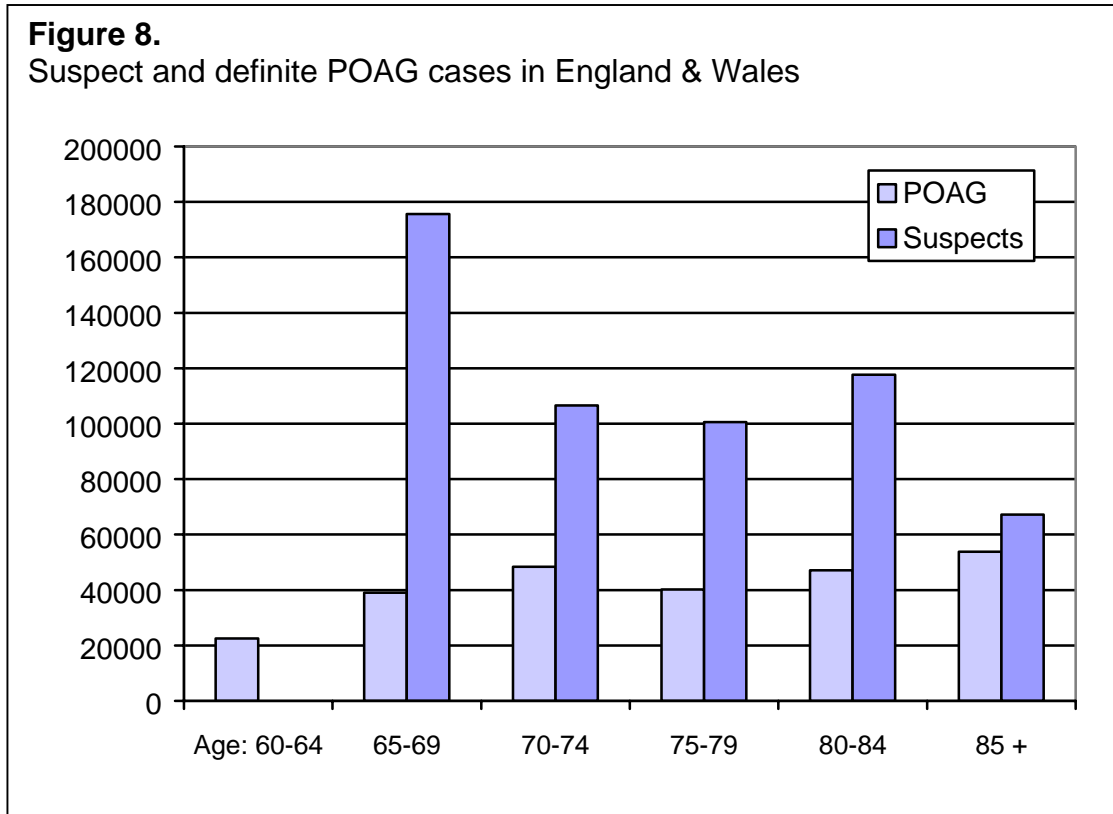
Figure 7 shows the number of ‘definite’ POAG cases in the population aged 60 and older in England and Wales. The data (sources 1 and 2), based on age-specific prevalence figures from the North London Eye Study, and predictive logistic equations derived from a number of studies in Europe, Australia, and USA, indicate that 250,000 have definite POAG. At least half of these do not come forward for timely diagnosis.



We estimate that about 15,000 new definite cases are expected to occur each year. Glaucoma accounted for 1517 (13%) of the 11744 new blindness certifications in one year for those aged 65 and older (Table 1).

Findings from the NLES (source 1) suggest that there are 570,000 suspect cases of POAG, and that one in five of these unconfirmed cases are known to the eye services and are being monitored through repeated visits to eye clinics, usually for life.

Figure 8 shows the distribution of the suspect POAG cases by age, in relation to the definite cases, for the older population of England and Wales.



The annual costs of treatment for those aged 60 years and over in England and Wales (source 9, ref 12, and source 2, ref 3).

For those diagnosed and in treatment an estimate of the total yearly cost to the NHS is **£50 million**. For those who do not meet the present clinical criteria for diagnosis but are considered as suspected glaucoma and are receiving treatment the estimate of yearly costs to the NHS is **£90 million**. The pool of morbidity in the population is considered to be at least twice that which is detected and at present treated. Increased detection in primary care through the General Practitioner and optometrist without corresponding advances in diagnosis and treatment could result in a doubling of the above estimates to a yearly total figure nearing **£300 million**.

2.3 Research Priorities

The epidemiological and service research priorities in the context of the main eye disorders are mentioned in the relevant chapter. Here, we outline the importance and direction of further epidemiological research.

In aetiological research the general approach has been to focus each study on a particular eye disorder and to investigate the possible determinants. A useful complementary approach would be to consider all disease or health outcomes of exposure to a particular risk factor or protective factor. Such exposure-oriented research should lead to a more holistic appreciation

of the exposure factor's importance for public health. The approach would require the working collaboration of disease experts and exposure experts (e.g. nutritionists) or 'aetiologists', i.e. epidemiologists with special interest in public health aspects of a particular exposure or risk factor complex. The methodology would focus on major cohort follow-up studies and large-scale randomised trials with long-term outcome assessment. Potential candidates for this research approach may include nutritional / dietary factors, alcohol consumption, and hormone replacement therapy, with a wide spectrum of ocular and other health indicators included as outcomes.

Large eye surveys planned primarily for estimation of the prevalence of visual impairment and eye disease in countries within Europe would probably fail to attract major funding. Those planned to form the initial cross-sectional phase of analytical cohort studies should have a higher chance of success. Generally, the approach in the past has been to limit the study scope to matters of vision and eye disease. Future large sample surveys should be multidisciplinary, aiming to obtain data on the population burden of a broader spectrum of disability or dysfunction (hearing, mobility etc.) and the causal disorders, so that the 'general functional health' status of the population may be assessed.

Health authorities may increasingly tend to base the planning of future levels and type of service on sound epidemiological models of population need (see source 2). Such models are scarce, and the very few which exist, are in great need of more diverse, precise and reliable input data. Consequently, studies designed specifically to generate such data and to enable the development of new models may become favoured, particularly if they are made germane to the requirements of the owner-users of the intended model, i.e. the health provider / commissioner.

In general medicine several biological measures exist, which can herald the coming of a disease, indicate its presence, or quantify the severity of disease or dysfunction. Many of these measures are 'continuous'. Their population mean values (norms) have had to be established, and the cut-offs that indicate abnormality have had to be defined. Discovery and development of such new objective measures for eye disorders is a reasonable expectation, in view of the advances in molecular biology and genetics. Population-based cross-sectional studies should play a central initial role in establishing the 'norms' and critical cut-off values. Biological measures that are permanent markers for transient exposures or quantify cumulative life-time exposure may be developed, and may require initial assessment through cross-sectional studies. Other developments may also require future cross-sectional studies for assessment and exploration of relationships. An example of such new advances would be the development of a sensible scoring system for visual function or for vision related quality of life, such that may be applicable across the spectrum of the major eye disorders and cultures.

Epidemiological research will be of increasing importance in the evaluation of interventions, both preventive and curative. These large-scale studies should not only measure clinical effectiveness but should also incorporate an economic evaluation. A feature of modern epidemiological studies is that they need to be consistently and comprehensively funded. We would hope that professional bodies, universities and funding agencies continue to work collaboratively to ensure this.

2.4 Sources of Data and Study References

Source 1. The North London Eye Study (NLES)

1. Reidy A, Minassian DC, Vafidis G, Joseph J, Farrow S, Wu J, Desai P, Connolly A. Prevalence of serious eye disease and visual impairment in a north London population: population based, cross sectional study. *BMJ* 1998;**316**:1643-1646

Source 2. Epidemiological Modelling of Eye Disease for Public Health Planning

2. Minassian DC, Reidy A, Desai P, Farrow S, Vafidis G, Minassian A. The deficit in cataract surgery in England and Wales and the escalating problem of visual impairment: epidemiological modelling of the population dynamics of cataract. *Br J Ophthalmol* 2000;**84**:4-8

3. Minassian DC, Reidy A, Coffey M, Minassian A. Utility of predictive equations for estimating the prevalence and incidence of primary open angle glaucoma in the UK. *Br J Ophthalmol* 2000;**84**(10):1159-1161.

4. Rohan TE, Frost CE, Wald NJ. Prevention of blindness by screening for diabetic retinopathy: a quantitative assessment. *BMJ* 1989;**299**(6714):1528.

5. Bachmann MO, Nelson SJ. Impact of diabetic retinopathy screening on a British district population: case detection and blindness prevention in an evidence-based model. *J Epidemiol Community Health* 1998;**51**(1):45-52.

Source 3. The National Cataract Surgery Survey

6. Desai P, Minassian DC, Reidy A. National cataract surgery survey 1997-8: a report of results of the clinical outcomes. *Br J Ophthalmol* 1999;**83**:1336-1340

7. Desai P, Reidy A, Minassian DC. Profile of patients presenting for cataract surgery in the UK: national data collection. *Br J Ophthalmol* 1999;**83**:893-896

Source 4. Diabetes UK internet library

Source 5. Royal National Institute for the Blind (RNIB)

8. Bruce I, McKennell A, Walker E. Blind and partially sighted adults in Britain: the RNIB survey volume 1. HMSO London 1991.

Source 6. Office for National Statistics

Source 7. NHS Executive, 'Reference Costs 2000'

Source 8. Blind and partial-sight registration

10. Evans JR, Wormald RP. Epidemiological function of BD8 certification. *Eye* 1993;**7**(1):172-179.

11. Evans J. Causes of blindness and partial sight in England and Wales 1990-1991. HMSO, London 1995.

Source 9. Cost of illness studies.

12. Jonsson B, Kriedlstein. Primary open-angle glaucoma: differences in international treatment patterns and costs. Isis Medical Media, Oxford 1999.

13. Minassian DC, Reidy A. Visual impairment from cataract in England and Wales: the NHS surgical burden. *CE Optometry* 2001;**4**(2):52-54

3 Retinal Disorders

3.1 Background

Disease affecting the retina causes the majority of the visual disability and blindness in the UK population. Although, retinal disease is mostly untreatable (vision can rarely be restored by clinical intervention once visual loss has occurred), it can sometimes be prevented, as in an effective screening strategy for diabetic patients. Inflammatory retinal disorders may also be improved with appropriate treatment. Through recent unprecedented advances in research into healthy and diseased retina, to which UK-based clinicians and scientists have made major contributions, real opportunities for the development of novel treatments now exist. The spectrum of disease includes the following classes of disorders.

3.1.1 Age-related macular degeneration

The recent past has seen an upsurge of interest in the function and dysfunction of the macular retina. This small region of the retina centred around the visual axis is responsible for fine and discriminant vision encompassing the functions of resolution, colour perception, contrast sensitivity, scanning, reading and detection of motion. Diseases of the macula, which were previously under-researched are now the focus of attention particularly owing to the identification of degenerative age-related macular disease as the major visual public health problem of the 21st century. Age-related maculopathy (ARM) is a common disorder of the macular retina accounting for the majority of blindness and partial sight in the developed world. The disease is responsible for over 50% of all blind and partially-sighted registration in the UK and is estimated to affect over three million people in the UK. The magnitude of the problem will grow significantly as the number of elderly people increases; one study projects an increase of over 29% in the number of people over the age of 65 years in the next 20 years in the UK. Moreover, the disease may be increasing in prevalence in real terms over and above that due to changing demographics. The fact that the disease is untreatable and non-preventable increases the frequency of the contact of sufferers with the medical and social professional services. The resulting disability requires symptomatic amelioration of, and ongoing social support with. Although not life threatening, age-related macular degeneration (AMD) has been judged, on the basis of a spectrum of measures of patient disability, as the third most disabling disease in the US population after diabetes and cancer. For these reasons, funds into AMD research have been targeted recently as a high priority in the distribution of US NIH/NEI national funding. Clearly, the development of measures to prevent or a strategy to treat even a small proportion of sufferers of AMD, will produce a large saving in health care costs and a substantial reduction in disability of a large proportion of the population. Research into the genes and proteins underlying the disorder offers the most promising hope for the development of such novel treatment strategies.

3.1.2 Vascular retinal disease

Disease of the retina due to complications arising secondary to retinal vascular disease include common disorders such as diabetic retinopathy and retinal vein occlusion. Diabetic retinopathy is the leading cause of blindness in the working population of the UK. Diabetes affects over 2% of the British population and, as with age-related macular degeneration, the prevalence of Type II disease is likely to increase in the future in the UK with the changing demographics of the population. It is estimated that a diabetic person has a 10-20 times greater likelihood to be registered blind than a non-diabetic person. Unlike AMD, clinical research has identified at least partially effective preventive treatments, including intensive diabetic control, control of hypertension and retinal laser photocoagulation for proliferative diabetic retinopathy and macular oedema (responsible for 70% of visual loss in diabetic patients). Secondly, vascular occlusion occurring in the venous and arterial retinal vasculature is also a common cause of visual loss in the Western population although it is rarely bilateral. Occlusion of the central retinal vein or a branch of the retinal venous system are the most common events, with the incidence of central retinal vein occlusion (CRVO) being approximately 30/100,000 persons/year. Only 6% of eyes with CRVO recover at least 3 lines of visual acuity at one year.

3.1.3 Inherited retinal disease

Monogenic retinal disorders including retinal dystrophies, chorioretinal dystrophies and stationary retinopathies although less common than AMD and diabetic retinopathy, affect approximately 1 in 3000 persons. Because these disorders are untreatable and often severe, they place a high burden in terms of rehabilitation and care for those people affected. Over and above the direct burden of disease, these disorders also allow a special opportunity for the identification of key molecules in retinal biology and disease. Through the strategies of linkage analysis and physical mapping, many causative genes for retinal disease have been determined; each discovery elucidates a key molecule in retinal biology which directs further research into protein structure, interaction, function and pharmacology. To date, over 69 such genes have been characterised as causing retinal disease and a further 59 distinct chromosomal loci have also been identified. The impact of these discoveries on all retinal disease and the development of novel therapies is likely to be highly promising if funding is directed towards research programmes targeted at strategies that follow-on from gene discovery.

3.1.4 Inflammatory retinal disease

This is a major cause of severe visual loss in patients of working age. Intraocular inflammation is largely an autoimmune condition, which may or may not be associated with systemic disease. Many types of intraocular inflammation can result in inflammation in the retina and cause breakdown of the blood-retinal barrier (BRB). This is normally very tight but when its integrity is breached due to active inflammation, retinal oedema can result and cause visual loss. The pathogenesis of these conditions is very similar to that of other autoimmune disorders such as thyroiditis and insulin dependent diabetes. It is unknown as to the initial stimulus but infection with an unknown agent may be implicated in triggering the immune response which affects the eye in individuals who may be genetically susceptible to this

insult. CD4+ T-cells infiltrate all layers of the eye and secrete cytokines which may recruit in other cell types as well as directly affecting the retinal tissues and disturbing function. Treatment is aimed at reducing the activity of these infiltrating cells and have to be given systemically in patients with bilateral disease. Although current immunosuppressive therapy may help many patients, the drugs themselves have many unpleasant side effects and in about 30 % of patients with severe inflammation they may be ineffective. The most common cause of visual loss, which responds poorly to treatment, is chronic macular oedema due to intractable BRB failure.

3.2 Research Potential

3.2.1 Age-related macular degeneration (AMD)

Susceptibility to AMD is determined partly by a person's genes as shown by a number of family- and twin-based studies. Although many candidate genes have been generated by the study of monogenic disorders (see below), association studies for AMD have so far been negative, although a protective effect of ApoE4 has been suggested. The genetic study of AMD is challenging due to the absence of DNA and clinical data from parents of affected people, the difficulty in classification and quantification of disease and the likely ethnic variability in the disease and the underlying genetic factors. A careful collection of phenotypic data and DNA/RNA and the recruitment of affected sibships is required to make further progress in this challenging area. Studies of many polymorphisms in many distinct candidate genes as well as the identification of further loci using linkage analysis in sibs, will be required to elucidate the genes involved. Following the discovery of any new gene implicated in the disorder further laboratory research is required to elucidate its expression, function and pharmacology (see below - inherited retinal disease).

As well as the need for laboratory research to elucidate molecular mechanisms underlying AMD, the evaluation of novel and established clinical treatments will require further careful evaluation in the future five years. Such treatments involve those aimed at destroying the growth of choroidal blood vessels beneath and within the ageing retina such as photodynamic therapy (PDT), external beam irradiation, transpupillary thermotherapy and vitreoretinal surgery. In the case of PDT, in a multicenter international trial comparing patients who had undergone PDT to control subjects with AMD having sham treatment, the percentage of subjects who experienced moderate loss of vision (three lines or less) was 61% in the PDT group and 46% in the control (untreated) group. This benefit was significant only for patients who had a type of choroidal neo-vascularisation (CNV) lesion defined as "predominately classic". Although statistically significant, the technique requires further evaluation for AMD and other causes and types of choroidal neovascularisation. The understanding of the molecules involved in cell death (apoptosis), scar-formation and neovascularisation, processes which contribute to the destruction of functioning retinal tissue in AMD, has increased recently and there exists real opportunities to examine, in the laboratory and then clinic, the manipulation of these processes through pharmacological means. Unlike the neurosensory retina, which histologically resembles the central nervous system (CNS), the retinal pigment epithelium layer is a monolayer of cells that has the potential to regenerate and can be successfully grown in culture. The exploration of retinal pigment epithelium (RPE) transplantation, in close collaboration between cell biologists

and retinal clinicians, will be important to investigate this potential treatment for those cases of AMD in which cell death (atrophy) is the predominant feature.

3.2.2 Vascular retinal disease

In diabetic retinopathy, unlike AMD, clinical research has identified at least partially effective preventive treatments, including intensive diabetic control, control of hypertension and retinal laser photocoagulation for proliferative diabetic retinopathy and to a lesser extent macular oedema (responsible for 70% of visual loss in diabetic patients). The National Screening Guidelines for Diabetic Retinopathy will lay down, for the first time, countrywide targets for screening and treatment but implementation and optimisation of the proposals remains a major objective. The UK is well placed to investigate screening strategies. Topics of investigation include validation (grading strategies, training), incidence and prevalence (establishing optimum screening intervals, NSF targets), cost-effectiveness, detection systems and automated grading. Diabetic macular oedema, even with timely laser treatment, often leads to a poor visual outcome. The effectiveness of alternative treatments such as vitrectomy/membrane peel will require careful assessment.

Continued investigation of the molecular mechanisms and the role of growth factors such as VEGF and the angiopoietins in diabetic retinal angiogenesis and macular oedema will suggest key molecular targets for pharmacological therapeutic intervention. Inhibition of intracellular molecules upregulated by VEGF, such as Protein Kinase C, will undergo more investigation and clinical trial appraisal before introduction as medical treatments. Finally viral vector introduction of VEGF receptors and other growth factor antagonist genes into the retina provides a method of longterm prevention of retinopathy progression.

Treatment of vein occlusion is currently limited to the use of scatter retinal photocoagulation to prevent neovascularisation, and macular laser treatment has some bearing on visual outcome in branch retinal vein occlusion. The pathogenesis of CRVO remains obscure and future research will continue to examine patients for prothrombotic tendencies and systemic risk factors, in an attempt to develop strategies that will reduce disease incidence. VEGF has been implicated in the occurrence of neovascular complications and inhibitors will likely be used to prevent this. Chorio-retinal anastomosis, either by laser or surgical means to bypass CRVO will be further examined and systemic and intravitreal clot lysis agents refined and reassessed.

3.2.3 Inherited retinal disease

Each newly discovered gene generates further research opportunities. Downstream projects include determining the expression profile of the gene in different tissues; characterising the structure of the expressed protein and localisation of the protein within the cell, the identification of interacting and homologous proteins; and the effect on protein function; structure and interaction of the genetic mutations found in families from the clinic. Only with the further investigation of gene function and protein biochemistry will understanding emerge to develop therapeutic strategies. Further genes and loci remain to be found for retinal disease, and although the techniques for linkage

analysis and positional cloning have improved, the standard technologies of DNA and RNA analysis and sequencing remain expensive and hence the costs of such research remain large. The experimentation needed to realise those laboratory projects downstream of gene discovery include the use of animal models. Animal models with naturally occurring mutations in retinal genes or those with generated knock-out mutations, allow the assessment of novel treatment approaches. Such techniques include gene-replacement therapy in which the missing gene is inserted into a viral vector and injected into the animal (for instance the sub-retinal space or vitreous cavity). Encouraging results have been shown for the replacement of the rds gene in rds $-/-$ mice, and more recently the RPE65 gene in RPE65 $-/-$ dogs (Nature Genetics May 2001) and this approach is a paradigm for the treatment of disorders that occur due to reduced gene dosage in the retina in humans (the majority of autosomal and X-linked recessive retinal disease). Other approaches include the insertion of genes designed to express ribozymes capable of catalysing mutant alleles in vivo such as those with missense mutations that cause the majority of autosomal dominant retinal disease. Also, the use of genes and proteins designed to interfere with and suppress apoptosis of retinal cells (such as ciliary neurotrophic factor - CNTF) is a promising strategy. Novel drugs designed on the basis of the laboratory investigations described above will also require evaluation in animal models as in the recent evaluation of systemic diltiazem on the retinal degeneration of mice lacking rod photoreceptor phosphodiesterase (rd $-/-$).

Following the determination of causative genes, in parallel with further laboratory investigation, there remains an important opportunity to study the clinical phenotype of resulting disease in the light of genetic discovery. The work of the interested clinician, in concert with the genetic laboratory, can identify subsets of patients with particular molecular diagnoses and carefully characterise the disease phenotype given such specific molecular data. Only with these phenotype-genotype correlation studies will the ultimate effect of genetic mutation on human biology be elucidated and the appropriate families and individuals for future novel therapies be identified. Such careful clinical characterisation of selected patients and families in terms of retinal imaging, psychophysics and electrophysiology is not inexpensive and requires substantial devoted funding.

3.2.4 Inflammatory retinal disease

The research priority in this area is to devise novel therapeutic strategies which are more effective at controlling the inflammation and thereby preventing visual loss. A greater understanding of the disease mechanisms can be achieved by examination of the cells that infiltrate the eye and are present in the ocular fluids. This may identify a cytokine profile produced by the cells which results in aggressive disease and switching these off may be achieved by using other downregulatory cytokines. In some types of retinal infection, implants containing the therapeutic agent are inserted into the eye and deliver the drug constantly over 6 months. To be able to treat eye inflammation inside the eye has many advantages in that it is likely to be more effective as reliable drug levels are achieved where the drug is needed and all the systemic side effects are avoided.

New immunosuppressive drugs can be assessed against current therapy in clinical trials. Many patients are young and healthy apart from their chronic eye problem and therefore it is of major importance that the side effect profile is acceptable for long term

treatment. Drugs which could induce disease remission, as has been suggested for interferon alpha, and/or could considerably reduce or replace the need for corticosteroids, which are the mainstay of treatment, would be ideal.

Patients with the same clinical phenotype of disease can have very different responses to treatment and visual outcome. Although few types of intraocular inflammation have a strong HLA association, there must be other genetic factors which determine disease outcome. This maybe genes that control levels of cytokine production or other immune signals or genes which control processes that metabolise drugs or a myriad of other processes which are involved. By dissecting out these parameters in carefully phenotyped patients, it may be possible to identify patients who will do badly and lose vision. The aim then would be to target these patents for earlier more aggressive treatment to try and prevent this from occurring.

3.2.5 Ocular oncology

Uveal melanomas are the most common primary intraocular malignancy in adults and pose a significant threat with approximately 50% of patients ultimately dying from their disease. In the past two decades there has been considerable progress in developing therapeutic options which avoid the need for removal of the affected eye. Whilst this has, in many cases, led to the preservation of a cosmetically acceptable eye and/or useful vision there has been no impact on patients' survival. The identification and treatment of high risk patients with adjuvant therapy at the time of their initial diagnosis may ultimately lead to improved survival in these patients.

In the last few years certain cytogenic abnormalities have been detected within uveal melanomas and these have been found to have a profound prognostic significance. Further research is directed into the characterisation of these and other abnormalities within the tumour genome. Increasing our understanding of the molecular genetic events which lead to the genesis of these tumours may provide us with greater means for identifying high risk individuals. In addition, an increased understanding of the molecular mechanisms responsible for the development of these tumours may provide us with opportunities to control tumour growth at a molecular level.

Adjuvant therapies must be developed to address the problem of micrometastatic disease present at the time of primary therapy. Such therapeutic options may include: immunotherapy, anti-angiogenic therapy, chemotherapy and gene therapy.

Retinoblastoma is the commonest intraocular tumour in childhood with a frequency of approximately 1 in 20,000 – 1 in 30,000 live births. Present treatment is highly successful in controlling the primary tumour and survival rates in affected children is extremely high. Primary treatment that may include radiotherapy, laser therapy, cryotherapy and chemotherapy may have a secondary adverse affect on visual function. Future treatment strategy will aim to eradicate the primary tumour, but at the same time minimise normal tissue damage. Again, in recent years there has been a considerable increase in our understanding in the genetic and molecular events that determine the development of retinoblastoma. Future research should be directed at increasing our understanding of these molecular genetic events that in turn may provide us with therapeutic options for eradicating the primary tumour with a minimal disturbance of normal tissues.

3.3 Research Priorities

3.3.1 Epidemiological and Service Issues

- Evaluation of novel treatments and improvement of existing treatments in AMD, diabetic retinopathy and vein occlusion including:
 - Photodynamic therapy
 - External beam radiation, proton beam irradiation
 - Transpupillary thermotherapy
 - Chorioretinal anastomosis (surgical and laser)
 - Intraocular administration of tissue plasminogen activator, other clot-lysis agents and anti-angiogenic, anti-scarring agents
- Assessment of most efficient delivery of diabetic screening and ophthalmic management in the UK diabetic population.
- Clinical trials of new immunosuppressive agents to control intraocular inflammation

3.3.2 Clinical and Laboratory Issues

- Elucidation of novel genes and chromosomal loci causing monogenic retinal disease.
- Elucidation of population genetic polymorphisms influencing the susceptibility to age-related macular degeneration and diabetic retinopathy.
- Evaluation of gene function, protein structure, chemistry and interaction in cell systems and animal models.
- Elucidation of novel therapies including gene replacement therapy, modulation of retinal cell apoptosis, catalysis of harmful gene mutations in vivo (ribozymes) and retinal cell transplantation.
- Characterisation of molecules involved in neovascularisation occurring in AMD, diabetic retinopathy and vein occlusion (e.g. vascular endothelial growth factor).
- Identification of cytokine profiles of the infiltrating cells from ocular fluids
- Devising strategies to switch off particular cytokines by these cells using other downregulatory cytokines
- Identification of cytokine and other genetic polymorphisms that might influence disease outcome
- Phenotype-genotype characterisation of monogenic retinal disorders
- Characterisation of phenotype of AMD genetic polymorphisms (eg ApoE4).
- Elucidation of genes conferring susceptibility of diabetics to sight-threatening retinopathy.
- Phenotype-genotype characterisation of ocular inflammatory disorders
- Development of RPE transplantation strategies in AMD
- Development of drugs to use in intraocular devices to control intraocular inflammation

4 Vitreoretinal Disease

4.1 Background

Vitreoretinal surgery continues to evolve rapidly on a global scale. In recent years there has been a further refinement and development of surgical technology as well as increasing interest in the use of adjunctive agents for vitreoretinal disease. There has also been increased interest in the application of vitreoretinal surgical techniques to a wider range of diseases with the potential for much greater levels of service requirement. Within the United Kingdom several multi-centre studies have now been completed and the potential exists for further collaboration between UK vitreoretinal surgical centres. The BEAVRS (Britain and Eire Vitreoretinal Surgeons) group offers a basis for future collaborative work. A number of UK based vitreoretinal surgeons are now involved in international collaborations and UK vitreoretinal surgery is well placed to play a central role in future international studies. A number of centres continue to work collaboratively with laboratory scientists and an increasing number of trained vitreoretinal surgeons with laboratory experience should strengthen this work in the future.

4.2 Research Potential

It is proposed that the following areas deserve co-ordinated research over the next five years:

4.2.1 Retinal detachment

Vitreoretinal surgical units throughout the United Kingdom now audit the results of primary retinal detachment. The results of these audits together with further work on the investigation of service delivery should result in guidelines on best practice in the treatment of primary retinal detachment. Level of service recommendations will be made and guidelines in accordance with clinical governance proposed.

The potential for further investigation on the causes and epidemiology of retinal detachment as collaborative research within the United Kingdom should be exploited. The BEAVRS group potentially forms a basis for this.

A pan-European multi-centre study on the indications for scleral buckling versus primary vitrectomy for rhegmatogenous retinal detachment (the SPR trial) is currently running, and one site within the UK (Liverpool) is taking part in this. The potential exists for further investigation of the indications for vitrectomy in primary detachment within the UK.

Clinically driven investigation into the basic science of retinal detachment should also be undertaken. The pathology of posterior vitreous detachment and the intra and peri-retinal pathological changes which determine the outcome of retinal detachment surgery are as yet uncertain. A better knowledge of these will help future vitreoretinal surgeons to improve the outcome of surgery in a variety of areas of vitreoretinal disease.

4.2.2 Proliferative vitreoretinopathy

Proliferative vitreoretinopathy (PVR) remains the most common cause of failure in retinal detachment surgery. Additionally the visual outcome for eyes with PVR is poor. A prospective randomised controlled trial on the use of adjunctive agents (5 fluorouracil and low molecular weight heparin) between Liverpool and Moorfields Eye Hospital is currently underway and should provide additional information on the use of adjuncts to treat and prevent PVR. The potential also exists to trial neuroprotective and growth factor strategies to improve the visual outcome in PVR and this depends on the continued development of adequate animal models for this condition.

4.2.3 Trauma

The visual outcome in many cases of trauma requiring vitreoretinal surgery remains unsatisfactory. A central problem is the development of severe proliferative vitreoretinopathy. A major pan-European multi-centre trial, centred on Moorfields Eye Hospital, is currently being organised and awaits funding. This will provide important information on the use of adjuncts in the management of trauma and will additionally give high quality data on the outcomes of vitreoretinal surgery in eyes having sustained trauma.

4.2.4 Age-related macular degeneration

Various techniques of retinal translocation are now under investigation to deal with age-related macular degeneration (the leading cause of blindness in the developed world). The United Kingdom in general has lagged behind the United States, Germany and Japan and other European countries in the development and investigation of these techniques. It is recommended that pilot work is undertaken in this area which is rapidly evolving. This could potentially lead to further developments in translocation surgery such as the use of adjuncts to prevent proliferative vitreoretinopathy (a major complication of the technique), or the use of anti-angiogenic agents. The future potential also exists for a randomised controlled trial of retinal translocation against other novel forms of treatment for macular disease such as photodynamic therapy.

The initial optimism that transplantation of retinal pigment epithelial and neural retinal cells to deal with macular disease has not met with favourable results in initial clinical trials. Such transplantation strategies may however in the future play an important role in the treatment of macular degeneration and other forms of retinal disease.

4.2.5 Diabetes

Few advances have been made in vitrectomy for proliferative diabetic retinopathy in recent years. The increasing availability of anti-angiogenic agents however provides the potential to improve the outcomes of vitrectomy surgery. As these agents become available prospective trials on their use as adjuncts to vitreoretinal surgery (which is usually performed on eyes with severe diabetic retinopathy) should be organised.

Favourable initial results on the role of vitrectomy in the treatment of diabetic macular oedema has lead to pilot studies at both Moorfields Eye Hospital and St Thomas' Hospital. Favourable results from these pilot studies should lead to further investigation of this area and it is recommended that a multi-centre randomised controlled trial should be organised.

4.2.6 Retinal vascular disease

Vitreoretinal surgical techniques now allow the cutting of the sheath of retinal vessels and this has lead to the proposal that this should be undertaken for cases of branch retinal venous occlusion. Initial unrandomised trials provided encouraging data that this leads to an improvement in the fundal picture. No centres in the UK are currently investigating this technique and a co-ordinated approach to this investigation is recommended. Surgical techniques now also allow for cannulation of retinal vessels and the delivery of agents to them, this allows the potential for treatment of a wide range of retinal vascular conditions by a vitreoretinal surgical approach.

4.2.7 Macular holes

A major prospective randomised clinical trial on the use of adjunctive serum to treat macular holes has now been completed at Moorfields Eye Hospital. This showed no significant advantage of adjunctive agents. Various questions remain unanswered in macular hole surgery, for example, the use of inner limiting membrane peeling, combined cataract surgery and vitrectomy for macular holes and the best posturing regime for tamponade agents used. Since surgery for macular hole is now undertaken by many centres throughout the United Kingdom it is recommended that a multi-centre approach to the investigation of these areas would be appropriate.

4.2.8 Uveitis

Small scale series over the years have reported a beneficial effect of vitrectomy in the management of various forms of uveitis. No large scale series has yet reported on this and again the potential exists within the UK to co-ordinate a large scale investigation on the role of vitrectomy surgery in the management of uveitic disease.

4.2.9 Tamponade agents

A number of heavier than water agents now exist which have the potential to provide interior tamponade following vitrectomy surgery. It is likely that this will be investigated on a pan-European level and United Kingdom investigators will play a role in this.

4.2.10 Gene delivery.

As the potential for gene delivery to deal with retinal disease becomes a clinical reality it is likely that vitreoretinal surgery will play a key role in strategies of delivering genetic material. Such strategies have the potential to treat a wide range of disease which is currently not amenable to vitreoretinal treatment, for example, genetic conditions such as retinitis pigmentosa and degenerative conditions such as age-related macular disease. These investigations will require close collaborations between laboratory scientists and vitreoretinal and medical retinal clinicians.

4.2.11 Molecular genetics

The characterisation of various retinal diseases at a molecular level will continue. As this area of science expands, conditions which have primarily required vitreoretinal intervention, for example, Stickler's syndrome, which is currently the subject of major ongoing molecular genetic trials in Cambridge, and other diseases where genetic background plays a major role, will require accurate phenotypic characterisation and co-ordinated molecular and epidemiological investigation.

4.3 Research Priorities

4.3.1 Epidemiological and Service Issues

- The use of adjunctive medications in vitreoretinal surgery especially posterior segment trauma and PVR and slow-release vehicles for adjuncts.
- Analysis of the surgical management of age-related macular degeneration.

4.3.2 Clinical and Laboratory Issues

- Further investigation of the causes and management of retinal detachment and proliferative vitreoretinopathy (PVR), including a fundamental study into combined gliosis and fibrosis.

5 Lens And Cataract

5.1 Background

The lens is composed of a single layer of epithelial cells attached to a basement membrane (lens capsule). The epithelial cells differentiate into lens fibres, after which proliferation ceases and there is terminal differentiation with a restriction of protein synthesis with the formation of crystallins. With aging of the cell protein synthesis and proteolysis is terminated, although deposition of new cells continues at the periphery of the lens.

The essential properties of the lens are its transparency and ability to focus light. A cataract is defined as opacity within the lens that interferes with vision. Cataract can occur in children, or be associated with inherited disease, but the vast majority are age-related. Age-related cataract has enormous economic and public health significance and it is the major treatable cause of blindness worldwide. Even in developed countries cataract is the most common reason for ophthalmic referral. Surgical removal of the lens with implantation of an artificial lens within the eye is the treatment of choice. Unfortunately, although this treatment is cheap and cost effective, delivery to the people most in need is difficult and the number of people blind with cataract continues to rise. In addition, posterior capsular opacification is a significant cause for late visual loss and a further drain on resources. Reducing the growing backlog of patients with cataract will require radical changes in the delivery of surgery. The safety and efficacy of these changes must be proven.

There is no validated medical treatment for cataract. Although prevention or a cure may not be possible in the foreseeable future, an intervention that delayed the onset of cataract would have a major impact. Any approach would almost certainly depend on an understanding of the molecular processes that occur in the normal lens and alterations associated with cataractogenesis.

Presbyopia is the loss of accommodation of the lens, which is the ability to change focus from distance to near. An understanding of how the physical properties of the lens and its support structures change with age may lead to developments that delay or prevent the onset of presbyopia. In addition, the artificial lens that is implanted following cataract extraction is typically a monofocal lens, and glasses are normally required for reading. The restoration of a full range of focus following cataract extraction would be a major advance. Multifocal intraocular lenses are available but not widely accepted. Intraocular lens implants that can accommodate are being developed, although they have not been perfected and further research is required.

The projects listed below anticipate that an understanding of the basic mechanisms of lens physiology will provide a framework to delay the processes of ageing and subvert the complications of cataract surgery. However, it is recognised that the developing these advances to clinical practice may be delayed. Therefore, for pragmatic reasons, consideration is also given for service provision and new technologies that may provide more immediate relief for affected patients.

5.2 Research Potential

5.2.1 Determine how markers of cataractogenesis interact with environmental influences to confer a susceptibility to age-related cataract.

The α A- and α B-crystallins of the lens act as chaperone proteins to prevent denaturation and aggregation of proteins associated with cataract. The chaperone property of α -crystallin decreases with age and it accumulates in cells that are stressed. The structural and physiological importance of the other major lens proteins, β - and γ -crystallin, is uncertain. The role of the minor cytoskeletal components, the lens specific intermediate filaments (phakinin and filensin) and membrane proteins MIP and MP20, in cataractogenesis is also unclear. Scientists in the UK have established that opacification of the human lens in cortical cataract is associated with a loss of protein which has led to an investigation of the role of proteases in the lens (e.g. calpain). Similar research may help identify the molecular and structural changes associated with presbyopia.

Differences in DNA coding sequences for enzymes or structural proteins may be associated with age-related cataract. DNA and RNA could be obtained from surgical specimens and amplified by polymerase chain technology and probed for sequences that were associated with cataract. Identification of the role of these proteins in cataractogenesis may lead to the development of animal models of cataract useful for screening anti-cataract drugs.

More data are required on the regulatory pathways that control the internal circulation of fluid within the lens, and how are they controlled. Gap junctions are the pathways that allow the passage of ions and small molecules between cells. Three structural proteins of the gap junction (connexins 43, 46, and 50) have been sequenced. 'Knockout' mice defective for connexin 46 have demonstrated the importance of this protein in maintaining lens transparency. The development of cataract is associated with the accumulation of intracellular sodium and calcium and the loss of potassium. Interfering with this signalling mechanism via g-protein coupled receptors carries an increased risk of cataract.

5.2.2 Determine if there are genetic factors that interact with environmental influences to confer a susceptibility to age-related cataract

The United Kingdom has a lead in the identification of the genetic basis of congenital cataract. Nine loci for autosomal dominant cataract have been mapped. The involvement of genetic influences in age-related cataract is also evident. It has been established that the pax-6 gene and other homeobox genes and transcription regulators are essential for normal eye development. Studies of congenital cataract may help determine the genes and their regulators that determine the formation of the lens.

5.2.3 Identify environmental risk factors for age related cataract formation and understand their influence on lens homeostasis

The relative significance of environmental influences and age in determining the onset of cataract is a matter of debate. Information has been derived from epidemiological studies. Age, nutrition, myopia, UV, drugs, stress, smoking, and hormones are all implicated in the development of cataract. It is not known if the initial change is in the epithelial cell and then transferred to fibres, or whether epithelial cells accumulate defective DNA and transmit this to the fibre cells. Investigating the links between environmental insults and cataract development may yield valuable new preventive strategies. Unfortunately, the late onset and multifactorial nature of age-related cataract makes it difficult to test the causal relationship of risk factors.

5.2.4 Characterise the mechanism of scarring responses following cataract surgery at a cellular and molecular level

Residual lens epithelial cells at the lens equator act as the source for fibrosis after surgery. Clinically significant posterior capsular opacification (PCO) develops in 25% of eyes within two years of cataract surgery. Laser therapy is normally required to restore vision in affected patients. The problem of PCO limits the adoption of modern surgical techniques in developing countries.

Lens epithelial cells express receptors for platelet-derived growth factors (PDGF), which may stimulate proliferation in the mature lens. Autocrine transforming growth factor- activated by surgery induces epithelial cells to assume a spindle cell phenotype and synthesize collagen and smooth muscle actin. Retinoblastoma protein pRb prevents lens epithelial cells entering into the cell cycle and from proliferating. The regulation complexes for pRb are Cdk4/cyclin D and Cdk5/p35, and these may be involved in the apoptosis that is a feature of terminal differentiation. Details of the other kinases (bcl-2 and capsases) implicated in apoptosis may help. Knowledge of these processes may lead to specific pharmacological targeting to prevent PCO.

5.2.5 Evaluate intraocular lens technologies for the prevention of posterior capsular opacification after cataract surgery

Advances in our understanding of the mechanism of lens fibre proliferation and differentiation may help explain the mechanism of PCO after cataract extraction. However, the application of this understanding to clinical practice may be restricted by the potential for diffusion of any pharmacological treatment delivered in solution within the eye, where it may influence adjacent structures. Linking agents to proteins that bind specifically to lens fibres may be an alternative approach. An important *in vitro* model of PCO has been developed in the United Kingdom, which may help evaluate potential therapies.

Alternative strategies to prevent PCO include the development of intraocular lens designs and materials to inhibit the migration of proliferating lens fibres across the posterior lens capsule. The possibility of linking toxic or inhibitory agents to the surface of the intraocular lens needs to be further developed.

5.2.6 Evaluate strategies to reduce the impact of the major complications of cataract surgery

Surgical complications that have a potential impact on vision develop in approximately 4% of procedures. Cystoid macular oedema (CMO), often following posterior capsular rupture, is the most common visually important complication. The role of preoperative treatment with non-steroidal agents needs to be defined. The role of an attached vitreous in determining the risk of CMO following posterior capsular rupture needs to be defined.

More serious complications, such as infectious endophthalmitis, are rare and establishment of a national database for surgical activities is essential if new therapeutic strategies are to be evaluated effectively.

5.3 Research Priorities

5.3.1 Epidemiological and Service Issues

- Evaluate intraocular lens technologies for the prevention of posterior capsular opacification after cataract surgery.
- Evaluate strategies for the effective delivery of resources to patients with cataract.
- Evaluate strategies to reduce the impact of the major complications of cataract surgery.
- Identify environmental risk factors for age related cataract formation and understand their influence on lens homeostasis.

5.3.2 Clinical and Laboratory Issues

- Determine how markers of cataractogenesis interact with environmental influences to confer a susceptibility to age-related cataract.
- Determine if there are genetic factors that interact with environmental influences to confer a susceptibility to age-related cataract.
- Characterise the mechanism of scarring responses following cataract surgery at a cellular and molecular level.

6 Glaucoma

6.1 Background

6.1.1 Classification of disease

'Glaucoma' is a term that covers a heterogeneous group of conditions that have in common an irreversible, and usually progressive, optic neuropathy, characterised by distinctive patterns of structural change at the optic nerve head (ONH) and by distinctive patterns of loss of visual function (visual field loss). The glaucomas include primary open-angle glaucoma (POAG, high- and normal-pressure types), acute and chronic angle-closure glaucoma, and secondary glaucomas. Most glaucoma is associated with raised intraocular pressure.

6.1.2 Disease prevalence

POAG (the most common form in the UK) increases in prevalence with increasing age. Around 1% of white subjects has POAG at the age of 50 years, rising to around 4% at the age of 80 years. Estimates for black subjects are 3% and 13% at the equivalent ages. In the context of the ageing population the prevalence of glaucoma will rise. POAG is asymptomatic early in the course of the disease, and patients frequently present late with irreversible loss of vision. Glaucoma is the most common cause of irreversible blindness in the world, and a leading cause of blindness in the UK. In the United States, it has been estimated that 4% of white Americans and 8% of black Americans with glaucoma are blind in both eyes.

6.1.3 Cost of glaucoma morbidity

In the UK, the annual cost associated with blindness due to glaucoma probably exceeds £100 million. The real impact of the disease is almost certainly greater, since visual field loss can have a profound impact on the quality of life of the affected patient, such as loss of the driving licence, even when visual acuity is relatively unaffected. In addition, treatments given for glaucoma whether they are surgical or medical (drops) can further reduce the patient's quality of life. The importance of glaucoma to the individual is the impact of suffering a chronic disease and the functional limitation resulting from loss of vision, which may be postponed or prevented by early diagnosis and appropriate treatment.

Once glaucoma is diagnosed, a patient has to be followed for the rest of his/her life. At present, between a quarter and a third of all patients attending ophthalmology clinics have glaucoma. This proportion, and the number of patients, is set to increase as the population ages.

6.1.4 Funding perspective

In the US, the National Eye Institute spends approximately \$30 million US dollars a year on glaucoma research for a population of 250 million. This contrasts with approximately \$0.5 to 1.0 million spent by charitable organisations in the UK for a population of 60 million.

Investment in glaucoma research in the UK is likely to be productive given the characteristics of the UK population and the international standing of its medical and scientific researchers. The combination of a structured health service and a population willing to participate in medical research is essential for the study of a chronic progressive disease such as glaucoma. The strength of glaucoma research in the UK, manifest by the large number of papers in high-impact peer-reviewed journals and the strong presence of UK glaucoma specialists presenting research at international scientific meetings, is much greater than would be expected from the current levels of funding. Investment in UK glaucoma research is required if this international lead is to be maintained.

6.2 Research Potential

6.2.1 Scope of Research

Biomedical research is largely focussed on biological models of disease. However, other areas of research can influence the health of the population. Health is not determined by one single factor, but by the interplay of many, including genes, development, diet, and lifestyle; the cultural and socio-economic environment; and the public health and healthcare systems available. Thus research needs to include areas such as risk factors for disease, interventions to change individual and population behaviour, and research into the efficacy and cost-effectiveness of medical and health-care interventions. Disease prevention, treatments, and strategies to cope with the disease can affect the level of disability resulting from a disease. These approaches need to be included in the broader picture.

Research activity needs to include the development of mechanisms to ensure the application of the results of research to clinical practice, to ensure that public health and health services benefit from 'state of the art' and best practice developments. The application of research results can be facilitated by the Royal College of Ophthalmologists through best practice guidelines, and by collaboration of researchers with industry. Research findings also need to be disseminated to inform the public, and this is best done via governmental and charitable organisations already involved in the field.

Research falls into three broad areas – epidemiological (causes, distribution, and control of disease in populations), clinical, and laboratory (molecular, cellular and genetic) research.

6.2.2 Epidemiological research

- i.** The definition of the size of the problem and its relation to determinants of disease at a population level is of fundamental importance. Some risk factors for disease are only measurable at the population level, and some interventions are only possible at the population level. Large-scale population studies are needed to establish significant risk-factors for disease.
- ii.** Prevalence and incidence estimates for the different types of glaucoma in different populations need to be established. More accurate estimates are becoming possible with the advent of more refined diagnostic techniques (visual field testing and ONH imaging). The UK is becoming increasingly multicultural and the prevalence and behaviour of glaucoma needs to be defined for each population.
- iii.** The proportions of diagnosed and undiagnosed glaucoma sufferers, and the relationship of diagnostic status to health care usage and risk factors for disease, is of great importance for the planning and design of health care resources. The introduction of new diagnostic technologies into the primary care setting may improve the rate of early diagnosis and reduce the burden of visual disability. The impact of new technologies should be investigated, and should include cost/benefit analyses.
- iv.** The impact of health interventions on the population needs to be evaluated. Whether there are variations in the quality of care across the country and whether best practice guidelines are adhered to need to be established. The delivery of health care, including the development of diagnostic and management strategies with paramedical ophthalmic practitioners, is an area for continuing research.
- v.** The economic and social burden of glaucoma needs to be quantified, particularly in the light of an ageing population, so that health resources can be better planned.

6.2.3 Clinical research

- i.** The natural history of POAG (and risk factors for progression), and to some extent the other glaucomas, has yet to be defined. Accurate measurement of disease progression is becoming possible with the advent of more reproducible measurement of ONH structure and visual function. Improved clinical definitions (phenotyping) of the glaucomas will aid the process. Identification of the relative importance of raised intraocular pressure and non-pressure risk factors will enable better risk profiling of individual patients.
- ii.** Accurate phenotyping (description of the observable physical or biochemical characteristics) of the glaucomas is essential to determine the relationship of disease state to genotype and environmental influences. The development of robust phenotyping techniques is needed. This will permit the association of particular ocular features with patterns of disease and/or responsiveness to treatment.
- iii.** Continuing research is required into more accurate and reproducible techniques to define structural (retina/ONH) and functional (psychophysical / electrophysiological) changes in glaucoma. These techniques will provide greater insight into the

pathophysiology of retinal and optic nerve damage in glaucoma. The relationship of structural to functional measurements remains poorly defined. More accurate estimation of disease progression will result from improved measurement techniques and this will, in turn, permit better-defined outcomes of therapeutic interventions. The role of new measurement technologies in clinical practice needs to be investigated.

iv. Little is known about the burden of the disease on the individual. The relationship between the degree of visual field loss and quality of life needs to be determined. The impact on the individual of the diagnosis and treatment interventions also needs to be elucidated.

v. Continued research into the effect of therapeutic interventions is required, as the therapeutic options available are continually changing. These need to be large studies with sufficient statistical power to answer the questions asked. Historically, the intraocular pressure has been the main measured outcome of treatment. Other outcome measures, such as ONH/retina structural and functional measurements, may be more appropriate. The efficacy and safety of new surgical techniques and methods of modulating wound healing need to be compared. New classes of medicine, with different side-effect profiles, need to be compared to existing standards. Gene and cell therapies will become available once the mechanisms of glaucoma have been elucidated.

vi. Information technology is an instrument that can be used to improve data management and should result in improved care of individual patients. New software tools need to be developed to synthesise and display the results of diagnostic techniques used to detect and characterise the disease, with an aim to generate clinical risk profiles for individual patients, either for the development or progression of disease.

6.2.4 Laboratory research

Molecular and cellular research

i. The pathophysiology of glaucoma is poorly understood. More research is needed into the normal and abnormal functioning of the retina, in particular into the ganglion cells and their relationship with the structural/functional supporting cells of the retina and optic nerve head, so that the molecular and biomechanical mechanisms that lead to retinal ganglion cell death can be defined. A multidisciplinary approach to research questions will make use of insights gained into biological mechanisms achieved in other related fields, such as ageing and senescence, developmental biology and regeneration, and neuro-immunology and neurology. Research into neurobiology and nerve regeneration is essential if treatments are to be developed to reverse glaucomatous cell death.

ii. The exploration of cellular mechanisms of disease, and of new therapeutic strategies, will depend on the development of cost effective and ethically acceptable animal models of glaucoma. Much of the structural change seen in glaucoma occurs at the ONH. Research is needed to better define these changes and investigate the effect of raised intraocular pressure on the ONH, and the response of the tissues to bio-mechanical stresses. This approach should include study of donated post-mortem eyes

of glaucoma patients. There is a pressing need to institute a national eye donor program to benefit basic research into the cellular changes that occur in glaucoma.

iii. There is much evidence that abnormal ocular blood flow may be implicated in the pathogenesis of some of the glaucomas, although the relevance of currently available methods of measurement of blood flow is uncertain. Research in this area may elucidate important pathogenic mechanisms.

iv. Raised intraocular pressure is one of the most important risk factors for glaucoma. Research into aqueous humour dynamics, trabecular meshwork structure and function, and uveoscleral outflow pathways may eventually lead to treatments that prevent the onset of disease. Work in this area is likely to benefit from advances in techniques for the analysis of differential gene expression, such as microarrays, to identify cellular changes in the trabecular meshwork and ciliary body that occur in glaucoma.

Genetic research

The human genome has now been published and, with the advent of techniques such as microarray technology, there is now the opportunity to link genotyping with phenotyping and relate these to the natural history of glaucoma and its response to therapy. There is a unique opportunity in the UK to do this in the context of The UK Population Biomedical Collection (Wellcome).

i. Almost all diseases have a major genetic component, with a gene responsible alone, or in combination with other genes, for disease or disease susceptibility. Open angle glaucoma is likely to be a complex disorder in which environmental factors and age interact with several genes to generate glaucomatous optic neuropathy. Our understanding of the genetic basis of glaucoma is at an early stage. There is a need for high quality genetic epidemiology to determine the heritability (the variation in any given phenotype that has a genetic basis) of aspects of the ocular phenotype that are relevant to glaucoma.

ii. It is likely that subtle variation in coding regions, the control of gene or post-translational modification will generate subtle cellular defects that will in time result in glaucomatous damage. The identification of these changes will require the application of complex mathematical techniques that have been developed to analyse other complex genetic traits (eg psychological disease). Linkage studies will remain an important aspect of this work but will be complemented by data from other methods of analysis – for example those relying on association models and sibling-pair models of analysis.

iii. The most powerful genetic epidemiological studies are based on twin data. These are a scarce resource, collaboration between interested groups is essential for this to succeed. Furthermore, collaboration should also be encouraged to recruit families for the identification of candidate genes. It is important that we collaborate with others as twin registers are established in the UK and overseas.

iv. The understanding of the cellular mechanisms that result in raised intraocular pressure and tissue damage will allow the development of gene therapies to alter aqueous secretion and outflow, and modulate tissue responses to physical and molecular damage.

6.3 Research priorities

Priorities in the plan are determined by the gaps in the current evidence base and the timeliness and feasibility of research in the light of scientific developments, and also reflect the strengths of existing research teams.

6.3.1 Epidemiological and Service Issues

- Natural history of glaucoma and risk factors for progression
- Optimal treatment strategies to arrest disease progression

6.3.2 Clinical and Laboratory Issues

- Mechanisms for raised intraocular pressure
- Genotype/phenotype correlation
- Cellular mechanisms of optic nerve damage

7 Cornea & External Eye Disease

7.1 Background

Corneal and external eye disease includes a diverse range of conditions affecting both the ocular surface (lids, conjunctiva and associated organs such as the lacrimal gland) together with the layers of the cornea deep to its epithelial surface. The biological role of these tissues is to ensure that the cornea, the “window of the eye” remains clear. A range of infective, inflammatory, degenerative and dystrophic disorders may interfere with the normal function of these tissues resulting in a spectrum of disease. This spectrum extends from minor short term conditions causing irritation, discharge, foreign body sensation, dryness, itching and discomfort in bright light (photophobia), through diseases resulting in identical but chronic symptoms lasting many years, and resulting in demoralisation and fear of blindness, to the most severe problems of corneal perforation and corneal blindness. Unlike many other eye diseases pain and discomfort, as well as blindness, are common.

Classification of disease: Ocular surface disease is a new term that has been coined in the last 10 years to describe the diverse conditions that affect the surface of the eye. Ocular surface disease can be defined as “a group of disorders, of diverse pathogenesis, in which disease results from failure of the mechanisms responsible for maintaining a healthy ocular surface”. The group of disorders causing ocular surface disease not only comprise the bulk of referrals to the primary eye care services, due to minor conditions that result in discomfort and absence from work, but also result in ocular surface failure in which blindness results from failure to maintain a normal corneal epithelium leading to ulceration, infection, scarring and loss of sight.

Examples of minor conditions include: lid margin inflammation, dry eye disease, hay fever conjunctivitis, and bacterial or viral infections of the conjunctiva. Sight threatening ocular surface disease includes Sjogrens syndrome, atopic eye diseases other than hay fever conjunctivitis (particularly common in Asian British), ocular cicatricial pemphigoid and Stevens-Johnson syndrome. Although these disorders are uncommon individually they lead to blindness through the common pathway of ocular surface failure requiring common treatment strategies.

Corneal and external diseases also comprise a further group of conditions in which the corneal tissues deep to the epithelium are the site of primary involvement causing loss of sight. These include inherited and degenerative diseases of the cornea, which result in corneal distortion (keratoconus) or corneal opacity (dystrophies such as macular and granular dystrophy), leading to blindness

Lastly, corneal & external eye disease is a subspecialty in ophthalmology notable for the impact of socio-cultural and lifestyle factors on health. The widespread use of contact lenses for correction of refractive errors (in most cases, short- or long-sightedness) in the past two decades has resulted in striking increases in incidence of both bacterial and protozoal corneal infections whilst freeing millions of individuals from dependence on spectacles. More recently surgical or laser ‘treatment’ (refractive surgery) of the normal cornea in individuals with refractive errors has provided an alternative to contact lenses. These refractive surgery

techniques may lead to new and sight-threatening abnormalities of corneal structure and function and complicate management of individuals later developing cataract or who become potential corneal donors.

7.2 Research Potential

Priorities in the national plan are determined by gaps in the current knowledge base, including disease prevalence, the evidence base for clinical practice and feasibility in the light of scientific developments. Research on interventions needs to be directed at both the primary care level, in order to impact on the majority of patients with minor problems, and at the tertiary level to improve treatment strategies for those with blinding disease. The latter requires collaboration with a range of other disciplines to investigate pathogenesis and develop more effective treatments.

Although some of these research projects fall initially into one discipline, such as epidemiology, often, for example, epidemiological studies may lead both to identification of the size of the problem and to risk factors for a disease. This may then require further investigations of pathogenesis in clinical and laboratory studies integrating with an understanding of the condition at the molecular level. For this reason study areas have been outlined with reference to the particular disciplines that will be needed to address the problem.

7.2.1 Incidence, prevalence and morbidity

The morbidity and burden on the population of some of the corneal & external eye disorders has been the subject of few studies. Studies that have been performed include the impact of this group of disorders in general practice, the incidence of corneal infection in contact lens wearers, and the prevalence of dry eye disease. Disease quantification is, however, lacking in many disorders; a notable example, which is of current public health importance, is our ignorance of the prevalence of disabling complications of refractive surgery, itself almost exclusively undertaken outside the NHS.

7.2.2 Healthcare delivery

Support by ophthalmologists for delivery of primary eye care in the community, by optometrists and general practitioners, has been shown in pilot studies to be effective and accessible. A priority of the national research programme is to evaluate whether introduction of this service on a wider scale, with audit of costs and outcomes, shows both cost benefit and clinical effectiveness. Examples of conditions that are amenable to this approach are conjunctivitis and blepharitis.

7.2.3 Refractive surgery

Refractive surgery is a rapidly developing field in the private sector. The place of refractive surgery in the clinical care of patients with eye diseases, such as very short

sight, and quality of life assessments for different methods of correcting refractive errors should be assessed.

7.2.4 Prevention

Identification of risk factors for iatrogenic disease such as contact lens wear, refractive surgery and inappropriate use of topical therapy are likely to have the greatest impact on prevention of corneal disease and toxic keratoconjunctivitis.

7.2.5 Pathogenesis, treatment & management strategies

These areas, in particular, require an integrated clinical and laboratory approach. Some of the most accessible, in view of the availability of current opportunities, are described here.

- Continuing research is required into the pathogenesis of many corneal & external eye disorders. Areas where investigation of pathogenesis is currently leading to the introduction of new treatment strategies are severe dry eye, other autoimmune disorders such as pemphigoid, and allergic eye disease, where investigations of pathogenesis at the cell biology level are leading to the introduction of new anti-inflammatory therapies which hold substantial promise of an improvement in treatment. These surface disorders also lead to ocular surface failure which is the factor that results in blindness. New therapies are being developed, such as in vitro amplification of corneal epithelial stem cells that are dependent on understanding the biology of the normal and abnormal ocular surface and integrate with the current drive to stem cell therapies in other tissues. Amniotic membrane is now freely available in the UK since the development of a national service for its provision which is also linked to evaluation of the technique.
- Corneal wound healing is critical to ocular surface disease and also to refractive surgery and corneal graft surgery. New strategies involve advances in understanding of the biology of this area, facilitated by the ability to develop micro-array technology to measure multiple relevant factors ie growth factors and proteases simultaneously. This understanding is now relevant with the ability to modulate metalloproteinases and growth factors in wound healing. There has been too much inference from skin wounds (which are vascular, with a less ordered collagen architecture) in the past: we need more specific corneal wound healing studies.
- Management of ocular infections has now achieved an evidence base with the recent completion of some randomised controlled trials of therapy for severe corneal infection. However it has been shown outside the UK that antibiotic resistance patterns are constantly changing and that these need to be monitored for emerging resistance patterns as part of the co-ordination of new drugs and disinfectants for the management of surface infections of the eye; this is ongoing in some large centers but enlarging the database, to include data from the smaller centers and community, may identify different patterns of emerging resistance.

Rapid diagnosis of ocular infections is being developed and is needed to improve rational prescribing by targeting therapy appropriately.

- Storage of donor corneas prior to transplantation is currently undertaken by various methods, but discard rates from eye banks using unselected donors indicate that major improvements might be made (approximately one third of corneas may be discarded because of poor endothelial function). This is especially necessary if the case if rates of donation of tissues for transplantation continue to decline. Research is therefore needed to improve or enhance survival rates in corneal graft material, not only for endothelium but also for the limbal tissue required for surface reconstruction techniques.
- Corneal graft survival and rejection. Currently there is a multicentre nation-wide evaluation of tissue matching for corneal transplantation in progress There is increased interest in lamellar corneal graft surgery using both new manual and automated techniques which promise to avoid the problem of endothelial rejection for stromal disorders and reduce the rehabilitation time for endothelial disorders; research in this area can be expected to bring improvements into corneal graft surgical technique and outcomes for the first time in four decades. Complementary to this and to the problems of severe corneal disease is the development of the artificial cornea with bio-integrable devices that have the potential to circumvent the problems of graft failure and supply. The potential threat of prion diseases to corneal graft recipients, and the potential for transmission of these diseases from corneal graft recipients by instrument contamination is being evaluated.
- Advances in molecular genetics facilitate research on the pathogenesis of corneal dystrophies and degenerations ranging from monogenic recessive disorders (such as stromal dystrophy) to polygenic disorders with an environmental component (keratoconus is probably such a disorder). Such research will not lead to new interventions for patients within five years. However such research is significantly facilitated both by publication of the human genome sequence in 2001 and also the superficial position of the cornea and external eye. The latter makes gene-based approaches to treatment an order of magnitude more feasible than 'gene therapy' initiatives for other ocular tissues.

7.3 Research priorities

7.3.1 Epidemiological and Service Issues

- Identification of risk factors for iatrogenic disease such as refractive surgery, contact lens wear and inappropriate use of topical medications.
- Rapid diagnosis and improved treatment strategies for ocular infections.

7.3.2 Clinical and Laboratory Issues

- Corneal wound healing mechanisms
- Factors affecting corneal graft survival and strategies to prevent rejection
- Molecular genetic analysis of the corneal dystrophies and degenerations

8 Ocular Adnexal Diseases

8.1 Background

The main areas of research required in ocular adnexal diseases are either in the causation and treatment of more common diseases (such as eyelid tumours) or of the rarer, but potentially blinding, diseases (such as orbital inflammatory disease or optic nerve tumours).

8.2 Research Potential

8.2.1 Tumours of the eyelid and orbit

Basal cell carcinoma and squamous carcinoma are the commonest eyelid tumours, with a rising incidence worldwide -- in common with skin tumours elsewhere in the body. Moreover, squamous carcinoma of the conjunctiva is reaching epidemic proportions wherever immunocompromised young patients (generally with HIV infection) are exposed to sunlight. Research needs to be directed towards the epidemiology of these tumours and into the mechanisms of tumourgenesis and its prevention in "at risk" individuals. Further research into the tumour syndromes, such as Gorlin's syndrome or xeroderma pigmentosum would help in the understanding of tumour induction.

Orbital lymphoma, with or without systemic involvement, appears to be a much commoner disease than in the past. There is a significant morbidity and mortality with this condition and further investigation of the epidemiology and causation is merited.

Optic nerve meningiomas and gliomas, although rare, cause loss of vision and may be associated with systemic genetic abnormalities -- such as neurofibromatosis. There remains considerable uncertainty as to the cause of the tumours and their natural history; with this uncertainty, the methods of treatment (particularly the role of radiotherapy) remain controversial.

8.2.2 Orbital inflammatory disease

Orbital inflammation can present as a wide spectrum, affecting one or more tissues within the orbit and, when active, these conditions are painful, impair function and threaten vision. In some cases there is a relentless fibrosis of orbital tissues with severe impairment of orbital function and blindness.

The most common orbital inflammatory disease is thyroid orbitopathy, for which there is increasing understanding of the mechanisms involved. Future research is required to elucidate the immune mechanisms of this disease and to direct therapy towards "blocking" this immune response before it arises. Current therapies treat the inflammation only after it is established and after the complications of the subsequent "healing" response have developed.

Other orbital inflammations that cause particular problems are myositis, scleritis and panorbital scirrhous inflammation. Myositis affects young people and can lead to dense scarring of the extraocular muscles, with consequent ocular motility problems and diplopia. Scleritis can present a significant risk of blindness and may be a primary process, or part of a more widespread orbital inflammatory disease. Pan-orbital scirrhous inflammation is relatively rare, but can cause relentless fibrosis with effect on ocular motility and optic nerve function. Treatment is often poor and these patients can be blinded by this painful condition.

The cause of orbital inflammatory diseases remains a mystery. Certain features suggest a “driving” antigen, with recruitment of a spectrum of inflammatory cells. Eosinophils appear to be prominent in certain types of orbital inflammation (particularly scirrhous inflammation) and the various substances generated by these cells may be potent factors in fibrosis. Research directed at elucidating this mechanism, and its therapeutic blocking, might be of value not only in these conditions, but also in other diseases characterised by excessive scarring.

Treatment of orbital inflammation is currently largely systemic therapy and often has gross side effects that may limit the duration and efficacy of treatment. An improved understanding of the mechanisms and “drivers” for the inflammation may encourage the development of better and “targeted” therapies

8.2.3 Anophthalmos/microphthalmos

Although very rare, children with microphthalmos or anophthalmos are blind or grossly visually handicapped. Currently there is controversy as to whether the causes of these conditions are genetic or environmental and research should be directed towards clarifying this issue. The treatment of these conditions is poor, and these children undergo multiple operations to try and improve their life and social acceptability. Linked to this rehabilitation is the role of orbital implant and prosthetics materials.

8.2.4 Trauma and reconstructive surgery

Tissue contracture during healing remains one of the most significant problems with trauma (either primary or surgical); not only is the healed area distorted, but it also tends to be of incorrect compliance – both of which affect function. Understanding of the healing processes might allow development of methods to prevent contracture of tissues and improve functional results after trauma and surgical reconstruction.

Other areas of significant research related to trauma and reconstructive surgery would be the development of periocular tissue expansion and the establishment of methods for tissue culturing (from the patient) for use in subsequent reconstruction. Biomaterials research for tissue substitution and implants requires more investigation.

The treatment of orbital wall fractures remains controversial and, in view of the frequency of this condition, merits further investigation.

8.3 Research Priorities

8.3.1 Epidemiological and Service Issues

- The epidemiology and risk factors for ocular and adnexal tumours

8.3.2 Clinical and Laboratory Issues

- Research into the mechanisms of tumour induction
- Studies in the immunological mechanisms causing orbital inflammatory disease
- Studies into the mechanisms of scar formation following eyelid trauma.

9 Neuro-Ophthalmology

9.1 Background

Neuro-ophthalmologists devote much of their time to the eye manifestations of neurological disorders, including stroke, migraine, multiple sclerosis, cerebral tumours and head injury. Intensive investigations into the aetiology and pathogenesis of these disorders continues and this will inevitably impact on the prevalence of untreatable neural blindness.

In addition to this research activity three areas of direct relevance to ophthalmic research can be identified for neuro-ophthalmology. In each of these areas preliminary achievements over the past twenty years can be further developed over the next five years, at least at a basic science level, pointing a way to clinical trials in the future.

9.2 Research Potential

9.2.1 Neuro-transmission, apoptosis and neuro-protection

Pharmacological treatment to sustain the vitality of retinal ganglion cells following focal ischaemic or toxic injury.

9.2.2 Neural regeneration

Neurons in the visual pathways have yet to be re-generated but preliminary studies have now reported successful regeneration of optic nerve axons in mammals and also the re-establishment of synaptic connections between these axons and cells in the brain proper. The capacity to re-establish appropriate rather than random connections after ganglion cell regeneration remains a crucial issue in the achievement of a meaningful return of visual function.

9.2.3 Electronics and bionics

The concept of a bionic eye or electronic visual prosthesis has long been a part of popular culture. Efforts continue focusing primarily on individuals with no residual vision following loss of function.

9.2.4 Gene therapy

Patients with hereditary familial optic neuropathy and in particular young adults with Leber's hereditary optic neuropathy represent a high priority for the application of these therapies. After the loss of one eye, the same clinical event in the fellow eye is virtually inevitable and this offers a highly suitable targeted group for the application of gene therapy techniques.

9.2.5 Clinical research in neuro-ophthalmology

There remains an urgent need to refine and make more systematic the wide-range of clinical psychophysical and electrophysiological tests currently available to assess afferent visual function. Perimetry remains the most reliable clinical means of localising lesions in the visual pathways. Unfortunately the sophisticated techniques in use remain subjective and time-consuming and not tolerated by a significant portion of patients. Efforts to develop accurate rapid objective mapping and quantification of sensitivities throughout the field of vision continue, most likely through the modification of the visual evoked response test. These results could be correlated with psychophysical and pupil perimetry abnormalities to further refine and rationalise the present array of tests in use.

In contrast to subjective psychophysical techniques, confocal scanning laser ophthalmoscopy, optical coherence tomography and retinal thickness analysis are all evolving objective techniques, which are likely to prove to be of direct relevance to the assessment and treatment of patients with acquired optic neuropathies.

9.3 Research Priorities

9.3.1 Epidemiological and Service Issues

- Visual rehabilitation in untreatable neural blindness.

9.3.2 Clinical and Laboratory Issues

- Protection of vision in chronic raised intracranial pressure syndromes.
- Rehabilitation of binocular function in neurogenic squint.
- Immunotherapies for inflammatory optic neuropathies.

10 Vision Impairment And Rehabilitation

10.1 Background

Vision impairment can be defined as any chronic visual deficit that impairs everyday function and is not correctable by ordinary glasses or contact lenses. Although there have been important strides in the treatment and prevention of eye disease over the past few decades, there still exist many causes of loss for which there is no cure, and thus even with the best medical treatment, many people must live with impaired vision. The leading causes of vision impairment are diseases that are common in the elderly: age-related macular degeneration (AMD), cataract, glaucoma, diabetic retinopathy, and optic nerve atrophy. Over two-thirds of those with vision impairment are over age 65 years of age.

Vision impairment is included in the ten most prevalent causes of disability in the UK. For older adults, vision impairment has a negative impact on the quality of life equivalent to that of life-threatening conditions such as heart disease and cancer. In children, vision impairment is associated with developmental delays and the need for special educational, vocational, and social services, often beyond childhood into adulthood. In adults, vision impairment is associated with loss of personal independence and difficulty maintaining employment, often leading to the need for disability pensions, vocational and social services, and nursing home or assistive living placement

10.2 Research Potential

10.2.1 Basic research and theoretical issues

The area of issues is a fundamental yet often under-appreciated pillar of research on vision impairment and blindness. A major goal of this area is to develop a theoretical understanding of normal visual functioning that can be extended to explain the disabilities experienced by people with low vision, blindness and other visual processing deficits. Examples include the role of vision in spatial cognition, factors that underlie text legibility and reading performance, and the role of visual attention in impaired vision. Ultimately, such a theory should explain how visual deficits affect performance of everyday activities and how to optimise the visual environment to enhance performance, especially in those with vision impairment. It should guide the development of appropriate training and rehabilitation strategies, guide the development of adaptive technology and assessment tools, and indicate when it is more effective to convey information by non-visual means. It is likely that the necessary insights for ameliorating the effects of vision impairment will emerge from interdisciplinary studies combining traditional approaches to vision research with methods from research on cognitive science, motor control, development and ageing, psychology, neurology, computational modelling, and broader perspectives from neuroscience.

10.2.2 Visual assessment and everyday task performance.

Another primary research area in vision impairment and rehabilitation is visual assessment and everyday task performance. Because vision plays an important role in most everyday activities, people with visual problems are routinely faced with significant challenges in their daily lives, problems such as recognising objects and people, getting around (mobility), reading, socialising, working, and taking care of their daily needs such as preparing meals and managing finances. Difficulties with daily activities can lead to serious reductions in quality of life, including depression, social isolation, educational problems, and employment challenges, all of which underscore the critical importance of research designed to minimise these difficulties among the visually impaired. There is considerable variability among visually impaired persons in their ability to perform everyday tasks, depending on their eye condition, its severity, duration and age of onset, task lighting conditions, as well as compensatory strategies and the existence of other medical problems and disabilities. The challenge for the clinician is to identify which tasks are problematic for a given patient so that a rehabilitation plan can be developed and implemented. Research on valid and reliable assessment tools that allow clinicians to properly identify and treat problems in performing daily visual tasks is essential to improving clinical care.

10.2.3 Rehabilitation process

The logical partner of visual assessment is the rehabilitation process. Rehabilitation of the visually impaired, just as the rehabilitation of a physical problem, is directed at optimising the functional capabilities and quality of life of the patient. The rehabilitation process is a multifaceted process involving the assessment of visual capabilities and the evaluation of functional performance (e.g., reading, writing, and mobility) within the context of lifestyle (e.g., employment, family activities), attitudes, and psychological well-being. Rehabilitation goals are defined in terms of what matters most in a person's life, and attempts are made to solve functional problems through adaptive options (e.g., vision enhancement and substitution devices, environmental modifications) and coping strategies. The research challenge is to develop rehabilitation mechanisms proven to be effective in enhancing quality of life, to determine which approaches are most successful with different types of individuals, and to improve the delivery of these services to those in need.

10.2.4 Technology and assistive devices

The area of technology and assistive devices is a critically important research area because of its central role in the rehabilitation process. This research focus includes the development of new devices, the application of advanced technologies to visual or sensory substitution aids, and the continuous development and exploitation of new technologies, including communication, information, and computer technology. In addition to the development of assistive devices, it is essential that research in this area addresses how to optimise training in the effective use of devices, including a special emphasis on the training of the elderly, who comprise a substantial portion of the visually impaired population. Other issues central to research in this area are cost and

accessibility, cosmesis and personal acceptance of visual rehabilitation devices, and to what extent they are user-friendly.

10.2.5 Environmental access and modifications

Research on environmental access and modifications addresses the effects of vision impairment on accessing the environment in the home, the workplace, and while travelling, and explores environmental modification strategies for increasing independence of visually impaired persons. Loss of independence, including mobility throughout one's environment, seriously degrades the quality of life in far-reaching ways, among them reducing access to social networks and vision rehabilitation and other health services. Most vision rehabilitation strategies involve prescribing "personal" assistive devices (e.g., magnifiers and other optical devices), or providing training or other adaptations to the visually impaired individual. Environmental interventions, however, may serve to allow those with vision impairment to function better in the home, the workplace, and in spaces that are intended for public access such as shops, malls, hospitals, and transportation facilities. Research on this topic seeks to identify the most effective environmental modifications, to evaluate the ease of their implementation, and their acceptability and use by visually impaired persons.

10.2.6 Outcomes assessment

Recent changes in health care financing have intensified public interest in the human costs of disability and the effectiveness of treatments and rehabilitation strategies for those affected. In order to address these issues, research on vision impairment must include outcomes assessment. Outcomes include measures of the individual's self perception of quality of life, assessments of the performance of everyday activities, employment status, independent living status, and educational attainment.

10.3 Research Priorities

10.3.1 Epidemiological and Service Issues

- Conduct clinical trial research and other intervention evaluations to examine the effectiveness of rehabilitation processes for the visually impaired, especially in terms of which strategies are most (vs. least) effective for various sub-populations of patients.
- Conduct epidemiological studies on the prevalence and incidence of vision impairment, visual disability and identification of sub-populations that may be at heightened risk.

10.3.2 Clinical and Laboratory Issues

- Carry out research on the visual mechanisms underlying object recognition, locomotion and mobility, skilled movement, and reading, and on the interaction of vision with sensory, motor, and cognitive systems in these complex behaviours. This research should include an examination of neural plasticity, especially how the central nervous system is reorganised after visual processing is disrupted or drastically impaired, and how this plasticity could be exploited to enhance the use of residual vision or other sensory/cognitive systems in the visually impaired.
- Develop effective assistive devices and techniques to maximise residual vision and/or substitute for visual information, in order to facilitate the performance of everyday tasks by the visually impaired.
- Develop environmental designs and modifications that facilitate access in the home and workplace, and while travelling in public places, in order to enhance independence among the visually impaired.

11 Paediatric Ophthalmology

11.1 Background

Paediatric ophthalmology is a subspecialty that encompasses a very broad group of eye disorders that affect children. It is difficult given the breadth of the specialty to decide on research priorities. There are wide areas of overlap with disease affecting adults and many current areas of research such as molecular genetics, wound healing, stem cell biology and tissue transplantation are important to all areas of ophthalmology and will not be considered here.

Research priorities in paediatric ophthalmology should include disorders that relate either to the major causes of childhood blindness or to less severe disorders, such as amblyopia and strabismus, that consume a large amount of health service resources. There is also a need for more information about the prevalence of childhood visual impairment, the major causes, and best strategies for delivering high quality ophthalmologic services for children.

11.2 Research Potential

11.2.1 Epidemiology

It is important as a starting point in planning research strategies to have good information about the major causes of childhood visual impairment. Similarly in planning screening and treatment programs for amblyopia and strabismus it is important to have good information about the prevalence and incidence of the disorders. There have been few good epidemiological studies in this area. Epidemiology is an important area of ophthalmology research, which needs to be encouraged and supported and should have a high priority. The following sections: 11.2.2 to 11.2.5, deal with the major causes of childhood blindness in the UK.

11.2.2 Inherited eye disease

40-50% of childhood blindness is due to inherited eye disease. The inherited retinal dystrophies are the most important group of disorders. Current research is focussed on mapping causative genetic mutations, identifying the effects of specific mutations on the eye and thereby improving understanding of disease mechanisms. Research priorities for the next five years should involve: -

i. Identification of genetic mutations causing eye disease

This will include identifying the genetic basis of monogenic disorders and also the identification of the genotypes which are associated with increased risk of developing polygenic disorders such as refractive errors and strabismus.

ii. Exploring disease mechanisms

This will require a multifaceted approach which would include the investigation of protein function in vitro, the study of transgenic animal models of human disease and careful phenotypic studies of children with known genetic mutations. The latter studies will be dependent on detailed electrophysiological and psychophysical testing and novel methods of imaging ocular structures.

iii. Identification of novel treatment strategies

The major focus will be to identify treatments for inherited retinal dystrophies a major cause of childhood blindness. Treatments could be generic such as gene therapy, retinal or RPE transplantation or the use of growth factors or be more specific guided by knowledge of the underlying disease mechanism, for example biochemical or pharmacological treatments. The effectiveness of novel treatments will need to be assessed in formal randomised trials.

11.2.3 Visual pathway damage

Brain injury associated with perinatal hypoxia is a very common cause of childhood visual impairment which may be due to direct damage to the visual pathway and abnormal brain processing of visual information. Brain injury causing visual impairment may be seen in full term infants but ischaemic brain injury (periventricular leukomalacia) is a very important cause of visual morbidity in pre-term infants where it is a more common cause of visual impairment than ROP. Many children with visual impairment associated with visual pathway damage are also developmentally delayed and have other neurological abnormalities. Assessment of such children is difficult and this may explain why little good quality research has been carried out in this area. The mechanism of brain injury is of interest to paediatricians and obstetricians and this is one area where ophthalmologists should be involved in collaborative multidisciplinary research. There is an urgent need to raise the profile of research in the area of brain injury and visual abnormalities. Research in this area may include correlation of visual function with neuroradiologic abnormalities; visual development in normal and brain damaged infants and the effects of brain injury on oculomotor function. Research relating to neuroprotection and nerve repair will relate to this topic.

11.2.4 Developmental abnormalities

Many developmental abnormalities of the eye such as cataract, glaucoma and anterior segment dysgenesis have a strong genetic component and the identification of the underlying mutations is one research priority. Most developmental eye disorders are not amenable to treatment but two disorders, congenital glaucoma and congenital cataract are treatable and remain the commonest treatable cause of childhood blindness. Treatment however is still problematic; the processes involved in tissue repair, regeneration and scarring play a part in the failure of treatment. Modification of the scarring process can for example improve the outcomes for congenital glaucoma and further research in this area is important not only in childhood disorders but across the whole range of adult ophthalmology.

11.2.5 Retinopathy of prematurity (ROP)

The current priorities for research in this area are:

- i.** Investigation of disease mechanisms - much of this overlaps with research into the mechanism of neovascularisation in other disorders such as diabetic retinopathy and retinovascular disease and the mechanism of scarring at the vitreo-retinal interface.
- ii.** As newer forms of prevention and treatment come on stream for example by modulating the production and /or effect of vascular endothelial growth factors there will be a need for further randomised controlled clinical trials. (see below)

11.2.6 Amblyopia and strabismus

Amblyopia and strabismus affect 2-5% of the childhood population and the investigation and treatment of these disorders consumes a large amount of health service resources. Further research in this area is a high priority. This would include:

- 1** Controlled clinical trials of the effectiveness of screening for and treatment of amblyopia.
- ii** Further controlled trials investigating the effect of early treatment of refractive errors on the later development of amblyopia.
- iii** Psychophysical testing combined with novel brain imaging (functional MRI) to investigate the underlying neurological deficit in the different forms of amblyopia.
- iv** Expanding the evidence base in the management of strabismus. To date there have been few good randomised controlled clinical trials of treatment of strabismus. Most changes in practice such as the use of adjustable sutures and botulinum toxin have been introduced without any formal assessment in a clinical trial. The indications and benefits have therefore not been clearly defined.

11.2.7 Treatment trials in the paediatric age group

It is hoped that advances in molecular and cell biology and other scientific disciplines will lead to an increasing number of new treatment options. Their efficacy will need to be tested in controlled clinical trials. We will need to develop techniques, including ocular imaging, psychophysics and electrophysiology for detecting treatment effects. Techniques designed for use in adults may be difficult or impossible to utilise in infants and children and more research is needed to develop techniques applicable to children.

11.2.8 Health service delivery in paediatric ophthalmology

The provision of services for the screening, diagnosis and treatment of childhood eye disorders involves several different professional groups including orthoptists, optometrists and ophthalmologists. Further research is needed to identify the most cost-effective model for the provision of screening, diagnosis and treatment of amblyopia and strabismus.

11.2.9 Functional deficits in visually impaired children and visual rehabilitation

There is limited information on the effects of unilateral or bilateral visual impairment on childhood development and later attainment of educational qualifications and social skills. It is important to develop tools for assessing the impact of visual impairment on children and their families not only to improve understanding of the impact of visual impairment but also to be able to measure the effectiveness of therapeutic interventions.

11.3 Research priorities

11.3.1 Epidemiological and Service Issues

- Epidemiology of childhood visual impairment
 - Understanding the extent and the causes of childhood visual impairment
- Amblyopia and strabismus
 - randomised controlled trials of treatment of amblyopia and strabismus
 - randomised controlled trials of screening for amblyopia
 - Health-care delivery in management of strabismus and amblyopia
- Effects of childhood visual impairment : educational, emotional and social
- Visual rehabilitation

11.3.2 Clinical and Laboratory Issues

- Inherited eye disease
 - identification of disease causing mutations
 - investigation of disease mechanisms
 - development of novel treatment strategies
- Brain injury and visual impairment
 - multidisciplinary research to understand the mechanism of brain injury
 - investigation of visual development and visual performance in brain injured children

12 Squint And Amblyopia

12.1 Background

Most squints start in childhood and result from abnormalities in the development of the brain mechanisms controlling eye movements and binocular vision. These mechanisms can break down in a number of different ways and at different ages resulting in different types of squint. Others result from weakness of, or damage to, the muscles moving the eyes or the nerves controlling them. These latter types of squint are more common in adults. In children under seven the vision in one eye may deteriorate because the abnormal visual experience resulting from misalignment of the eyes, differences in focus between the eyes or other abnormal visual experience may lead to changes in visual connections in the brain and to poor vision in that eye known as amblyopia or "lazy eye".

Squint and amblyopia are common conditions, affecting 3 to 5% of children. Both have a lifelong impact on visual function and appearance, with consequences for education, career choice, employment, self-esteem and personal relations. The aim of research is to find ways of preventing or minimise the impact of these conditions. This will have lifelong benefits for the patient and society.

12.2 Research Potential

12.2.1 Squint and amblyopia in children

The scientific basis: starting with the pioneering work of Hubel and Wiesel in the early 1960's, studies on the development of the visual system and its modification by abnormal visual experience using animal models have contributed greatly to our understanding of the development of vision and of brain development in general. The impact of this work on clinical practice has been considerable, mainly with the recognition of the need for early diagnosis and intervention. However more detailed correlations have so far been difficult to establish. In particular, most of the animal work on the effects of visual deprivation probably relates to human amblyopia having its onset in the first 12 to 18 months of life. But many children present with amblyopia of later onset, commonly between 3 and 5 years of age, and studies are needed in non-human primates to examine the underlying pathophysiology of amblyopia starting at these later stages of visual development. Studies that can produce directly comparable data from primates and man will be of particular value.

i. Understanding amblyopia in children

Studies of the pathophysiology of amblyopia in man using psychophysical and clinical electrophysiological methods are demonstrating abnormalities affecting a range of visual functions other than acuity. These are likely to lead to a better understanding of the underlying abnormalities, particularly the differential involvement of the parvo and magnocellular pathways, and are likely to lead to better ways of monitoring and treating these patients. In particular, patients with squint and amblyopia rely on their

fellow eye for visual function and most suppress their amblyopic eye. Several studies, both in animals and man, have demonstrated abnormalities affecting the fellow eye. Studies are needed to define these abnormalities and to see if they are intrinsic to the condition or related to patching and to define the effects of amblyopia on the overall visual function of the patient.

ii. Finding and treating amblyopia

Aspects of clinical research into amblyopia and pre-school vision screening have recently been reviewed (Pre-school Vision Screening: Results of a Systematic Review; NHS Centre for Reviews and Dissemination, University of York). This identified a number of areas where research is needed. Clinical studies were recommended into the extent of disability attributable to amblyopia, the incidence of blindness or partial sight due to amblyopia with subsequent loss of the fellow eye and the prognosis for vision in the amblyopic eye under these circumstances. Although randomised control trials of the treatment of amblyopia have been recommended, reservations have been expressed with respect to denying children in an untreated control group what is generally considered to be an effective treatment. Studies comparing outcomes for non-compliant and compliant children are of value in this context. The cost-effectiveness of pre-school vision screening and treatment also needs to be examined.

Outcome studies of the effectiveness of amblyopia treatment show a residual group who fail to respond even with apparently good compliance with patching. This group deserves further study to identify reasons for the poor response.

iii. Understanding and treating squint

Most children with a squint lose binocular function and this is rarely restored following squint surgery. The ultimate aim of research in this area is to understand the mechanisms underlying this loss and to find ways of preventing it or reversing it. Not only will this approach have the potential to restore stereoscopic function, but it will also prevent the development of consecutive divergence in adulthood, with the need for further surgery. Studies of very early intervention either with surgery or using Botulinum toxin have produced encouraging results and this area deserves further study.

A number of types of childhood squint are intermittent, with apparent partial loss of binocularity and development of a degree of suppression. Studies of the underlying pathophysiology of binocular function in such patients are likely to give important information as to why and how binocular function is lost both in these and other groups of patients. The largest group of such children are those with intermittent divergent squints. Many of these remain stable, but some progress to a total loss of binocular function. There is currently no good evidence as to whether early surgical intervention in children with intermittent squints is beneficial and studies are needed to establish the optimum management of such children.

iv. Preventing long and short sight

Animal studies are demonstrating that visual feedback has a major effect on the development of correct focussing of the eyes and the elimination of refractive errors. Evidence is appearing which suggests that similar mechanisms operate in man. These studies are potentially of great importance, in particular studies which aim to understand why these mechanisms break down, leading to refractive errors.

v. Treating nystagmus (wobbly eyes)

Nystagmus remains a significant cause of visual disability in both children and adults. Studies are needed of the underlying disorders of oculomotor control and of whether surgical intervention offers significant benefits.

12.2.2 Adult Squint

In the majority of adults with a squint, the condition represents the continuing effect of a childhood onset squint. A substantial proportion of patients require further surgery as an adult to improve their appearance and minimise the impact of the squint on their employment and personal relationships. Although the benefits of adult squint surgery are well recognised by anecdotal reports from patients, a systematic study is needed to evaluate the incidence of untreated adult squint and its social impact, in particular its effects on employment prospects, self-esteem and personal relations and the benefits from surgery.

i. Understanding and treating double vision

A substantial proportion of these adult patients suffers from double vision because of incomplete suppression of the image from their squinting eye. This causes problems with employment and driving. Studies are needed of the mechanisms underlying suppression and factors which cause it to change. Some adult patients lose the ability to fuse the images from their two eyes and suffer intractable double vision. This may occur after removal of an adult onset cataract in patients with no previous history of squint. Understanding the changes in the central visual pathways that underlie such plastic changes in adults is likely also to be of importance in the visual rehabilitation of patients with conditions such as macular degeneration. Studies have shown comparable plastic changes in the central visual pathways of adult primates following macular lesions.

ii. Unresolved clinical problems

Two particular conditions that pose continuing problems for clinical management are thyroid eye disease and orbital blowout fractures. Thyroid eye disease is a sight threatening condition associated with auto-immune thyroid disease. As well as damaging the optic nerve, it causes considerable morbidity through its effects on the extraocular muscles, giving double vision, and the swelling of orbital structures results in disfiguring proptosis and lid deformities. It commonly affects younger patients, causing problems with employment and driving. With the rapid advances that are occurring in immunology, studies are required to apply these to the investigation of the pathophysiology of thyroid eye disease. The clinical management of the active

inflammatory phase of the disease remains controversial and studies are required to determine the balance between benefit from treatment and the risk of potentially major side-effects for aggressive and conservative management strategies using steroids and other immunosuppressive agents and orbital radiotherapy. These studies will require general medical input adequately to evaluate the systemic impact of these treatments. In particular studies are needed to evaluate the role of newer immunosuppressive agents.

iii. Orbital blowout fractures

These most commonly affect young men and have a major impact on employment prospects and the ability to drive. The indications for early surgical intervention remain controversial and studies are needed to determine which patients benefit from early surgical intervention. These need to be carried out in collaboration with maxillo-facial surgeons, who often see these patients at their initial presentation.

iv. Disorders of accommodation and convergence

The pathophysiology of disorders affecting accommodation and convergence is presently poorly understood. Both insufficiency and spasm of accommodation and convergence cause considerable visual morbidity in patients of working age and deserve more study.

12.3 Research Priorities

12.3.1 Epidemiological and Service Issues

- Determining whether very early squint surgery gives better outcomes for binocular function.
- Determining the optimum management of intermittent squints.
- Determining optimum management for thyroid eye disease.
- Cost-benefit analysis of visual screening in children and determining the optimum age(s) for screening.

12.3.2 Clinical and Laboratory Issues

- Understanding the changes in the brain underlying amblyopia and determining why some children fail to respond to patching.
- Understanding why binocular function breaks down in some children.
- Understanding mechanisms underlying development of correct focussing of the eye and why this fails in some children.

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