DIABETIC EYE DISEASE

IN THE WEST OF SCOTLAND

BY

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The work reported in this Thesis is entirely that of the author except for the following sections in Chapter 5 which were carried out in collaboration with other Ophthalmologists, Physicians, and Opticians from both the Tennent Institute of Ophthalmology and Glasgow Royal Infirmary:

1. Assessment of efficiency of Ophthalmologists and Physicians in the use of Ophthalmoscopy in the screening for diabetic retinopathy in a hospital diabetic clinic.
2. Perimetry.
3. Fluorescein Angiography (partly).

Material from this thesis has been published and presented at Conferences as shown below.

1. Contrast Sensitivity in diabetic subjects with and without retinopathy.
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2. Potential retinal damage from the use of ophthalmic instruments.
(In conjunction with N.M. McKechnie) Trans Ophthalmol Soc UK (1982); 102: 140-146.

3. Common causes of blindness and visual handicap in the West of Scotland.
(In conjunction with D. Allan and W.S. Foulds) Br J Ophthalmol (1983); 67: 209-213.

4. Blood viscosity in proliferative diabetic retinopathy and complicated retinal vein thrombosis.
(In conjunction with G.E. Trope, G.D.O. Lowe, W.S. Foulds, and C.D. Forbes) Trans Ophthalmol Soc UK (1983); In Press.

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SUMMARY

This thesis reports the results of an investigation into some aspects of diabetic eye disease.

The first three chapters give an account of the present state of knowledge of diabetes mellitus and diabetic retinopathy.

In chapter 4 the multifactorial aetiology of diabetic retinopathy is discussed. In relation to this a study of the possible role of blood and plasma viscosity in the pathogenesis of diabetic retinopathy is reported. It was found that in diabetes blood and plasma viscosities are increased. Diabetics with proliferative retinopathy were found to have higher blood viscosity, at both high and low shear rates, than diabetics with background or no retinopathy. Diabetics with serious forms of retinopathy had higher fibrinogen levels than controls.

Chapter 5 reports results of a study carried out in general practice to determine the prevalence of diagnosed diabetes in the West of Scotland. 7139 files of patients attending one group practice were searched for evidence of diabetes. 76 diabetics were found to attend this practice. This gave a figure for the prevalence of known diabetics of 1.06 per cent.

In Chapter 6 results of an investigation into the most practical means for the screening and detection of diabetic retinopathy are reported. This work was carried out in collaboration with ophthalmologists, opticians, physicians, and technicians from the Tennent Institute of Ophthalmology and Glasgow Royal Infirmary. Ophthalmoscopy was found to

be a reliable tool for the purpose of screening for diabetic retinopathy. Ophthalmologists and trained and interested physicians were equally efficient in this respect. Other investigations such as fluorescein angiography, tests of colour vision, contrast sensitivity to grating patterns, and measurement of visual fields were time consuming, costly and needed highly specialised instruments which might not necessarily be available in centres concerned with early detection of serious diabetic retinopathy.

Diabetic subjects had lower contrast sensitivity to grating patterns, compared to normal subjects, as measured by the Arden grating test. Contrast sensitivity was inversly proportional to the degree and severity of retinopathy. The severity of diabetic retinopathy also affected colour discrimination. The most seriously affected were those with exudative retinopathy. The study also confirmed that measurements of visual acuity are not a good indication of the severity of retinopathy.

On the basis of results of the above study funduscopic examination of 400 consecutive diabetics attending a large hospital diabetic clinic, Glasgow Royal Infirmary, was performed (Chapter 7). This work was carried out to determine the prevalence of diabetic retinopathy in this population of diabetic individuals. 32 per cent of these patients were found to have diabetic retinopathy and of these one third had "serious" retinopathy. Serious diabetic retinopathy was defined as a sight-threatening retinopathy which included cases with ischaemic, proliferative, and maculopathy (exudation and/or macular oedema); this is more clearly defined in chapter 3. Patients who had different severity of diabetic retinopathy in the two eyes

were classed according to the more severe retinopathy.

Males developed diabetes 7 years earlier than females and median age of males with diabetic retinopathy was 7 years younger than females with retinopathy. The prevalence of diabetic retinopathy increased steadily with the duration of diabetes in both sexes.

Blood pressure and smoking were found to have no relation to the prevalence of diabetic retinopathy in this population and hypertension had a similar prevalence among diabetics as in the rest of the population in the West of Scotland.

A similar study was carried out on diabetics attending general practice (chapter 8). Identified diabetics were asked to attend for a full physical, including an eye examination. 35 per cent of patients were found to have ophthalmoscopically recognisable diabetic retinopathy. One third of patients with retinopathy had "serious" forms of the disease. This suggested that about 10 per cent of the diabetic population in the West of Scotland might be expected to show these changes.

Patients with a family history of diabetes were found to have developed diabetes about one decade earlier than those who did not have a positive history of diabetes in their families.

In this part of the study glycosylated haemoglobin and random blood sugar were measured. No relation was found between the type of diabetic retinopathy and the level of glycosylated haemoglobin. A positive association was found between the level of random blood sugar and the presence and severity of diabetic retinopathy.

It is possible that short term fluctuations of blood sugar are more important in the pathogenesis of diabetic retinopathy than the level of hyperglycaemia over the last few weeks of the diabetic illness.

A study of the causes of blind registration with a special reference to diabetes - induced blindness was carried out in the "Society for the Blind in Glasgow and the West of Scotland". 2118 B.P.1 Forms were studied. Forms available from the years 1960 and 1980 were analysed. The commonest causes of blindness were senile macular degeneration, glaucoma, cataract, diabetic retinopathy, and myopia. Diabetic retinopathy was found to be the first cause of blindness in the working age 20-64. The onset of blindness was earlier in diabetic males than females. Diabetics were found to be registered as visually handicapped at an earlier age than the non-diabetic blind individuals (Chapter 9).

In Chapter 10 an account is given of the indications, techniques, and advantages of photocoagulation in the treatment of diabetic retinopathy. Visual results of major studies carried out in this respect are summarised.

A study of the short-term effects of laser therapy and exposure to high intensity light from ophthalmic instruments was carried out on patients attending the Tennent Institute (Chapter 11). Normal volunteers and diabetic patients were exposed to the tungsten light of a slit-lamp microscope. Also diabetics who received laser treatment for proliferative diabetic retinopathy were studied. Visual acuity on Snellen's Chart, colour vision as determined by the Farnsworth-Munsell 100-Hue test, and contrast sensitivity measured by Arden grating test were all determined before,

20 minutes, and 24 hours after exposure. These visual functions were not found to be significantly affected by laser therapy or exposure to ophthalmic instruments during photocoagulation or a slit-lamp examination although the majority of normal and diabetic patients showed a temporary drop in visual acuity 20 minutes after light exposure, in all cases returning to within 1 line of Snellen's Chart.

In the final chapter (12) various conclusions from the preceeding chapters are discussed and some recommendations are made with regard to the desirability and design of screening programmes for the early detection of diabetic retinopathy.

DIABETIC EYE DISEASE

IN THE WEST OF SCOTLAND

CHAPTER 1

INTRODUCTION

Diabetic eye disease is one of the four commonest causes of blindness in England and Wales (Sorsby 1966). It is now the first cause of blindness in the age group 20-64 (Sorsby 1972; Ghafour, Allan, and Foulds 1983).

It is known that in the Western World the prevalence of diabetes mellitus is between 0.5 and 2 per cent of the population (West 1978). The exact prevalence of diabetes in Scotland is not known nor is the prevalence of diabetic retinopathy or the incidence of blindness from this cause.

Although the various clinical features of diabetic retinopathy were recognised after the introduction of the ophthalmoscope by Helmholtz in 1850 (Henkind 1980) there is still no consensus on the underlying pathogenesis of the disorder. Considerable advances have occured in our understanding of the disease process as a result of the introduction of fundus fluorescein angiography (Novotny and Alvis 1961), vitreous fluorophotometry (Cunha-Vaz, de Abreu, Campos, and Figo 1975), and by the application of modern techniques of tissue preparation (Ashton 1963), light and electron microscopy to diseased retinal tissue.

It appears likely that diabetic retinopathy is multifactorial in origin and such factors as age of onset, length of diabetic history, control of diabetes, insulin dependence, environmental, and possibly haematological parameters may all play a role in its genesis (Garner 1981).

Until the introduction of retinal photocoagulation (Meyer-Schwickerath 1959) little could be done to influence the progress of proliferative diabetic retinopathy. In several multicentre controlled trials it has been claimed

that both exudative and proliferative forms of retinopathy may be favourably influenced by retinal photocoagulation (Diabetic Retinopathy Study 1976; Multicentre Controlled Study 1977).

These trials have been concerned with efficacy of laser or other types of photocoagulation in diabetic retinopathy; little attention has been paid to the possible adverse effects of these forms of therapy.

This thesis sets out to determine as accurately as possible the prevalence of diagnosed diabetes in the general population of the West of Scotland and the prevalence of diabetic eye disease in this population and in a population attending a large hospital diabetic clinic. This included the relation of some parameters, such as the influence of coexisting hypertension and smoking, to the frequency of different types of diabetic retinopathy. The relation of blood viscosity and some other rheological factors to diabetic retinopathy was studied in a group of patients who were matched for age, sex, duration of diabetes, and smoking habits.

From blind registration statistics an attempt is made to assess the incidence of blindness from diabetic eye disease in relation to other causes of blindness in the West of Scotland. From these studies the size of the diabetic population and numbers of patients with different types of retinopathy are calculated and the relative risk of diabetes-induced blindness is estimated.

A study was also carried out, in collaboration with some colleagues, of the different tools used for the

identification of diabetic retinopathy and an assessment is made as to the most practical of these investigations for the screening of diabetic retinopathy.

An account is given of photocoagulation treatment which is now the most widely used therapy for diabetic retinopathy.

Finally a study of the possible adverse effects of laser therapy on some visual functions, such as visual acuity, contrast sensitivity, and colour vision is reported.

CHAPTER 2

DIABETES

2.1. Definition

Diabetes is a disease which affects both humans and some animals. In man it is the third most common metabolic disease after obesity and thyroid disorder and may be diagnosed for the first time at any age (Meier 1960).

The disorder in diabetes consists of a metabolic and vascular component, which are probably interrelated. The metabolic syndrome is characterised by an inappropriate elevation of blood glucose level, associated with alterations in lipid and protein metabolism for which a relative or absolute lack of insulin is responsible. The vascular syndrome consists of accelerated non-specific atherosclerosis (premature ageing), and a more specific microangiopathy affecting the eye and kidney.

2.2. History

Diabetes has been recognised for more than two thousand years. It was mentioned in Chinese medical writings as a syndrome of polyuria, polyphagia and polydipsia. Its name which comes from a Greek root meaning "To run through" was given to it by Aretaeus (A.D.70). The diabetic urine was described by Thomas Willis "As if imbued with honey", and was proved to contain sugar by Dobson (1776). Claud Bernard in 1859 recognised hyperglycaemia as the cardinal sign of the disease and Langerhans in 1869 described the islets of the pancreas which now bear his name.

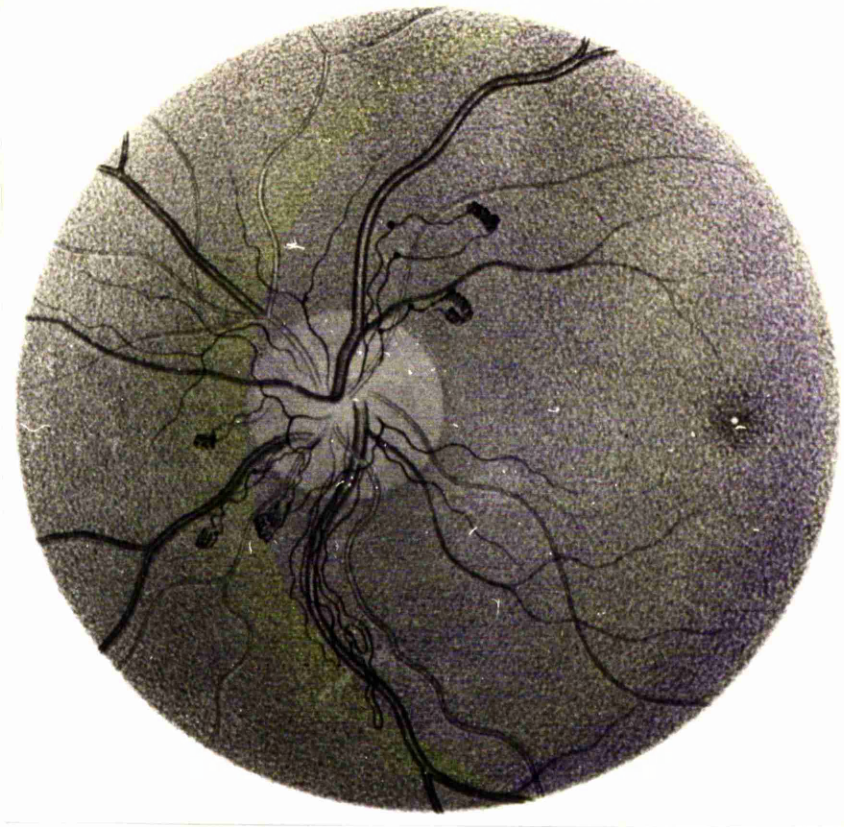

Figure 1. Drawing of a fundus by Hirschberg (1877).

Important contributions to the management of diabetes were made by Banting and Best when they managed to prepare an extract from dog pancreas capable of reducing an elevated blood glucose level (Banting and Best 1921), by Hagedorn who introduced the first long-acting insulin in 1936, and Nicol and Smith who described the chemical structure of human insulin in 1960. It is interesting to note that carbutamide was accidentally discovered by Franke and Fuchs in Germany in 1955 and that this initiated the use of Sulphonylureas as oral hypoglycaemic agents.

2.3. Diagnosis

The degree of hyperglycaemia is probably relevant to the development of microangiopathy, as shown mainly in the eye and kidney. A two-hour postprandial capillary whole-blood concentration of glucose greater than 11 mmol/L has been identified as the point above which the relative risk of retinopathy rises and a two-hour postprandial capillary whole blood glucose concentration of 7.5 mmol/L (135 mg/100 ml) is the value above which a diagnosis of diabetes becomes more likely (Bennett, Rushford, Miller, and Le Compte 1976; Jarrett and Keen 1976; Jarrett, Keen, Fuller, and McCartney 1979).

The following procedures are recommended as diagnostic tests for diabetes.

A. Testing a morning urine specimen for sugar.

B. Measuring blood glucose level.

1. Fasting blood sugar. A fasting venous plasma concentration of 8 mmol/L (144 mg/100 ml) or greater is regarded as diagnostic of diabetes. If the concentration is below 6 mmol/L (108 mg/100 ml) the diagnosis is excluded (W.H.O. 1980).

2. There is a general agreement that a 1-hour postprandial blood glucose level of 11 mmol/L (198 mg/100 ml) or higher indicates diabetes.

C. Oral glucose tolerance test. A patient whose fasting blood sugar is between 6 and 8 mmol/L is given 50 or 100 g (the W.H.O. 1980 recommends 75 g) of glucose orally. Venous blood samples are withdrawn at 1/2, 1, 1.1/2, and 2 hour intervals. If the two hour venous plasma concentration is greater than 11 mmol/L the test is diagnostic of diabetes.

Patients who have a fasting blood sugar between 6 and 8 mmol/L and a 2-hour glucose concentration between 8 and 11 mmol/L after a 75 g oral glucose load are categorised as having impaired glucose tolerance and need to show another abnormal value after a 75 g glucose load (for example a one-hour concentration of 11 mmol/L or greater) before a diagnosis of diabetes is made.

D. Estimation of glycosylated haemoglobin: In diabetes, abnormal concentrations of various glycosylated haemoglobins can be identified. Haemoglobin A_{1c} is a glycosylated haemoglobin whose concentration in diabetic patients reflects the mean blood glucose level for up to 120 days previously (Day 1981) - a value easily ascertained using the standard indices of carbohydrate metabolism. Unlike blood and urine sugar measurements, HbA_{1c} determinations are highly reproducible and require little patient compliance since only one blood sample is needed to ascertain mean glucose level for the preceeding weeks or months. Data may be used to ascertain the degree of glycaemic control and, thus, the effectiveness of a particular thapeutic regimen. It has been suggested that better management of the disease

is possible and the prevention or amelioration of chronic diabetic complications is anticipated (Schanzlin, Jay, Fritzand, and others 1979), and that HbA_{1c} determination is a convenient tool with which to screen patients for diabetes (Bunn, Gabbay, and Gallop 1978; Gonen and Rubinstein 1978; Cole 1979; Wardle 1982).

2.4. Classification

Diabetes can be classified as follows:

(a) Genetic type: Diabetes in this category is usually subdivided into type I insulin-dependent diabetes which is commonly diagnosed before the age of 30, and type II which can be managed by restriction of diet, oral hypoglycaemic agents or insulin depending on the achievment of an acceptable level of blood sugar and the presence of complications and is not insulin-dependent.

(b) Pancreatic diabetes in which the carbohydrate intolerance may be attributed directly to destruction of the pancreatic islets by chronic inflammation, carcinoma, haemochromatosis or surgical removal.

(c) Endocrine diabetes which is associated with endocrinopathies such as hyperpituitarism (acromegaly, basophilism), hyperthyroidism, hyperadrenalism (Cushing's syndrome, pheochromocytoma), and pancreatic islet-cell tumour of A-cell type. Under this category may also be included gestational diabetes and the various forms of stress diabetes listed above.

(d) Iatrogenic diabetes - precipitated by administration of corticosteroids, certain diuretics of the benzothiadiazine type and possibly also by oestrogen-progesterone combinations.

Type I, Insulin-dependent diabetes (IDD)

This type is characterised by a rapid onset, with symptoms such as polydipsia, polyuria, polyphagia, loss of weight and strength, and in children, frequently, recurrence of bed wetting. It is apt to be of the unstable or brittle type, being quite sensitive to the administration of exogenous insulin and easily influenced by physical activity. The patient is liable to ketoacidosis.

For adequate treatment diet and insulin therapy are mandatory.

Diagnosis is usually not difficult and death can occur due to cardiovascular and renal complications althougth the mortality rate has been favourably influenced by the introduction of insulin therapy.

Type II, Non insulin-dependent diabetes (NIDD)

This type has a less stormy beginning, frequently symptoms are minimal or absent. The chief complaint may be moderate loss of weight or occasionally, weight gain. There may be some nocturia. Vulvar pruritus in the female or vascular complications may lead the patient to seek medical advice. It may occasionally be diagnosed as a consequence of blurred vision resulting from diabetic retinopathy or an early onset of senile cataract (Cotlier 1981). Anaemia and fatigue may be associated with fairly advanced diabetic nephropathy; and the disease is sometimes diagnosed as a result of diabetic neuropathy which may present as paresthesia, loss of sensation, impotence, nocturnal diarrhoea, postural hypotension or neurogenic bladder.

The patient with maturity-onset diabetes usually does not present the dramatic, acute metabolic syndrome observed in the juvenile-onset patient but rather a chronic vascular

syndrome. It is therefore important to suspect diabetes as an underlying disease in a wide variety of circumstances.

2.5. Treatment

Correction of the underlying metabolic abnormalities to reduce symptoms, maintaining an ideal body weight, prevention of complications and the nonspecific accelerated atherosclerosis to which a diabetic patient is liable should be the aims of diabetic management. To achieve these, dietary restriction, oral hypoglycaemic agents and/or insulins are used for the treatment of diabetes.

Diet: The chief aims of a diabetic diet are:

1. To prevent excessive postprandial hyperglycaemia.
2. To prevent hyperglycaemia if the patient is on exogenous insulin.
3. To obtain an ideal body weight.
4. To normalise serum cholesterol and triglycerides.
5. To prevent or delay premature atherosclerosis.

It has recently been reported (Simpson, Mann, Chakrabarti, and others 1982) that a high fibre diet has an effect on lowering some clotting values and they reduce the cardiovascular morbidity and mortality.

According to ideal body weight, physical activity and occupation of the patient the basic caloric requirement is determined. Detailed consideration of diet will not be discussed as it is beyond the scope of this work.

Oral hypoglycaemic agents

These are used in the treatment of NIDD if it is of the nonketotic type and when dietary treatment alone is unsuccessful in achieving adequate control.

Insulin

Insulin is a polypeptide, and if taken by mouth is digested to its constituent amino acids. A patient is usually admitted to hospital for education and adjustment of the dose when insulin is needed for the treatment of diabetes (Peacock, Tattersall, Taylor, Douglas, and Reeves 1983).

2.6. Complications of diabetes, Fig. 2.

Listed below are the complications to which a diabetic is susceptible. Some of these can actually be the presenting symptoms of the disease.

A. Acute

1. Diabetic ketoacidosis and coma due to lack of insulin. It may be seen in a person with a) undiagnosed diabetes, b) known diabetes, but who fails to increase his insulin dosage despite poor urine or blood tests, c) known diabetes who suffers from nausea and vomiting and fails to take his daily insulin because he does not eat.
2. Hyperglycaemic nonketotic coma.
3. Complications of insulin therapy.

Repeated use of the same site for insulin injections may lead to a gross thickening of subcutaneous tissue chiefly fat, so called lipohypertrophy. The subcutaneous fat, on the other hand, may rapidly disappear at the site of injections giving rise to the condition called lipoatrophy. This may be due to the intradermal injection of insulin.

Hypoglycaemia may result from an insulin overdose caused, in turn, by mismeasurement using insulin of the wrong strength or too rapid action of insulin,

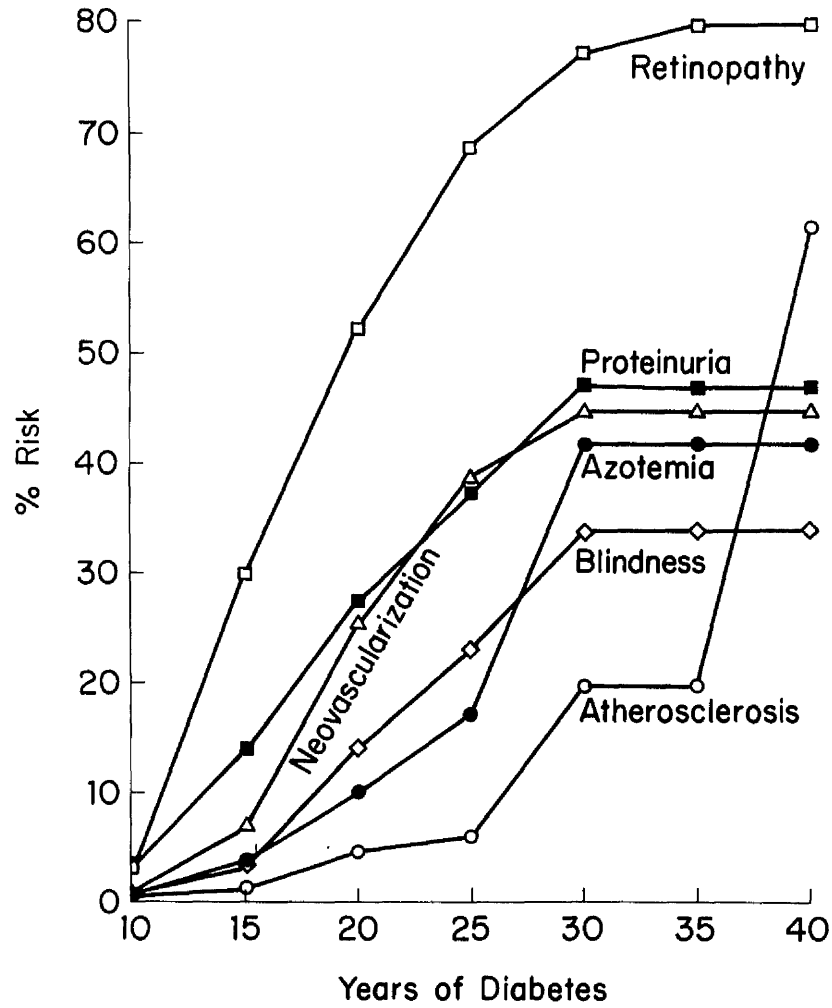

Figure 2. Relation of duration of diabetes to increasing incidence of complications (From West 1978).

from increased physical activity or from failing to take an expected meal, usually the mid-day snack.

B. Chronic

1. Diabetic retinopathy. This is the topic of this Thesis and will be discussed in detail in the following chapters.
2. Diabetic nephropathy. Intercapillary glomerulosclerosis (Kimmelstiel - Wilson disease), characterised by proteinuria and hypertension is the result of a distinctive nodular glomerular lesion of the kidneys with a typical basement membrane (Root, Pote, and Frehner 1954).
3. Diabetic neuropathy. Although it most frequently involves peripheral nerves, it may involve any portion of the nervous system. If an intracranial aneurysm can be ruled out by an angiogram then diabetic neuropathy is most probably the underlying cause for an ocular palsy in a known diabetic patient.

It is difficult to assess the degree of neuropathy and figures vary widely&considerably in different clinical surveys (Bruyn and Garland 1970).

Diabetic neuropathy may be primarily vascular which is potentially reversible or primarily metabolic which is less amenable to treatment (Thomas and Ward 1975).

Clinically diabetic neuropathy may present with peripheral and/or autonomic manifestations.

Peripheral

Sensory : Loss of vibration sense, paresthesia, pain, loss of pain sensation.

Neuromuscular : Weakness, paralysis, diabetic amyotrophy, extraocular palsies.

Autonomic

Eye : Pupillary changes

Gastrointestinal : Delayed gastric emptying, gall bladder dysfunction, nocturnal diarrhoea.

Genitourinary : Sexual impotence, atonic urinary bladder, retrograde ejaculation.

Vascular : Orthostatic hypotension.

Bones and Joints : Neuropathic joint (Charcot).

Skin : Neurogenic ulcer, absent sweating, dependant oedema.

2.7. Death from diabetes

It is generally accepted that diabetics tend to die at an earlier age than a comparable group of nondiabetic individuals in the general population (Sharma, Archer, Hadden, and others 1980).

Myocardial infarction and other vascular diseases, renal complications, ketoacidosis, and hyperglycaemia are the major causes of death in a diabetic population of any age group. Recently the Medical Services Study Group and British Diabetic Association conducted a study on the more important causes of death among diabetics under the age of 50 in the United Kingdom, and found that myocardial infarction and large vessel disease were the cause of death in 41 per cent, renal disease in 19 per cent, diabetic ketoacidosis and coma in 15 per cent, and hypoglycaemia in 4 per cent. Associated factors included smoking, hypertension, obesity, and peripheral vascular disease. Those who

die before the age of 50 do not smoke more heavily than a comparable group in the general population (Tunbridge 1981).

Depending on the prevalence of diabetes in different communities of the world (West 1978) diabetes contributes variably to mortality compared to other causes of death. Listed in Appendix 1 are the death rates from diabetes and its complications in some countries (World Health Annual Statistics 1976) from which it can probably be noted that rice eating communities, in contrast to industrialised countries, have lower rates of death from diabetes.

CHAPTER 3

DIABETIC RETINOPATHY

3.1. CLINICAL FEATURES

Some or all of the following abnormalities are found in the fundus on clinical examination.

3.1.a. Venous changes

Dilatation of the retinal veins is said to be an early feature but early venous dilatation is sometimes difficult to detect ophthalmoscopically. As the dilatation increases however, especially if it is associated with increasing tortousity, it will lead to fusiform dilatations which sometimes occur in close proximity along the vein giving it the appearance of a "string of sausages" (Ballantyne and Lowenstein 1943), Figure 3. The blood in the veins is darker in colour than normal.

Severe changes are sometimes seen in the veins when intraretinal neovascularisation is not detectable. Loops may form, and eventually become so engorged and twisted around the base that they strangulate and slough.

Finally when contraction of fibrous tissue occurs, (this accompanies or follows new vessel formation) Figure 4, the veins are displaced from their original course and loops, coils, and varicose changes become more frequent.

These venous changes indicate a serious development in the course of diabetic retinopathy because they are usually associated with areas of capillary nonperfusion and may preceed new vessel formation.

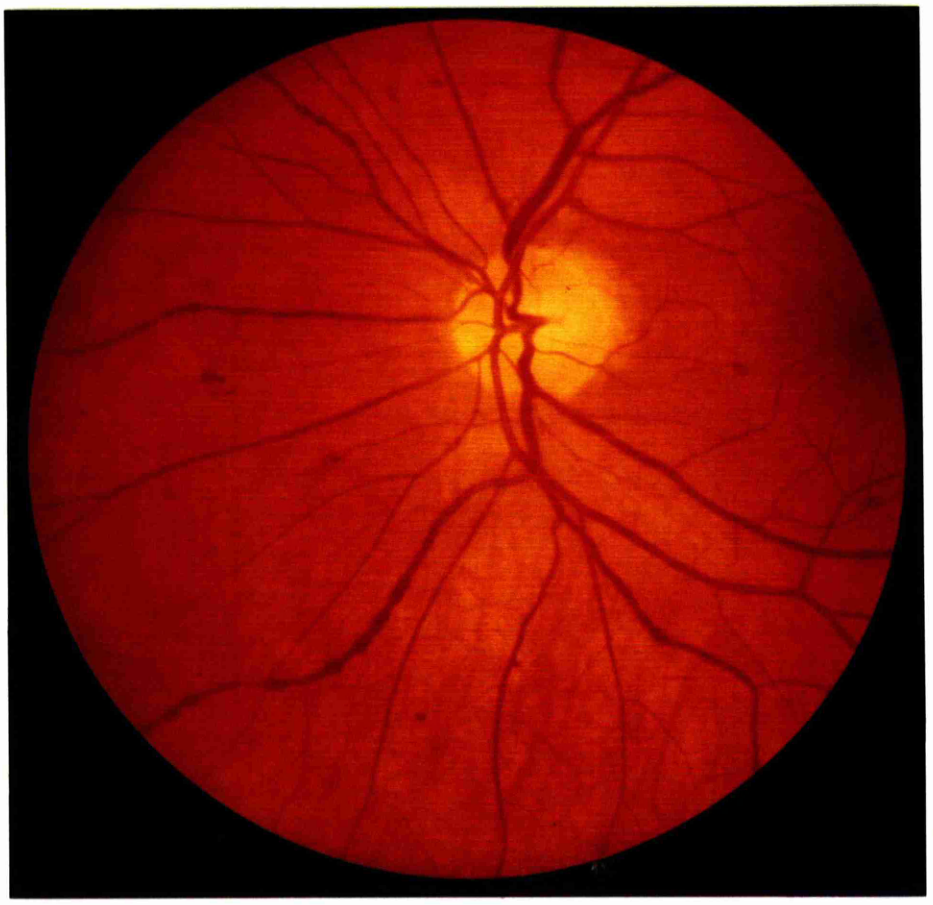

Figure 3. Fundus photograph showing the "string of sausages" appearance of veins.

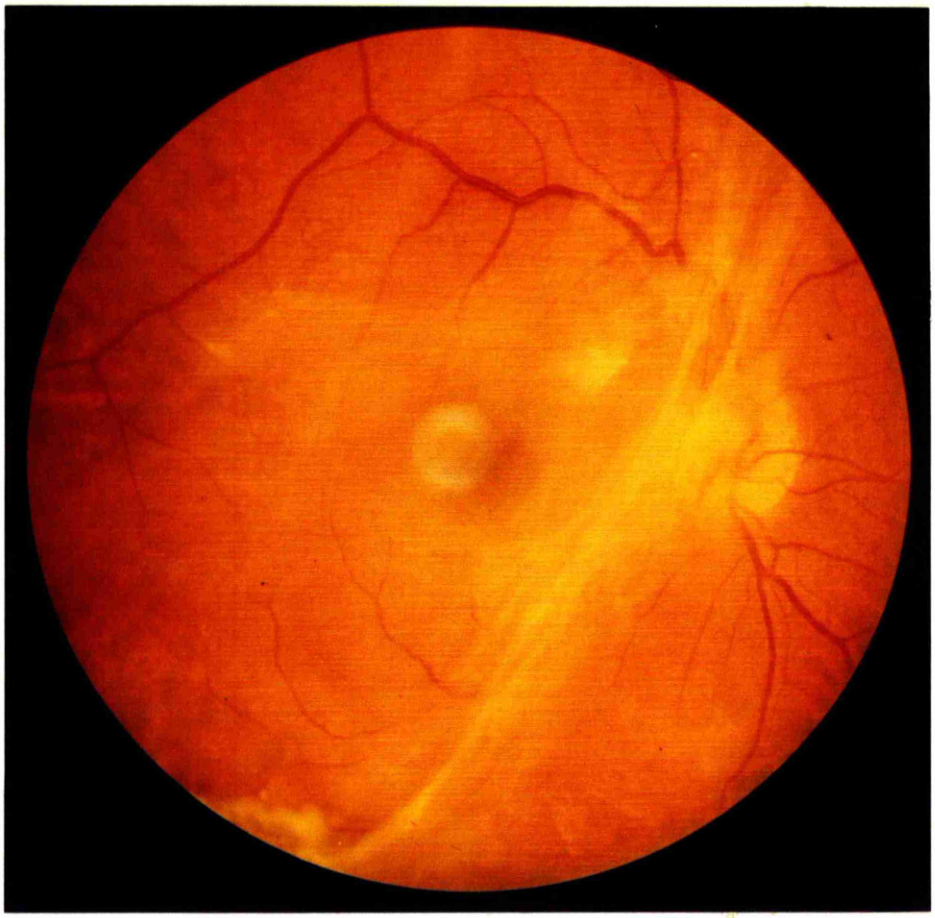

Figure 4. Fundus photograph . Advanced proliferative diabetic retinopathy;formation of fibrous tissue and traction on the macula.

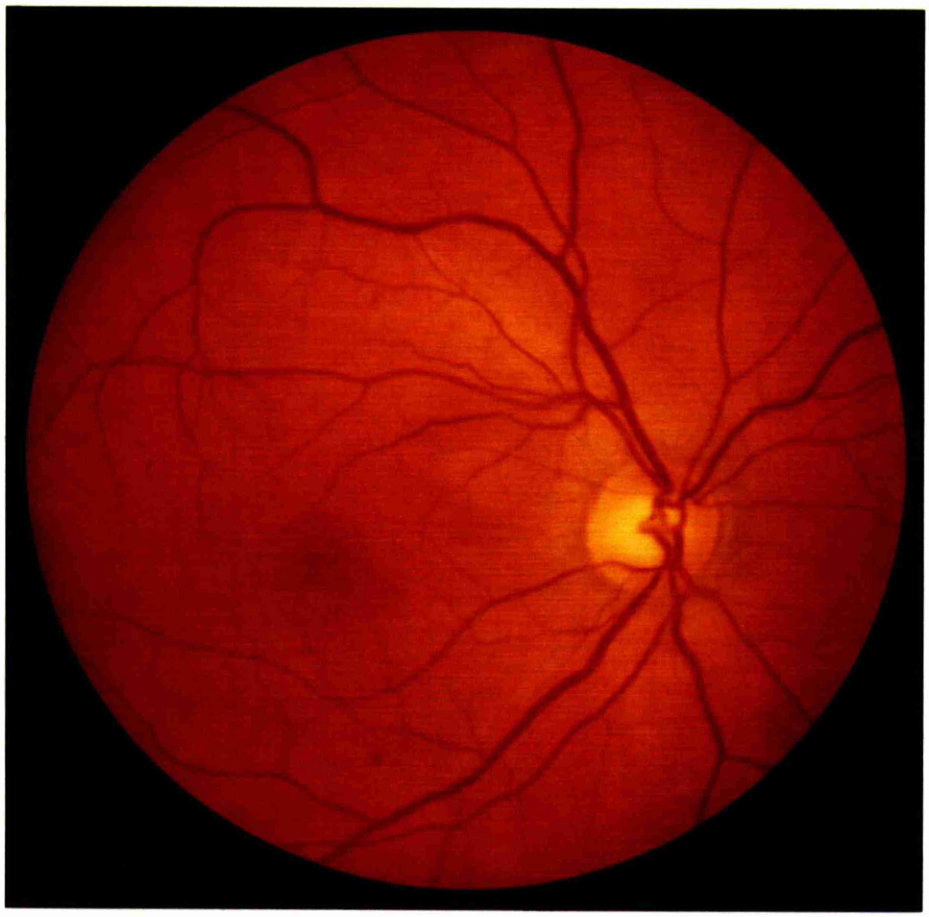

Figure 5. Fundus photograph. Simple diabetic background retinopathy;only a few microaneurysms are seen. This was the fundus appearance of a woman with a 34 years history of diabetes.

3.1.b. Microaneusysms

Microaneurysms can develop in diabetic animals (Barnett 1981). In 1962 Patz and Maumenee demonstrated microaneurysms in a spontaneously diabetic dog. Hausler, Sibay, and Campbell (1964) demonstrated their presence in a dog rendered diabetic by the administration of growth hormone, and retinal changes similar to those occuring in man have been obtained in a dog rendered diabetic by alloxan or metasomatotropin by Engerman and Bloodworth (1965), and by Bloodworth and Molitor (1965).

The presence of microaneurysms (Nettleship 1882) in a diabetic eye, in the absence of other vascular changes, is highly suspicious of diabetes. They are the first unequivocal sign, althougn not pathognomonic of the retinopathy of diabetes.

They range in size from a few to 100 microns with an average of 50 microns (Fig. 5). Those 20-30 microns in diameter can be seen with the ophthalmoscope especially if the pupil is well dilated. The smaller ones are not seen. However, fluorescein angiography shows them all and may disclose a tenfold increase in their number (Scott, Dollery, Hill, Hodge, and Fraser 1963). Microaneurysms may be seen on fluorescein angiography even if the fundus is clinically normal (Tani 1976).

Microaneurysms do not affect vision in the absence of other changes although in one fundus there may be a few hundred of them. They may disappear following strict diabetic control (Dollery and Oakley 1965) or may remain

unchanged for years. With time they fade and some may disappear altogether. Sometimes their previous existence is indicated by whitish spots in the fundus. This is because they form as a blow out of the capillary wall which is later filled in by endothelial cell proliferation and later with basement membrane material.

Microaneurysms are round in shape, clearly outlined sometimes by a single layer of endothelial cells and sometimes by a thin but double contoured wall. They may assume a saccular form arising from the side of a capillary or an ampulliforum shape (Ashton 1949); in their early stage their walls may be thin so that erythrocytes may pass through them (Bloodworth 1962), but as they develop they tend to acquire thickened laminated coats formed by the deposition of PAS-positive material. At a later stage they thrombose and their lumina are occluded by laminated hyaline material.

Two mechanisms for the formation of microaneurysms have been suggested. The first is a localised outpouching of capillary wall. It could be due to focal weakness of the wall due to pericyte degeneration (Cogan 1961), capillary obliteration to leave a residual stump and/or abortive attempts at neovascularisation of areas of capillary closure (Yanoff 1969). An alternative suggestion for the formation of capillary microaneurysms is by fusion of the opposed sides of a capillary loop (Ashton 1958). Although Ashton (1974) has withdrawn this suggestion, he originally thought that this type is preceeded by varicosity and kinking of the capillary.

Figure 6. Formation of microaneurysms. From Ashton 1963.

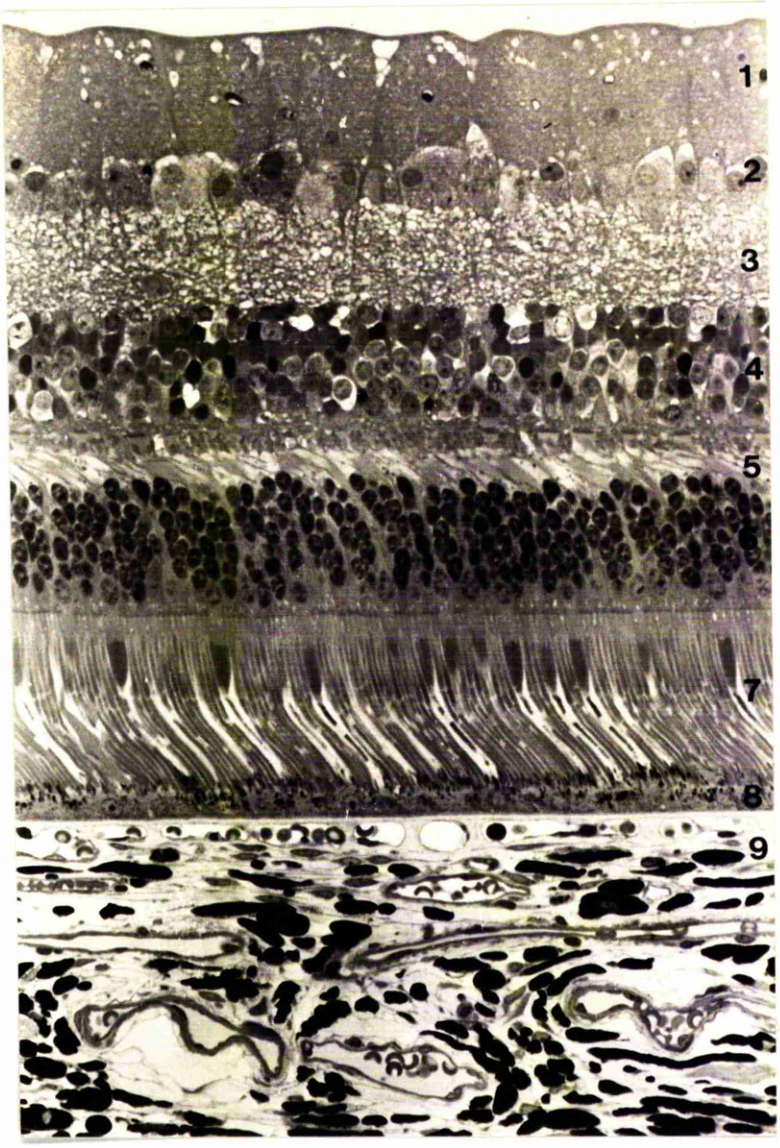

Figure 7. Histological section of the layers of a normal primate retina(Courtesy of N. McKechnie).

1. Nerve fibre.
2. Ganglion cell.
3. Inner plexiform.
4. Inner nuclear.
5. Outer plexiform.
6. Outer nuclear.
7. Rods and cones.
8. Pigment epithelium.
9. Choriocapillaris.

The start may be a limited hyperplasia causing both circumferential dilation and longitudinal growth which would result in tortousity and kinking fusion of the opposed walls of the resulting loop. This leads to the development of an aneurysm which appears to be an outpouching of the wall of the affected capillary (Fig. 6).

Microaneurysms always occur in areas where at least one or two capillaries are nonperfused. They are particularly numerous at the edge of microinfarcts in the nerve fibre layer (cotton wool spots).

3.1.c. Retinal Haemorrhages

Haemorrhages in diabetic retinopathy occur in the mid-retina from the deep capillary plexus or in the nerve fibre layer from the superficial capillary plexus (Fig. 7). The former are typically round. They may be of the "dot and blot" type or "sponge mark" which looks like a blood soaked sponge imprint. They are usually located at the posterior pole of the retina but have recently (Roy and McCulloch 1982) been described in the periphery of the retina next to the ora serrata. More superficial haemorrhages are less common and are flame-shaped. These, however, may so dominate the picture that some ophthalmologists have applied the term "haemorrhagic retinopathy" to describe the diabetic fundus in which they feature.

It is unusual for haemorrhages in the diabetic fundus to have the striate or linear form which is characteristic of haemorrhages in the nerve fibre layer, and this appearance should suggested another aetiology such as systemic hypertension.

The individual haemorrhage takes 6-8 weeks to disappear and may be replaced by others. The spontaneous resolution of retinal haemorrhage makes the interpretation of therapeutic measures difficult.

Haemorrhages may break through the confines of Muller cells and become large and confluent. The may also break through the internal limiting membrane into the subhyaloid space.

3.1.d. Hard exudates

These have well defined edges and are composed of lipid material. They are seen in three forms.

A cluster of small exudates, may be seen in more than one area and may or may not be associated with haemorrhages. Fluorescein angiography always shows the presence of microaneurysms in the same area. Hard exudates, in contrast to microaneurysms do not fluoresce.

Hard exudates may also be seen as a ring or circinate arrangement called circinate retinopathy (Fig. 8). Exudates may form a ring enclosing an area of visible vascular disturbance such as a collection of varicose capillaries, microaneurysms, or haemorrhages (Houston and Wise 1957). On other occasions hard exudates may form larger lesions with a wreath-like structure which may be more than two disc diameter across. These are usually single and enclose the macula. Ring-shaped exudates are more stable and may remain unchanged for more than two years.

A third type of hard exudate is the solitary plaque. It is usually found at the posterior pole and may lie quite close to the macula which is usually oedematous (macular oedema). They may take some years to absorb and should they do so, fine shining cholesterol crystals are left behind.

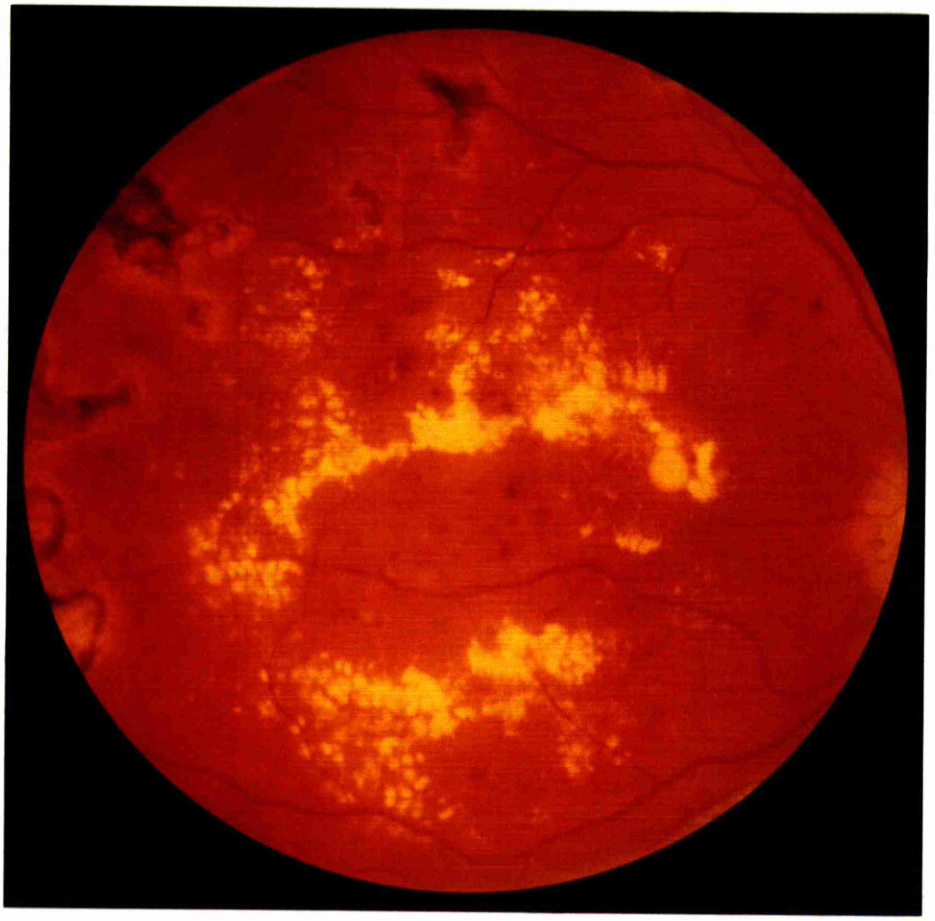

Figure 8. Fundus photograph. Exudative diabetic retinopathy. Formation of a ring of hard exudates. This is a dangerous sign; it may cause severe loss of visual acuity.

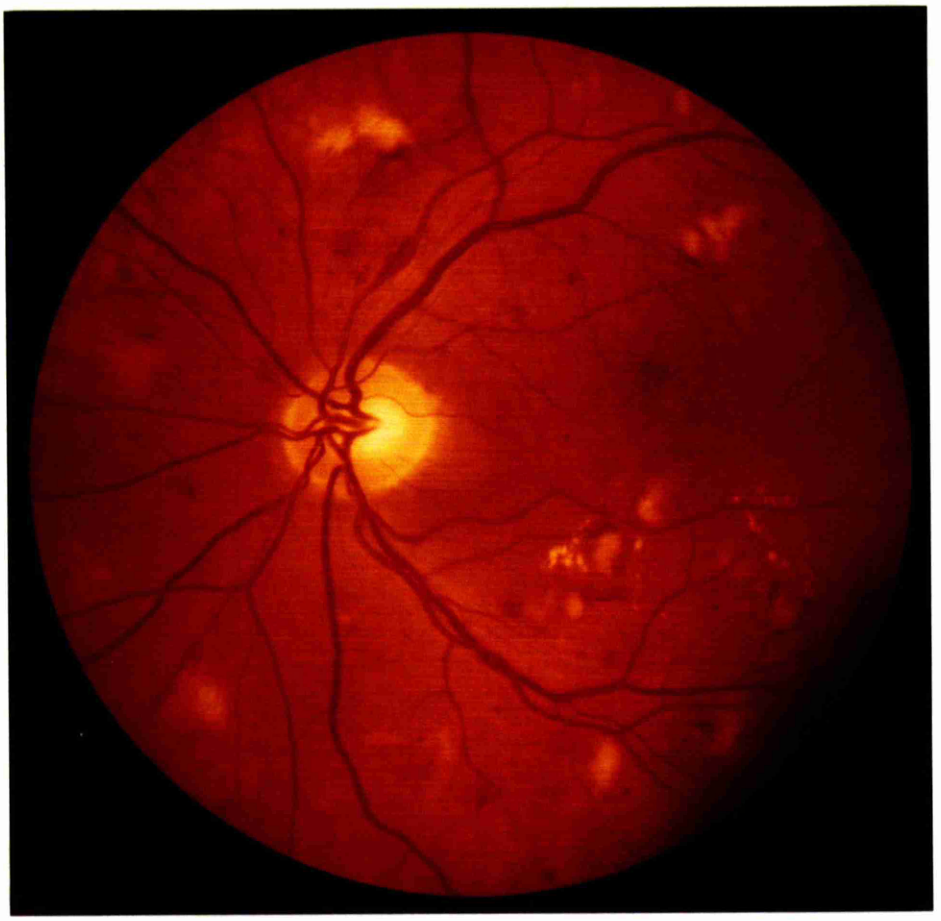

Figure 9. Fundus photograph. Ischaemic diabetic retinopathy with normal blood pressure. Note absence of blood vessel changes characteristic of hypertension.

These plaques are serious sight threatening lesions. Even if they are absorbed they leave a scotoma in the visual field (King, Dobree, Kok and others 1963).

The exudates of diabetic retinopathy are situated for the most part in the outer reticular layer (Ballantyne and Michaelson 1962), in the first place filling individual cystic spaces and forming compact masses which are known clinically as "waxy" patches. Duke-Elder (1967) states that diabetic exudates differ from hypertensive exudates which are predominantly fibrinous and when confluent are granular in appearance and of silvery grey colour. Waxy diabetic exudates are smooth and of homogenous texture. From my own limited experience in histopathology the suggested differences are not at all obvious.

Flat preparations show that hard exudates have finger-like processes winding through the outer plexiform layer but as they enlarge all the retinal layers are eventually invaded and deposits are also found as a localised sheathing along the adventitia of larger vessels. The fatty material is partly intracellular and partly extracellular. The intracellular fat is contained in large rounded cells with small nuclei, phagocytic in function and microglial in origin. These cells are stuffed with fat and occur in clusters. Some workers believed that hard exudates were deposits from the blood stream but the fact that these waxy plaques are always found in areas of neuronal degeneration suggests that they are breakdown products of degenerate nervous tissue which is gradually removed by the phagocytic action of the microglial cells (Bloodworth 1962). However part of their content may emanate from abnormally thin-walled microaneurysms.

3.1.e. Cotton wool spots

Cotton wool spots previously known as soft exudates are greyish yellow in colour with an indistinct margin different from the sharply demarcated edges of hard exudates (Fig. 9).

They are commonly related to areas of acute focal ischaemia and are not specific to hypertensive retinopathy as their presence has been demonstrated in normotensive diabetics (Kohner, Dollery, and Bulpitt 1969). Pathologically they consist of areas of swollen degenerate axons in the nerve fibre layer of the retina. This swelling of the individual axons of the nerve fibre layer of the retina is dueto intracellular oedema and also to failure of axoplasmic transport which is dependent on local energy provision (McLeod, Marshall, Kohner, and Bird 1977). The failure of axoplasmic transport results in an acummulation of axoplasmin in the affected area and is largely responsible for the gross swelling of affected axons. Histologically these swollen axons look like cells and have been called cytoid bodies.

3.1.f. Macular oedema

Diabetic macular oedema is the most serious of the manifestations of nonproliferative retinopathy (Rubinstein and Myska 1972; B.J.O., Editorial 1974; Rubenstein and Myska 1974). If it involves the macular area diffusely, oedema is likely to have a general origin and results from abnormal capillary permeability (Kearns, Hamilton, and Kohner 1979). The oedema may also come from the subjacent choroidal circulation due to a breakdown in the blood-retinal barrier presented by the pigment epithelium (Tso, Cunha-Vaz, Shih, and Jones 1980).

Localised macular oedema probably results from leakage of plasma from microaneurysms and shunt vessels and may be accompanied by hard exudates (lipid), cystoid maculopathy or both.

The oedema fluid accumulates in the outer plexiform layer and finally spreads to adjacent retina. The accumulation of extracellular fluid in the outer plexiform layer and the peculiar arrangement at the macula of the fibres in this layer may give the appearance of cystoid maculopathy (Schatz and Patz 1976; Ticho and Patz 1973).

3.1.g. Proliferative vessels (Figure 10).

In the normally developing retina the vascular network is formed by a process of budding from embryonic mesoderm. In the foetus the new vessels normally develop from an advancing matrix of vasoformative mesenchyme which forms solid cords of endothelial cells that bud out from the parent vessels. The same basic origin is found in neovascularisation in the retina. Vasoproliferation is almost never seen in diseases where total anoxia occurs, for example, in central retinal artery occlusion.

In diabetic retinopathy, neovascularisation is almost always found posterior to the equator, characteristically on the optic disc and along the course of the major retinal vessels, usually within three disc diameters of the disc. These blood vessels do not share the permeability characteristics of normal retinal vessels (Henkind 1981; Garner 1981). Thus, they leak fluorescein, sometimes so profusely as to rapidly obscure retinal details during angiography. They usually remain flat and do not bleed but contraction of the vitreous and detachment of the posterior hyaloid produces

elevation of the newly formed fibrovascular tissue (Wallow, Greaser, and Stevens 1981; Foos, Kreiger, Forsyth, and Zakka 1980).

New vessels appear on the venous side of the circulation. They are usually seen at the edge of areas of capillary nonperfusion and they grow on the surfaces of the retina and of the vitreous which provide a scaffolding on which the vessels can spread.

In addition to their abnormal permeability, which is associated with fenestrations in the basement membrane and absence of the tight endothelial cell junctions which characterise mature retinal vessels (Cohen, McMeel, and Franks 1979), new vessels are prone to bleed.

Initially new formed blood vessels are unaccompanied by a fibrous tissue support but before long fibroblastic activity lays down a collagenous framework around vessels attaching them to the tissue at the posterior pole of the eye and to the posterior hyaloid which is usually detached (Beetham 1963; Dobree 1964), Fig. 11. The evolution of vasoproliferation is always associated with changes in the vitreous which consist of contraction of the vitreous body and detachment of the posterior hyaloid surface and thickening of the posterior hyaloid membrane. Progressive traction on the fibrovascular tissue may eventually lead to a localised area of retinal detachment. Vitreous traction on the neovascular membrane or upper retinal vessels frequently causes avulsion of the vessels and vitreous haemorrhage.

3.2. CLASSIFICATION

Different types of diabetic retinoathy may have a different prognosis (Kohner 1978). It is therefore important to classify these retinal pictures. Each form of retinopathy may vary greatly in severity and it is also important in the assessment and follow-up of diabetic retinopathy to grade the severity of the changes present.

Because the signs may vary greatly from one area of the fundus to another and vary greatly in their relative proportion, it is difficult to devise a wholly satisfactory classification.

There are difficulties in devising a classification of diabetic retinopathy which takes full account of the lack of uniformity and of the variability in the various signs which may be present in the eye. A fundus which might be described as showing no retinopathy on the most detailed ophthalmoscopic examination could demonstrate many anatomical and functional changes if further sophisticated methods of examination are used e.g. fluorescein angiography, contrast sensitivity testing, and colour vision assessment (Tani 1976; Ghafour, Foulds, Allan and McClure 1982; Yamazaki, Adechi-Usami, and Chiba 1982; Lakowski, Aspinall, and Kinnear 1972; Roth 1969).

Many different systems of classification based on different methods of examination have been proposed.

Hirschberg (1891) attempted the first classification when he described three clinical signs namely inflammatory, haemorrhagic, and pigmentary changes. Proliferative changes were not described although clearly illustrated (Fig. 1). In the first group, inflammation of the central part of the retina with small clear spots and punctate

haemorrhages were included; "retinitis puncta diabetica". The second group was described with retinal haemorrhages and consequent inflammation and degeneration, "retinitis haemorrhagica diabetica". The last group included those with inflammation and degeneration of the retina and whose connection with diabetes required, he thought, further investigation. He stated that "a single small haemorrhage in the retina permits us to recognise glycosuria" (Hirschberg 1891).

Ballantyne and Lowenstein (1943) classified diabetic retinopathy into five stages:

1. Microlesions with microaneurysms with or without haemorrhages and punctate exudates.
2. Macrolesions: waxy exudates which, sometimes, can be circinate but never form a macular star.
3. Venous changes: among which variation - in blood vessel calibre, in the course of the main veins, was the earliest change. It takes the form of intermittent enlargement rather than intermittent constriction. These two authors also described increasing tortousity and the formation of loops as well as plexuses and leashes of newly formed vessels. In this category also included were periphlebitis, phlebosclerosis, and increase in haemorrhages in the retina.
4. Destructive changes: Intraocular haemorrhages, retinitis proliferons, detachment of the retina and vitreous, and secondary glaucoma constituted this stage.
5. Mixed form in which the changes of arteriosclerosis and hypertension are added to the diabetic ones.

Ballantyne and Lowenstein thought that the above changes appear in a sequence of events in that manner.

Scott's classification (Scott 1951), which is strictly a grading system, takes into consideration the different course diabetic retinopathy might take, as follows:

Stage 1.a : Capillary microaneurysms

1.b : Changes in the larger veins like phlebo-sclerosis, loops, coils, and distension.

Stage 2.a : Punctate haemorrhages with or without discrete flecks of exudates.

2.b : Larger round or 'blot' haemorrhages with confluent exudates.

Stage 3.a : More numerous haemorrhages and exudates.

3.b : Haemorrhages into the vitreous.

Stage 4 : Retinitis proliferans, retinal detachment and gross degenerative changes.

In Lee's 'classification' (Lee, McMeel, Schepens, and Field 1966) four types of changes are described : Angiopathic , exudative, proliferative, and vitreous haemorrhage. An attempt was made to classify and grade the severity of diabetic retinopathy by taking account of the area of fundus affected by each of the recognisable ophthalmoscopic signs which may be present, for example vascular changes, exudation, proliferation and haemorrhage. Each of the signs was graded as not present (0), mild (1), moderate (2), advanced (3), far advanced (4), and end stage (5). This grading was specifically designed for binocular indirect ophthalmoscopy, with its large field of observation, and aimed at specifically describing the components of retinopathy rather than of the fundus as a whole. Thus a more meaningful description of the status of the retinopathy could be obtained. It appears to be an admirable grading scheme for recording the severity of retinopathy in relation to response to

treatment. It is undoubtedly too complex for use in a screening programme.

In his "System of Ophthalmology", Duke-Elder (1967) classifies diabetic retinopathy as follows:

1. Pre-proliferative stage comprising
   a. Changes in veins and vessels : Distension of the larger veins and their main branches.
   b. Other visible evidence of diabetic retinopathy may or may not be present.
   c. Normal retinal functions other than a decrease of retinal activity.

The arterio-venous ratio changes from 3:4 to 2:4, fullness of veins is especially seen in young diabetics and could be reverted when their diabetic state is well controlled (Larsen 1960).

2. Simple diabetic retinopathy, composed of:
   a. Capillary microansurysms.
   b. Retinal haemorrhages.
   c. Retinal exudates.
   d. Late changes in the retinal veins.
   e. Hypertensive and arteriosclerotic lesions.
   f. Lipaemia retinalis.
   g. Xanthosis retinae.
   h. Pigmentary changes.
3. Proliferative diabetic retinopathy in which the newly growing bloodvessels pass into three stages of evolution (Dobree 1964):
   a. Naked vessels.
   b. Condensation of connective tissue around these vessels.
   c. Cicatrisation and rectraction of fibrous tissue.

Venous changes were considered by some to occur after background retinopathy is relatively advanced (Ballantyne and Lowenstein 1943), while others noted that venous changes may occur early in the course of retinopathy or even as the first detectable sign of retinopathy (Brown and Jones 1964) and independently from other background changes (Scott 1951). Burditt, Caird, and Draper (1968) noted that venous changes tend to regress spontaneously and occasionally evolve into background retinopathy but never into proliferative retinopathy.

A less complex classification and one which might be useful for clinical grading was proposed by Scuderi (1973) as follows:

I Background retinopathy:

- A. Early.
  - 1. Microaneurysms, punctate haemorrhages.
  - 2. Punctate retinitis.
- B. Advanced.
  - 1. Haemorrhagic.
  - 2. Exudative.
- C. Severe.
  - 1. Retinal and preretinal haemorrhages, venous changes.
  - 2. Vitreous haemorrhages.
  - 3. Venous thrombosis.

II Proliferative retinopathy:

III Mixed retinopathy:

- A. Diabetic and atherosclerotic.
- B. Diabetic and renal.

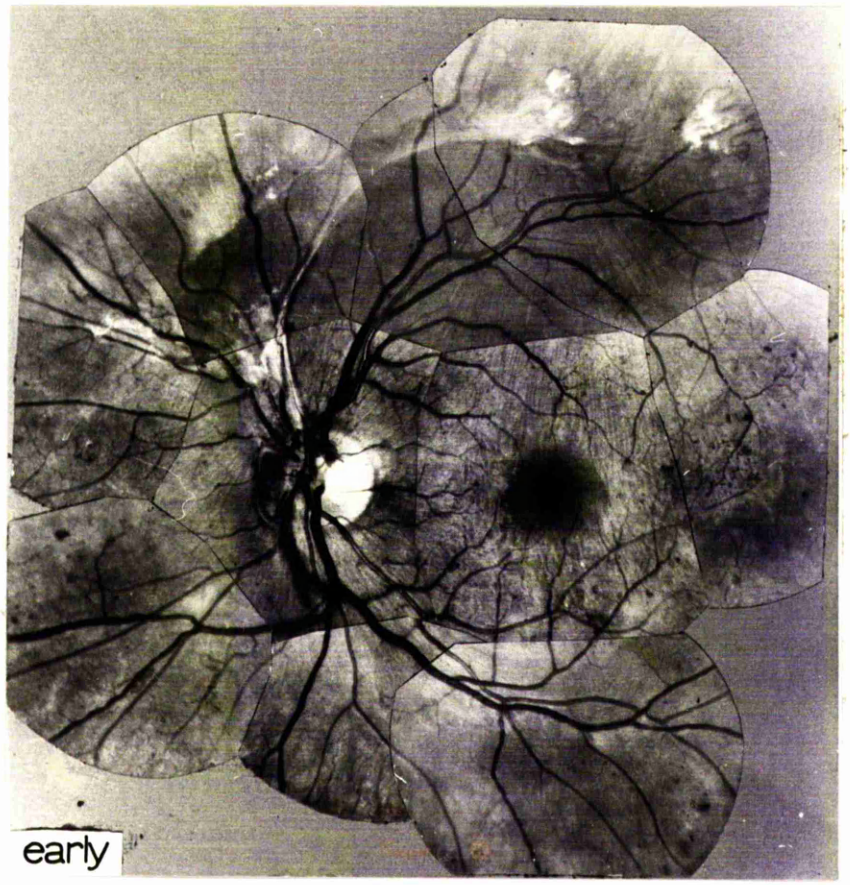

Figure 10. Composite fundus photographs. Early proliferative diabetic retinopathy.

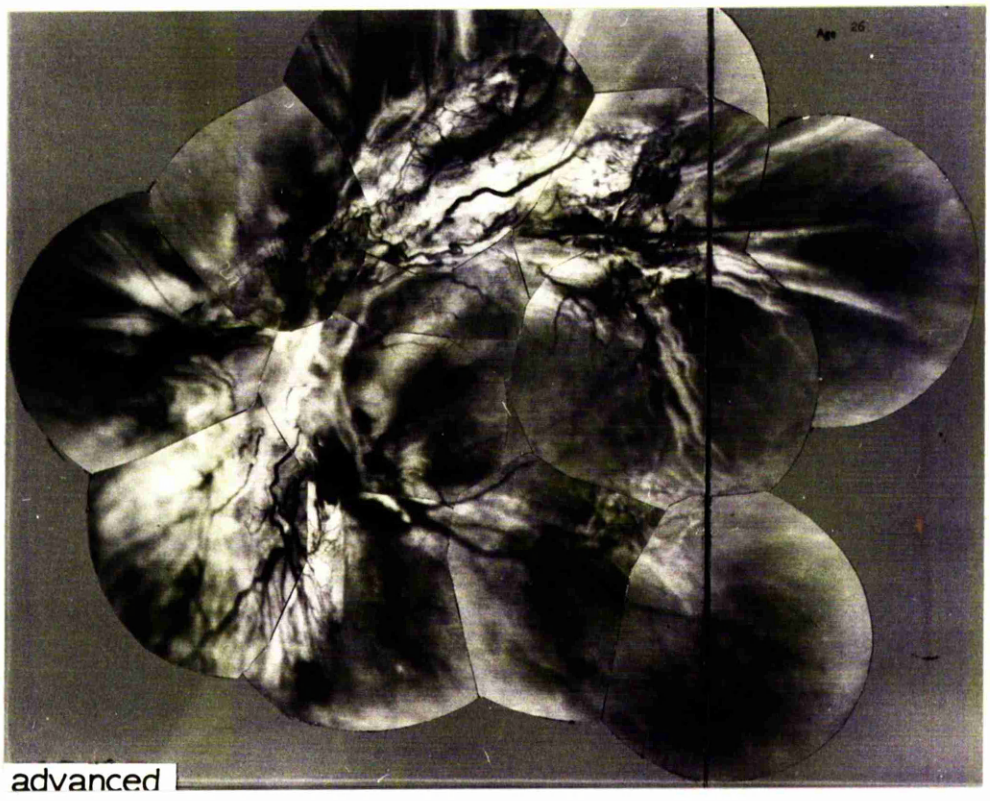

Figure 11. Composite fundus photograph showing advanced proliferative diabetic retinopathy. Same patient as in Figure 10, ten months later.

Figure 12. Fundus fluorescein angiography. Areas of advanced capillary nonperfusion with proliferation of new vessels (leaking fluorescein) at the edge of the ischaemic area. Note also leakage of dye (staining) of blood vessel walls indicated by an arrow.

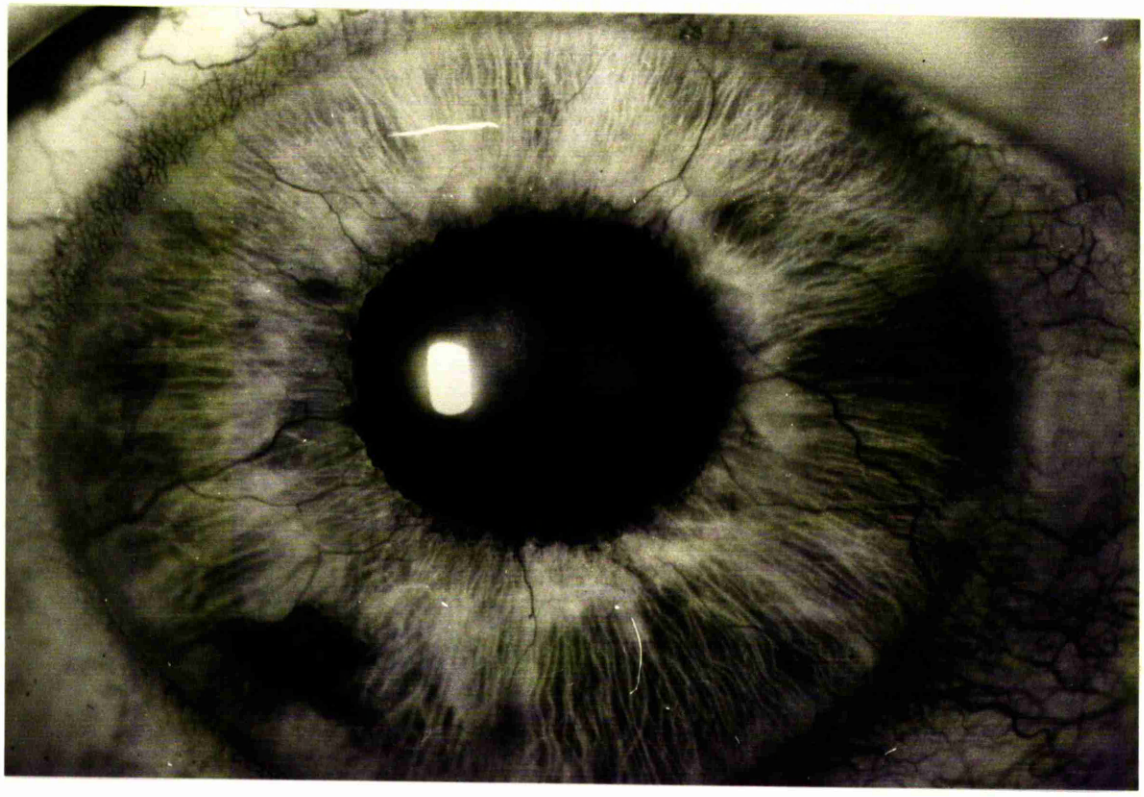

Figure 13(a). A photograph of iris neovascularisation (rubeosis iridis).

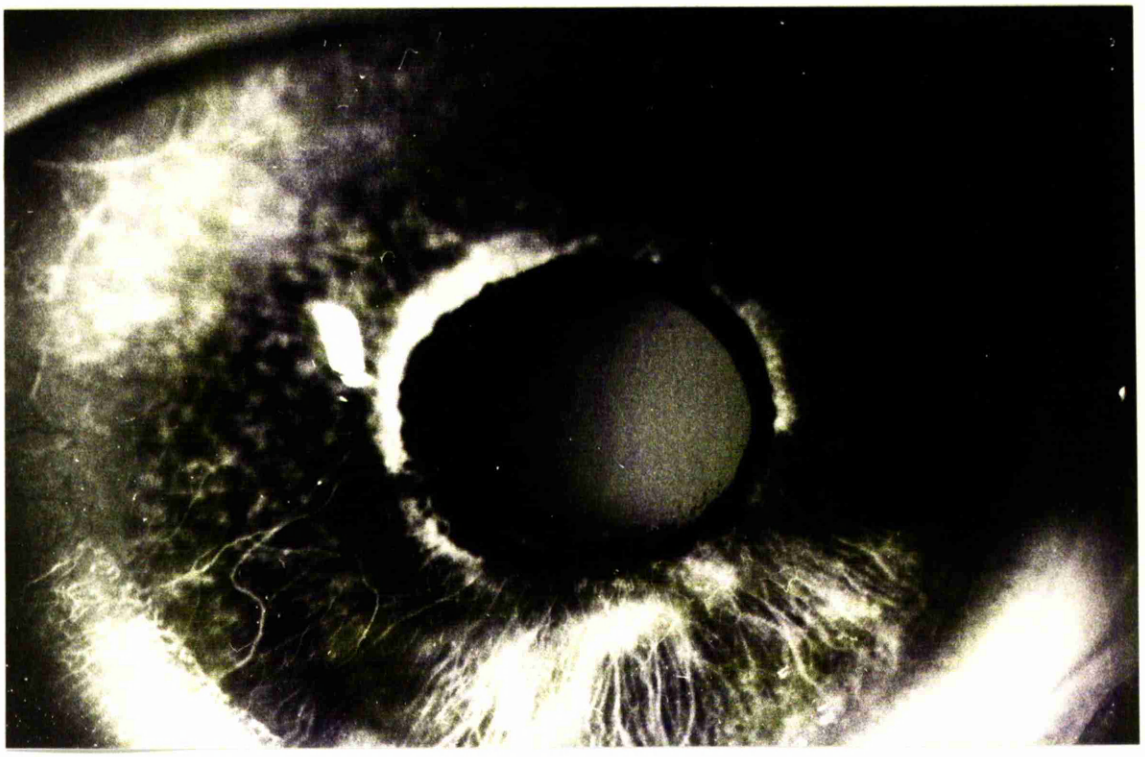

Figure 13(b). Fluorescein iridogram(late stage)of the same patient in Figure 13(a). See leakage of the dye from the iris new vessels.

Many systems of classification are based on grading of the changes which are seen either ophthalmoscopically or by colour photographs.

In the Hammersmith grading system (Oakley, Hill, Joplin, Kohner, and Fraser 1967) twenty colour photographs serve as standards to define four degrees of severity (A to D) for each of the five components of retinopathy. Patient's colour photographs are obtained in nine pre-determined photographic fields around and including the optic disc. Photographs are then graded for each component of retinopathy by comparison with four degrees of severity in the standard photographs. These components are:

1. Microaneurysms and haemorrhages; their number is directly counted in the photographic field regardless of their size.
2. Exudates - Hard exudates only are assessed according to the area of retina involved rather than their number. Cotton wool spots (soft exudates) are ignored.
3. New vessels. These are graded according to the area of field involved. All abnormal vascular channels are included, except those forming in relation to previously established fibrous retinitis proliferans.
4. Venous irregularities. Dilatation, segmental irregularities, and sausaging are assessed according to the percentage of vein, in a particular field, thought to be involved and graded 1 -3. Grades 4 and 5 are reserved for fields in which all the vein is thought to be abnormal according to the severity of involvement of the vein.

5. Retinitis proliferans. Regardless of the amount of its vascular component, any fibrotic lesion in front of the retina is graded according to the area involved in a particular photographic field.

Grading in this system was defined as follows:

Grade 0 .... No lesion

Grade 1 .... Less than standard "A".

Grade 2 .... Equal or worse than "A" but better than standard "B".

Grade 3 .... Equal or worse than "B" but better than standard "C".

Grade 4 .... Equal or worse than "C" but better than standard "D".

Grade 5 .... Equal or worse than "D".

In the initial assessment of this grading system observers were designated the "inside group" if they were familiar with the system, or the "outside group" and these were associated with London diabetic clinics other than Hammersmith Hospital. There was a "satisfactory" consistency between the two groups in the assessment of microaneurysms, haemorrhages, and exudates. A fair consistency was observed in the assessment of new vessels; the outside group of observers made twice as many errors than the inside group in this respect. The consistency was however unsatisfactory in the assessment of venous changes and the outside group experienced particular difficulties in this respect (Oakley, Joplin, Kohner, and Fraser 1968).

In my opinion the Hammersmith system is useful provided the observer is satisfactorily trained. It, however, requires a lot of technical backup and financial support.

The Airlie grading system represented a joint effort from both the United States and the United Kingdom to find a comprehensive, generally accepted classification and grading system for diabetic retinopathy (Davis, Norton and Myers 1968). The Airlie system proposes more extensive recording methods and patient evaluation than any other system (direct and indirect ophthalmoscopy, slit-lamp biomicroscopy of the retina, fundus diagrams, and where indicated, detailed written descriptions). The list of components of retinopathy for grading is more comprehensive than that of any other system. Components amenable to photographic assessment are graded by reference to one standard colour photograph; grade 2, components more severe than standard photograph. Other components are graded by reference to standard written descriptions.

This system was further modified (Diabetic Retinopathy Study Research Group 1981) by the addition of subdivisions to the original grading; it was uncertain whether all components listed in this system could be accurately graded by different observers (Kohner 1968). This system has however, enabled the people involved in the assessment of the effects of photocoagulation therapy on diabetic retinopathy to perform accurate statistical analyses of their results. Without this system it would probably not have been possible to reach the conclusion that photocoagulation is of value in the therapy of diabetic retinopathy. For some purposes and in particular the screening of diabetic patients for the presence or absence of sight-threatening retinopathy a simpler classification and grading system may be appropriate.

For screening purposes the following classification which is used in the Tennent Institute of Ophthalmology has been found satisfactory.

1. No retinopathy. Patients with good visual acuity in whom no diabetic retinopathy is found on funduscopy and who fail to show changes on fluorescein angiography are included under this heading.
2. Background retinopathy. Characterised by the presence of one or a combination of microaneurysms, scattered small hard exudates, and scattered haemorrhages with retention of good visual acuity.
3. Exudative retinopathy.
   (a) Many small or large hard exudates encroaching upon the macula and causing deterioration of visual acuity or threatening to do so.
   (b) Diabetic macular oedema; in the form of focal of cystoid oedema causing deterioration of visual acuity.
4. Ischaemic retinopathy (Fig. 12). Cotton wool spots, large areas of capillary nonperfusion on fluorescein angiography, presence of ghost vessels, rubeosis iridis (Fig. 13), venous loops or beading and multiple areas of intraretinal microvascular abnormalities (IRMA). This might be associated with retention of good visual acuity.
5. Proliferative retinopathy. Detected on ophthalmoscopy and/or fluorescein angiography. Proliferating blood vessels are seen on the optic disc and/or the retina with or without rubeosis of the iris. This also might be associated with retention of good visual acuity.

6. End-stage retinopathy. Manifested by an unresolving vitreous haemorrhage, proliferation of fibrous tissue, retinal detachment, or rubeotic glaucoma.

This classification includes an "ischaemic" category which would obviously necessitate a close watch on the progress of the retinopathy because it is in this group of patients that a better control of the diabetic state might cause arrest or even reversal of the changes (Irsigler, Kritz, Najemnik, and Freyler 1979) while a persistent hyperglycaemia might lead to a rapid deterioration of the retinopathy and appearance of neovascularisation.

For screening purposes a very simple grading system was used namely division of patients into serious and non-serious retinopathy. The purpose of this grading was to make it simple for relatively untrained observers to decide whether or not a patient's retinopathy was a "sight-threatening" retinopathy and needed further investigation with a view to possible laser therapy.

3.3. NATURAL HISTORY OF DIABETIC RETINOPATHY

3.3.a. Introduction

To study the natural history of untreated diabetic retinopathy, it may be convenient to consider some of the variables which may contribute to the frequency and evolution of diabetic retinopathy.

In spite of the vast amount of literature on diabetic retinopathy it is not exactly known what precise role the duration of metabolic disorder, the age at which the disorder first appears, the line of management adopted for each diabetic patient, the severity of the diabetic state, or the existence of high blood pressure, pregnancy, and other factors, like smoking, play in the appearance and progression of diabetic retinopathy.

3.3.b. Variation with Sex

No study shows any substantial sex difference in the proportion of diabetics with retinopathy. A particularly low frequency and severity of retinopathy in diabetic males over 59 years of age has, however, been reported (Nilsson, Nilsson, Frostberg, and others 1967). Seftel and Walker (1966) also found that retinopathy is more common in women. Blindness from diabetes is far more common among black women in the United States, than among black men although much or all of this difference may be due to higher frequency of diabetes among black women (Kahn and Bradley 1975). In some communities (Ghafour, Allan, and Foulds 1983) women may predominate among the diabetic blind perhaps only because women form a greater proportion of older diabetics among whom retinopathy is more common. This perhaps is due to the fact that diabetic men die at an earlier age than diabetic women.

3.3.c. Effect of age at diagnosis and duration of diabetes

It has been accepted that diabetic retinopathy is infrequent in persons with juvenile-onset insulin-dependent diabetes, within the first few years after the onset of the disease, but becomes more prevalent with increasing duration (Caird, Garrett 1963; Caird, Pirie, and Ramsell 1969; Miki, Fukuda, Kuzuya, and others 1969). In a recent study (Dorf, Elmer, Ballintine, and others 1976) no relation between the age of onset of diabetes and the frequency of diabetic retinopathy has been found.

Malone, van Cader, and Edwards (1977) reported that 67 per cent of juvenile patients had retinopathy within one year of the diagnosis. Their study was based on ophthalmoscopy. Other studies based on ophthalmoscopy have suggested that over the age of 40 retinopathy can sometimes be observed at the time of diagnosis of diabetes (Caird et al 1969). There are a few studies of patients over 60 at the time of diagnosis of diabetes, but here the frequency in the first 5 years after diagnosis is higher than in juvenile-onset diabetes and increases to reach 60 per cent or so after 15 years (Burditt, Caird, and Draper 1968).

Studies based on the use of fluorescein angiography have found lower rates of retinopathy in the early years after the onset of diabetes; prevelance rate of zero per cent after zero to four years, 27 per cent for five to nine years, and 71 per cent for more than ten years (Palmberg, Waltman, Krupin, and others 1979; Frank, Hoffman, Podgor, and others 1980).

Comment

It does not seem that a large proportion of diabetic patients would have diabetic retinopathy within at least the first few years after the diagnosis of diabetes is made. The observation of Malone et al (1977) was shown to be invalid (Frank et al 1980) since that study was carried out by inexperienced physicians who were not quite capable of interpretation of many fundus changes. Malone et al (1977) interpreted minor retinal changes, not due to diabetes, as being signs of diabetic retinopathy. This work is an indication of the benefits of properly training individuals involved in the screening and detection of diabetic retinopathy.

Diabetic microangiopathy is believed to be a function of the duration of the metabolic disorder in diabetes (Garner 1982). Almost all studies on the prevalence of diabetic retinopathy have stressed the influence of the duration of diabetes on the development and progress of diabetic retinopathy, irrespective of the racial, environmental, dietary habits or other factors among the sample of patients studied.

A positive relation between the prevalence of diabetic retinopathy and the duration of diabetes was reported in Japanese diabetics (Miki et al 1969), Pima Indians (Dorf et al 1976; West, Erdreich, and Stober 1980), Americans (Kahn and Bradley 1975; Frank et al 1980), and Portugese (Cunha-Vaz, Fonseca, de Abreu, and Ruas 1978).

A prevalence, incorrectly termed incidence, as low as 4.6 per cent was reported among Nigerian diabetics (Osuntokun 1969) and was related not only to duration of diabetes but in addition to a possible alteration in the immunological system or to dietary habits of the population

in that country which include for an average Nigerian much unsaturated vegetable fats as well as a liberal quantity of carbohydrates, vegetables, and pulses but little protein and it was thought that this diet also contributed to the low serum cholesterol found in most Nigerian diabetics. Vegetable fats have been found to cause a decrease in the number and size of hard exudates in ptients with diabetic retinopathy (King, Dobree, Kok, and others 1963).

In the United Kingdom, the relation between duration of diabetes and diabetic retinopathy has, as would be expected, been documented and in a study carried out by the author a linear and positive correlation between the prevalence of diabetic retinopathy and duration of the disease among diabetics attending a General Hospital diabetic clinic has been found (see Chapter 7).

3.3.d. Influence of diabetic control

Reports in the literature on the effects of good diabetic control on the prevalence of diabetic retinopathy and on its progression are conflicting.

Observation of 4,400 diabetics for more than 20 years has suggested that better control of diabetes favourably influences the chances of development of diabetic retinopathy (Pirart 1977). Good control of the diabetic state, specially during the first 5 years after diagnosis, has also been claimed to delay the onset of retinopathy by approximately two and a half years especially in young diabetics (Caird et al 1969).

In recent years there has been increasing evidence that maintaining a patient in a near normoglycaemic state, whether by continuous subcutaneous insulin infusion, CSII (Pickup 1982), or other means for as long as possible may retard the

appearance of diabetic retinopathy (Cahill, Etzwiler, and Frienkel 1976; Jones, Carter, Haitas and Mann 1983) and improve eye and kidney function (Steno Study Group 1982). In a study involving 289 Japanese diabetics, Miki and co-workers found that progression of retinopathy was significantly more frequent in the fair and poor control group than in the good control group (Miki et al 1969). Other workers reported an almost linear correlation between the severity of retinopathy at the time of examination and mean blood sugar level (Hardin, Jackson, Johnston, and Kelly 1956; Szabo 1970), and studies by vitreous fluorophotometry Cunha-Vaz, de Abreu, Campos, and Figo 1975) on blood retinal barrier have shown that the degree of breakdown of the blood retinal barrier, not only correlated with the duration of the diabetes but was accelerated by poor metabolic control (Cunha-Vaz, Fonseca, de Abreu, and Ruas 1978).

Even a reversal of some serious forms of diabetic retinopathy after strict control of hyperglycaemia has been reported. Thus maculopathy disappeared in a patient 65 days after CSII (White, Kohner, Pickup, and Keen 1981), and a reversal of florid proliferative changes has been noted after a few months of strict diabetic control (Irsigler et al, 1979), although this has been challenged recently (Lawson, Champion, Canny et al 1982).

It has also been found that poor control of diabetes is associated, in addition to hyperglycaemia, with higher levels of plasma lipids (Sosenko, Breslow, Miettinen, and Gabbay 1980), and that restoration of normal lipid and aminoacid metabolism was achieved by the establishment of a near normoglycaemic state (Tamborlane, Sherwin, Genel, and Felig, 1979).

Some animal studies support the view that poor diabetic control is important in the initiation and evolution of diabetic retinopathy (Engerman, Bloodworth, and Nelson 1977).

Some other reports have however failed to establish the beneficial effects of good diabetic control on the prevalence and progression of diabetic retinopathy (Constam 1965).

Comment

There is little doubt that maintenance of a near normoglycaemic state in a diabetic subject delays the appearance and progression of diabetic retinopathy. This should not, however, be achieved at the expense of the diabetic individual's wellbeing; a diabetic should not be subjected to the adverse effects near normoglycaemia might cause namely frequent hypoglycaemic episodes.

3.3.e. Co-existing high blood pressure

Some authors have thought that diabetics have an increased liability to hypertension and that diabetic hypertensives are more liable to develop retinopathy than normotensive diabetics especially patients over the age of 40. Ballantyne and Lowenstein (1943) found hypertension in 50 per cent of diabetics showing retinal changes. Kornerup (1957) comparing a large series of diabetics with normal individuals found that in a group under the age of 40, hypertensive retinal changes were present in 17 per cent of diabetics and in 6 per cent of normals.

A recent study of risk factors among Pima Indians of Oklahoma sub-divided subjects into those who had a systolic blood pressure of 170 mm Hg and who did not have

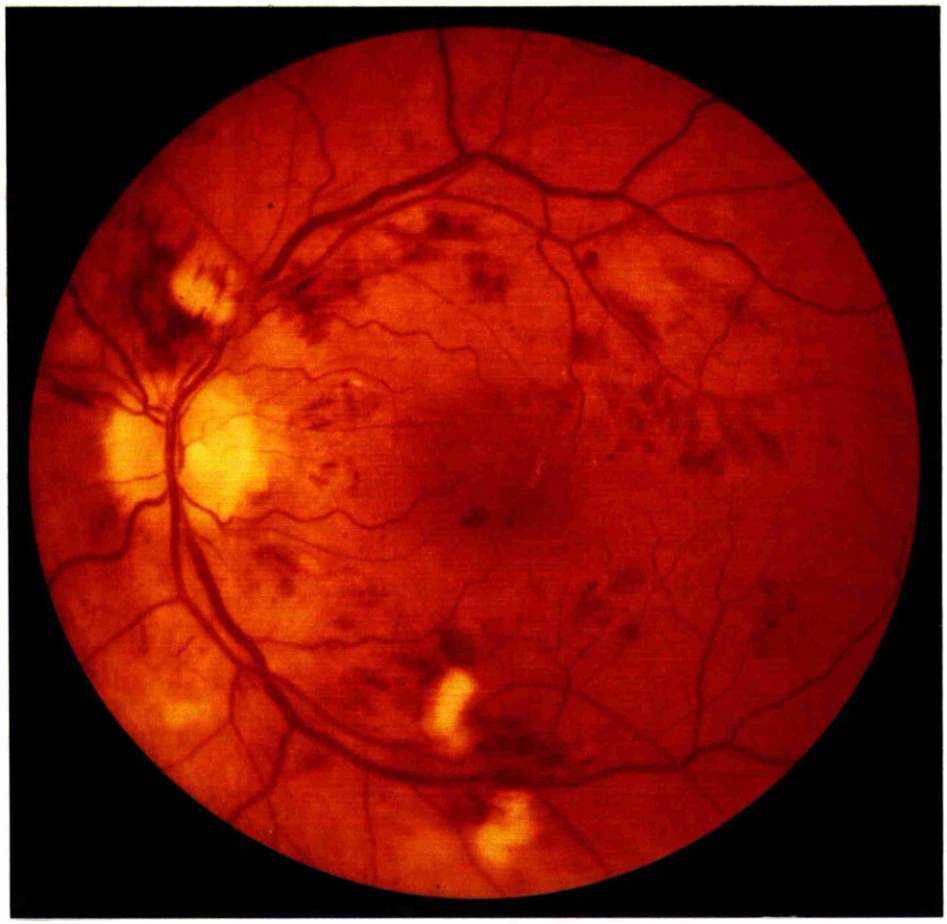

Figure 14. Fundus photograph. Ischaemic diabetic retinopathy in a hypertensive patient aged 46 . Many cotton wool spots are seen. Retinal arterioles are narrow and numerous linear haemorrhages are noted.

proteinuria and those whose systolic blood pressure was greater than this. On ophthalmoscopy it was found that the prevalence of retinopathy was significantly higher among those with raised systolic blood pressure (West and Stober 1978; West et al 1980). Pima Indians might however not represent the diabetic population elsewhere; this might be due to the very high prevalence rate among Pima Indians.

It does not seem, however, that either hypertension or arteriosclerosis have a "direct" influence on diabetic retinopathy (Oakley, Pyke, Tattersall and others 1974) although the retina may become affected by the addition of a hypertensive retinopathy, in which case the components of retinopathy referrable to the diabetes and hypertension can be separately identified. Cotton wool spots which are commonly related to areas of acute ischaemia are not exclusive to hypertensive diabetics (Larsen 1960) since they have been shown to exist in normotensive diabetics as well (Kohner, Dollery, and Bullpitt 1969). Harrold found that increased systemic blood pressure made little difference to the appearance of the retina in diabetics with retinopathy beyond altering the incidence of linear haemorrhages (Harrold 1971), Fig. 14. Others (Knowler, Bennett, and Ballantine 1980) reported an increase in hard exudates among hypertensive diabetics not treated by insulin.

3.3.f. Pregnancy and diabetic retinopathy

Females who develop diabetes during the first, second, or even the third decade of their lives are susceptible to the development of diabetic retinopathy, for the first time during their child-bearing life.

Pregnancy and diabetes certainly complicate each other in many ways. The severity of complications increases with

the duration of the diabetes and the lack of consistent control. It has been stated that retinopathy and its severity correlate with the presence of angiopathy elsewhere in the body, and the outcome of pregnancy is related to the presence of retinopathy and its severity (Caird, et al, 1969; Moloney and Drury 1982). Beetham (1950) found that during 63 pregnancies in 44 patients with simple retinopathy, there were only 8 instances of marked progression with the development of "malignant" retinopathy, and 4 instances of progression in 18 pregnancies in 12 women with "malignant" retinopathy.

Since the introduction of photocoagulation and other forms of treatment this unfavourable prognosis was altered. In order to allow most women the option of motherhood, there is now agreement (Cassar, Kohner, Hamilton, and others 1978; Johnston 1980; Hovart, Maclean, Goldberg, and Crock 1980; Singerman 1981) that:

1. Diabetic women should undergo planned pregnancies early in life.
2. If proliferative retinopathy is seen prior to pregnancy, prompt laser treatment is indicated until the disease is quiescent.
3. Treatment should continue during the pregnancy because it minimises the risk of severe visual loss.
4. Women whose proliferative retinopathy is in spontaneous or laser-induced remission before pregnancy may undertake pregnancy and maintain good vision provided that careful observation and appropriate laser therapy are available.
5. If proliferative diabetic retinopathy is seen, for the first time during pregnancy, prompt laser therapy is indicated.

6. Consideration of therapeutic abortion is restricted to women with progressive proliferation despite treatment.

3.3.g. Effect of smoking

It is not, yet, certain if smoking plays any role in the development of diabetic retinopathy.

Because many blood values, including blood viscosity, are said to be increased by cigarette smoking (Dintenfass 1975) and blood viscosity has been found to be increased in diabetics with and without retinopathy (Lowe, Lowe, Drummond, and others 1980), diabetics are therefore advised not to smoke.

It has been claimed that the risk of development of diabetic retinopathy might be enhanced by cigarette smoking, and that it increases relative to the number of cigarettes smoked per day. The same study (Paetku, Boyd, Winship, and Grace 1977), which involved 181 patients, of whom 65 were long-duration cases of twenty or more years, reported a significant association between smoking and proliferative retinopathy in diabetes of long duration.

Another study on the relation of microangiopathy to HLA-associated genetic factors (Gray, Starkey, Rainbow, and others 1982) has suggested that smoking is a risk factor in the development of diabetic retinopathy and this agrees with the finding (Christiansen 1978) that smoking is more prevalent among diabetics with microangiopathy than among those who did not have signs of angiopathy.

On the other hand, however, an examination of the relationship between retinopathy and cigarette smoking in a consecutive series of 695 Oklahoma Indians with adult-onset diabetes (West and Stober 1978) showed strikingly negative results both for retinopathy and proliferative retinopathy.

Although smokers had slightly lower levels of blood pressure and blood glucose, it did not seem likely that these differences were sufficient to hide an effect of smoking on retinopathy. Similar results were also reported in another study which involved 973 diabetics (West, Erdreich, and Stober 1980).

Summary

It would appear that the development of diabetic retinopathy is related to the duration of diabetes, age at diagnosis, and the state of diabetic control. It may be made worse by pregnancy and possibly systemic hypertension. The roles of diet (particularly dietary fat) and smoking are unclear.

3.3.h. Prognosis of untreated diabetic retinopathy

It can be seen from the previous account that it is not exactly known what determines the onset, rate of progression, or regression, of diabetic retinopathy once diabetes is established.

It seems that the presence and site of diabetic retinopathy are probably more important than its extent in determining the prognosis for vision (Caird and Garrett 1963; Beetham 1963; Tamura and Tamura 1982).

Background retinopathy is the earliest clinically recognisable form of diabetic retinopathy; only a small proportion of eyes with mild background changes advance to the sight threatening forms of retinopathy. Over a 5 year period 36 per cent of eyes with microaneurysms alone will show spontaneous disappearance of all clinically visible lesions and 50 per cent will develop haemorrhages and/or exudates (Caird and Garrett 1962). In Bedford, England, 116 diabetics were discovered in 1962 and were re-examined in 1967; no microaneurysms were observed initially

in 26 persons with two hour post load glucose levels of 200-239 mg/100 ml (11.1 - 13.3 mmol/L), but 3 had microaneurysms five years later. In those with still higher blood glucose levels about one quarter had microaneurysms after 5 years (Keen 1972). Keen also reported that about 8 per cent of the newly discovered diabetics with two hour glucose level greater than 13.3 mmol/L had microaneurysms at the time of discovery of diabetes. In the entire group of 116, 3 developed impairment of vision from retinopathy during the first five years of known diabetes. Arrest or very slow progression of background retinopathy has also been reported by other observers. Kohner (1978) found that 12 out of 106 eyes studied over a 5-year period deteriorated in vision and the majority did so due to the development of cataract rather than worsening of the retinopathy itself.

In a large series of patients Burditt, et al. (1968) observed 3907 eyes of 2184 patients; they showed that in patients with microaneurysms alone, the chances of progression with the development of haemorrhages or exudates increase, with increasing age at diagnosis, from about 40 per cent in those 29 and under at diagnosis to over 60 per cent in those aged 30 to 59. Regression, on the other hand, of retinopathy in these patients with disappearance of all microaneurysms to leave normal fundi was less common in older patients than in the young. When haemorrhages or exudates were present progression with the development of "malignant" retinopathy occured in less than 20 per cent of patients and was least common in the oldest patients. Regression with disappearance of all haemorrhages and exudates to leave either microaneurysms alone or normal fundi was again commoner in the youngest group

(40 to 50 per cent), but not infrequent, in the older (15 to 30 per cent) (Burditt, Caird, and Draper 1968).

Both small hard exudates and haemorrhages may be reduced in number and appearance with a better control of the hyperglycaemic state or when a co-existing high blood pressure is adequately treated (Tamborlane et al 1979; Knowler et al 1980; Sosenko et al 1980). Larger hard exudates may take many years to resolve (King et al 1963; Kaback and Tanenbaum 1974).

Certain clinical signs indicate that a patient with mild retinopathy is in danger of development of the more serious forms of retinopathy. An increase in the number of haemorrhages, increase in the number and size of hard exudates, encroachment of hard exudates upon the fovea, appearance of cotton wool spots, venous beading, and clinical or subclinical collection of fluid in the macular region all herald deterioration of visual acuity and indicate a worse prognosis.

The development of diabetic maculopathy with even minor damage to vision is a danger sign and tends to involve both eyes. It is more common in patients with onset of diabetes after the age of 40 and in only about a quarter of those with maculopathy is diabetes diagnosed before this age (Sigelman 1980).

Maculopathy is more commonly seen with Type II than with Type I diabetes. In the Hammersmith Hospital, 75 per cent of patients with maculopathy had their disease diagnosed after the age of 40. In 30 per cent of these patients, the known duration of diabetes was 10 years or less. In 25 per cent of patients with maculopathy, diabetes was diagnosed under the age of 40 (Kohner 1978).

Kohner (1978) suggested that these younger patients fall into three distinct groups. The largest sub-group is composed of type I patients with a long duration of diabetes (over 15 to 20 years). Most of these patients have impaired renal function and in most of them maculopathy decreases vision, though rarely beyond 6/36. The final cause of visual loss in these patients is usually haemorrhage from new vessels.

The second group is composed of either type I or type II diabetics who develop maculopathy after diabetes of relatively short duration that commonly is poorly controlled. Their visual loss is usually not severe, and impeccable diabetic control may have marked beneficial effect.

The third sub-group is the smallest. In these patients there is a form of macular oedema with little in the way of obvious lesions. In contrast to the more common type of retinopathy in which leakage becomes more marked in the late frames of the angiograms, these patients' capillaries all leak fluorescein profusely, even in the capillary stage. This type of maculopathy does not usually respond to any form of treatment and carries a very bad prognosis for vision (Kearns, Hamilton, and Kohner 1979) because neovascularisation is very soon added to the picture making the outcome even worse.

Recently a simpler classification (Blach, Whitelocke, and Hamilton 1981) of diabetic maculopathy has been proposed:

1. Focal diabetic maculopathy: This consists of usually circinate exudates, microaneurysms, and haemorrhages. Oedema is at the centre of the ring exudates and may often be present at the macula. Fluorescein angiography demonstrates adequate capillary perfusion but areas of

leakage are seen.

2. Cystoid diabetic maculopathy: This has marked oedema with cystic changes at the macula. Exudates are not a feature, but microaneurysms and haemorrhages occur with a marked increase in permeability of the capillaries on fluorescein angiography.

3. Ischaemic diabetic maculopathy: This consists of microaneurysms, haemorrhages, and a few exudates - often with macular oedema and cystoid changes together with deep retinal haemorrhages. Fluorescein angiography reveals areas of capillary nonperfusion in the para-macular area.

An important factor in further progression, stabilisation, or regression of diabetic maculopathy is the state of perfusion of the perifoveal network; progression of capillary nonperfusion in the perifoveal zone correlated with poor visual prognosis (Tamura and Tamura 1982). Good final visual acuity without treatment was recorded in 63 per cent of eyes with diabetic maculopathy and good perfusion while poor results were obtained in 100 per cent of centrally nonperfusing eyes (Ticho and Patz 1973).

The appearance of capillary nonperfusion and cotton wool spots is a dangerous sign since it signals the development of new vessel formation. Cotton wool spots should always be regarded as an indicationthat neovascularisation is likely to develop in 6 to 12 months.

In addition to capillary nonperfusion other signs of retinal ischaemia are large blot haemorrhages, sheets and clusters of haemorrhages, sheathed vessels and white lines replacing blood vessels. Venous loops (Whittington 1964) may be an additional sign. Regression of venous loops

however can sometimes occur (Joplin, Oakley, Hill, and others 1967).

New vessels may develop on the disc or in the retinal periphery. Those on the disc carry a worse prognosis than those in the retina which may remain flat and hardly advance at all over a period of 5 years (Beetham 1963).

Haemorrhages complicate disc vessels more readily and the subsequent advance to fibrosis makes the prognosis worse than in the case of retinal vessels (Diabetic Retinopathy Study 1976). Out of 21 untreated eyes followed for 5 years, 13 lost vision while of 17 eyes with retinal vessels only 5 lost vision in 5 years (Kohner 1978). A follow-up of patients with moderate and severe proliferative diabetic retinopathy for an average of 44.3 months showed that one third of the patients retained a good level of vision, another third were left with a moderate visual acuity of 6/60 or better, and the rest were almost blind (Spencer, McMeel, and Frank 1981).

Regression of neovascularisation has, however, been seen in some patients. Gerritzen (1973), see Table 1, in an 8 year follow-up of 459 diabetic patients with different forms of retinopathy, including cases with neovascularisation, reported the disappearance of new vessels in some cases.

Proliferative retinopathy more commonly progresses to advanced disease if untreated. This depends on changes in the vitreous and internal limiting membrane of the retina. Neovascularisation passes through three stages of evolution (Dobree 1964) in the first of which the newly formed vessels, whether on the disc or in the retina are naked; fibrous tissue then starts to invest the vessels, second stage, and may be seen extending on the detached vitreous;

recurrent vitreous haemorrhage may take place in this stage causing sudden partial or complete loss of vision. A small vitreous haemorrhage usually clears up but a severe haemorrhage may not be absorbed and may leave permanent blindness (Diabetic Retinopathy Study 1979). Ziemianski, McMeel, and Franks (1980) followed up eighty five eyes with severe vitreous haemorrhage at the initial visit and found that vision improved in 30 per cent of cases, was unchanged in 28 per cent, and worsened in 42 per cent. When, in the third stage, the fibrous tissue contracts retinal tears, traction retinal detachment, and blindness result. Thrombotic glaucoma resulting from new vessels growing at the anterior chamber angle usually associated with rubeosis of the iris is another dangerous development and there are usually areas of retinal capillary nonperfusion. These patients have new blood vessels at the disc at the same time. Severe visual loss occurs and only rarely is a patient left with a visual acuity of 6/60 or better.

Period (years)	Progression	Stationary	Amelioration
2	14-29	60-69	7-17
4	32-39	47-57	10-12
6	39-50	40-47	10-14
8	48	38	14

Table 1. Follow-up results of untreated diabetic retinopathy shown as percentages of patients with different clinical outcome. From Gerritzen 1973.

CHAPTER 4

PATHOGENESIS OF DIABETIC RETINOPATHY

4.1. INTRODUCTION

The pathogenesis of diabetic retinopathy is poorly understood. It is an extremely complex series of changes in which many factors contribute to the final picture.

The changes that occur in diabetic retinopathy are not unique to diabetes and some are found in other diseases. However, it is only in a diabetic fundus that all the following features can exist at the same time : Venous dilatation, capillary nonperfusion, focal retinal ischaemia, proteinaceous and lipid exudates, microaneurysms, retinal oedema, haemorrhages, and retinal and optic disc neovascularisation.

Retinal hypoxia seems to be the insult common to diabetic retinopathy and similar diseases (Ashton 1963, 1980). The suggested mechanisms by which retinal hypoxia is produced in diabetes are as follows:

1. There is impaired ability of red blood cells to release oxygen. This is caused by reduced levels of 2, 3 - diphosphoglycerate in erythocytes, which results from lowered plasma inorganic phosphate in poorly controlled diabetics; this reduction is associated with impaired release of oxygen by haemoglobin and may be found in recently diagnosed diabetics (Ditzel, Anderson, and Daugaard 1973; Standl and Kolb 1973; Ditzel, Hau, and Daugaard 1977).

2. There is an abnormal distribution of haemoglobin A in diabetics with increased haemoglobin A_{1c}. This has a greater than normal binding power for oxygen, further impairing the diffusion of oxygen to tissue.

3. Insulin insufficiency or insulin-insensitive cells lead to shunting of glucose into polyol pathways with accumulation of sorbitol and fuctuse (Gabbay 1973; Rossio, Morrison, and Winegrad 1972). Increased osmotic pressure from intracellular sorbitol causes cellular oedema, probably including oedema of endothelial cells. This may further contribute to tissue hypoxia by impaired diffusion.

4. There are changes in blood consisting of altered plasma proteins, increased red cell aggregation, altered platelet function, and impaired fibrinolytic response. These changes possibly play a significant role in the pathogenesis of diabetic retinopathy by impairing blood flow in the microcirculation, particularly in the presence of thickened capillary basement membrane with a narrowed lumen (Ditzel 1967; Little, Sacks, Vassiliades, and Greer 1977).

The pathogenesis of diabetic retinopathy will be discussed in this chapter under the following headings : Microangiopathy, the influence of genetic factors and carbohydrate metabolism, the role of growth hormone, and the role of some rheological factors.

4.2. MICROANGIOPATHY

Blood vessels in most parts of the body are subject to disease as a function of the duration of the metabolic defect in diabetes and are at the root of the renal complications, neuropathy, and tendency to gangrene, as well as the retinal disturbance. Largely because the vascular complications are far less amenable to therapy that lowers the blood sugar than is the metabolic disorder, it was

suggested that these are distinct aspects of the diabetic process under the control of related but separated genes (Sabour, MacDonald, and Robson 1962; Siperstein, Unger, and Madison 1968). It is difficult to sustain this view because angiopathy can also develop in diabetes of other types in which genetic factors are not involved (Duncan, Macfarlane, and Robson 1958) and is also seen in artificially induced diabetes in animals (Bloodworth and Molitor 1965). Moreover, microangiopathy develops after the onset of diabetes mellitus and may be delayed if the carbohydrate metabolism is kept under rigid control (Caird et al 1969). Consequently there is good reason to attribute the small vessel involvement to the metabolic abnormality, but the mechanism by which this is brought about is still not entirely clear.

Apart from microangiopathy, the larger vessels of arterial size are prone to develop excessively severe atherosclerosis, and there is evidence that plaque formation at the origin of the ophthalmic artery may aggravate an established diabetic retinopathy (Garner and Ashton 1972). There is however, little that is absolutely specific to diabetes in either small or large vessels.

Venous, capillary, and arteriolar changes are early manifestations of the diabetic retinopathy process.

4.2.a. VENOUS CHANGES

Dilatation of the veins is one of the early changes in the process of diabetic retinopathy and may amount to about 10% in some patients (Skovborg, Nielson, Lauritzen, and

Hartkopp 1969). Initially, the dilatation appears to be functional since it may be reversed with improved control of the diabetic state (Larsen 1960), but eventually the abnormality is likely to become fixed as sclerotic changes take place within the wall.

At one time it was usual to regard the venous dilatation as indicating a venous stasis retinopathy. If this is the case, failure to detect any sign of structural impediment to outflow would mean that any stasis must be due to a functional disturbance, such as hyperviscosity or sluggish perfusion due to arteriolar inadequacy in a manner comparable to the venous stasis retinopathy associated with carotid artery disease (Kearns and Hollenhorst 1963). Demonstrations of increased blood flow in early diabetic retinopathy (Kohner, Hamilton, Saunders, Sutcliff, and Bulpitt 1975), however, are opposed to any concept of stasis from whatever cause and the mechanism of venous dilatation remains unexplained. There is a distinct possibility, nevertheless, of its being a reflection of the increased blood flow shown to be prominent in early diabetic retinopathy.

4.2.b. CAPILLARY CHANGES

The capillary changes which can be recognised clinically are, dilatation, which can be generalised or localised, and capillary closure.

Capillary dilatation

Capillary dilatation is evidenced by the finding of an

increase of blood flow in minimal and preclinical retinopathy and in recently diagnosed diabetes (Kohner et al 1975). It is also found in maculopathy and sometimes in young diabetics with early proliferative retinopathy and is usually associated with capillary closure.

Capillary dilatation on fluorescein angiography is an early change in diabetic retinopathy and may occur in the absence of other signs.

It is possible that vasodilatation and increased blood flow are both autoregulatory mechanisms to compensate for an abnormal metabolsim and/or increased hypoxia since it has been found that increased retinal blood flow is associated with raised levels of blood glucose (Atherton, Hill, Keen, Young, and Edwards 1980), and with lactic acid accumulation (Keen and Chlouverakis 1965). It is also possible that raised whole blood viscosity could play some part in the process of dilatation. (Trope, Lowe, Ghafour, Foulds, and Forbes 1983).

Localised capillary dilatations appear in the form of microaneurysms and, like generalised dilatation, are usually associated with one or more areas of capillary nonperfusion.

Capillary dilatation is not associated with visual deterioration unless other changes like increased permeability are present as in macular oedema, when visual loss is a common result. Increased capillary permeability, again, is possibly an autoregulatory response to tissue hypoxia secondary to insulin dependent intraretinal metabolic processes and perhaps increased levels of glycosylated haemoglobin (HBA_{1c}) and hyperglycaemia (Hill and Atherton 1979).

Dilatation of the capillaries is associated with the following structural changes : Basement membrane thickening, pericyte degeneration, microaneurysms, and intraretinal microvascular abnormalities (IRMA).

Basement membrane changes

The hallmark of capillary abnormality in diabetes is thickening of the basement membrane (Siperstein, Raskin, and Burns 1973), a development that accompanies the metabolic disturbance and occurs in many tissues. It can be detected in renal glomeruli and appears to be secondary to the metabolic abnormality and is a feature of secondary diabetes. It is retarded by therapeutic prevention of hyperglycaemia and can be reversed by grafting of pancreatic islet cells in experimentally induced diabetes in animals (Lee, Mauer, Brown, Sutherland, Michael, and Najarian 1974). The normal width of the basement membrane is of the order of 80-120 nm; in diabetes it may be up to five times this and is due to an accumulation of collagenous glycoprotein distinguished by an increased proportion of hydroxylysine-rich subunits. Two mechanisms for increased synthesis are suggested (Spiro 1976):

1. The high levels of growth hormone (Somatotrophin) common in diabetes induce both increased synthesis of peptides and subsequent hydroxylation of the lysine residue.

2. Hyperglycaemia is associated with metabolic pathways which are independent of insulin and involve glycosyl and galactosyl transferases. This could result in the linking of disaccharide units to the hydroxylysine-peptide units and the formation of basement membrane protein.

It has been suggested that a humoral factor might be involved in basement membrane synthesis in experimental work on the lens of diabetic rats (Fisher 1979). However, it is doubtful whether this is important in the development of retinal lesions since there is a barrier to protein movement across the capillary wall provided mainly by the capillary endothelium.

Ashton's comment (1974) on the presence of recognisable haematogenous elements such as lipid, fibrin, haemosiderin, and even cellular constituents within the thickened membrane supports the view that part of the thickening represents insudation through an unduly permeable endothelium. Such elements are, however, by no means invariable, and commonly the thickening appears to be caused by accumulation of true basement membrane material. It is possible, therefore, that both insudation and increased synthesis are involved.

The thickened membrane can also include cellular remnants presumed to originate from degenerate pericytes, giving the membrane a laminated appearance in electron micrographs; an alternative hypothesis is that the laminated appearance of the thickened membrane could be caused by waves of endothelial cell degeneration and renewal, each new layer of endothelium secreting its own membrane (Vracko 1974).

Added to the thickening of the amorphous component of the basement membrane is an increase in the network of reticulin fibres normally demonstrable around the vessels on their external aspects (Ashton and Tripathi 1975). Reticulin is argyrophilic and is a collagenous protein with a fibrillar organisation, individual fibres measuring about 10 nm in diameter. It possibly has the same origin as does the basal lamina. Fibres of this type may frequently be

observed extending into the interstices of the adjacent neural tissue and when present in large amounts appear to contribute to the formation of capillary loops (Ashton 1961).

Pericyte degeneration

The increased permeability of the capillaries was postulated (Ballantyne 1948) to be a result of endothelial injury, and a specific and differential decrease in the number of pericytes of the capillary wall (Cogan, Toussaint, and Kuwabara 1961) which might be preceeded by an increase in the size of these cells (Fisher 1980) is a persistent change of the capillary wall in diabetic retinopathy.

Pericytes are normally wrapped about the outer circumference of the vascular channel; they probably function to provide structural integrity to the vessel (Yanoff 1969). The ratio of pericytes to capillary endothelial cells in a normal young individual is approximately 1:1. In a normal ageing process, there is a relative decrease of capillary endothelial cells. This is reversed, however, in diabetic retinopathy in which there is a gradual loss of retinal capillary pericytes or mural cells. The small number of pericytes may create a weakness in the wall that would predispose to the formation of aneurysms and the tendency to fluid leakage or haemorrhage.

Microaneurysms

Capillary aneurysms are a constant feature of diabetic retinopathy and are commonly its presenting clinical sign.

The propensity for microaneurysm formation is a feature not so much of diabetes as of the retinal capillaries, since on the one hand, they occur in several other retinal disor-

ders and, on the other, are rare in the capillaries of diabetic patients elsewhere in the body. They are sometimes found in the conjunctiva, kidney, and heart (Factor, Okun, and Minase 1980). They predominate on the venous side of the circulation in the posterior retina and are usually most frequent around foci of closed capillaries. They begin as saccular outpouchings from a capillary wall. The wall of the aneurysm consists of an endothelial lining and a relatively thin basement membrane. Patent microaneurysms show positive fluorescence on fluorescein angiography; some gradually hyalinise due to thickening of their walls by deposition of PAS -positive material. They then appear as yellow or white spots that do not fluoresce and may give a misleading impression of regression.

The importance of microaneurysms lies in their excessive permeability and liability to rupture, resulting in focal serous exudation and haemorrhage. Accumulated thrombus within the aneurysmal sac causes many aneurysms to be obliterated, the life of individual lesions being of the order of several months (Kohner and Dollery 1970).

Intraretinal microvascular abnormalities (IRMA)

The closure of precapillary arterioles and capillaries creates a state of relative ischaemia and hypoxia. Later formation of intraretinal vascular shunts and the process of neovascularisation characteristic of proliferative diabetic retinopathy occur in relation to ischaemic retina. Formation of non-leaking or very slowly leaking intraretinal vascular channels (intraretinal microvascular abnormalities: IRMA) can be demonstrated by fluorescein angiography. These shunt vessels often show a retarded rate of flow. Apple (1981)

suggests that these represent a compensatory response to a hypoxic stimulus. It is important that IRMA should be distinguished from proliferating blood vessels on one hand and from shunt vessels on the other to avoid photocoagulating an area with shunt blood vessels or delay photocoagulation of an area with proliferative vessels which must be treated as soon as their presence is confirmed by careful ophthalmoscopy and angiography (Henkind 1981).

Capillary closure

Capillary closure or nonperfusion is the most important development in the course of diabetic retinopathy. It predisposes to neovascularisation and other serious complications.

Ashton (1953) first demonstrated multiple small foci of nonperfused capillaries in diabetes using Indian ink injection of the blood vessels in enucleated eyes. He found capillary closure to be a predominant pathological feature of diabetic retinopathy.

Clinical evidence supporting the role of focal retinal ischaemia in diabetic retinopathy include the presence of ischaemic retinal infarcts (cotton-wool spots) in all stages of retinopathy (Esmann, Lundbaeck, and Madsen 1963) and the presence of capillary nonperfusion in both early and late stages of retinopathy (Kohner et al 1975). These findings may suggest (Little 1981) that focal ischaemia and nonperfusion proceed from areas of microinfarction to large zones of macroinfarction and influence the development of retinal neovascularisation, since zones of capillary nonperfusion are always found in association with neovascularisation.

It is not exactly known what causes capillary closure but abnormalities of blood coagulation and changes in the endothelial lining of the capillaries are important associations.

Blood retinal barrier

The blood retinal barrier is located at two different levels. In the outer barrier the main structure involved is the retinal pigment epithelium. The inner blood retinal barrier is composed of the endothelial membrane of the retinal vessels. In both of these membranes the constituent cells have tight junctions of the "non-leaky" type.

At present, abnormal function of the blood retinal barrier is widely accepted as one of very important changes in the development of retinal vascular disease and macular pathology. Vitreous fluorophotometry (Cunha Vaz et al 1975) has demonstrated that a breakdown in the blood retinal barrier takes place early in the disease process before any clinical change in the retina is detectable (Cunha Vaz 1976; Krupin, Waltman, Osterich, Santiago, Ratzan, Kilo, and Becker 1978). Krogsaa, Lund-Andersen, Mehlsen, Sestoft, and Larsen (1981) reported that the degree of blood retinal barrier permeability correlates with the degree of retinopathy, being higher in those with proliferative diabetic retinopathy and lowest in diabetics who had simple background retinopathy. In all cases the permeability was higher than in normal controls. In the human eye, the amount of fluorescein entering the vitreous after injection into the systemic circulation in early diabetes is increased and it was suggested that this is due to an increased permeability of the retinal vessels (Cunha Vaz 1978). A fault in the

pigment epithelium which allows the diffusion of fluorescein into the vitreous was also suggested by other workers (Tso, Cunha Vaz, Shih, and Jones 1980). Support for this view comes from the finding of an increase in vitreous fluorescein in streptozotocin induced diabetes in the guinea pig since these animals are devoid of retinal vessels (Klein, Engerman, and Ernest 1980). Fresh photocoagulation burns, by damaging the pigment epithelium of the retina, also allow the diffusion of fluorescein into the vitreous until the burns have healed (Foulds, Moseley, Edie, and McNaught 1980).

4.2.c. ARTERIOLAR CHANGES

Arteriolar hyalinosis (Ashton 1953) of the type commonly identified with the benign phase of hypertension is a common feature in diabetes. It is likely to represent the insidious insudation of plasma through an abnormally permeable endothelial lining. The leakage may be enhanced by the increased transmural pressure gradient associated with the arteriolar dilatation characteristic of early diabetic retinopathy (Skovborg, Nielson, Lauitzen, and Hartkopp 1969).

4.3. RETINAL ISCHAEMIA AND PROLIFERATIVE CHANGES

Vasoproliferation is almost never seen in diseases where total anoxia occurs, for example, in central retinal artery occlusion; however, in diabetic retinopathy and other diseases mimicking it hypoxia plays a major role in the pathogenesis.

As arteriolar and capillary changes progress there is an associated increase in the extent of inadequate perfusion of the retinal vascular bed; the increased blood flow noted

in early diabetic retinopathy is replaced by a decrease. This decrease of retinal perfusion may be so much that the retinal circulation becomes below normal (Cunha Vaz 1978) and, at this stage, new blood vessels start to appear on the venous side of the circulation from the previously dilated vessels (Michaelson 1948; Ashton, Ward, and Serpell 1954).

It is presumed that a viable but metabolically impoverished retina liberates a diffusable angiogenic factor which is capable of accumulation in the vitreous space and which may also stimulate endothelial proliferation on the retinal surface (Glaser, D'Amore, Michels, Brunson, Fenselau, Rice, and Patz 1980). This hypothetical factor has not been isolated but some ocular tissues have been proved to possess angiogenic activity while extracts of skeletal muscle, cardiac muscle, and liver have not (Glaser, D'Amore, Michels, Patz, and Fenselau 1980; Chen and Chen 1980). Cartilage (Langer, Brem, Falterman, Klein, and Falkman 1976), aortic extracts (Eisenstein, Goren, Shumacher, and Choromokos 1979), and vitreous (Patz 1980) were found, on the other hand, to have an inhibitory effect on neovascularisation.

Evidence of a causal relationship between ischaemic retina, producing a vasculogenic diffusable "factor", and neovascularisation is also derived from the following clinical observations.

1. Fluorescein angiography frequently demonstrates areas of capillary nonperfusion before the development of retinal neovascularisation.

2. The conditions associated with retinal neovascularisation such as retrolental fibroplasia, sickle cell disorders, retinal vein occlusion and, of course, diabetic retinopathy, always include areas of retinal capillary nonperfusion.

3. Retinal neovascularisation occasionally occurs at a distance from the ischaemic areas, such as when disc neovascularisation occurs after branch vein occlusion.

4. The iris rubeosis seen with diabetic retinopathy appears to respond to ablative photocoagulation of the retina (Kohner, Shilling, and Hamilton 1976; Henkind 1978; Merin, Ber, and Ivry 1978; Tasman, Magargal, and Augsburger 1980).

4.4. ROLE OF GROWTH HORMONE

Growth hormone (Ganong 1979) is produced by the pituitary gland and its secretion is controlled via the hypothalamus. It has a molecular weight of 21,500 and can now be synthesised. Radioimmuno-assay is used to measure the plasma levels of growth hormone, the normal basal level of which in adults is less than 3 ng/ml; metabolism of growth hormone takes place, at least in part, in the liver.

It promotes growth, is a protein anabolic hormone, and affects electrolyte, fat, and carbohydrate metabolism.

Growth hormone has a diabetogenic effect. 25% of patients with growth hormone-secreting tumours of the pituitary gland have diabetes and human growth hormone makes diabetes worse. Hypophysectomy ameliorates diabetes and increases sensitivity to insulin. It decreases glucose uptake into some tissue (anti-insulin action), increases

hepatic glucose output and may decrease tissue binding of insulin. Growth hormone may stimulate insulin secretion indirectly, and the hyperglycaemia it produces secondarily stimulates the pancreas and may eventually exhaust the B cells.

It was reported (Campbell, Lei, and Davidson 1951) that within 3 to 7 days of daily injection of growth hormone, dogs developed hyperglycaemia and glycosuria.

Serum growth hormone levels three to four times greater in diabetic subjects than in nondiabetics have been found (Johansen and Hansen 1969) and exercise (Lundback 1973) accentuates the abnormally high secretion of human growth hormone in diabetics.

Evidence indicates that the relationship of abnormal carbohydrate metabolism to the development of diabetic retinopathy hinges on growth hormone. Hansen (1971) showed that following rigid control of blood sugar levels, the hypersecretion of growth hormone in juvenile diabetics was neutralised. This observation was made on hospitalised patients from whom blood sugar was measured three times daily and on whom growth hormone determinations during exercise were made in the course of regulatory metabolic control. Increasing dosage of soluble insulin and isophane insulin suspension were given by three to four injections daily. After several days of strict diabetic control with blood sugar levels ranging between 4.4 to 6.6 mmol/L (80 to 120 mg/100 ml), no rise of serum growth hormone occured during exercise, and fasting serum growth hormone levels were normalised. It was, hence, concluded that abnormalities of serum growth hormone in juvenile diabetics are metabolic in origin.

4.5. ROLE OF GENETIC FACTORS AND CARBOHYDRATE METABOLISM

There is a disagreement about the contribution of carbohydrate metabolism and genetic factors to the development of diabetic retinopathy. Some workers believe that it is the disturbance of carbohydrate metabolism, rather than a genetic factor, that determines the onset of retinopathy, while others studying, for example, diabetic twins concluded that genetics play an essential role in the development of the diabetic retinal changes.

Caird, et al (1969) found, in diabetic retinopathy, no greater similarity among diabetic siblings than among unrelated diabetics, although on the other hand, Pyke and Tattersall (1972) reported significant similarities in the development and pattern of retinopathy between many pairs of identical diabetic twins with duration of diabetes of more than 15 years.

A higher incidence of vascular complications among poorly controlled juvenile diabetics than among well controlled subjects was found and it was concluded that to achieve a better control of carbohydrate metabolism many patients require more than one insulin injection daily (Paz-Guevara, Hsu, and White 1975). Also experimental models of diabetic retinopathy have shown a statistically significant greater number of microaneurysms, acellular capillary zones, and pericyte cell loss in dogs that were poorly controlled than in those which had a better control (Engerman 1976).

In the absence of genetic diabetes, microangiopathy was produced in rats (Cohen, Michaelson, and Yanko 1972) which were fed a 72% sucrose diet for 12 months, again stressing

the importance of carbohydrate in the pathogenesis of diabetic retinopathy.

Thickening of the perivascular basement membrane is a common development in the course of diabetic vasculopathy. It is also noted in advancing age, and is related to hydrostatic pressure (Ashworth, Erdmann, and Arnold 1960; Ashton 1974); although it is inconstant and nonspecific for diabetes it, undoubtedly, is most common and pronounced in this condition and has been described in the diabetic kidney, skin, muscle, and nerve (Fagerberg 1956; Aagenaes and Moe 1961). It has also been seen in prediabetics and very early after the onset of diabetes and has not been found to occur in hyperglycaemia in the absence of genetic diabetes mellitus even after many years suggesting that the thickening is a basic genetic defect rather than a complication of diabetes (Sabour, MacDonald, and Robson 1962; Siperstein, Unger, and Madison 1968) although it has been noted in many types of diabetes including experimentally produced diabetes in dogs and that due to haemochromatosis, pancreatitis (Duncan, MacFarlane and Robson 1958; Bloodworth, Engerman, and Power 1969; Walsh and Malins 1978), and randomly selected diabetics (Gray, Starkey, Rainbow and others 1982).

4.6. ROLE OF HAEMATOLOGICAL FACTORS

4.6.a. Introduction

Prostaglandins: Prostaglandins are a series of closely related 20-carbon unsaturated fatty acids containing a cyclopentane ring. They were first isolated from semen but have been shown to be synthesised in all organs of the body. Three main groups of prostaglandins are identified, PGA, PGE, and PGF; the common biologically active prostaglandins are PGA_1, PGE_1, PGE_2, $PGF_{1\alpha}$, and $PGF_{2\alpha}$. The biologically important products synthesised are PGE_2, thromboxanes, and prostacyclin which is called PGI_2.

Prostaglandin synthetases are enzymes that catalyse prostaglandin formation. The first of these enzymes involved in this process is called cyclooxygenase; it catalyses the conversion of arachidonic acid to a cyclic endoperoxide. This process is inhibited by aspirin, indomethacin and various other drugs (Lewis 1982).

Prostaglandin PGE_1 inhibits platelet aggregation while PGE_2 augments aggregation.

Prostaglandins may play a role in regulating the capacity of red blood cells to undergo deformation in passing through capillaries. They also stimulate renin secretion.

Prostacyclin, PGI_2, inhibits blood clotting and stimulates renin secretation.

Thromboxane A_2 promotes clotting, and clot formation apparently depends on the balance between it and PGI_2.

Thromboxane is a vasodilator and stimulator of platelet aggregation.

The clotting mechanism: When a blood vessel is damaged, the exposed layer of collagen attracts platelets which liberate serotonin and adenosine diphosphate (ADP). The ADP rapidly attracts other platelets and a loose plug of aggregated platelets is formed. The aggregated platelets are bound together and converted into the definitive clot by fibrin.

The insoluble fibrin is formed from the soluble plasma protein fibrinogen and this process is catalysed by thrombin which, in turn, is formed from its circulating precursor prothrombin by the action of activated factor X. Factor X is activated through two pathways, an intrinsic and an extrinsic pathway. The initial reaction in the intrinsic pathway is conversion of factor XII to active factor XII which then activates factor XI. Factor XI then activates factor IX. In the presence of factor VIII and platelets, active factor IX activates factor X which in the presence of platelets, Ca ions, and factor V, catalyses the conversion of prothrombin to thrombin. The extrinsic pathway involves the activation of factor VII by tissue thromboplastin, a protein-lipid complex released from damaged blood walls. Active factor VII activates factor X which catalyses the conversion of prothrombin to thrombin.

Anti-clotting mechanism: Reactions that tend to prevent clotting inside the blood vessels and to break down any clot that may form include formation from activated factor X of

an antithrombin and removal of some activated clotting factors from the circulation by the liver. There is also a reduction in the supply of clotting factors because of their use during clotting.

Thromboxane A_2 promotes platelet aggregation and hence clotting but its action is opposed by the simultaneous formation of PGI_2 (prostacyclin) which inhibits aggregation.

Reduction of prostacyclin level might upset the balance which it maintains with platelet thromboxane which is a vasodilator and stimulator of platelet aggregation and hence the action of the latter would be enhanced.

There is in addition a fibrinolytic system that limits clotting, the active components of which is plasmin or fibrinolysin. This enzyme lyses fibrin and fibrinogen producing fibrinogen degradation products (FDP) that inhibits thrombin. Plasmin is formed from its inactive precurser, plasminogen, by the action of thrombin and possibly substances in the tissue. There is also an activator in plasma that normally circulates as inactive proactivator. Proactivator is converted into activator by the action of proteolytic fragments of active factor XII called prekalkrein activators which are also involved in the formation of kinins; they are formed by the action of plasmin on active factor XII.

4.6.b. Abnormal prostacyclin levels

Reduced levels of prostacyclins, which tend to increase after the administration of insulin, but not to normal levels have been found in diabetic animals (Harrison, Reece, and Johnson 1978). Prostacyclin levels have also been found to be reduced in diabetic patients, the reduction being

most marked in those with proliferative retinopathy (Webster, Lewis, McDermot, Hensby, Porta, and Kohner 1980). In vessels of amputated legs of diabetic subjects a reduced prostacyclin activity was reported by Johnson and co-workers (Johnson, Harrison, Raferty, and Elder 1979).

4.6.c. Plasmin activator

Although plasmin activator was not found to be significantly reduced in diabetic subjects without or with only minimal retinopathy, a slight reduction however could play a role in the reduction of plasmin, the active fibrinolytic agent (Almer, Pandolfi, and Nilsson 1975).

4.6.d. Red blood cells

Increased red blood cell aggregation was found in the conjunctival vessels of diabetic dogs (Ditzel 1967). In humans an increase of erythrocyte aggregation, reflected in increases in erythrocyte sedimentation rate, has been reported. Increased aggregation was associated with the severity of diabetic retinopathy in the patients studied (Little 1976).

In addition to red cell aggregation, the deformability of these cells was noted to be reduced (McMillan, Utterback, and LaPuma 1978).

For circulation to occur, red cell aggregates must be disrupted in order that blood flows through the microcirculation. When blood flow is sludged, transfer of oxygen is probably impaired; when aggregates are not disrupted then focal areas of ischaemia occur. Impaired blood flow by rigid and clumped red cells is probably exacerbated in the

presence of a narrowed lumen and rigid cells caused by the thickened capillary basement membrane (Little 1981).

4.6.e. Platelets

It has been shown that about ninety per cent of adult-onset diabetics have platelet aggregation-enhancing activity (Dobbie, Kwaan, Colwell, and Suwanwela 1974). The same study also showed a positive association between platelet aggregation-enhancing activity and nephropathy or retinopathy and with the duration of diabetes.

von Willebrand factor VIII (vW-VIII) - related protein and antihaemophilic factor (AHF) - activity in diabetics with retinopathy were found to be higher than in those without retinopathy and generally higher in diabetics than in a nondiabetic group (Pandolfi, Almer, and Holmberg 1974). Since the vW-VIII factor is involved in the mechanism of platelet adhesion and aggregation, these findings may contribute to an explanation of the increased platelet stickiness known to occur in diabetics and especially in those with retinal changes (Colwell, Sagel, Crook, Chambers, and Laimins 1977; Burrows, Chavin, and Hockaday 1978; Creter, Pavlotzky, and Savir 1978).

4.6.f. Abnormal fibrinolytic system

Longstanding diabetics of ten or more years who did not develop retinopathy were shown to have a significantly higher and almost normal fibrinolytic response to venous occlusion and also a higher spontaneous fibrinolytic activity than those who have developed retinopathy (Almer et al 1975). The fibrinogen and alpha-2 macroglobulin levels were higher in the retinopathy group. There have, however, been

other reports on elevated concentrations of fibrinogen or reduced fibrinolytic activity in patients with diabetic retinopathy (Jones and Peterson 1979).

4.6.g. Blood and plasma viscosity

Skovborg, Nielson, Schlichtkrull, and Ditzel (1966) reported a twenty per cent increase in whole blood viscosity in diabetics when compared with control patients. They correlated increased viscosity with concentrations of serum proteins and observed that the average concentrations of fibrinogen and alpha-2 globulin were higher in the diabetic group.

Blood viscosity was found to be higher in diabetic children, in groups of diabetics with various durations of diabetes, and in patients with increasing severity of retinopathy (McMillan 1974; Lowe, Lowe, Drummon and others 1981; Trope, Lowe, Ghafour, Foulds and Forbes 1983).

Factors such as trauma which are known to increase blood viscosity could cause an acceleration of the retinopathic changes (Dintenfass 1975; Alexander, Kearns, Kohner, and Asplin 1979). Reduction of blood viscosity, on the other hand, may reduce the occurrance of retinopathy (Ariga, Oshiba, and Tamada 1981; Kobayashi, Hirai, Terano, Hamazaky, Tamura, and Kumagai 1981).

Blood viscosity was studied, by the author and others, in a group of 18 patients with proliferative diabetic retinopathy confirmed by fluorescein angiography. The group comprised 12 males and 6 females aged 29-73 years with a mean age of 53 ± 3 years. The duration of diabetes ranged from 2 to 31 years with a mean of 17 ± 2 years. 9 of the patients were insulin-dependent, type I diabetics; the other 9 were non-insulin dependent. The group was matched

for age, sex, smoking habits, duration, type, and treatment of diabetes with another group of 18 diabetics of whom 8 had no clinically detectable retinopathy and 10 had background retinopathy.

Venous blood was sampled between 2 and 5 pm after 10 minutes' rest from a forearm vein with a 19 gauge 'butterfly' needle (Abbott) without a tourniquet. Blood was anti-coagulated with edetic acid (EDTA, 1.5 mg/ml) for viscosity studies, which were performed within 2 hours of vene-puncture. Whole blood viscosity was measured at a high shear rate (94 s^{-1}) and at a low shear rate (.0.94 s^{-1}) in a Contraves LS 30 rotational viscometer at temperature 37°C. Haematrocrit (Hawksley microhaematrocrit 13,000 g for 5 minutes), plasma viscosity (Coulter-Harkness capillary viscometer, 25°C) were measured.

Table 2 shows the blood whole blood viscosity, at high and low shear rates, of the group of diabetics with proliferative retinopathy and of those with a milder form of/or no retinopathy. Significant differences were found btween the two groups. Plasma viscosity, also, was significantly different when the two groups were compared ($P < 0.001$).

The mean plasma fibrinogen level of the group with proliferative diabetic retinopathy was 3.69 ± 0.25 g/L and of the control group, 3.07 ± 0.17 g/L. The difference was found to be significant ($P < 0.05$).

There is controversy about the role of increased viscosity in the pathogenesis of diabetic retinopathy. In this study different parameters which could contribute to the differences in blood and plasma viscosity have been excluded; subjects ages, smoking habits, duration of

	Proliferative group	Background or no retinopathy group	
Blood viscosity (m Pa.s)			
- High shear 94 sec^{-1}	6.12 ± 0.18	5.35 ± 0.21	$P < 0.01$
- High shear PCV = 45	6.25 ± 0.15	5.57 ± 0.15	$P < 0.01$
- Low shear 0.94 sec^{-1}	20.8 ± 1.2	17.8 ± 0.9	$P < 0.05$
- Low shear PCV = 45	21.7 ± 0.8	19.3 ± 0.6	$P < 0.05$
Plasma viscosity (m Pa.s)	1.89 ± 0.03	1.71 ± 0.02	$P < 0.001$
Fibrinogen (g/L)	3.69 ± 0.25	3.07 ± 0.17	$P < 0.05$

Table 2. Comparison of blood viscosity at high and low shear rates, plasma viscosity, and fibrinogen levels of diabetics with different severity of retinopathy.

diabetes, type, and treatment of diabetes were similar. In an earlier study (Lowe et al 1981) it was shown that whole blood and plasma viscosities were higher in established diabetics than in matched normal controls. It would however be interesting to see if these values were raised in recently diagnosed diabetics.

4.6.h. SUMMARY AND CONCLUSION

Blood and blood vessel changes occur in diabetic patients. These changes include:

1. Increased erythrocyte aggregation and rigidity.
2. Increased blood and plasma viscosity.
3. Altered platelet activity with increase of their aggregation and stickiness, with increased release of thromboxane and prostaglandin E.
4. Increased levels of plasma fibrinogen.
5. Changes in the blood vessel wall.
6. Changes in the blood-retinal barriers.

These changes may be related to altered carbohydrate metabolism in the presence of insufficient insulin and/or hyperglycaemia, and growth hormone.

CHAPTER 5

THE IDENTIFICATION OF DIABETIC RETINOPATHY

As for other diseases of the retina, many clinical investigatory tools can be used for the identification of diabetic retinopathy.

In a joint effort with other Ophthalmologists, Physicians, Opticians, and Technicians a study was carried out to assess the usefulness of the following ophthalmic parameters in the diagnosis and assessment of diabetic retinopathy.

1. Assessment of structure by:
   a. Ophthalmoscopy
   b. Fluorescein angiography
2. Assessment of function as shown by measurement of
   a. Visual acuity
   b. Quantitative perimetry
   c. Colour vision using the Farnsworth-Munsell 100 Hue Test
   d. Contrast sensitivity using the Arden grating test

5.1. OPHTHALMOSCOPY

Although fluorescein angiography gives a higher rate of detection of diabetic retinopathy (Klemen, Freyler, Scheimbauer, and Prskavec 1980) than ophthalmoscopy, ophthalmoscopy in a darkened room with the patient's pupils well dilated has been found useful in the diagnosis and grading of retinopathy in cases with clinically detectable diabetic changes of the retina (Barrie, Scobie, Green, MacCuish, and Foulds 1981). This is especially true if strict criteria for the definition of the different types of retinopathy are used.

To determine the accuracy of identification of diabetic retinopathy by ophthalmoscopy and to compare ophthalmoscopy performed by trained general Physicians with that carried out by Ophthalmologists two groups of patients were examined:

1. A group of 182 diabetics seen by both Ophthalmologists and Physicians, each being unaware of the results of the other.

2. 349 diabetics examined by Physicians using direct ophthalmoscopy and 635 by Ophthalmologists using both direct and indirect ophthalmoscopy.

In each case patients were those referred from the general diabetic clinic of Glasgow Royal Infirmary for an annual eye examination.

On the basis of ophthalmoscopic examination patients were sub-divided into those without retinopathy, those with background retinopathy, and those with serious retinopathy as defined on page 63 .

The same patients were examined separately by a Physician and an Ophthalmologist.

There was reasonable agreement in the total amount of retinopathy diagnosed (Physicians 23 per cent, Ophthalmologists 25 per cent). There was however, some disparity in the numbers thought to have serious retinopathy (Physicians 4 per cent, Ophthalmologists 10 per cent).

The results of a study on group 2 composed of separate but comparable patients examined by either Physicians or Ophthalmologists are detailed in Table 4.

Comment

In the study on group 1 there is a disparity between

the prevalence of serious retinopathy diagnosed by the Physicians and that diagnosed by the Ophthalmologists.

The Physicians involved in this study included an experienced Consultant Diabetologist and a Senior Registrar in general medicine who had attended the retina clinic at the Tennent Institute. - The Ophthalmologists included a Senior Ophthalmic Registrar and a recently appointed Research Registrar in ophthalmology. In retrospect it is possible that judgements made by the less experienced observer were not as accurate as they might have been.

In the study on group 2 where separate but comparable groups of diabetic patients were examined by observers who were by then experienced in the application of the diagnostic criteria to diabetic fundi, better agreement was found between the two sets of observers although some disparity remained.

Although the numbers of patients in group 2 (984) is large there remains a definite possibility that the prevalence of diabetic retinopathy was different in the group examined by the Physicians from that examined by the Ophthalmologists.

To test the accuracy of diagnosis by Physicians or Ophthalmologists all patients labelled as having serious retinopathy were re-examined in the Tennent Institute of Ophthalmology using, in addition to ophthalmoscopy, bio-microscopy with a diagnostic contact lens, colour fundus photography, and fluorescein angiography.

On the basis of this further examination, the diagnosis of serious retinopathy was confirmed in 72 per cent of patients referred by Physicians and 63 per cent of patients referred by Ophthalmologists.

	Physician	Ophthalmologist
No retinopathy	141 (77)	136 (75)
Background retinopathy	33 (18)	28 (15)
Serious retinopathy	8 (4)	18 (10)
Total	182	182

Table 3. A comparison of prevalence of retinopathy as determined by Ophthalmologists and Physicians using conventional ophthalmoscopy (percentages) are shown in brackets).

	Physician	Ophthalmologist
No retinopathy	259 (74)	511 (80)
Background retinopathy	55 (16)	88 (14)
Serious retinopathy	35 (10)	36 (6)
Total	349	635

Table 4. Prevalence of different types of diabetic retinopathy of two groups of patients examined by either Ophthalmologists or Physicians using conventional ophthalmoscopy (percentages are shown in brackets).

	No retinopathy	Background retinopathy	Serious retinopathy
Prevalence of retinopathy in the random sample	72	17	11
Prevalence of retinopathy as found by Physicians	75	17	8
Prevalence of retinopathy as found by Ophthalmologists	79	14	7

Table 5. A comparison of the percentages of different categories of retinopathy between a random sample of 93 diabetics fully investigated, and ophthalmoscopic findings in 1166 patients examined by Physicians and Ophthalmologists.

Category	No. of eyes.	Range of corrected visual acuity	Mean corrected visual acuity
No retinopathy	242	6/5 - 6/9	6/6
Background retinopathy	79	6/5 - 6/9	6/6
Exudative retinopathy	13	6/9 - 6/60	6/18
Ischaemic retinopathy	12	6/6 - 6/12	6/9
Proliferative retinopathy	34	6/6 - 6/18	6/9

Table 6. Visual acuities of diabetic patients with different grades of retinopathy.

It appeared that both Ophthalmologists and Physicians were overdiagnosing serious retinopathy on the basis of ophthalmoscopy alone, but both were comparable in the accuracy of their assessment.

Having identified a false positive rate of around 24 per cent it was important to estimate what proportion of patients with serious retinopathy were being wrongly classified as having non-serious retinopathy. This figure could only be determined indirectly as patients classified as having non-serious retinopathy were not routinely investigated in the Tennent Institute. However, extrapolating from the prevalence of serious retinopathy found in a group of diabetic patients randomly selected from the diabetic clinic and fully investigated in the Tennent Institute whether or not there was any visual problem it again appeared (Table 5) that there was comparability between the prevalence of serious and background retinopathy diagnosed by Physicians or Ophthalmologists in the total population of diabetic patients examined (1166 patients) but both sets of observers appeared to be underdiagnosing serious retinopathy by around 3 per cent as compared with the prevalence found in the randomly selected group.

In addition to the interobserver error estimated in these studies it would undoubtedly have been of value to have estimated the intraobserver error by having the same observer to classify and grade the same patients for example on the basis of retinal photography; the author carried out such a study.

Fifty colour fundus photographs of diabetic individuals were randomly selected to test the repeatability of

grading by one observer.

A slide viewer which enlarged the view x 3 was used. The type of retinopathy was classed as indicated in Chapter 3 of this Thesis. The slides were then mixed up and the classification of photographic signs of diabetic retinopathy was repeated.

In 13 instances (26 per cent) there was inconsistency in the grading of retinopathy. In most of the cases (10 cases) the difference in grading occurred when a photograph showed an abundance of hard exudates (diabetic maculopathy). A difficulty was particularly experienced in classing the changes as an exudative retinopathy or as a diabetic macular oedema.

It is re assuring however that most of the inconsistencies were related to cases of diabetic maculopathies. This perhaps stresses the occasional need for further investigation, for example by fluorescein angiography, in such cases since a reasonable degree of certainty should be obtained before a decision can be made as to whether a diabetic patient with such changes would benefit from photocoagulation therapy.

5.2. FLUORESCEIN ANGIOGRAPHY

Fundus fluorescein angiography (Novotny and Alvis 1961) is used for the display of anatomical, physiological, and pathological features of the fundus in vivo. It offers an opportunity for independent and objective measurements, and evaluation of data collected from different centres. It also makes possible re-evaluation and revision of methods and criteria during the course of a study, if this proves desirable. Fluorescein angiography gives an opportunity to make subsequent measurements and assessments not requiring

the presence of the subject (Wetzig and Jepson 1966; Kahn and Hiller 1974; ffytch, Shilling, Chisholm, and Federman 1980).

3 ml of a 20% or 5 ml of a 10% solution of the soluble dye sodium fluorescein are injected into an arm vein and a series of fundus photographs are taken, usually at 1-2 second intervals. During photography the fundus is illuminated by a flash of blue light of 420-490 nm which maximally excites the fluorescence in the sodium fluorescein as it passes through the tissue. Sodium fluorescein fluoresces at 510-530 nm and the emitted fluorescence is photographed on black and white film via a barrier filter transmitting maximally at 510 nm. The time the dye takes to first appear in the retinal arteries is called the dye-arrival or arm to retina time, and the interval between its appearance in the arteries and the veins is the intraretinal circulation time.

In the blood fluorescein is bound to albumin the large molecules of which can not cross the endothelial barrier of the retinal capillaries so that in health fluorescein in the retinal circulation remains intravascular. Although it escapes readily from the capillaries of the choroid it is prevented from entering the retina from this source because of the barrier function of the retinal pigment epithelium. Any increase in retinal capillary permeability may allow intravascular albumin-bound fluorescein to diffuse into the retinal tissue (Scott, Dollery, Hill, Hodge, and Fraser 1963; Rosen 1977). The amount of unbound fluorescein in the plasma, also, plays a role in the penetration of systemically administered fluorescein sodium into the eye and this concentration has been found to differ from person to person (Palestine and Brubaker 1982).

Fluorescein angiography is superior to many other investigations (Wisznia, Liberman, and Leopold 1971) in the detection of very early diabetic retinopathy; in more than one third of diabetics with apparently normal fundi fluorescein angiography may show hyperpermeability, occlusion of the capillaries, and arterio-venous shunts (Klemen et al 1980).

Not only is the technique capable of demonstrating abnormality of retinal capillary permeability, it may reveal pathological changes such as capillary abnormalities including capillary microaneurysms, fine neovascularisation, or areas of capillary underperfusion not readily detected by ophthalmoscopy. Of 181 eyes of 93 patients selected at random from a diabetic clinic, 28 per cent showed no visible retinopathy on ophthalmoscopy. However, fluorescein angiography revealed the presence of simple diabetic changes in 20 per cent of this proportion. No case was shown to be without retinopathy on fluorescein angiography when on ophthalmoscopy the presence of diabetic retinopathy was suspected (see Chapter 7).

Although retinal colour photography was used routinely in the assessment of all patients initially classified as being serious retinopathy, it was not used in the initial screening of diabetic patients attending the diabetic clinic. These patients were examined in a general medical unit which did not have any sophisticated ophthalmic equipment and in any case retinal photography was not considered suitable for the screening of a large number of diabetic subjects by general physicians.

5.3. VISUAL ACUITY

The visual acuity of 438 eyes (219 patients) was measured using Snellen's test chart. Patients were diabetics attending for investigation or screening from the following sources: 93 randomly selected for a pilot study into the prevalence of diabetic retinopathy among diabetics attending Glasgow Royal Infirmary, 54 consecutive patients attending Woodside Health Centre for a study of the prevalence of diabetes in general practice (see Chapter 6 and 8), and 72 diabetics attending the Tennent Institute of Ophthalmology for assessment of the state of their retinopathy or for treatment and follow-up. 58 eyes with cataract or other pathology had to be excluded because fundus details could not be seen so that the presence or degree of retinopathy could not be determined. The visual acuities of the remaining 380 eyes in relation to the different stages of retinopathy present are shown in Table 6.

As expected, patients without retinopathy or other pathology had unimpaired vision. Patients showing background, ischaemic, or even proliferative retinopathy, if this was not complicated by vitreous haemorrhage or rubeotic glaucoma, tended also to have normal acuities so that the use of visual acuity measurment was not a useful guide to the presence of these forms of diabetic retinopathy. Only in patients with exudative maculopathy was reduced visual acuity a common finding.

5.4. PERIMETRY

Roth (1969) reported that all diabetics with retinopathy showed central visual field defects and that approximately half of the diabetic patients without retinopathy also had

visual field defects. King and others (1963) found that scotomata persisted even after disappearance of exudates from some diabetic fundi following the use of certain dietary regimes. ··Arcuate field defects which are similar to those found in glaucoma have also been reported to occur in some diabetic subjects with preproliferative retinopathy (Wisznia et al 1971).

To investigate the usefulness of testing the visual field in the screening of diabetic retinopathy quantitative perimetry was carried out using the oculus Tubinger perimeter and it was found that of 150 ophthalmoscopically normal eyes 126 gave a normal result, and 24, 16 per cent, showed scotomata. 5 out of 58 eyes with background retinopathy, 9 per cent, showed visual field defects. 7 out of 9 eyes with exudative retinopathy, 78 per cent, had field defects. When eyes with retinal ischaemia were tested it was found that only 2 eyes of 6 tested showed any field defect. The results are summarised in Table 7.

The high false normal results in patients with serious forms of retinopathy together with the number of patients without retinopathy showing visual field defects makes perimetry unreliable in the identification and assessment of severity of diabetic retinopathy.

5.5. COLOUR VISION

Colour discrimination may be adversely affected in congenital colour defects (Palmer 1977; Pokorny, Smith, and Verriest 1979). The ability to discriminate colours has also been found to deteriorate in many acquired disorders affecting the eye (Lakowski 1962; Foulds 1969; Chisholm, Pronte-Stewart, and Awduche 1970; Weale 1970; Birch 1981).

Measurement of colour vision is thought to be a sensitive index of visual function.

In diabetes, an acquired dyschromatopsia of the tritanopic type (blue defect) affecting the discrimination of blues from reds, yellows, and greens is said to be commonly present and, sometimes, to preceed the appearance of clinically detectable diabetic retinopathy (Kinnear, Aspinall, and Lakowski 1972). It has also been found that among a diabetic population those with retinopathy perform worse on colour vision testing than those without ophthalmoscopically detectable retinopathy (Lakowski, Aspinall, and Kinnear 1972/73). Some diabetics have been reported to have difficulty in accurately measuring their blood and urine sugar (Taylor 1972).

To establish whether assessment of colour vision was useful for the screening of diabetic retinopathy and particularly for differentiating serious from non-serious retinopathy, colour vision in 98 eyes of 57 diabetics was tested. In addition 24 eyes from 14 normal individual from the Department's staff were tested for comparison of colour vision performance with the diabetic group; these were found to have normal colour vision as defined by Verriest, Van Laethem, and Uvijls (1982).

Colour vision testing was carried out using the Farnsworth-Munsell 100 Hue Test (Farnsworth 1943) under standard conditions of artificial daylight. The test consists of 85 coloured "caps" arranged in four sets. The first set contains 22 caps and the other three contain 21 caps each. The caps are 1.25 cm in size. All colours are of equal luminosity and saturation and can be so arranged that they form a continuous sequence of hues. At

the ends of each set, coloured reference caps are placed and the patients' task is to arrange the caps, which are presented in a predetermined random manner, in order of hue to form a colour sequence between the reference hues in each set. Each coloured cap has a number on its reverse side and if perfectly arranged the caps will form a numerical sequence from 1 to 85. Departures from the correct order are indicated by errors in this sequence and the total error score gives a measure of the colour loss and the particular wavelengths affected can be seen in a graphical representation. A normal untrained observer can rarely attain the perfect sequence but the few errors made are usually distributed randomly around the hue circle, Fig. 15. The colour defective will make numerous errors but usually cocentrated in two parts of the hue circle (Voke 1981).

Of the 98 diabetic eyes tested 27 eyes (16 patients) had normal visual acuity and no diabetic retinopathy on ophthalmoscopy, 27 eyes (16 patients) had background retinopathy and good vision, 15 eyes (9 patients) had diabetic exudative retinopathy with low visual acuity, and finally 29 eyes (16 patients) had ischaemic or proliferative retinopathy. The patients were obtained from the following sources: Those with background or no retinopathy were diabetics attending Woodside Health Centre or Glasgow Royal Infirmary; patients with exudative or proliferative diabetic retinopathy were subjects attending for laser treatment or were referred by the author, other Ophthalmologists, or Physicians from Woodside Health Centre and Glasgow Royal Infirmary for investigation and photocoagulation. An eye

which had already received photocoagulation or other forms of therapy was excluded from the study.

No time limit was given to the patient for the completion of the test and patients used their available spectacle correction where appropriate.

Total error scores from each of the eyes tested are shown in Appendix 2. It was found that 63 per cent (17/27 of eyes without retinopathy on ophthalmoscopy showed abnormal total error scores. Two thirds of the defective eyes had a diffuse type of dyschromatopsia, the other third showed an abnormality of the blue/yellow axis. Similar figures were obtained from those with background retinopathy; 70 per cent of eyes had abnormally high scores. More than a half of these had a diffuse dyschromatopsia (Fig. 16). 87 per cent and 79 per cent respectively of eyes with exudative or proliferative retinopathy demonstrated poor colour discrimination (Fig. 17). In most cases the faulty colour discrimination was of a diffuse type. In only 10 per cent of instances was it a blue/yellow defect. The results are summarised in Table 8.

In Table 9 are shown the mean, median, standard deviation, and square roots of total error scores from the individual groups. Figure 18 shows the mean square roots and standard deviation of each of the groups tested. Significant statistical differences, at the level of $P = 0.05$, were found when figures from normal individuals were compared with figures from different groups of diabetics except on Mann-Whitney test when normal

Category	No. of eyes tested	No. of eyes with normal results	No. of eyes with abnormal results
No retinopathy	150	126	24
Background retinopathy	58	53	5
Exudative retinopathy	9	2	7
Ischaemic retinopathy	6	4	2

Table 7. Results of visual field tests of 223 diabetic eyes.

Category of subjects	No.of eyes tested	No.of eyes with high scores	No.of eyes with diffuse chromat-opsia	No.of eyes with poor blue/yellow axis	No.of eyes with red/green normality
Normal subjects	24	8 (33)	7 (29)	1 (4)	-
No retinopathy	27	17 (63)	12 (44.5)	5 (18.5)	-
Background retinopathy	27	19 (70)	11 (40)	8 (30)	-
Exudative retinopathy	15	13 (87)	13 (87)	-	-
Proliferative retinopathy	29	23 (79)	19 (65)	3 (10)	1 (4)

Table 8. Abnormalities of colour vision in normal and diabetic subjects. (Percentages are shown in brackets).

	Mean	Median	Standard deviation
Normals (24 eyes, 14 patients)	88.6 (9.41)	83 (9.11)	31 (5.56)
No retinopathy (27 eyes, 16 patients)	110 (10.48)	98 (9.89)	43 (6.55)
Background retinopathy (27 eyes, 16 patients)	138 (11.74)	106 (10.29)	78 (8.83)
Exudative retinopathy (15 eyes, 9 patients)	305 (17.46)	322 (17.94)	117 (10.81)
Proliferative retinopathy (29 eyes, 16 patients)	190 (13.78)	184 (13.56)	117 (10.81)

Table 9. Different parameters of error scores of the groups of individuals examined on the Farnsworth-Munsell 100-Hue test. The square roots are in brackets.

	t-test	Mann-Whitney test
Normal Vs no retinopathy	P=0.0426	P=0.1129 *
Normal Vs background retinopathy	P=0.0049	P=0.0165
Normal Vs exudative retinopathy	P=0.0000	P=0.0000
Normal Vs proliferative retinopathy	P=0.0000	P=0.0004
No retinopathy Vs background retinopathy	P=0.1165 *	P=0.2394 *
No retinopathy Vs exudative retinopathy	P=0.0000	P=0.0000
No retinopathy Vs proliferative retinopathy	P=0.0015	P=0.0059
Background retinopathy Vs exudative retinopathy	P=0.0000	P=0.0000
Background retinopathy Vs proliferative retinopathy	P=0.0538 *	P=0.1117 *
Exudative retinopathy Vs proliferative retinopathy	P=0.0044	P=0.0024

Table 10. Comparison of mean scores from different groups of individuals. Non-significant differences of mean scores are indicated by *.

vs. the no retinopathy group were compared (P = 0.1129) although the Student t-test showed significant differences (P = 0.0426), Table 10. On comparing figures from the diabetic groups with each other the only non-significant result was found when the background retinopathy group was compared with the proliferative group, see Table 9.

The square root was used because it has been found that the square root of the Farnsworth-Munsell 100 Hue-test error score is statistically more informative than either the total error score or its logarithm (Kinnear 1970; Aspinall 1974). In addition it makes graphical representation of the data easier.

Because no particular attention was paid to the age factor in this study, the relatively high scores from "normal" eyes might be due to age distribution among the sample studied; age has been shown to affect colour vision steadily with advancing years (Lakowski 1958; Verriest 1963; Pinkers 1980), Table 11. Colours are perceived and discriminated most accurately between the age of 16 and 35, and after 55 years there is a rapid deterioration in fine colour discrimination which affects mainly blue/yellow or violet/blue/green discrimination. Red/green discrimination which is characteristically affected in for example tobacco amblyopia (Chisholm et al 1970) remains reasonably stable and is the least affected by age. Age should also contribute, to some extent, to the high error scores of the diabetic subjects especially the older ones with severe exudative

retinopathy. Patients with exudative retinopathy tend to be older than other groups of diabetics at the time of diagnosis of diabetes (Bodonsky, Cudworth, Whitelocke, and Dóbree 1982) and would thus be more affected by the age factor than others and it might be true that the deterioration of colour-vision of diabetics is an accelerated version of loss of colour discrimination associated with ageing (Kinnear, Aspinall, and Lakowski 1972). Further work in progress suggests that this may be the case.

In conclusion, colour vision of diabetic subjects seems to be affected to a significant extent. Even before the appearance of ophthalmoscopically detectable retinopathy high error scores are found on the Farnsworth-Munsell 100-Hue test. Because of the large overlap in the total error scores of patients with and without retinopathy and with serious as compared to non-serious retinopathy the test was found not to be of value for screening purposes.

Age range (years)	95th Percentile
16-20	100
21-25	74
26-30	92
31-35	106
36-40	120
41-45	134
46-50	144
51-55	154
56-60	164
61-65	174

Table 11. Upper limit of error scores (95th percentile) made by normal trichromats of different ages. From Verriest (1963): Further studies on acquired deficiency of colour discrimination. J.Opt.Soc.Am. 53: 185-195.

	Mean values	Arden's figures
Plate 2	11.96 (2.27)	11.50
Plate 3	10.26 (1.89)	10.00
Plate 4	11.33 (2.08)	11.50
Plate 5	10.90 (1.98)	11.50
Plate 6	9.08 (2.25)	10.00
Plate 7	9.19 (2.56)	9.00

Table 12. Results of contrast sensitivity measurements. Mean values for normal controls in this study are compared with those of Arden and Jacobson (1978).

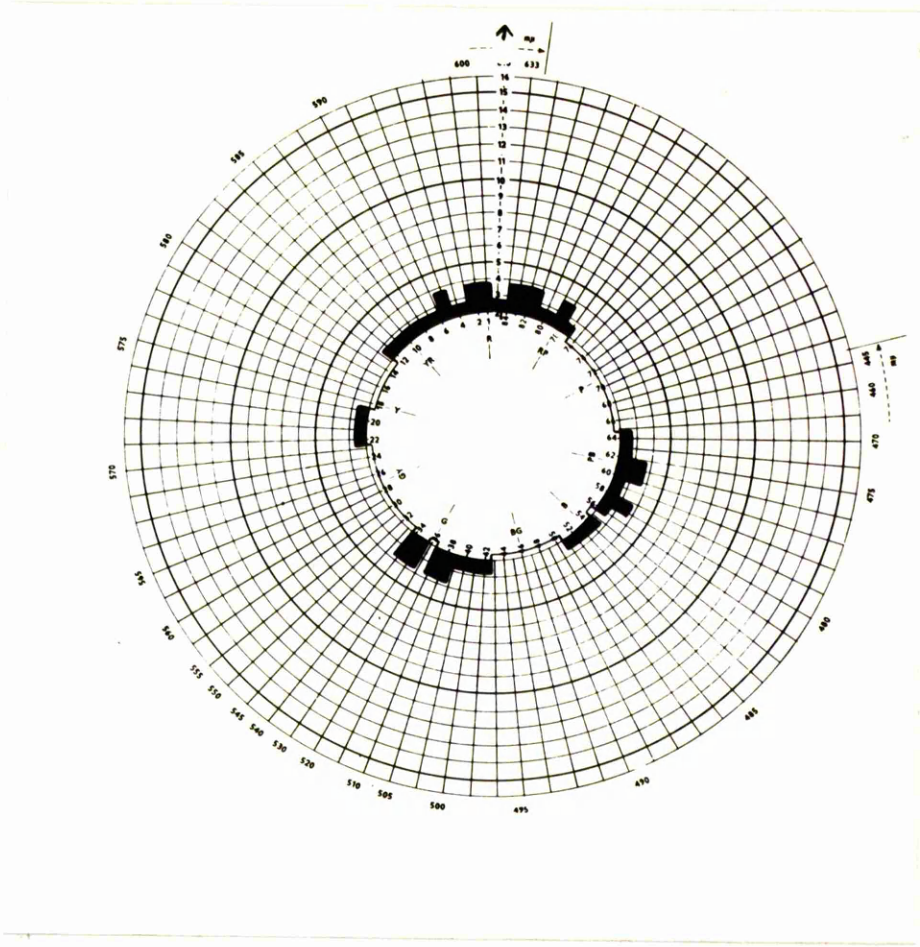

Figure 15. Farnsworth-Munsell 100-Hue test trace of a normal untrained subject. Random distribution of error score.

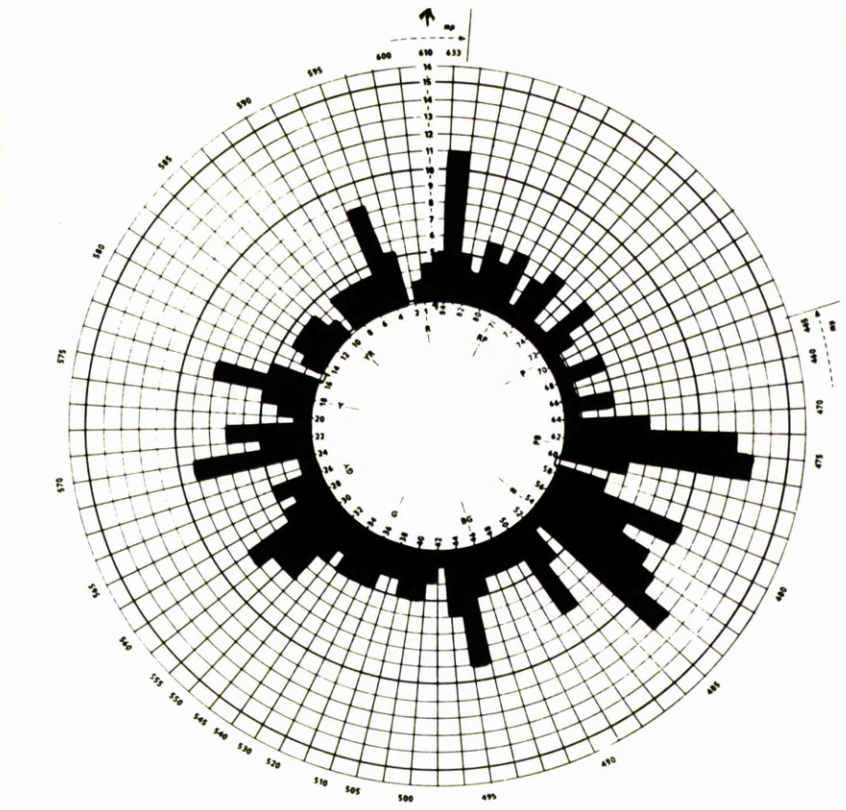

Figure 16. Fanrsworth-Munsell 100-Hue test trace of a diabetic patient with background retinopathy. Diffuse dyschromatopsia.

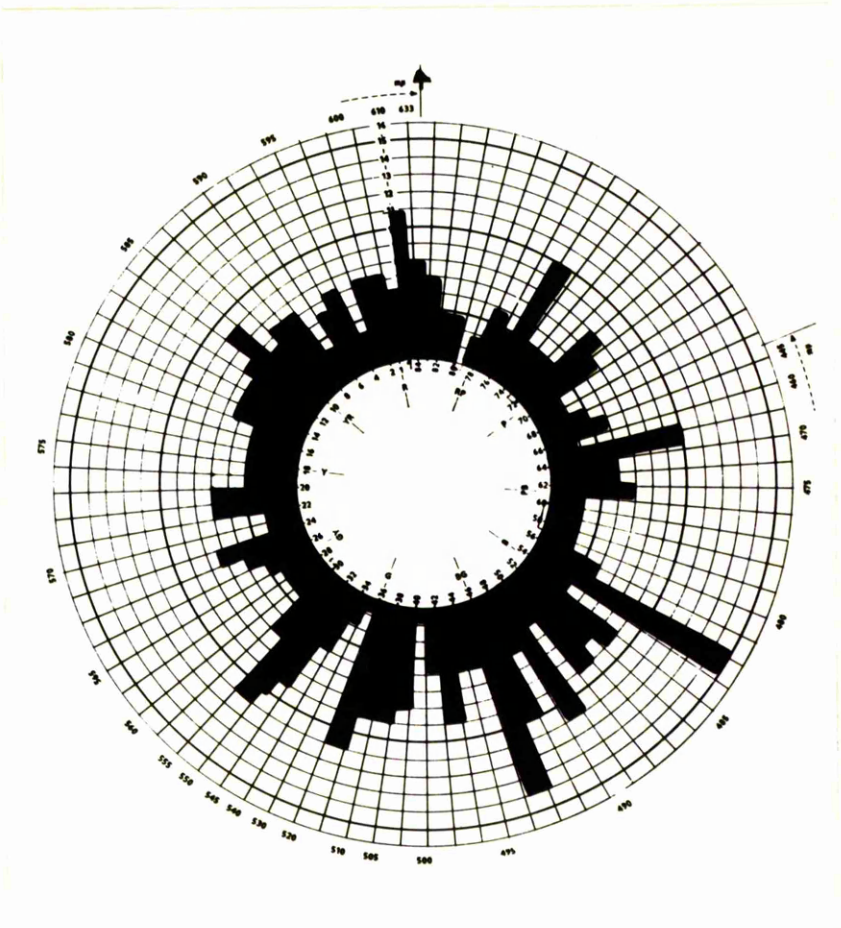

Figure 17. Farnsworth-Munsell 100-Hue test trace of a diabetic with maculopathy. High total error score with absence of a definit polarity.

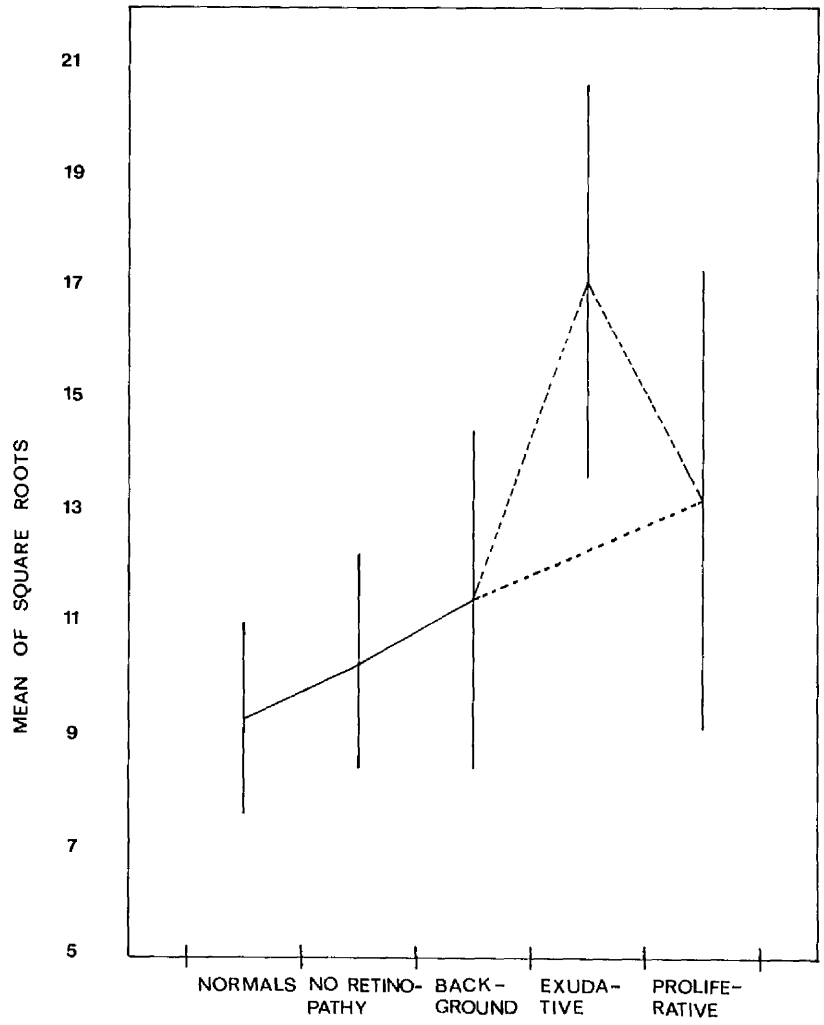

Figure 18. Square roots of means of total error scores of normal individuals and diabetics with different types of retinopathy. Vertical lines represent standard deviations.

5.6. CONTRAST SENSITIVITY

Contrast sensitivity is an important visual function which is sometimes neglected in everyday clinical practice.

The ear acts as a frequency analyser and splits any complex sound into its harmonic components which are transmitted separately to higher levels of the nervous system and it is a matter of controversy whether a similar process occurs in the visual system (Spekeijse and van der Tweed 1977) because there is no obvious basis in retinal anatomy which would enable the eye to act as a spatial frequency analyser as there is in the structure of the cochlea. However, it has been established that single cells in the visual cortex do respond to narrow bands of spatial frequencies and may respond more vigorously to a sinusoidal grating of optimal frequency than to a square wave grating or to any single line, bar, or edge (Maffei, Fiorentini, and Bisti 1974; Glezer, Cooperman, Ivanov, and Tscherbach 1976; Glezer, Kostelyanets, and Cooperman 1977), and that maximum grating acuity is at 30 to 40 cycles per degree. It has, therefore, been postulated that there exist visual "channels" each handling information about bands of spatial frequency. Separate channels have also been postulated for the processing of luminance and colour information (Regan 1977).

Isolated losses of contrast sensitivity have been demonstrated in certain diseases, and in many others loss of contrast sensitivity is more prominent and disturbing to the patient than the loss of visual acuity. It has been reported that contrast sensitivity is reduced in cases of glaucoma before the patient notices impairment

of vision (Arden 1978), in macular and paramacular diseases even when foveolar function remains unaltered and the optotype acuity is normal (Sjostrand and Frisen 1977). It has also been shown that measurements of contrast sensitivity are a more sensitive indication of demyelination of the optic nerve than other psychophysical tests (Arden and Gucukogla 1978). Canavan and Archer (1980) reported loss of contrast sensitivity following contusional eye injury and noted that there was a significant difference in this aspect of visual function between the injured and uninjured eyes; the defect in contrast sensitivity could be demonstrated in the injured eye even when no structural abnormality could be detected on full clinical examination.

Although gratings such as those of the Arden test are unfamiliar as they are never seen in nature, they are a powerful investigatory tool. The Arden grating test has been shown to be useful in North West Iran (Minassian, Jones, and Zargarizadeh 1981) and Australia (Singh et al 1981) as a screening test. It also appeared to be the most sensitive of three tests, VER acuity, Snellen acuity, and Arden test scores, equalling VER performance in optic nerve diseases, and surpassing it in macular diseases and was, thus, recommended for use as a screening test in central visual disturbances (Skalka 1980), glaucoma (Arden, Siegel, and Scher 1977), retrobulbar neuritis, Arden and Gucokogla 1978), families of glaucoma patients (Hitchings, Powell, Arden, and Carter 1981), Minamata disease (Mukuno, Ishikawa, and Okamura 1981), and in retinitis pigmentosa (Lindberg, Fishman, Anderson, and Vasquez 1981).

A study was conducted by the author to determine whether diabetic subjects have a normal or an elevated threshold for different grating frequencies using the Arden grating book, by comparing a group of diabetics with normal individuals matched for age, and also to establish the usefulness of this test as a screening tool in a diabetic eye clinic and whether it can be used to differentiate serious from non-serious retinopathy.

Recently, Arden and Jacobson (1978) introduced a grating test which has been used for the evaluation and follow up of certain diseases of the eye. It consists of a book with seven plates. The first plate is used for quick initial screening of contrast sensitivity. Plate 2 is the first plate usually used. It shows a sinusoidal grating, in which the contrast varies in the Y dimension, being low at the top of the page and highest at the bottom of the page. The contrast changes in a logarithmic sequence, being 0.088 units per division.

The distance between the patient's eye and the plates is about 57 cm, and the spacing between the periods of the grating is nominally 0.2 cycles/degree. The successive plates show gratings of periods 0.4, 0.8, 1.6, 3.2, and 6.4 cycles/degree.

In conducting the test the examiner covers the plate with a card of roughly similar albedo to the test pattern and then moves it to expose the progressively higher contrast portions (scale reading 20 to 15). The patient, seated, looks at the plate, and follows with his eye as the card is moved slowly down the page and is instructed to report the moment he sees the grating bars. For a subject performing the test for the first time an initial run is usually permitted on the

first, low frequency, plate. The position of the card is read from the scale at the side of the plate and this is called the score. A reading of 25 is arbitrarily assigned if the grating could not be seen by the subject.

The Arden grating test is a subjective test requiring active participation by the patient, and to administer the test it was necessary that a range of values from normal individuals should be obtained. Eighty normal volunteers from the Department's staff, the author's relations, and relatives of patients were examined and informed of the nature of the study. The right eye from each of the normal individuals was used. Standard artificial daylight was used (Verivide Cabinet, Leslie Hubble Limited) and, when necessary, the subjects were wearing their appropriate near vision correction.

The subject's ages ranged between 24 and 68 years, mean age 46 and median 45 years.

Individuals with ocular diseases were excluded by checking for eye symptoms, visual acuity measurement using Snellen's test chart, slit lamp biomicroscopy, applanation tonometry, and ophthalmoscopic examination. No effort was made to perform the Arden grating test if a lens opacity, elevated intraocular pressure, or retinal disease was present.

Ninety nine diabetics ranging in age between 27 and 70 years (mean age 47, median 49 years) were also tested. Again the right eye was used and, like the control group, diabetics had no lens opacities or increased intraocular pressure but, of course, varying degrees of retinal diabetic involvement were present. Included in this series were 42 eyes with ophthalmoscopically no retinopathy, 28 eyes with

background retinopathy. The last group consisted of 29 eyes with proliferative diabetic retinopathy confirmed by fluorescein angiograms. Visual acuities among this group of diabetics ranged from 6/5 to 6/36 with mean and median levels of 6/9.

The mean results for the various plates and also the total scores from the normal controls and the different groups of diabetic subjects were compared using the Student t-test and F-test (Figs. 19 & 20). Normal probability plots confirmed that the data were essentially normally distributed. Mean scores on the individual plates from 80 normal eyes with standard deviation (in brackets) of each together with the original figures as suggested by Arden and Jacobson (1978) are shown in Table 12, see also Figure 21.

Assuming that Arden and Jacobson's figures were the result of a few hundred observations, as opposed to eighty subjects in this study, there were no statistically significant differences between Arden and Jacobson's mean readings and the mean readings from the present normal controls on plates 2, 3, 4, and 7 ($P > 0.1$, 0.2, 0.2, and 0.2 respectively), but differences were found to exist between the mean scores on plates 5 and 6 ($P < 0.001$ on both plates).

When mean contrast thresholds for plates 2 to 7 from the 99 right eyes of all diabetic subjects, irrespective of the presence or degree of retinopathy, are compared (Table 13) it is noted that as the grating frequency of the successive plates increases, the mean increases together with the standard deviation, i.e. large variances were noted, Fig. 22. Significant statistical differences were found between these readings and both Arden and Jacobson's figures for normals and the present series of 80 normal

controls at all spatial grating frequencies ($P < 0.001$ on all plates).

Mean scores on the six plates of the grating book of 42 diabetics who showed no retinopathy on ophthalmoscopy are as shown in Table 14. No significant differences could be detected between this group and normal individuals at low frequency spatial gratings viz plates 2 through 5 but mean thresholds on plates 6 and 7 were statistically different ($P < 0.001$), patients in this category having a higher threshold (lower contrast sensitivity) for high frequency patterns, Figures 23 a & b. The same conclusion results when these "no retinopathy" figures are compared with Arden and Jacobson's original means.

The group of diabetics with background retinopathy (28 right eyes) demonstrated significantly high thresholds for grating patternsalong the whole spectrum whether the mean values were compared with normal controls or with Arden and Jacobson's means, Table 15.

The most strikingly high scores on all plates were obtained from the 29 patients with proliferative diabetic retinopathy, Figure 20. Again, highly significant differences were found between the mean values of contrast threshold, Table 16, and those of both present normal controls and Arden and Jacobson's normals. A wide range of scores was obtained on all plates especially plates 6 and 7 (3.2 and 6.4 cycles/ degree respectively).

Comment

Scores of normal controls were comparable to Arden and Jacobsons figures on plates 2, 3, 4, and 7 but different from those on plate 5 and 6. Figures from a recent work

(Singh, Cooper, Alder, Crawford, Terrell, and Constable 1981) using plates 6 and 7 only, Table 17, did not differ from figures from the normal individuals in this work but showed significant differences when compared with the original figures of Arden and Jacobson.

The individuals who participated in the present study, whether normals or diabetics represented a wide range of ages so that it is unlikely that the mean scores were biased by age. The variation in the test results with age in normals is only slight (Arden 1978), although a significant increase in test scores with increasing age was noted by Arundale (1978) and Skalka (1980) who found that contrast threshold increased with age despite excellent Snellen acuity.

Differences in mean thresholds of normal subjects for plates 6 and 7 between the present study and that reported by Arden and Jacobson (1978) are likely to reflect minor differences in testing techniques such as the illumination used, the distance of subject from the test plate, and the rate at which the obscuring card was moved. It was thought important that comparisons between diabetic and normal subjects should be made only under the same test conditions.

The test was conducted by one examiner using the same standard illumination. This excluded the possibility of an interobserver difference in recording and judgement. The test was also carried out at different times of the day so that any effects of fluctuation of blood sugar causing varying errors of refraction and possible changes in test scores should average out.

	Mean	Standard deviation
Plate 2	13.42	3.72
Plate 3	11.17	3.39
Plate 4	13.37	3.54
Plate 5	13.73	3.99
Plate 6	13.91	6.39
Plate 7	15.80	7.31

Table 13. Figures obtained from 99 diabetic eyes with different grades of retinopathy on Arden grating test.

	Mean	Standard deviation
Plate 2	12.86	4.03
Plate 3	9.53	2.99
Plate 4	11.73	3.32
Plate 5	11.60	3.50
Plate 6	12.40	7.28
Plate 7	13.26	8.07

Table 14. Mean of contrast threshold on the Arden book from 42 diabetic eyes without clinically detectable retinopathy.

	Mean	Standard deviation
Plate 2	13.60	2.87
Plate 3	12.00	2.23
Plate 4	13.33	3.06
Plate 5	13.13	2.64
Plate 6	12.66	4.33
Plate 7	14.86	5.20

Table 15. Mean values and standard deviation of figures obtained from diabetes eyes with background retinopathy.

	Mean	Standard deviation
Plate 2	13.80	4.31
Plate 3	12.00	4.22
Plate 4	15.06	3.65
Plate 5	16.46	4.18
Plate 6	16.66	6.65
Plate 7	19.26	7.43

Table 16. Mean threshold figures from 29 diabetic subjects with proliferative diabetic retinopthy on the Arden grating test.

Normal subjects

	Present study mean values	Arden and Jacobson's mean values	Singh's mean values
Plate 6	9.08 (2.25)	10.00 (2.00)	9.50 (2.29)
Plate 7	9.19 (2.56)	9.00 (2.00)	9.44 (2.32)

Table 17. A comparison of different mean contrast threshold readings from normal individuals of this work, Arden & Jacobson (1978) and Singh et al (1981). Standard deviations are shown in brackets.

Plate	2	3	4	5	6	7
Mean	11.96	10.26	11.33	10.90	9.08	9.19
+ 1.96 x SD	4.45	3.70	4.08	3.88	4.41	5.02
giving normal range of	16.41 to 7.51	13.96 to 6.56	15.41 to 7.25	14.78 to 7.02	13.49 to 4.67	14.21 to 4.17

Table 18. 95% limits (mean + 1.96 SD) of normal range of contrast sensitivity obtained from normal individuals in this study.

The highest total scores for any one of the normal controls did not exceed 81 but with diabetics, especially those with well advanced retinopathy, much higher total scores were obtained; actually a few of those with background retinopathy and many with proliferative retinopathy were unable to see some of the grating patterns especially when the higher frequency plates 6 and 7 were used. They were, thus, assigned an arbitrary score of 25 for that particular plate.

Learning does not play a role in this test (Fiorentini and Berardi 1981). In the present study all patients were shown the plates only once after an initial run on plate 2 and consequently learing did not influence the results. Using electronically generated sinusoidal gratings Fiorentini and Berardi (1981) concluded that the spatial frequency discrimination does not improve with repetition.

When scores from normal subjects were compared with the various groups of diabetics it was found that there were significant differences on all plates and from all groups except that diabetics without retinopathy only differed from normals in respect of plate 6 and 7. In fact almost the same conclusion resulted when Arden's normals were used; significant differences being found on plates 2, 6, and 7. This would suggest that a functional deficit for higher frequencies may preceed ophthalmoscopically visible retinopathy and indeed loss of visual acuity.

It has been claimed (Arden and Jacobson 1978) that the test measures retinal integrative function and it would appear that in diabetes this aspect of retinal function

may be abnormal when visual acuity and some other aspects of function such as colour vision are still unaffected.

Although reduced contrast sensitivity on the Arden grating test is more marked in those with more advanced retinopathy than in those with background or no retinopathy the overlap in results between groups makes the test unsuitable for screening for retinopathy requiring treatment. The overlap arises from the variance of scores within groups. Thus using the standard range of $\pm$ 2 SD to categorise the results within each group would result in 50 per cent of diabetics in the no retinopathy group being classed as normals on plates 6 and 7 although as a group the mean scores for those plates are significantly different in these two groups. Even using the slightly less broad 95% confidence limits (1.96 x SD) considerable overlap remains between each group tested.

As already indicated this broad overlap between groups prevents the tests being useful for the routine clinical screening of diabetic retinopathy.

Plate	2	3	4	5	6	7	Comparison
						*	Normal Controls v. Arden Normals
	*	*	*	*	*	*	Arden Normals v. All Diabetics
	*	*	*	*	*	*	Arden Normals v. No Retinopathy
	*		*	*	*	*	Arden Normals v. Background Retinopathy
	*	*	*	*	*	*	Arden Normals v. Proliferative Retinopathy
	*	*	*	*	*	*	Normal Controls v. All Diabetics
	*	*	*	*	*	*	Normal Controls v. No Retinopathy
			*	*	*	*	Normal Controls v. Background Retinopathy
	*	*	*	*	*	*	Normal Controls v. Proliferative Retinopathy
					*	*	No Retinopathy v. Background Retinopathy
		*					No Retinopathy v. Proliferative Retinopathy
	*	*		*	*		Background Retinopathy v. Proliferative Retinopathy

Figure 19. A t-test comparison of mean contrast thresholds, on different plates of the Arden grating book, between different groups of individuals tested. Significant differences are indicated by an asterisk (*).

Plate	2	3	4	5	6	7	Comparison
				*	*		Normal Controls v. Arden Normals
	*	*	*	*	*	*	Arden Normals v. All Diabetics
	*				*	*	Arden Normals v. No Retinopathy
	*	*	*	*	*	*	Arden Normals v. Background Retinopathy
	*	*	*	*	*	*	Arden Normals v. Proliferative Retinopathy
	*	*	*	*	*	*	Normal Controls v. All Diabetics
					*	*	Normal Controls v. No Retinopathy
	*	*	*	*	*	*	Normal Controls v. Background Retinopathy
	*	*	*	*	*	*	Normal Controls v. Proliferative Retinopathy
		*	*	*			No Retinopathy v. Background Retinopathy
		*	*	*	*	*	No Retinopathy v. Proliferative Retinopathy
				*	*	*	Background Retinopathy v. Proliferative Retinopathy

Figure 20. An F-test comparison of mean contrast thresholds, on different plates of the Arden grating book, between different groups of individuals tested. Significant differences are indicated by an asterisk (*).

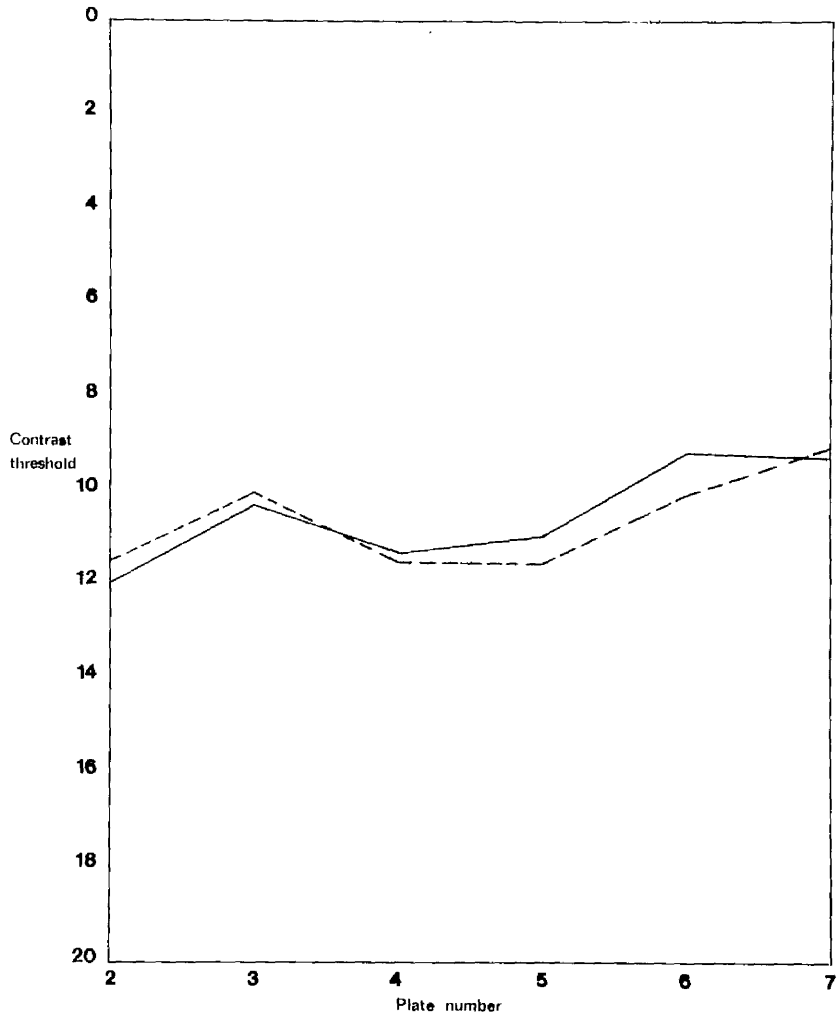

Figure 21. Mean contrast thrshold on the Arden grating book of :

_____ Normal individuals in this series.
----- Normal individuals in Arden and Jacobson's series(1978).

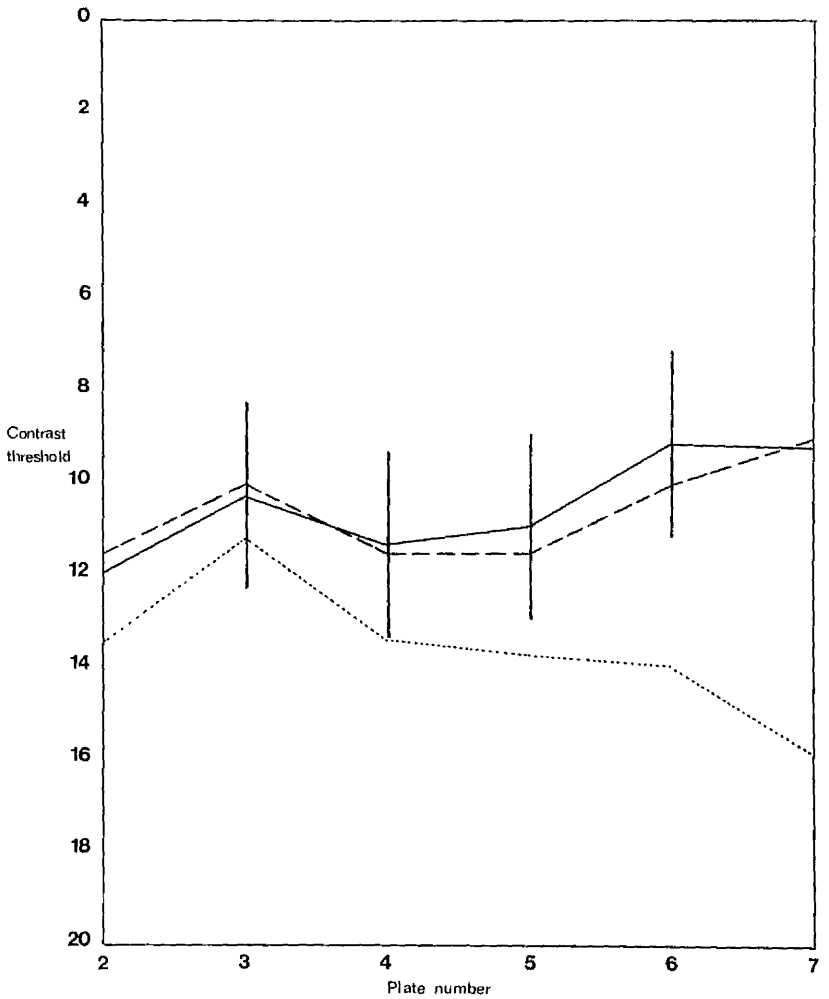

Figure 22. Mean contrast threshold on the Arden grating book of :

_____ Normals in this series.

----- Arden and Jacobson's normals.

..... All diabetics irrespective of presence or type of retinopathy.

Vertical lines indicate standard deviation.

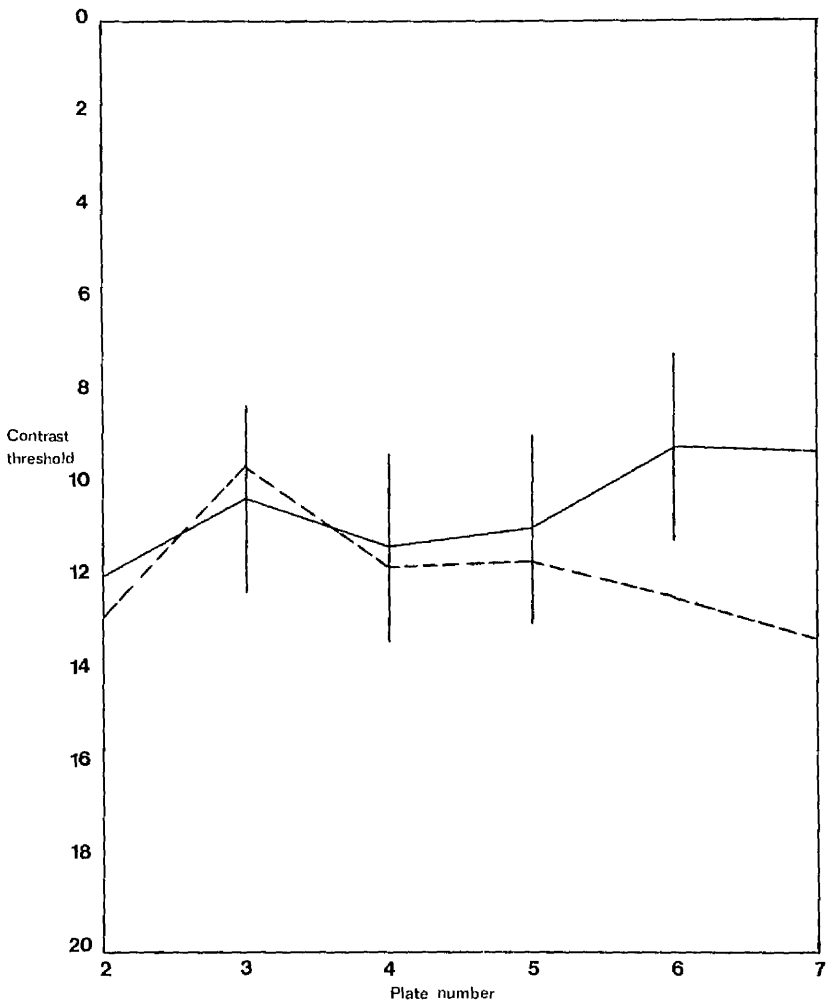

Figure 23(a). Contrast threshold of normal individuals and diabetic patients with no retinopathy.

_____ Normals.

----- Diabetics ; no retinopathy.

Vertical lines represent standard deviation.

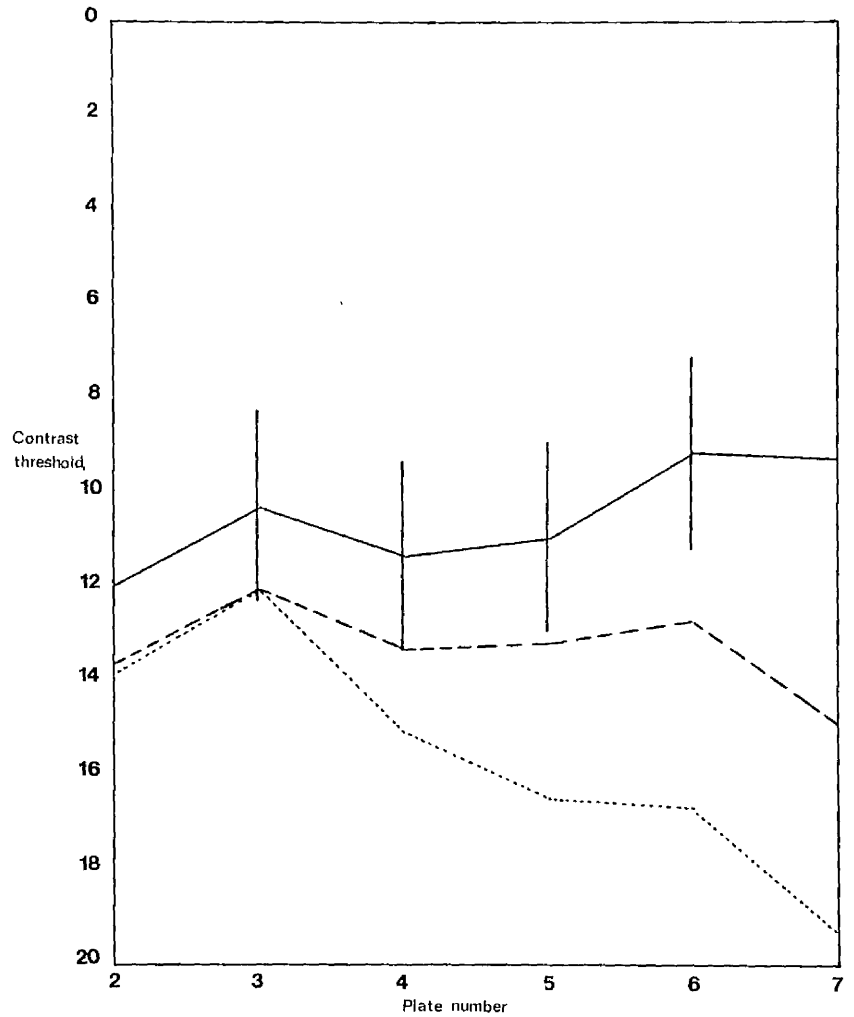

Figure 23(b). Mean contrast threshold of :

_____ Normal subjects.

----- Diabetics with background retinopathy.

..... Diabetics with proliferative retinopathy.

Vertical lines represent standard deviation.

CHAPTER 6

PREVALENCE OF DIABETES IN THE WEST OF SCOTLAND

6.1 INTRODUCTION

Diabetes is a disease which shows a great variation of frequency in different areas of the world and, depending on the criteria used for the diagnosis of diabetes in different surveys, the available figures show a wide range of prevalence rates in different countries. Factors such as race, environment, and socio-economics all play parts in modifying the rates.

To obtain up to date information on the prevalence of diabetes and diabetic blindness in different countries, a letter, see appendix 3, was sent to diabetic societies and to blind welfare bodies in 22 countries. Figures were received from the following countries: Canada; four states in the USA; Denmark; France; Italy; and Spain; India; Tunisia; and Barbados. No replies were received from East European countries.

In the United States of America it is estimated that there are 4.5 million diabetics, one third of whom are unaware that they have the disease. In terms of total population in America, slightly more than 2 per cent have diabetes (Amos 1974).

In Canada diabetes affects nearly one million people, or one in every twenty persons (CNIB 1981).

Several tribes of American Indians were shown to have very high frequencies of glycosuria and diabetes. Amongst the tribes of Pima, Cocopah, Cherokee, and Seneca, almost 50 per cent of those over the age of 30 had a venous plasma level of more than 8.8 mmol/L (160 mg/100 ml) 2 hours after a 75g

glucose load (Bennett, Burch, and Miller 1971). By contrast, the Athabaskan Indians and the racially dissimilar Eskimos in Alaska both have a very low prevalence of clinical diabetes; both groups also show a high degree of tolerance to a glucose load in comparison with all other population groups within the United States. The Eskimos of Greenland, like those of Alaska, have a very low prevalence of diabetes.

Using population sampling and defining diabetes as a blood sugar level of over 8.3 mmol/L (149 mg/100 ml) 2 hours after a glucose load, West and Kalbfleisch (1966) provided reasonably exact comparisons of the prevalence of diabetes in some countries of the world in those over 35 years of age. Their comparative prevalence rates were 2.0 per cent in East Pakistan, 3.3 per cent in Malaya, 4.1 per cent in Central America, 6.9 per cent in Uruguay, 7 per cent in Venezuela, 17 per cent in Bangor, Pennsylvania, and 25 per cent in Cherokee Indians.

Studies in South Africa have suggested that diabetes is excessively common among those of Indian origin. Indians showed a prevalence rate of 10.4 per cent, Malays of 6.6 per cent, and African blacks 3.6 per cent. No factor other than racial was found that might have explained this great variation. The same difference in prevalence rate was found to exist between the Busselton Whites of Australia, 2.3 per cent, and Davenport Aboriginals where the rate was found to be 19 per cent (Jarrett 1976).

Population sampling was used for the study of prevalence of diabetes in Bedford and in Birmingham, England, in each of which the prevalence of known plus new-found diabetes

ation	Prevalence of diabetes(%)	Comment	Reference
d States erica	2	About 4.5 million have diabetes	Amos(1974)
Cocopah, kee,and a Indians	50	Studied are those over 30 who had venous level of more than 8.8 mmol /L after 2 hour of a 75 g glucose load	Bennett(1971)
askan Indians ska Eskimos, land Eskimos	Very low !		Jarrett(1976)
Pakistan a l America y ela ,Pennslvania ee Indians	2 3.3 4.1 6.9 7 17 25	All had a blood sugar level of over 8.3 mmol/L	West and Kalbfleisch (1966)
Africa ians ays ican blacks ia es nport iginals	 10.4 6.6 3.6 2.3 19		Jarrett(1976)
	4-5		C N I B (1981) (personal communication)
ord ngham	1-3		Sharp et al (1964)
ath	1.06		Clark et al (1965)
urgh	0.6		Falconer et al (1971)

Table 19. Different prevalence rates of diabetes in some countries .

in all age-groups was in the order of 1-3 per cent (Sharp, Butterfield, and Keen 1964). In the United Kingdom, the incidence of diabetes in the first 26 years of life is about one tenth of these figures (Wadsworth and Jarrett 1974).

In Scotland (Clark, Taylor, Tocher, and Tocher 1965) a survey of glycosuria and diabetes was undertaken on the population of Arbroath, on the Angus coast of Scotland with a population of around 20,000, and showed that 3.8 per cent of the population, above 5 years of age, had glycosuria. Further investigations showed that 28 per cent of these were diabetics. By calculation this gives a prevalence rate of diabetes in this part of Scotland of 1.06 per cent (see Table 19). Falconer, Duncan, and Smith (1971) reported a prevalence of 0.6 per cent in Edinburgh.

A study was carried out to discover the prevalence of diagnosed diabetes in a general practice in the West of Scotland (Woodside Health Centre, Glasgow). The frequency of complications of diabetes, other than diabetic retinopathy (see the following chapter), was also studied as was the state of diabetic control using random blood sugar and glycosylated haemoglobin levels.

6.2. MATERIALS & METHOD

7139 medical records of patients attending one group practice, in which three general practitioners were involved, were searched for information indicative of diabetes. Records were analysed in batches of 150-200 selected alphabetically. Doctor's letters, hospital replies, urine and blood investigations, and medical prescriptions were looked at and a letter was sent to every identified diabetic

under the care of the group explaining the nature of the survey and requesting his/her attendance.

Special clinics for the examination of identified diabetic subjects were arranged. These clinics were held from 2 to 5 in the afternoon.

At these clinics a note was taken of the name, age, sex, duration of diabetes, age at which diabetes was first diagnosed, family history, smoking habits, type and frequency of treatment, treating body (whether general practitioner or hospital), history of chest pain, intermittent claudication, gangrene, or cardiovascular accident. Blood pressure was recorded (sitting) and samples of blood taken for random blood sugar and glycosylated haemoglobin measurements. A computer input was prepared from the information obtained and the results analysed on the Edinburgh University Computer.

6.3. RESULTS & DISCUSSION

Counts of diabetes in general practice of sample physicians is a recognised epidemiological procedure and has been used in previous studies (Adelstein 1975).

The age/sex distribution of people on the practice list is shown in the Appendices. 798 records (10 per cent) could not be inspected because more than 200 records of students on the practice list were kept at Baird Hall, a student's residence, about 250 records were usually withdrawn daily for consultant clinics, repeat prescriptions and surgery appointments, and about 200 files were permanently withdrawn because of patients moving or dying. The rest, about 150, constituted the "missing files" common to many clinics (Hannay and Maddox 1977; Scobie, Rafferty, Franks, and Fonksen, 1983).

6.3.a. Prevalence and sex ratio

Of 7139 records inspected, 76 diabetics were identified. These comprised 30 males and 46 females. Regardless of the type of diabetes, whether adult or juvenile - onset, this gives a male-female sex ratio of 1:1.55.

Comment

The male:female ratio in the general population of the West of Scotland is 1:1.1 (Registrar General, Scotland 1981). In Scotland and in England-Wales the male:female sex ratio in cases with "adult"-onset diabetes is 1:2 (World Health Organisation 1964).

Ratios with female predominance have been found in some countries e.g. Central America (West and Kalbfleisch 1970), Europe and the Soviet Union (World Health Organisation 1964) and Libya where the male:female ratio was reported to be 1:4 (Mekkawi and Aswad 1972). On the other hand, high male:female ratios were reported from some other parts of the world including Nigeria (Osuntokun 1971), Ethiopia (Belcher 1970), and Iraq and Jordan (W.H.O. 1964).

There is a possibility that in some countries social customs may make it more likely that men are diagnosed earlier than women.

Attendance rate

The number of people who were willing to participate in the study and who actually attended the clinic was 54 giving an attendance rate of 71 per cent. A search into the notes of those who defaulted showed that there was no specific reason for their failure to attend the clinic. Diabetics

are required, sometimes, to attend so many general and specialised clinics that some probably feel unwilling to undergo further tests; also some of the patients requested to attend had moved to other areas without notifying the Health Centre of their new address, a recognised bias in this sort of epidemiological survey (Hannay and Maddox 1977).

18 of the 30 diabetic males and 36 of the 46 females were able to attend the clinic, making the total number of persons examined 54. The default rate was 40 and 22 per cent among males and females respectively.

Comment

The number of patients studied is relatively small to draw conclusions about the default rate, but it will be seen from the next chapter that, on an average, diabetic males tend to be around 7 years younger than diabetic females and this could, perhaps, mean that relatively more males were at work at the time of the clinic and probably found it inconvenient to be available, the clinic being an "additional" one and not one of the routine clinics they usually visited.

The prevalence of diagnosed diabetes among the population of the practice studied is accordingly 1.06 per cent. This is similar to that found in Arbroath (Clark and others 1965) but higher than that in Edinburgh in which a prevalence rate of 0.6 per cent was found. In the Edinburgh survey the characteristics of 2932 diabetics were studied (Falconer and others 1971).

6.3.b. Age at time of examination

Patients' ages ranged between 21 and 86 years with a mean age of 62 and a median of 64 years, Table 20.

About 50 per cent of all diabetics examined were 66 years of age or more, see Table 21. Appendix 5 shows the age distribution of patients on the practice lists of Woodside Health Centre. It can be seen that the over 65 year olds constitute about 20% of the practice studied. Those over 65 years of age formed 14 per cent of the total Health Centre list.

6.3.c. Duration of diabetes

Duration of diabetes of the sample studied ranged between 6 months and 34 years with a median of 6.6 years. In Table 22 are shown the minimum, maximum, mean, and median duration of the diabetic illness. This range of duration of diabetes is similar to the range found in a recent study also carried out in Britain (Bodansky, Cudworth, Whitelocke, and Dobree 1982).

6.3.d. Age at diagnosis of diabetes

One patient, a female, had developed diabetes at the age of 11 and one, also a female, was diagnosed at the age of 83. However, the median age at diagnosis in males was 60 and in females 55 years (Table 23). No significant difference in the age at diagnosis of diabetes in males as compared with females was demonstrated (P = 0.1142, Mann-Whitney comparison of medians).

Comment

The failure to demonstrate a difference in age of onset

Ages in years	All patients	Males	Females
Minimum age	21	21	28
Maximum age	86	76	86
Mean age	62	59	63
Median age	64	64	66
Standard deviation	14	16	13

Table 20. Age and sex of the 54 diabetics studied.

Age group	No.	Percent	Males No.	Males Percent	Females No.	Females Percent
0-20	0	0	0	0	0	0
21-40	5	9.2	3	16.6	2	5.5
41-65	23	42.6	7	38.8	16	44.4
66 +	26	48.1	8	44.4	18	50.0
TOTAL	54		18		36	

Table 21. Actual numbers and percentages of the total of diabetics examined at different age groups, subdivided into male and female groups.

Duration	All Patients	Male	Female
Minimum	6 months	6 months	6 months
Maximum	34 years	14 years	34 years
Mean	8.2 years	7.1 years	8.8 years
Median	6.6 years	7.9 years	6.0 years
Standard deviation	7.3 years	4.6 years	8.4 years

Table 22. Details of known duration of diabetes in the sample studied.

Age at diagnosis in years	All	Male	Female
Minimum	11	18	11
Maximum	83	68	83
Mean	54	52	55
Median	60	60	55

Table 23. Age at diagnosis of diabetes.

Age Group (years)	ALL No. of patients.	ALL per cent	MALE No. of patients.	MALE per cent	FEMALE No. of patients.	FEMALE per cent
0-20	2	3.7	1	5.5	1	2.7
21-40	7	12.9	3	16.6	4	11.1
41-65	29	53.7	10	55.5	19	52.7
66 +	16	29.6	4	22.2	12	33.3

Table 24. Age at time of diagnosis of different age groups.

Age at diagnosis (years)	With positive family history (24 cases).	without family history (30 cases).
Minimum age	11	20
Maximum age	68	83
Mean age	50	57
Maximum age	50	60

Table 25. Ages at diagnosis of patients with and without a positive family history of diabetes.

of diabetes in males as compared with females may relate to the small sample size. The results differ from those of a study of 400 diabetics attending a general hospital diabetic clinic in which significant statistical differences in the age at diagnosis of diabetes was found between the two sexes ($P = 0.0001$), see Chapter 7.

In Table 24 it is noted that in more than half of the patients the diagnosis was made between ages 41-65 years and that more females, (33 per cent), experienced the onset of diabetes after the age of 65 than did males in the same age category. 16.6 per cent of males and 11.1 per cent of females were diagnosed between the ages of 21 and 40 years.

6.3.e. Family history of diabetes

Twenty four individuals, 44 per cent of the total, had a positive family history of diabetes. In twenty cases, 37 per cent, the father, the mother, a sister or a brother or both plus one of the parents or a grandparent, were diabetic; the rest, 4 cases, had one or more second degree relatives affected with the illness.

The median age at onset of diabetes tends to be about one decade earlier in those with a family history, as seen in Table 25 and Figure 24.

Five out of 24 subjects (21 per cent) who came from families with a positive history of diabetes were diagnosed after the age of 65, while 11 out of 30 (36 per cent) with no family history of diabetes were actually found to be diabetic after this age, see Table 26. This could be another indication that diabetic patients with a positive family history of diabetes tend to develop the illness at an earlier age.

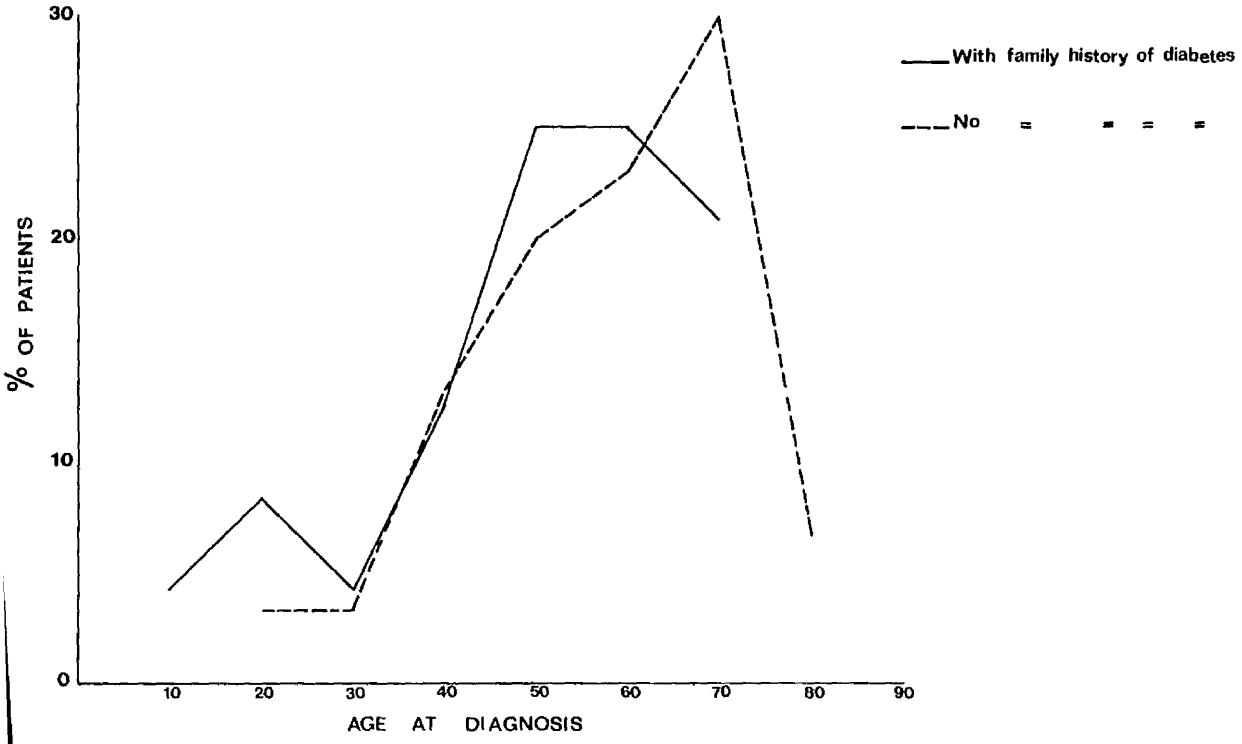

Figure 24. Different parameters of age at diagnosis of diabetes in 24 patients with and 30 patients without family history of diabetes.

Age at onset (years)	(+)ive family history Number	Percent	(-)ive family history Number	Percent
0-20	1	4.0	1	3.3
21-40	3	12.5	4	13.3
41-65	15	62.5	14	46.6
66 +	5	21.0	11	36.6
TOTAL	24		30	

Table 26. A comparison of ages at diagnosis of subjects with and without a history of diabetes in the family. Woodside Health Centre.

Comment

"Heriditability" rates of diabetes as high as 35-50 per cent were reported in some studies (Falconer 1967; Simpson 1969) and these figures related more to juvenile-onset than to adult-onset cases of diabetes. Simpson (1969) also reported that when diabetes was discovered after age 40, the risk for siblings and children was increased by a factor of 2-3; but when diabetes was discovered before age 20, risk was increased about 12-fold in siblings, and more than 30-fold in offspring of the diabetic.

It was not possible to study the age at the onset of diabetes in cases with juvenile diabetes because of the small number of patients studied. It is, however, reported that the incidence is about 6 times more frequent in the second five years than the first five years of life and that the incidence in the young onset patients rises with age reaching a peak at age 11 and there is, then, a decline in incidence after age 14. Recent data (Bloom, Hayes, and Gamble 1975) from a survey in Britain and Ireland suggest a plateau in incidence before the fourth and eighth years before a sharp rise with a peak during age 10-13.

There is no information in the present work of the frequency of diabetes in the offspring of the individual diabetics studied but nevertheless, the study showed that around 30 per cent of diabetics had a positive family history. Whether genetic or environmental factors such as fatness or socio-economic status (West 1978) determined these rates was not considered.

6.3.f. Smoking habits

Among the 54 patients 17 were smokers (32 per cent), 30 non-smokers (55 per cent), and 7 ex-smokers (13 per cent). Of the smokers, 14 smoked 10-25 cigarettes per day, 1 smoked pipe tobacco, and 2 had the habit of smoking cigars. I have, unfortunately, not been able to compare these figures with prevalence rates of smoking among the general population as these are, as yet, not available.

6.3.g. Blood pressure

As already mentioned, blood pressure readings were made with the patient seated. Diastolic blood pressure was taken as the pressure at which there was a change in the tone of the sound.

A systolic blood pressure of more than 180 mm Hg and/or a diastolic pressure higher than 95 mm Hg was arbritrarily considered to be elevated at the time of examination.

Although one might ordinarily accept higher values for normal blood pressure among older subjects, the criteria used in this study were chosen so that a comparison could be made with a large population study (Beevers 1978) in which these were the criteria selected.

It can be noted from Table 27 that 7 out of 36 females, 19 per cent, but none of the 18 males had a systolic pressure of more than 180 mm Hg, and that 9 of the females, 25 per cent, and only 1 male, 5.5 per cent, had a diastolic pressure higher than 95 mm Hg.

Comment

Among the population of Renfrew, West of Scotland, an extensive study which included 3001 subjects the frequency

of diastolic blood pressure of more than 95 mm Hg was found to be around 25 per cent (Beevers 1978). It seems, thus, that elevated blood pressure was not higher among the sample of diabetics under consideration than its prevalence in the general population. This is in agreement with some other recent studies in which blood pressure levels of diabetic twins were not significantly different from those of none diabetic twins (Pyke, Smith, Nelson, and others 1977) or in diabetics who have survived forty years or more (Oakley, Pyke, and Tattersall 1974).

6.3.h. Relation of smoking to blood pressure

No positive relationship was found between smoking habits and systolic and/or diastolic blood pressure readings. Seven out of thirty non-smokers, 23.3 per cent, had a diastolic pressure higher than 95 mm Hg, while 2 out of 17 smokers, 11.7 per cent, had a high diastolic pressure as defined.

When the systolic blood pressure is measured it can be seen from Table 28 that 16.6. per cent of the non-smokers and 5.8 per cent of the smokers had a systolic pressure higher than 180 mm Hg.

6.3.i. Type of treatment

35 per cent of patients were on dietary restriction nly, 50 per cent on oral hypogylcaemic agents (35 per cent n one daily dose of the drugs and 15 per cent on more than nce daily dose), and the rest, 15 per cent, on insulin (11 er cent on one injection and 4 per cent on two injections er day). Thus the great majority (55%) were cases of non-sulin dependent diabetes (NIDD) while only 15 per cent had sulin dependent diabetes (IDD). These figures are monstrated in Figure 25.

Systolic				Diastolic			
	All patients	MALE	Female		All Patients	MALE	Female
Less than 180 mm Hg	47	18	29	Less than 95 mm Hg	44	17	27
More than 180 mm Hg	7	0	7	More than 95 mm Hg	10	1	9
TOTAL	54	18	36	TOTAL	54	18	36

Table 27. Systolic and diastolic blood pressure measurements.

Systolic					Diastolic				
	Smokers	Non-smokers	Ex-smokers	TOTAL		Smokers	Non-Smokers	Ex-Smokers	TOTAL
Less than 180 mm Hg	16	25	6	47	Less than 95 mm Hg	15	23	6	44
More than 180	1	5	1	7	More than 95	2	7	1	10
TOTAL	17	30	7	54	TOTAL	17	30	7	54

Table 28. Normal and high systolic and diastolic blood pressure as related to smoking habits.

	Diet only	once O.H.	twice O.H.	once Insulin	twice Insulin	TOTAL
G.P. patients	15 (46)	12 (36)	4 (12)	1 (3)	1 (3)	33
Hospital patients	4 (19)	7 (33)	4 (19)	5 (24)	1 (5)	21

Table 29. A comparison between treatment policies of General Practice and Hospital clinics. Percentages are shown in brackets
O.H. : Oral Hypoglycaemic agents.
Percentages are in brackets.

	Number of patients affected with one or more of the listed complications.	Percent of incidence.
Angina	13	24
Infarction	8	15
Intermittent claudication	15	28
Gangrene	0	0
Cardiovascular accident	2	4

Table 30. Incidence of some diabetic complications excluding retinopathy.

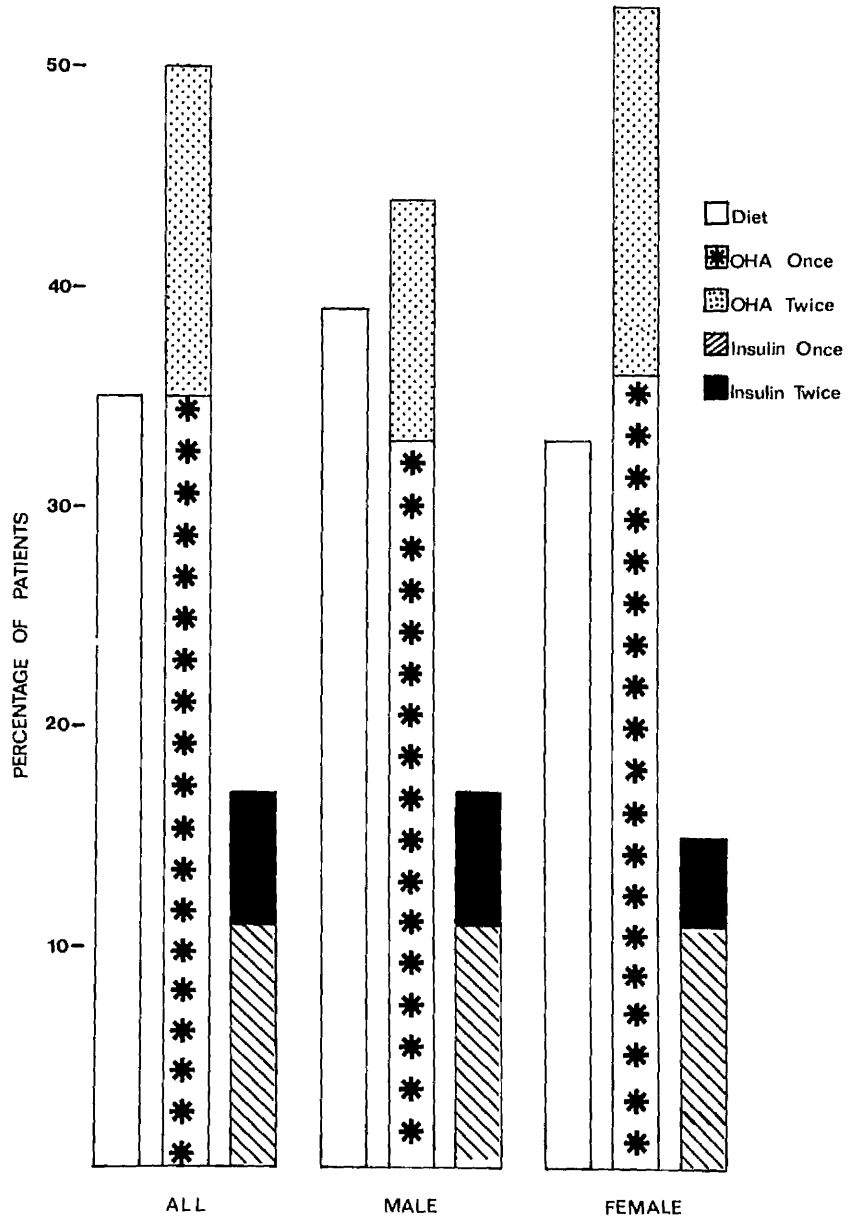

Figure 25. Treatment of a sample of 54 diabetic patients in general practice(Woodside Health Centre) ; for numbers see Table 29(page 160).

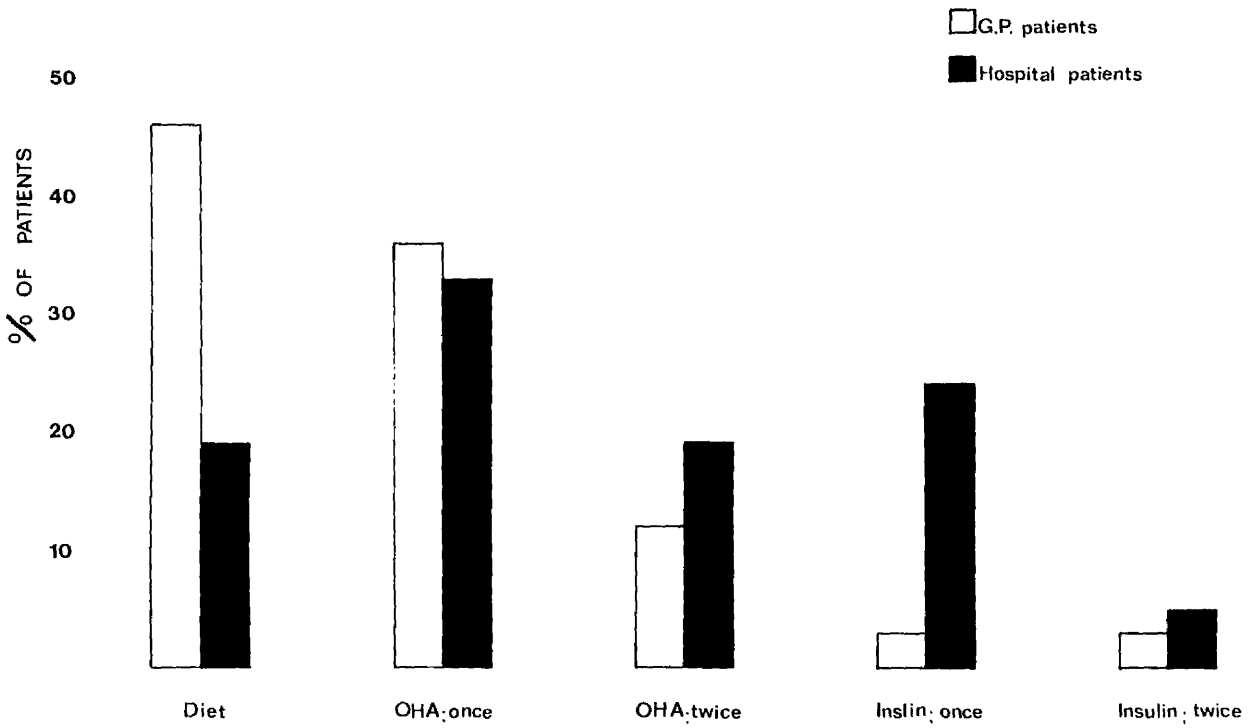

Figure 26. A comparison between treatment of diabetics attending general practice and a hospital diabetic clinic. Numbers of patients are shown in Table 29 (page 160).

6.3.j. G.P. and Hospital patients

61 per cent of the patients were exclusively looked after by their own general practitioners. The rest, 39 per cent, attended a hospital for the management of their diabetes but visited their own doctors only sometimes for routine check-up and repeat prescriptions.

Treatment policy was noted to be different among the two groups. Slightly less than a half of the patients who were under the general practitioners' care were on oral hypoglycaemic agents, 46 per cent on dietary restriction and only 6 per cent were insulin dependent while 29 per cent of hospital attending subjects were on insulin therapy and only 19 per cent were managed by dietary restriction alone. Table 29 and Figure 26 show a comparison of these figures.

This may be due to the fact that patients with milder NIDD usually attend medical practitioners and are referred to hospital once insulin therapy is required for one reason or another. (Thorn and Russell 1973). See Chapter 7.

6.3.k. Frequency of complications other than retinopathy

Questions were asked about the presence and/or a history of certain complications of diabetes. As seen in Table 30, coronary heart disease (39 per cent) and intermittent claudication headed the list of systemic complications. There was no case of gangrene and only two instances (4 per cent) of cerebrovascular accident, one male and one female. See also Table 31 for the incidence of occurrence of combinations of these complications.

Comment

Of patients with one or more systemic complications one was on insulin therapy (out of 11 patients with IDD). No significant difference was found in the prevalence of systemic complications between insulin dependent diabetics and non-insulin dependent ones.

Figures in this section are similar to those reported by others workers (Lewis and Symons 1958) and confirm that diabetes is one of the major causes of mortality in many communities. Diabetes has killed more people than the two world wars combined (West 1978).

6.3.1. Control of diabetes

Random blood sugar

None of the usual tests which are used in the diagnosis of diabetes was used here. Rather reliance was laid on the clinic records for the diagnosis. All cases studied were "labelled" as diabetic and treated by their physicians as such. A level of 11 mmol/L was considered the dividing line between normal and abnormal levels of blood sugar at the time patients attended the clinic and the samples of blood withdrawn.

In the West of Scotland lunch is usually taken about noon. Blood samples were taken between 2 p.m. and 3 p.m. so that patients in general were two to three hours post-prandial. As already noted the majority of patients had NIDD in whom a 2 hour post-prandial blood sugar level of 11 mmol/L would be grossly abnormal. Such a post-prandial blood sugar level would also be considered abnormal in insulin-dependent diabetics.

Table 32 shows that 19 patients (35 per cent) had a high blood sugar.

Random blood sugar levels of over 11 mmol/L were found in 30 per cent of the NIDD and in 65 per cent of the IDD. The difference however may be due to the small sample size and to the known difference in behaviour of post-prandial blood sugar levels in the two types of diabetes.

10 of 33 diabetics treated by their general practitioner and 9 of 21 individuals attending hospitals for their follow-up (30 and 43 per cent respectively) showed high blood glucose levels; this is shown in Table 34.

4 patients out of 6 treated at hospital with insulin had high glucose levels and in one of general practitioners' patients on insulin was the level high; the other patients had normal blood glucose. This makes the total number of subjects on insulin therapy 8.

No firm conclusion could be drawn from these figures since the number of patients was small. However, no great differences existed between the levels of blood sugar in patients attending general practice or hospital diabetic clinic.

Glycosylated haemoglobin

Corning Electrophoresis (Glytrac) set was used for the quantitative determination of glycosylated haemoglobin. Samples of blood were examined within 24 hours. The normal range was taken as 4.1 - 8.1 per cent.

21 patients were found to have high levels of glycosylated haemoglobin (38.8 per cent); 13 were general practitioners' patients and 8 were hospital attenders.

In Table 35 the levels of HbA_{1c} are related to hospital and practitioners' care. About 35 per cent in each group had abnormal levels of HbA_{1c}. In Table 36 the sex distribution of individuals with normal and abnormal levels of HbA_{1c} is shown; 30 per cent of males and 45 per cent of females had abnormal HbA_{1c} levels.

27 individuals were on oral hypoglycaemic agents and of these 17 (63 per cent) had abnormal HbA_{1c} while only 25 per cent of those on insulin had HbA_{1c} levels within normal limits, see Table 37.

Including patients on diet alone 30 per cent of non-insulin dependent diabetics showed abnormal HbA_{1c} levels as compared to 75 per cent of patients with insulin dependent diabetes.

Comment

It appears that more than 35 per cent of the diabetics under consideration are not well controlled whether random blood sugar or glycosylated haemoglobin levels were used for the assessment of control and further that on HbA_{1c} estimation IDD were less well controlled than NIDD. HbA_{1c} measurements give an indication of long-term control in NIDD but in IDD HbA_{1c} probably reflects the degree of control over the preceeding few weeks.

Number of complications	Number of patients	Percentage
One complication	15	28.0
Two complications	10	18.5
Three complications	1	2.0
TOTAL	26	48.5

Table 31. Frequency of occurrence of one or more of the systemic complications in a sample of 54 patients studied at Woodside Health Centre.

	Male	Female	All
Normal	13	22	35
Above normal	5	14	19
TOTAL	18	36	54

Table 32. Normal and abnormal random blood glucose levels of the 54 diabetics studied.

Glucose level	Diet	Oral/ Once	Oral/ Twice	Insulin/ Once	Insulin/ Twice	Total
Normal	12	16	4	1	2	35
High	7	3	4	5	0	19
Totals	19	19	8	6	2	54

Table 33. Normal and high random blood sugar levels as related to type and frequency of treatment.

	G.P. Patients	Hospital Patients	Total
Normal	23	12	35
High	10	9	19
Totals	33	21	54

Table 34. General practitioners'and Hospital's patients with normal and high random blood glucose levels.

HbAlc	G.P.'s	Hospital	Totals
Normal	20	13	33
Above normal	13	8	21
Totals	33	21	54

Table 35. Different levels of HbAlc related to hospital and general practitioner attenders.

HbAlc	All	Male	Female
Normal	33	13	20
Above normal	21	5	16
Totals	54	18	36

Table 36. Levels of HbAlc as related to sex. Normal range of HbAlc: 4.1 - 8.1 per cent.

HbAlc level	Diet	O.H. /Once	O.H. /Twice	Insulin /Once	Insulin /Twice	Totals
Normal	14	13	4	1	1	33
Above normal	5	6	4	5	1	21
Totals	19	19	8	6	2	54

Table 37. This table shows that 32 per cent of patients with non-insulin dependent diabetes (NIDD) had abnormal HbAlc while 75 per cent of insulin-dependent diabetics (IDD) showed abnormal levels (normal range of HbAlc 4.1 - 8.1 per cent).

CHAPTER 7

PREVALENCE OF DIABETIC RETINOPATHY IN A GENERAL HOSPITAL DIABETIC CLINIC

7.1 INTRODUCTION

Diabetes has been shown to be the commonest systemic disease causing blindness (Michaelson 1969) and diabetic retinopathy, one of the most dangerous complications of diabetes to be the cause of blindness in more than 80 per cent of cases of blindness due to diabetes (Nielson 1982). In England and Wales, where it was estimated that there were 8,700 blind diabetics (9.6 per cent of all blind people) 6,200 were blind from diabetic retinopathy alone; the rest, 2,500 from other causes with diabetic retinopathy as a contributory cause (Sorsby 1966).

Studies have been carried out (Lewis and Symons 1958; Osuntokun 1969; Cullen and Town 1975; Donovan 1978; Mitchell 1980; Scobie, MacCuish, Barrie, Green, and Foulds 1981; Jarah 1982; Bodansky, Cudworth, Whitelocke, and Dobree 1982) to determine the prevalence of diabetic retinopathy and, sometimes other complications of diabetes in general and special diabetic clinics. Results varied depending on many variables including the geographical situation of the clinic and whether it was a general diabetic clinic or one to which only selected cases of diabetes were referred including in some instances those with known retinopathy.

The prevalence of diabetic retinopathy is likely to be different among hospital patients as compared with those being cared for in general practice. Having ready access to a large hospital diabetic clinic it was decided in the first instance to establish the prevalence of retinopathy in a hospital clinic and subsequently to compare this with a study based on a general practice population. The aims

of the study were:

1. To determine the prevalence of diabetic retinopathy in a hospital diabetic clinic (Glasgow Royal Infirmary) in the West of Scotland.

2. To determine the frequency of different types of retinopathy.

3. To identify the different factors which might contribute to the development of diabetic retinopathy in diabetic subjects, for example age at examination, age at which diabetes was first recognised, and the duration of diabetes and its treatment and to relate these factors to the relative frequency of occurrence of retinopathy of different types and severity.

4. To identify patients requiring further ophthalmological examination and/or laser treatment.

7.2. MATERIALS AND METHODS

The study was carried out during the period 1st May to 31st December 1981 at the Glasgow Royal Infirmary diabetic clinic. Patients from this clinic who show serious forms of retinopathy or other diabetic eye complications are usually referred to the Tennent Institute of Ophthalmology for further assessment and treatment where appropriate.

In a previous work by diabetic physicians of Glasgow Royal Infirmary and Ophthalmologists from the Tennent Institute during the period August 1978 - March 1981, a certain proportion of patients was seen by each group of clinicians (Barrie, Scobie, Green, MacCuish, and Foulds 1981). In the present study there was no selection of cases because the author alone examined 400 consecutive diabetic subjects attending for their annual eye test.

A note was taken of the patients' diabetic clinic number for future reference, age at time of examination, duration of diabetes, type of treatment, frequency of intake of oral hypoglycaemic agents or administration of insulin, presence of or a history of hypertension, and smoking habits. Pupils were dilated using Tropicamide and a dark room was used for the ophthalmoscopic examination. A careful examination of the fundus was then carried out. In those who showed signs of diabetic retinopathy the retinopathy was classified as previously described. In addition a note was made of which abnormal features were most in evidence (microaneurysms, haemorrhages, exudates, cotton-wool spots, new vessels). The presence of cataract glaucoma as indicated by an operation or a history of taking drugs for its control, or other complications of diabetes was also recorded. A computer input (see Appendix 6) was prepared and the results analysed on the Edinburgh University Regional Computer.

7.3. RESULTS AND DISCUSSION

400 patients were examined. This figure comprised 190 males, 47.5 per cent of the total, and 210 females, 52.5 per cent, giving a male:female ratio of 1:1.1. This ratio is similar to that reported in a previous study in England (Caird and Garrett 1963) in which 1750 diabetics attending a general hospital diabetic clinic were examined. The male:female ratio in the community of the West of Scotland is also 1:1.1 (Registrar General, Scotland 1981).

7.3.a. Influence of age and duration of diabetes

The oldest of the patients was 85 and the youngest 13 years of age. The median age of all patients was 60 years (± 16).

Table 38 shows the minimum, maximum, mean, and median duration of age of the two sexes and Figure 27 demonstrates the age distribution of the patients.

29 per cent of patients were between 57.5 and 67.5 years of age and two thirds, 65.5 per cent, of them were within the working age, 21-65 years old. 75 per cent of men and 57 per cent of women fell within this age range and 85 per cent of patients were over 40. Ages of patients were comparable to the age range reported by Lewis and Symon (1958) who studied the frequency of different vascular diseases among 654 diabetics from the Royal Free and Hampstead General Hospitals. 90 per cent of their patients were over 40 years of age.

Median age of the 190 males was 55 years and of the 210 females was 62 years, see Tables 39 and 40 in which the age range is split up into the following categories: 0-20, 21-40, 41-65, and over 65 years. The majority of males (64 per cent) were in the age range 41-65 at the time of examination. In females 45 per cent were in this age range while 40 per cent were over 65 years of age.

7.3.b. Age at diagnosis of diabetes.

In Table 43 the ages at the time diabetes was first recognised are shown. There was a 7 year difference between the median age at diagnosis of male and female subjects. Males tended to develop diabetes at an earlier age than females; median ages being 49 and 56 years respectively and this was found to be statistically significant = 0.0001, Mann Whitney test). This can also be seen om Figures 29 and 30. In males the peak frequency of

age at diagnosis was at age 60 and in females at age 70. Again females generally developed diabetes a decade later than males.

Table 44 shows other interesting figures. About one tenth of men but almost a quarter of all women were diagnosed after age 65..

Comment

Bennett, Rushford, Miller, and LeCompte (1976) in a study of diabetes among Pima Indians found that the incidence of diabetes peaked at age 30 in men and at age 40 in women. Although much earlier than the median age of diagnosis obtained from the sample under consideration, their data also shows that males tend to develop diabetes at a younger age than females.

In this study the incidence of diabetes continued to rise with increasing age. This is in agreement with that reported by Gamble and Taylor (1969) and by Falconer and co-workers (1971), (Figure 31), but in contrast to the findings of Belcher (1973) in Ethiopian diabetics in whom the peak incidence of onset of diabetes was around age 30 followed by a continuous decline of incidence till the age of 60 around which the rate was lowest, Figure 32. More than one explanation for these differences have been offered the most probable of which is the lack of exercise and fatness among the relatively more prosperous communities (West 1978). In these communities old people also have more tests and this may contribute to the discovery of more diabetics. The Ethiopian figures may also reflect a high mortality from diabetes.

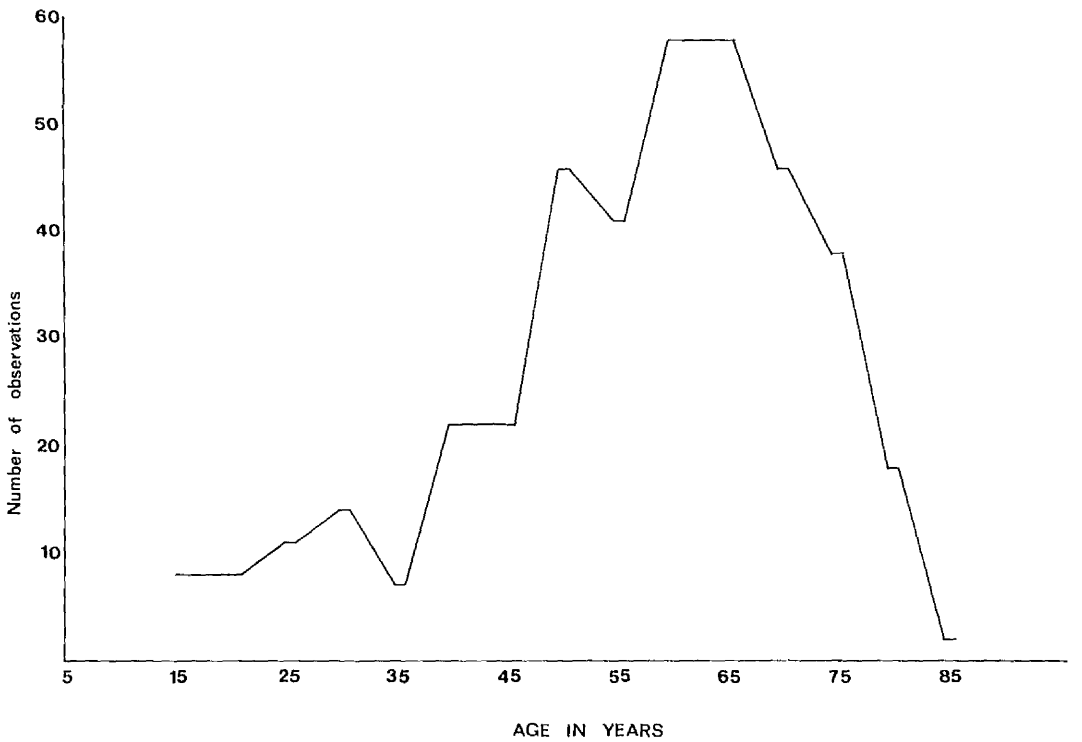

Figure 27. Distribution of ages, at the time of ophthalmic examination, of diabetics attending a Hospital Diabetic Clinic.

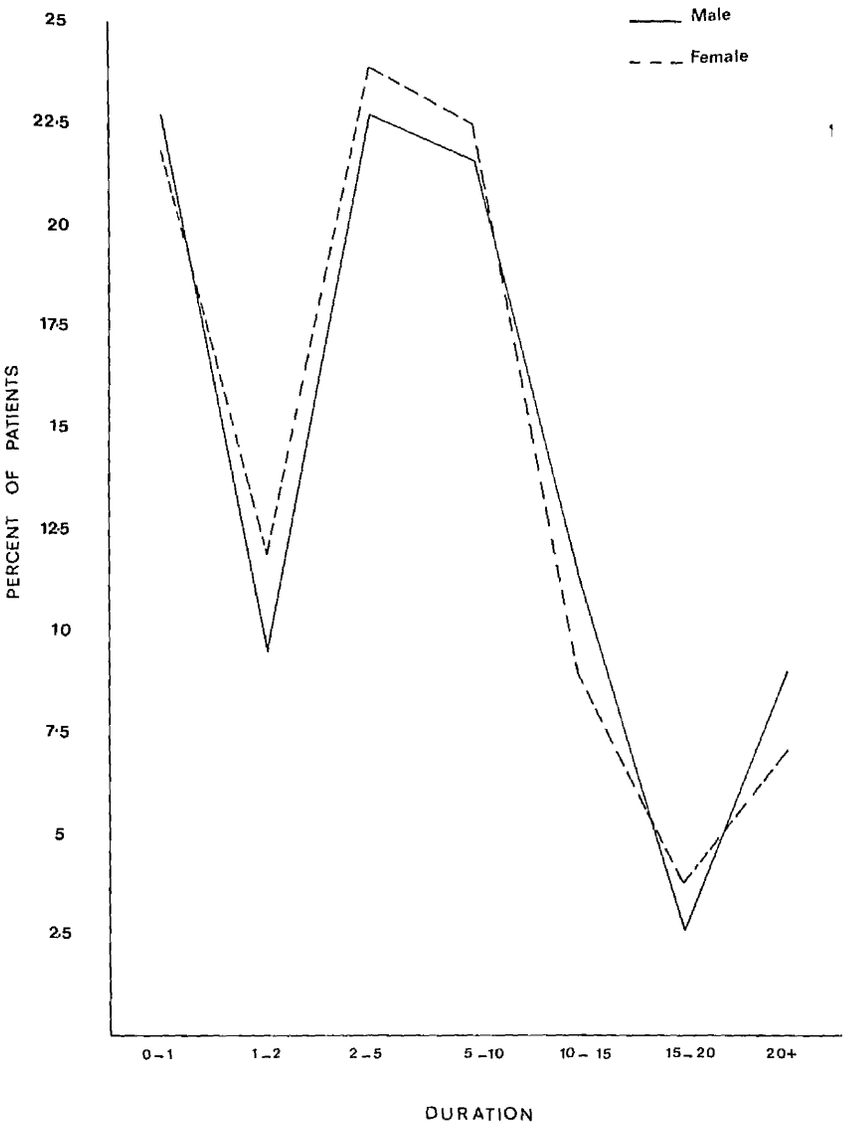

Figure 28. Distribution of duration of diabetes among patients attending Glasgow Royal Infirmary Diabetic Clinic.

Ages (years)	All patients	Male	Females
Maximum	85	81	85
Minimum	13	14	13
Mean	57	54	59
Median	60	55	62
Standard deviation	16	15	16

Table 38. Different age parameters of males and females. It is noted that females tend to be 7 years older than males at the time of examination.

Age (years)	Number of patients	Percentage
0-20	13	3.3
21-40	46	11.5
41-65	216	54.0
66 +	125	31.2

Table 39. Age distribution of 400 diabetics at time of examination.

Age (years)	Male Number	Male Percentage	Female Number	Female Percentage
0-20	8	4.2	5	2.4
21-40	21	11.0	25	11.9
41-65	121	63.7	95	45.2
66 +	40	21.1	85	40.5

Table 40. Age distribution by sex at examination.

Duration	All patients	Male	Females
Minimum	1 month	1 month	1 month
Maximum	40 years	35 years	40 years
Mean	7 "	7.2 "	6.8 "
Median	4 "	4.8 "	4.0 "
Standard deviation	8 "	7.7 "	7.8 "

Table 41. Different parameters of known duration of diabetes in the sample studied.

Duration (years)	All patients		Male		Female	
	No.	Percentage	No.	Percentage	No.	Percentage
0-1	89	22.2	43	22.6	46	21.9
1+-2	43	10.8	18	9.5	25	11.9
2+-5	93	23.2	43	22.6	50	23.8
5+-10	88	22.0	41	21.6	47	22.5
10+-15	42	10.5	23	12.1	19	9.0
15+-20	13	3.3	5	2.6	8	3.8
20+	32	8.0	17	9.0	15	7.1
Total	400		190		210	

Table 42. Distribution of known duration of diabetes, by sex, of patients examined at Glasgow Royal Infirmary Diabetic Clinic.

Age (years)	All	Male	Female
Minimum	2	2	5
Maximum	83	77	83
Mean	50	47	52
Median	53	49	56
Standard deviation	17	16	17

Table 43. Ages at diagnosis of diabetes of 400 diabetic individuals.

7.3.c. Duration of diabetes.

There was a wide range of durations of diabetes amongst the subjects. The shortest was one month and the longest (in a female) 40 years. Table 41 depicts the different durations of diabetes in all patients split up according to sex and in Table 42 the duration of diabetes is subdivided into zero to 1 year, more than 1 up to 2 years, more than 2 and up to 5 years, more than 5 and up to 10 years, more than 10 years and up to 15 years, more than 15 and up to 20 years, and finally more than 20 years. The numbers of patients encountered in each of these duration categories are shown in the Appendices.

In Figure 28 the distribution of durations is shown. The data show a biphasic distribution with a peak at 0-1 years and a second peak at around 5 years. This probably results from the fact that the diabetic clinic is composed of a population of patients with recently diagnosed diabetes referred for confirmation and initial stabilisation and a second group of patients who for various reasons continue to attend the clinics. As the average age at examination was 57 years and the average age at diagnosis 50 the average duration of diabetes among this population would be expected to be 7 years which agrees with the peak frequency of the second peak of the bimodal frequency curve in Figure 28.

.3.d. Age, duration of diabetes, and type of diabetes

101, 73, and 126 subjects constituting 25, 43, and 2 per cent respectively were on dietary restriction, ral hypoglycaemic agents, and insulin i.e. approximately per cent had NIDD and 32 per cent were IDD. These

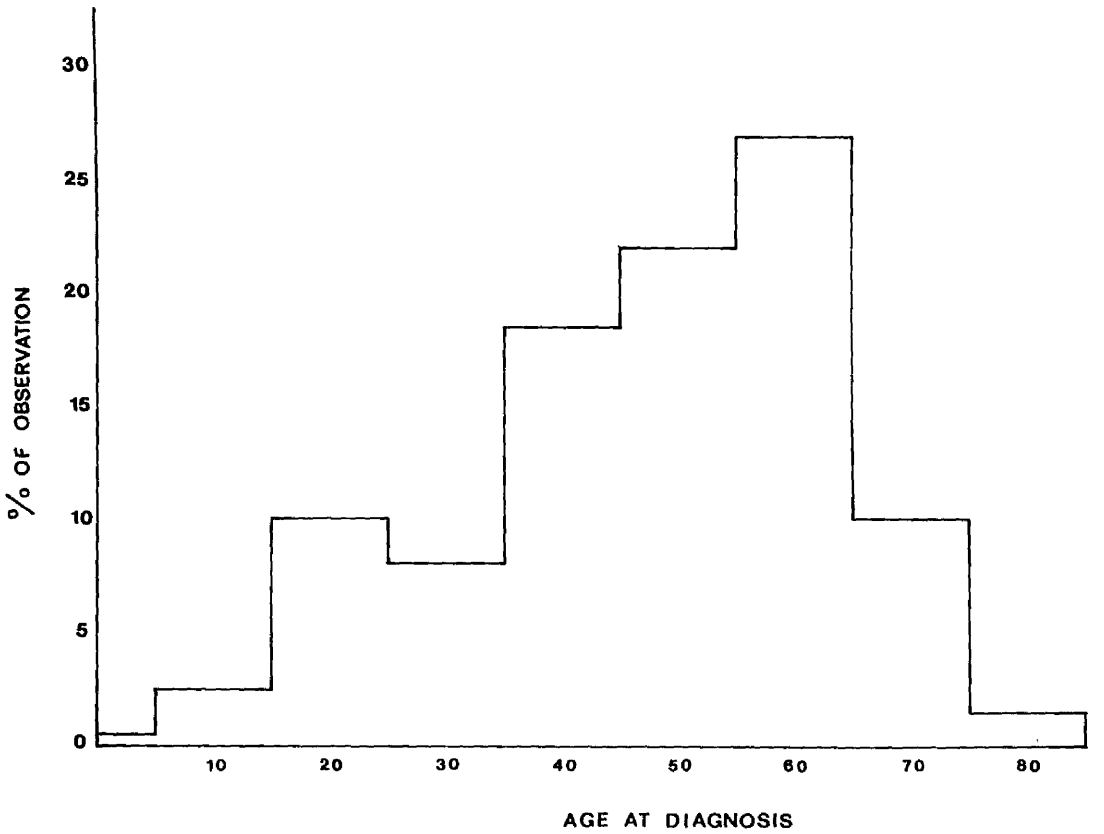

Figure 29. Distribution of age at diagnosis of diabetes in 190 diabetic males.

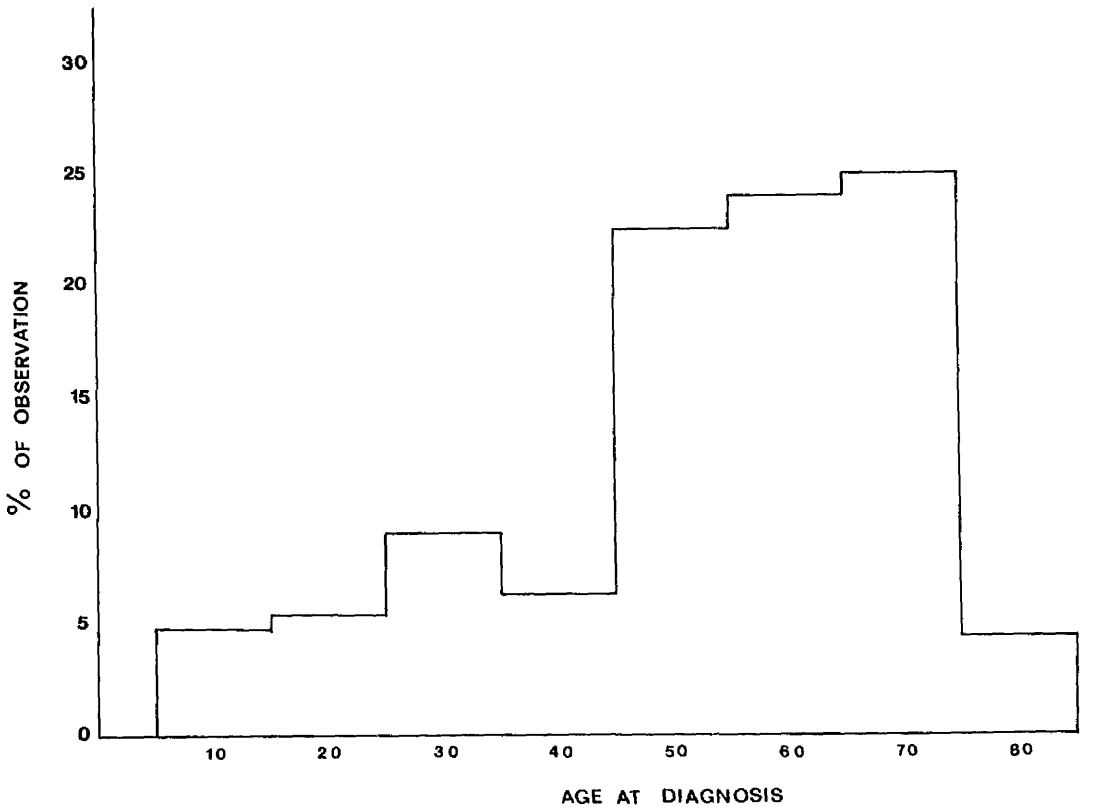

Figure 30. Distribution of age at diagnosis of diabetes in 210 diabetic females.

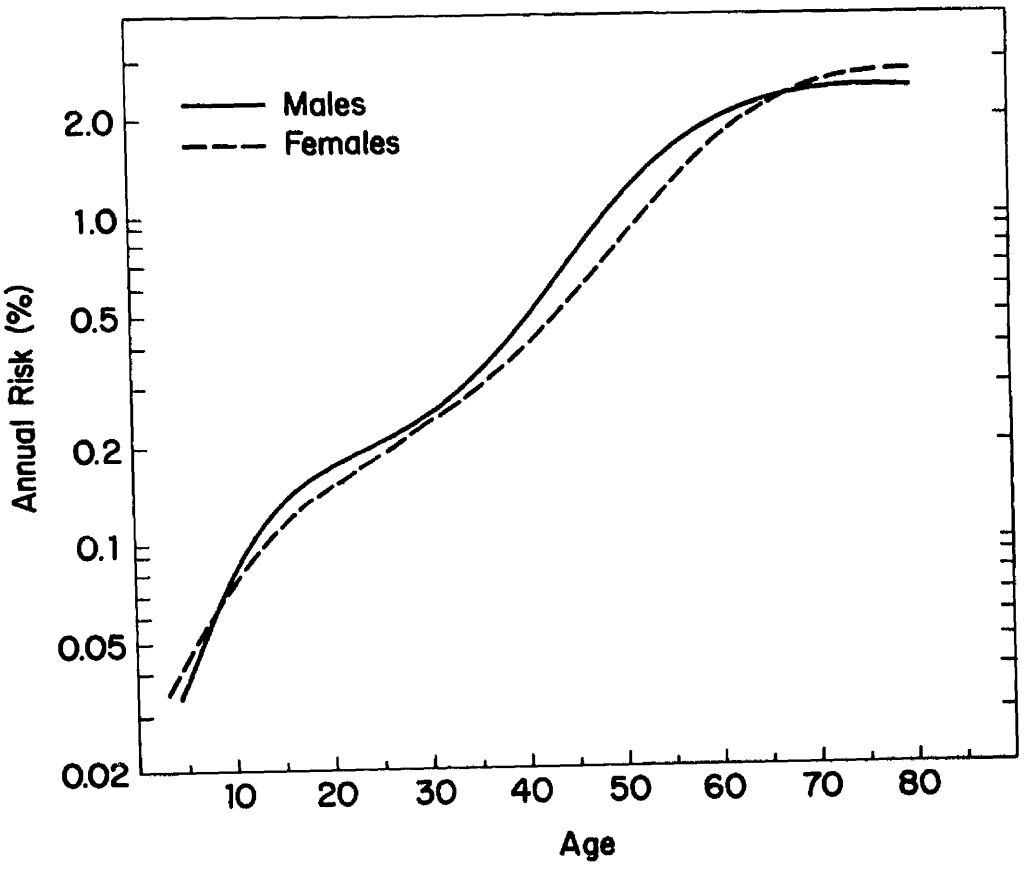

Figure 31. Increasing incidence of diagnosis of diabetes with age. From Falconer et al (1971).

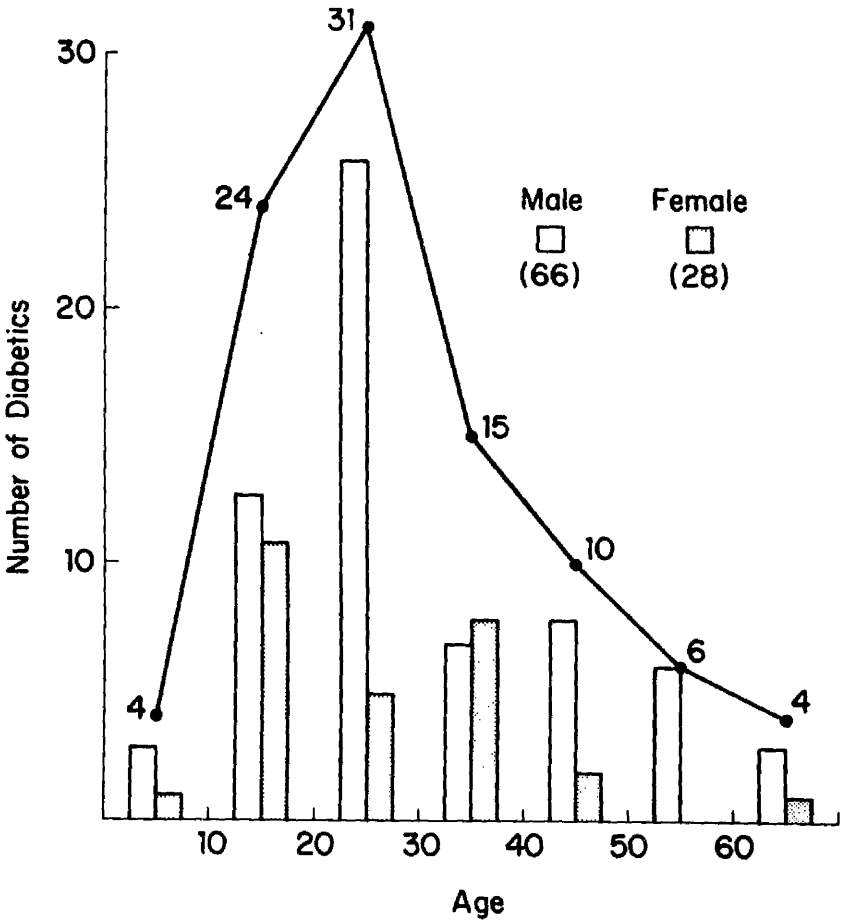

Figure 32. Age at first diagnosis of diabetes in Ethiopia. Note that diagnosis peaks in the third and fourth decades and that males are diagnosed relatively earlier than females (from Belcher 1973).

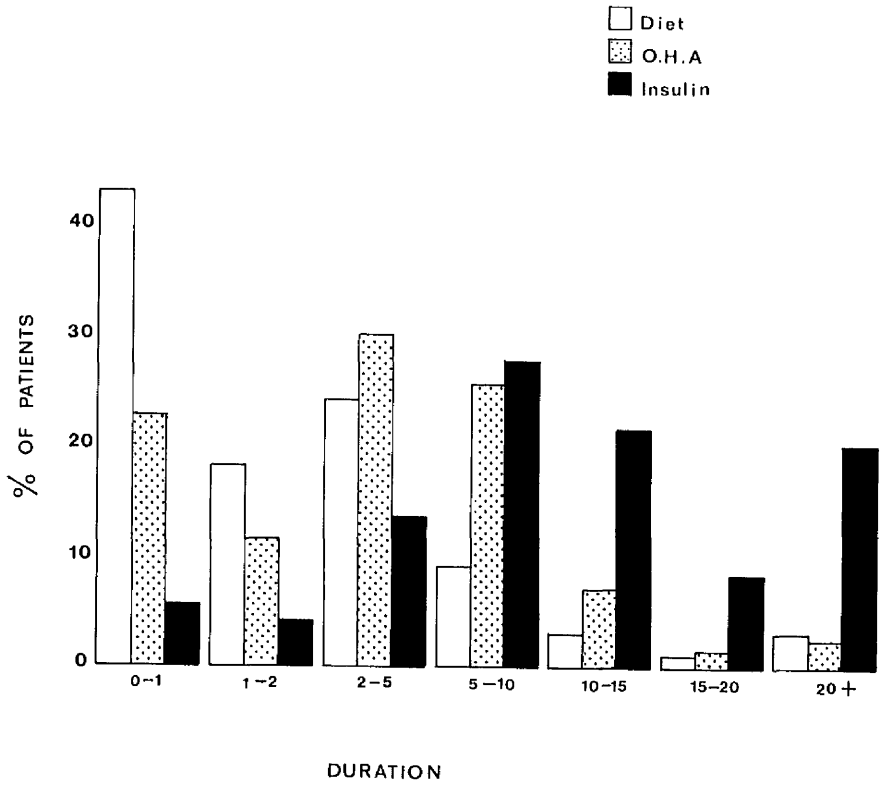

Figure 33. Relation of duration to treatment of diabetes. Number of patients in each category is listed in Appendix 8 .

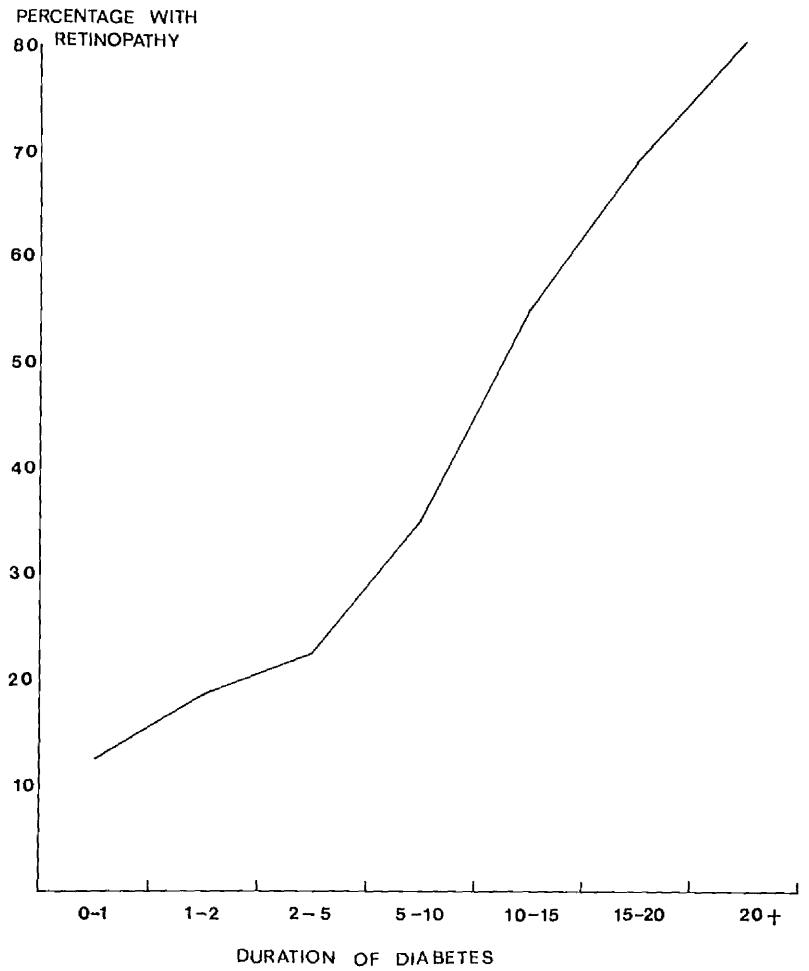

Figure 34. Shows higher prevalence of diabetic retinopathy with increasing duration of diabetes. Data from 400 patients.

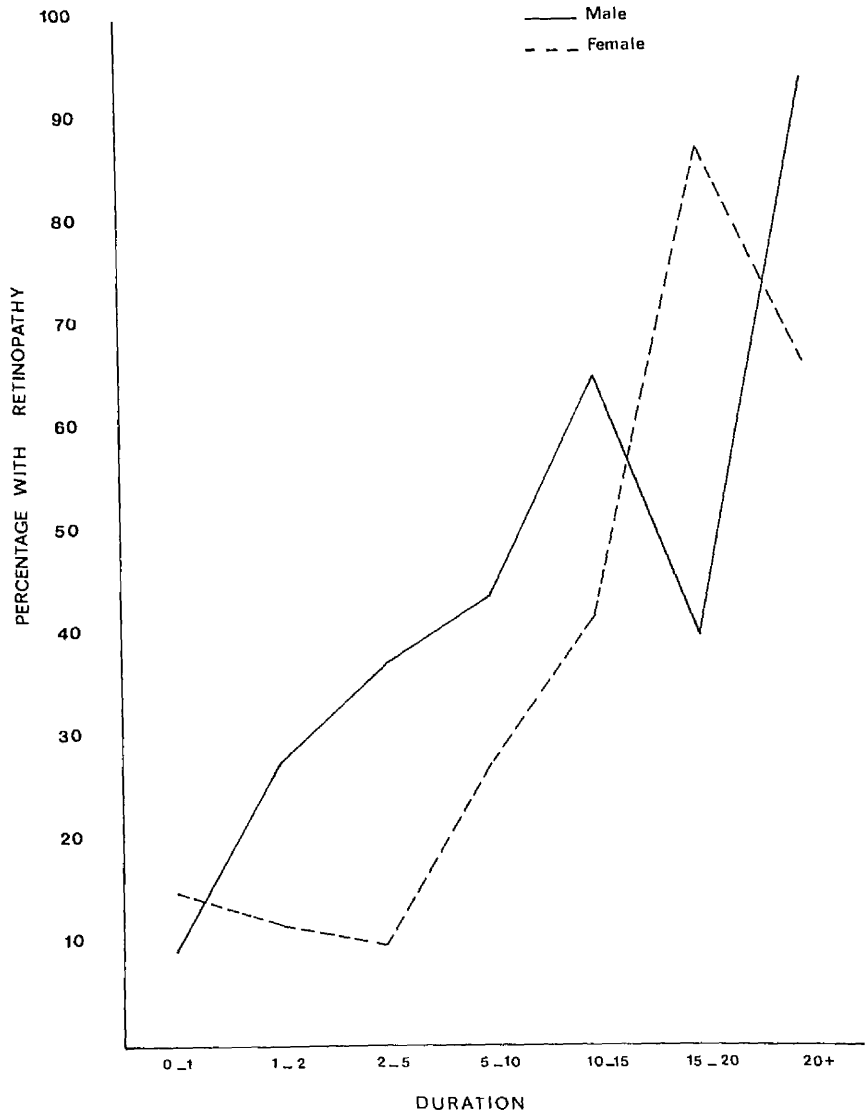

Figure 35. Males and females with diabetic retinopathy. Relation to duration of diabetes.

figures are relatively different from those found in general practice where a smaller population were IDD, Table 45.

7.3.e. Duration of diabetes and type of treatment

Diabetics on diet alone had a shorter duration of diabetes (median 1.8 years) than the NIDD on oral hypoglycaemic agents (median 3.1 years). IDD had longer duration of diabetes than did the NIDD patients (median 10 years), Figure 33. This is expected and has been reported in a previous study (Nilsson, Nilsson, and Frostberg 1967).

Non insulin dependent diabetes tends to present at a later age than does insulin dependent diabetes so that the duration of the disease in a mixed population containing both types of diabetics would be likely to show a prevalence of longer durations among the insulin dependent group. It may also be the case that increasing complication rate in longer standing diabetics might result in insulin therapy being instituted for these patients. The influence of age of onset of IDD as compared with NIDD is confirmed by a correlation of the age at examination and type of diabetes in the present data where it can be seen (Table 47) that the mean age at diagnosis of those on diet or oral hypoglycaemic agents was 61 years while insulin dependent patients had a mean age at examination of 46 years.

No patient whose age fell within the 0-20 years group was non insulin dependent while 10 per cent of subjects on insulin therapy fell within this age category. 16 per cent of insulin dependent patients were above 65 years of age and this figure is about a third and a half of those on diet or oral hypoglycaemic agents within this age bracket. This is shown in Table 48.

Age (years)	Male		Female	
	Number	Percentage	Number	Percentage
0-20	20	10.5	16	7.6
21-40	41	21.5	31	14.8
41-65	111	58.5	113	53.8
66 +	18	9.5	50	23.8
Total	190	100.0	210	100.0
Before 40	61	32	47	22
After 40	129	68	163	78

Table 44. Age at diagnosis of diabetes for both sexes. More males are diagnosed at an earlier age than females (Glasgow Royal Infirmary).

Treatment and frequency	Number of patients.		Percentage		Percentage in General Practice
Diet	101		25		35
Oral hypoglycaemic agents - once	101	173	25	43	50
- twice	72		18		
Insulin - once	58	126	15	32	15
- twice	68		17		

Table 45. Form of treatment.

Duration	Diet	O.H.	Insulin
Minimum	1 month	1 month	1 month
Maximum	40 years	28¼ years	40 years
Mean	3.5 "	5 "	12.4 "
Median	1.8 "	3.1 "	10.0 "
Standard deviation	5.7 "	5.0 "	9.3 "

Table 46. Comparison of different parameters of duration of diabetes and types of treatment. This table shows that patients on insulin tend to have longer duration of diabetes (O.H. : oral hypoglycaemic agents).

Age (years)	Diet	O.H.	Insulin
Minimum	29	29	13
Maximum	82	84	85
Mean	61	61	46
Median	62	62	48
Standard deviation	12	11	19

Table 47. Treatment related to age at examination.

Age at examination (years)	Percentage on diet	Percentage on oral hypoglycaemic agents	Percentage on insulin
0-20	0	0	10
21-40	6	4	26
41-65	54	58	48
66 +	40	37	16

Table 48. Percentages of diabetics of different age groups at time of examination on different treatment regimens.

	All Patients		Male		Female	
	No.	Percent	No.	Percent	No.	Percent
Smokers	110	27.5	63	33.2	47	22.4
Non Smokers	260	65.0	106	55.8	154	73.3
Ex Smokers	30	7.5	21	11.0	9	4.3
TOTAL	400	100.0	190	100.0	210	100.0

Table 49. Smoking habits of the 400 patient studied at Glasgow Royal Infirmary.

7.3.f. Smoking habits

The majority of patients were non smokers (65 per cent). Smoking was more prevalent among men than women, the percentages of those who smoked among men and women were 33 and 22 respectively. Table 49 depicts the smoking habits of the 400 diabetic patients.

7.3.g. Hypertension

A patient who was on antihypertensive treatment or who had high blood pressure using the same criteria as before, (Chapter 6),was considered to be hypertensive. The prevalence of hypertension is seen in Table 50. A higher percentage of females had a high blood pressure than males. Median age at time of examination and duration of diabetes of those with and without hypertension did not differ much and were as follows - 60 and 4; 59 and 5 years respectively.

Comment

Lewis and Symons (1958) defined hypertension as blood pressure of over 165/95 and reported that the prevalence of hypertension among diabetics was 36 per cent in men and 56 per cent in women and in those over 60 years of age 70 per cent of women and 50 per cent of men were hypertensive. They found no relation between duration of diabetes and hypertension. In this work I have been unable to demonstrate a relationship between the "presence" of diabetes and hypertension on one hand or between the "duration" of diabetes and hypertension on the other but, unlike Lewis and Symons (1958), have in addition failed to show any relationship between increasing age of patients and the presence of hypertension. It is difficult to define hypertension

(Beevers 1978) and there is a trend toward high blood pressure with age. It is possible, perhaps that older patients are not treated as "hypertensives" if their blood pressure is found to be relatively higher than younger people, and this might explain the failure to recognise higher rates of "hypertension" with increasing age of the patients, Table 51.

In Beever's study (1978) 20 per cent of normal subjects over the age of 65 had blood pressure of over 170/95. This is similar to the results presented in this study (19.2 per cent of diabetic patients), Table 51.

Table 52 shows that there was no increase in the frequency of hypertension with increasing duration of diabetes.

There is thus no support for the view that diabetes predisposes to systemic hypertension.

7.3.h. Prevalence of ocular abnormality among diabetics

During examination of the eye for the presence of diabetic retinopathy a note was made of any other ocular abnormality such as catarct, glaucoma, or extraocular palsy. Table 53 shows the numbers and prevalence rates of different ocular findings in all patients and in the two sexes separately. Some patients had more than one pathology in one eye. 83 patients (21 per cent) had one or a combination of the listed eye disorders. More females had lens opacities than males, 22.8 and 8.4 per cent respectively. This was probably due to the older age composition of females. Median ages of those with and without cataracts were 70 and 56 years respectively; the median duration of diabetes in those with cataract was 6.5 years and in the other group 4 years. This is shown in Table 54.

It is seen that about a fifth of all patients had ocular conditions other than diabetic retinopathy some of which, at least, could have been related to the diabetic process.

A comparison of figures of duration and age at diagnosis of diabetes from subjects with and without cataracts showed that, taken alone, the role of duration of diabetes was not significant in relation to the development of cataract ($P = 0.0655$, Mann-Whitney comparison of medians; $P = 0.0916$, two sample t - test comparison of means) but the age at diagnosis of diabetes was important. Cataract being significantly associated with a late age at diagnosis ($P = 0.0001$, both tests comparing median and mean ages).

It has been suggested (Cotlier 1981) that diabetes accelerates the development of senile catarct. The present study does not support this view; no association between duration of diabetes and prevalence of cataract being found.

Blood Pressure	All patients		Male		Female	
	No.	Percent	No.	Percent	No.	Percent
High	71	17.8	26	13.7	45	21.4
Normal	329	82.2	164	86.3	165	78.6

Table 50. Blood pressure measurements.

Age group	Number of patients studied	Number with hypertension	Percentage with hypertension
0-20	13	0	0
21-40	46	6	13.0
41-65	216	41	18.9
66 +	125	24	19.2

Table 51. Relation of age to blood pressure.

Duration (years)	No. of patients examined	Number with hypertension	Percentage with hypertension
0-1	89	21	23.6
1+-2	43	5	11.6
2+-5	93	18	19.3
5+-10	88	17	19.3
10+-15	42	6	14.3
15+-20	13	1	7.7
20+	32	3	9.4

Table 52. Relation between known duration of diabetes and hypertension.

	All Patients		Male		Female	
	No.	Percent	No.	Percent	No.	Percent
Cataract	64	16	16	8.4	48	22.8
Glaucoma	4	1	1	0.5	3	1.4
Other conditions	22	5.5	10	5.3	12	5.7

Table 53. Prevalence of some eye conditions among the 400 clinic patients.

Years	with cataract	without cataract
Median age at examination	70	56
Median age at diagnosis of diabetes	63	50
Mean age at diagnosis of diabetes	61	48
Median duration of diabetes	6.5	4.0
Mean duration of diabetes	8.6	6.6

Table 54. Different parameters from 400 diabetic patients with and without lens opacities.

	All patients	Male	Female
With retinopathy	129 (32)	76 (40)	53 (25)
Without retinopathy	271 (68)	114 (60)	157 (75)

Table 55. Prevalence of diabetic retinopathy from a series of 400 consecutive diabetics.

7.3.i. Diabetic retinopathy in the clinic

129 patients (32 per cent) had diabetic retinopathy in one or both eyes. Recently, Donovan (1978) reported a prevalence of 35.5 per cent among diabetics attending a general hospital diabetic clinic but higher rates have been found by others; 49 per cent among a diabetic clinic population and 36 per cent in a town hospital in Australia (Mitchell 1980).

Of the 129 diabetics with retinopathy 76 were males and 53 females; 40 per cent of the male and 25 per cent of female population, a difference of 15 per cent, see Table 55.

In spite of being relatively younger, with a median age of 55, a higher percentage of males had diabetic retinopathy than females whose median age was 62 years. This is probably because men had been diabetics for longer periods. The median duration of diabetes was 4.8 years in males and 4 years in females. It is known that the duration of diabetes is a more decisive factor than age at examination or age at onset of diabetes in those with retinopathy, Table 56. Bodansky and others (1982) examined 100 consecutive diabetic patients with severe retinopathy and reported a significant association between male sex and proliferative retinopathy which was also positively related to type I insulin dependent diabetes (IDD). It is well known that type I diabetes is more frequently related to early-onset which is usually associated with longer duration.

Slightly more than a fifth of the clinic population studied had only background retinopathy and 11 per cent showed what could be categorised as serious forms of retinopathy. Similar figures were found from a study of diabetic

retinopathy in general practice (Chapter 8) and are comparable to figures reported by Donovan (1978) from a study of 704 diabetic patients attending a district general hospital in England.

7.3.j. Relative frequency of different types of retinopathy

66 per cent of patients with retinopathy had simple background retinopathy. The other third had more serious types of retinopathy viz exudative, ischaemic, and proliferative. It can be seen from Table 57 that of those with diabetic retinopathy 15 per cent had proliferative retinopathy. Proliferative retinopathy also constituted 45 per cent of patients with serious retinopathy, Table 58.

The prevalence rates of all forms of diabetic retinopathy and proliferative retinopathy in some recent studies are listed in Table 59.

7.3.k. Duration of diabetes in patients with and without retinopathy

Diabetic retinopathy was seen in patients who had diabetes ranging between 1 month and 40 years. It is probable that those in whom diabetes was diagnosed only during the month prior to ophthalmoscopy had had "occult" diabetes for sometime (Anderson 1966).

When the number of patients with diabetic retinopathy in different duration categories was compared with the actual number of diabetics who fell within that category a steady increase in the prevalence of retinopathy was found; 12 per cent of those who had diabetes for one year or less showed retinopathy. This figure rose to 35 per cent after 5-10 years and to more than 80 per cent among patients with a duration of more than 20 years. This is shown in Table 60 and Figures 34 and 35.

Funduscopy	Actual number	Prevalence in the clinic
Background	85	21.2
Maculopathy	8	2.0
Ischaemic	16	4.0
Proliferative	20	5.0
Total number	129	32.2
No retinopathy	271	67.8

Table 56. Prevalence of different types of retinopathy in the clinic.

Retinopathy	Actual number of patients	Percentage among retinopathy patients
Background	85	65.9
Maculopathy	8	6.2
Ischaemic	16	12.4
Proliferative	20	15.5
Total	129	100.0

Table 57. Frequency of different types of retinopathy.

	Percentage among patients with serious retinopathy	
Exudative	18	(8)
Ischaemic	37	(16)
Proliferative	45	(20)
Total		(44)

Table 58. Relative frequency of different types of serious retinopathy among 400 diabetics. Actual numbers of patients in each category are shown in brackets.

Prevalence of retinopathy (per cent)	Prevalence of proliferative retinopathy in the clinic (per cent)	Reference
21.7	?	Lewis & Symons (1958)
35.5	4.4	Donovan (1978)
49)	7)	
)	)	Mitchell
36)	3)	(1980)
26.7	3.8	Scobie & others (1981)
32	5	This series

Table 59. A comparison of prevalence rates of diabetic retinopathy in different studies.

An almost similar pattern of increase in prevalence of retinopathy was noted in the two sexes but a higher population of men developed retinopathy within the first 5 years of diabetes. After 5 years 37 per cent of men but only 10 per cent of women had retinopathy. This is demonstrated in Table 61.

7.3.1. Comparison of duration and age at onset of diabetes in subjects with and without retinopathy

Patients with retinopathy had longer durations of diabetes than those who did not have retinopathy. Median duration was 9 and 3 years respectively in the two groups. This difference was found to be statistically significant ($P < 0.0001$, Mann-Whitney test). These figures are shown in Table 62.

Mean age at diagnosis of diabetes in those with retinopathy was 49 years and in those without retinopathy 55 years, a difference of 6 years, which was also found to be significant ($P = 0.0105$, Mann-Whitney test).

Males with retinopathy had longer duration of diabetes than males without retinopathy; median duration being 9 and 2.5 years respectively. In females those with retinopathy had duration of 10 years and those without retinopathy 3 years. These differences were statistically significant ($P < 0.001$). This relationship between duration of diabetes and prevalence of retinopathy was present in both males and females.

Males with retinopathy had a median age at onset of diabetes of 45 years while males without retinopathy had a median age of 48 years. Females with retinopathy had a median age at onset of 54 and those with no retinopathy a median age of 57 years. There was a significant relationship between the age of onset and prevalence of retinopathy

in females ($P < 0.0001$) but not in males ($P = 0.1508$).

When the mean duration of diabetes in patients with no retinopathy (4.7 years) was compared with the duration in patients with different severities of diabetic retinopathy, Table 63, significant results were obtained; no retinopathy versus background retinopathy, no retinopathy versus exudative retinopathy, no retinopathy versus ischaemic retinopathy, no retinopathy versus proliferative retinopathy ($P = 0.001$ in all cases). The mean age at onset for patients without retinopathy did not differ significantly from that of patients with any of the various types of retinopathy found ($P = 0.1$ in all instances).

It seems, therefore, that the duration of diabetes was of significant importance in relation to whether a patient would have retinopathy. There was no difference whether all patients with retinopathy were lumped together or whether males and females were compared separately. Younger onset goes with a greater tendency to develop retinopathy but this is less clear cut than the effect of duration especially in males.

7.3.m. Referrals

All patients classed as serious retinopathy were reffered to the Tennent Institute of Ophthalmology for further investigation and assessment for possible laser therapy with the exception of those patients who had already been so referred.

30 patients (7.5 per cent of the total) were referred for further assessment. In 22 (74 per cent) serious retinopathy was confirmed.

Duration of Diabetes (years)	Number of diabetics examined	Number with diabetic retinopathy	Prevalence of retinopathy in the duration category
0-1	89	11	12.3
1+-2	43	8	18.6
2+-5	93	21	22.5
5+-10	88	31	35.2
10+-15	42	23	54.7
15+-20	13	9	69.2
20+	32	26	81.2

Table 60. A steady increase of prevalence of diabetic retinopathy with increasing known duration of diabetes. Data from 400 patients.

Duration (years)	Percentage of men with retinopathy.		Percentage of women with retinopathy	
0-1	9.3	(4)	15.2	(7)
1+-2	27.7	(5)	12.0	(3)
2+-5	37.2	(16)	10.0	(5)
5+-10	43.9	(18)	27.6	(13)
10+-15	65.2	(15)	42.1	(8)
15+-20	40.0	(2)	87.5	(7)
20+	94.1	(16)	66.6	(10)
Total		(76)		(53)

Table 61. Prevalence rates of diabetic retinopathy in males and females with varying known duration of diabetes. Actual numbers are shown in brackets.

	RETINOPATHY			NO RETINOPATHY		
Years	All 129 patient	Male 76 patient	Female 53 patient	All 271 patient	Male 114 patient	Female 157 patient
Mean duration	11.6	11.5	11.7	4.7	4.3	5.1
Median duration	9.0	9.0	10.0	3.0	2.5	3.0
Mean age at onset	47	45	49	51	48	53
Median age at onset	49	46	54	55	51	57

Table 62. Comparison of mean and median durations and ages at onset of diabetes, of the two sexes, in patients with and without diabetic retinopathy.

Retinopathy		Mean duration	Median duration	Mean age at onset	Median age at onset
Background	All (85)	12.4	10.0	45	46
	Male (49)	12.0	9.0	45	44
	Female (36)	12.9	10.5	48	52
Exudative	All (8)	8.7	6	54	64
	Male (3)	14.8	14.0	43	36
	Female (5)	5	3.1	60	65
Ischaemic	All (16)	9.3	8.2	49	50
	Male (10)	8.6	8.2	48	48
	Female (6)	10.3	8.5	51	56
Proliferative	All (20)	11.1	8.8	49	60
	Male (14)	10.9	7.8	50	60
	Female (6)	11.6	9.6	46	52

Table 63. Duration and age at diagnosis of patients with varying severity of retinopathy. Numbers of patients are shown in brackets.

Patients	All	Male	Female
Number referred "	46	22	24
Did not need referral	343	160	183
Already attending	11	8	3
Total	400	190	210

Table 64. Disposal of patients.

Groups of Patients	Number of patients	Percent of referrals
Proved to be non-serious	8	26
Serious - need no treatment	11	37
Serious - need laser	11	37
Total	30	100

Table 65. Frequency and outcome of referrals.

On fluorescein angiography 8 patients failed to show any form of serious changes and were, therefore, returned to the Royal Infirmary Diabetic Clinic. Of the remaining 22 diabetics, 11 were found to have serious retinopathies which needed no treatment at the time of examination but for whom arrangements were made to be seen at regular intervals. The other 11 diabetics (37 per cent of the referrals) needed laser therapy; see Tables 64 and 65.

In 16 instances diabetics were referred for conditions other than diabetic retinopathy.

As 11 patients in the group of 400 (Table 64) had already been identified previously as having serious retinopathy and had been treated where appropriate the number of potential referrals was reduced by this amount.

In a diabetic clinic where no routine eye examination had been previously carried out one would expect a referral rate of 10 per cent of whom some 50 per cent would require laser treatment.

CHAPTER 8

PREVALENCE OF DIABETIC RETINOPATHY IN GENERAL PRACTICE

8.1. INTRODUCTION:

Many studies have been conducted in different countries to determine the prevalence of diabetic retinopathy in a given community.

The Pima Indians of Arizona have the highest rate of diabetes in the world, up to 50 per cent (Bennett, Rushford, Miller, and LeCompte, 1976). A survey of 1640 Pima Indian diabetics aged 15 years and over has shown that 18 per cent of those with a 2-hour postload plasma glucose level equal to or greater than 200 mg/100 ml (11 mmol/L) had some evidence of diabetic retinopathy. Of those with diabetic retinopathy 7 per cent were found to have proliferative or neovascular changes, the remaining having microaneurysms and/or exudates. The frequency of retinal changes was higher in those with higher glucose levels especially beyond the age of 35 years (Dorf, Ballintine, Bennett, and Miller 1976; Knowler, Bennett, Hamman, and Miller 1978).

Diabetic retinopathy ranks third, next to macular degeneration and glaucoma, as a leading cause of blindness in the United States; it is the responsible cause of blindness in 1 out of every 15 blind persons (7 per cent of the total number of the blind in the country) (NSPB 1980). At age 52-64 the prevalence of diabetic retinopathy is almost 2 per cent rising to about 3 per cent at age 65-74 years and 7 per cent at age 75-85 (Kini, Leibowitz, Colton, and others 1978; Kahn and Bradley 1975).

Racial and ethnic factors are important in the determination of the frequency in the same community. The

Population Studied	Prevalence of diabetic retinopathy and comment	Reference
Denmark	3/4 of patients who had survived 15-25 years of diabetes	Lundbaeck (1953)
Sweden	46.8%. A study of 1000 diabetics	Kornerup (1957)
Nigeria	4.6%	Osuntokun (1969)
Kristianstad, Sweden	34.3%	Nilson and others (1967)
Pima Indians	21% of those with a 2-hour postprandial glucose level of more than 200 mg/100 ml.	Dorf and others (1976)
Japan	33.9%	Kojima and others (1971)
Japan	45% (duration more than 7 years)	Seftel and Walker (1966)
Oxford, England	Diabetes of 5 or less years: 4% in those younger than 30 years 22% in those 30-59 years old 34% in those over 59 years old	Burditt and others (1968)
gypt	11.4%	Osman and others (1971)
lack South African	45% (duration more than 7 years)	Seftel and Walker (1966)

Table 66. Prevalence rates of diabetic retinopathy in some studies.

white diabetics of South Africa show a prevalence of diabetic retinopathy of 34 per cent while the prevalence for black South Africans is 45 per cent. In contrast, Nigerians show a prevalence of diabetic retinopathy of only 4.6 per cent (Osuntokun 1969). In Egypt, also in Africa, 11.4 per cent of 1140 diabetics showed signs of retinopathy, 1.7 per cent only was of the proliferative type (Osman, Seiam, and Mekkawi 1971). Low rates of diabetic retinopathy were reported in Libyans except in fat females in whom a high frequency of retinal exudates was found (Mekkawi and Aswad 1972).

Mann and Potter (1969) examining 333 Maoris of New Zealand found 9 diabetics, 4 of whom had retinopathy.

In a study of the prevalence of diabetic retinopathy in untreated Japanese diabetics it was found that in those with a fasting blood sugar higher than 170 mg/100 ml (9.4 mmol/L) and a duration of more than 5 years, 50 per cent showed evidence of retinopathy when first examined (Miki, Fukuda, Kuzuya and others 1969).

In Table 66 some prevalence rates from different studies are listed.

Although information on the prevalence of different types of diabetic retinopathy among hospital diabetic clinic patients in the West of Scotland has become available recently (Scobie, MacCuish, Barrie, and others 1981), data on the prevalence of diabetic retinopathy in the general population of this part of Scotland has not previously been available. In the study by Scobie et al (1981) it was suggested that the diabetic patients attendinng the Glasgow Royal Infirmary were representative of diabetics in general

but obviously such patients form a selected group and prevalence figures for retinopathy and its various types might well differ from those in the general population. It was thought useful to conduct a pilot study of all the diabetics in one general practice to see whether the prevalence of retinopathy and its various categories resembled or differed from the hospital based group.

8.2. MATERIALS & METHODS:

Diabetics attending a general practice clinic were examined for the prevalence of diabetic retinopathy which was subdivided into serious and nonserious subgroups as before.

The severity of diabetic retinopathy was related to measurements of random blood sugar and glycosylated haemoglobin at the time of ophthalmoscopic examination. It has been claimed recently (Schanzlin, Jay, Fritz, and others 1979) that levels of glycosylated haemoglobin are directly related to the severity of diabetic retinopathy especially in patients in whom diabetes was diagnosed before 30 years of age.

Ocular fundi were examined by direct ophthalmoscopy in a darkened room after dilating the pupil with cyclopentolate % and/or phenylephrine 10%. Visual acuities were measured sing Snellen's test chart before dilating the pupils. atients were informed of the nature of the study.

.3. RESULTS & DISCUSSION:

The 54 patients examined included 18 males and 36 females. ere was no statistically significant difference between e male : female ratio in this study and that encountered the study of diabetics of Glasgow Royal Infirmary hapter 7), P = 0.05.

8.3.a. Diabetic retinopathy

19 patients (35 per cent) showed ophthalmoscopically recognisable retinopathy. Among these were 5 males and 14 females constituting 28 and 39 per cent of males and females included in this study.

Background retinopathy

13 patients had background retinopathy, 24 per cent of the total diabetic population and 68 per cent of those with retinopathy. In no instance was it found necessary to refer any of these patients for further investigation.

Exudative retinopathy

Two patients, 10.5 per cent of subjects with retinopathy fell into this category.

Ischaemic retinopathy

In this category 3 patients were recognised, two of whom had laser treatment later.

Proliferative retinopathy

Only one patient had neovascularisation of the optic disc and he was already attending an ophthalmologist for photocoagulation.

Table 67, depicts the above figures and also the relative frequency in a diabetic population of different types of retinopathy.

8.3.b. Other ocular changes

10 patients (18.5 per cent) had ocular abnormality other than diabetic retinopathy (cataract, glaucoma, or extraocular muscle palsy), Table 68. In 6 cases the abnormality was unilateral.

Type of retinopathy	Number of patients	Percentage of the total number with retinopathy	Percentage of frequency among all diabetics frequency
Background	13	68.4	24
Exudative	2	10.5	3.7
Ischaemic	3	15.8	5.5
Proliferative	1	5.3	1.8
Total	1.9	100.0	35.0

Table 67. Prevalence of diabetic retinopathy in General Practice.

	All patients (54)	Males (18)	Females (36)
Cataract	5	2	3
Glaucoma	2	1	1
Extraocular palsy	3	0	3
Percentage of the total	18.5	16.6	19.4

Table 68. Frequency of ocular abnormalities other than diabetic retinopathy found in a study of 54 diabetic patients attending a Group Practice (Woodside Health Centre).

8.3.c. Association of systemic complications and retinopathy

Of patients with diabetic retinopathy 6 were on treatment for angina, 3 had had one or more attacks of myocardial infarction, and 7 suffered from intermittent claudication.

Although the number of patients studied was small, the frequency of occurrence of these vascular complications (Table 69) was generally higher in patients with diabetic retinopathy than those without it. Table 70 shows that the concurrent association of two or more systemic complications in patients who had diabetic retinopathy was higher than in those without it.

8.3.d. Age at examination

A comparison was made between the ages at the time of examination of patients with and without retinopathy. Table 71 depicts the different parameters of age at examination of the two groups. There was no significant difference between the mean or median ages in the two groups ($P = 0.2127$, two sample t - test comparison of means; $P = 0.6120$, Mann-Whitney comparison of medians).

8.3.e. Duration of diabetes

Median duration of diabetes of the 19 patients who had diabetic retinopathy was 10.2 years and of the 35 patients without retinopathy was 4.0 years. Mean duration of diabetes was 12.6 and 5.9 years respectively. This is shown in Table 72. As expected the effect of the duration of the diabetic illness on the presence of retinopathy was statistically significant when these figures were compared ($P = 0.0045$, t - test comparison of means; $P = 0.0011$, Mann-Whitney comparison of medians).

	Number of patients with				
	Angina	Infarction	Intermittent Claudication	Gangrene	CVA
Patients with retinopathy	6 (31.5)	3 (15.7)	7 (36.8)	0	0
Patients without retinopathy	7 (20.0)	5 (14.2)	8 (22.8)	0	2 (5.7)

Table 69. Association of systemic vascular disease in patients with and without retinopathy. Note that there are higher percentages of complications in diabetics with retinopathy than in those without diabetic retinal involvement

Number of associated complications	None	1	2	3	Total
Number of patients with retinopathy	9 (47.3)	5 (26.3)	4 (21.0)	1 (5.2)	19
Number of patients without retinopathy	19 (54.2)	10 (28.5)	6 (17.1)	0	35

Table 70. Multiplicity of systemic involvement with diabetic retinopathy.

	Patients with retinopathy (Ages in years)	without retinopathy (Ages in years)
Minimum age	45	21
Maximum	85	86
Mean	65	60
Median	67	62
Standard deviation	10	16

Table 71. Ages at examination (54 patients attending Woodside Health Centre).

	Diabetics with retinopathy (Duration in years)	without retinopathy (Duration in years)
Minimum duration	1.5	0.5
Maximum	34	22
Mean	12.6	5.9
Median	10.2	4.0
Standard deviation	8.4	5.5

Table 72. Comparison of known duration of diabetes with and without retinopathy.

	with retinopathy (Age in years)	without retinopathy (Age in years)
Minimum age	22	11
Maximum	71	83
Mean	52	55
Median	55	59
Standard deviation	13	17

Table 73. A comparison of age at diagnosis of diabetes of the two groups.

	Retinopathy group (19 patients)	No retinopathy group (35 patients)
Mean blood sugar (mmol/L)	12.0	8.86
Median blood sugar	12.4	7.60
Standard deviation	5.31	4.42
Mean HbAlc (per cent)	8.67	7.08
Median HbAlc	8.20	7.1
Standard deviation	2.86	2.56

Table 74. Values of random blood sugar and glycosylated haemoglobin from two groups of diabetics.

8.3.f. Age at diatnosis of diabetes

Table 73 depicts the ages at which the diagnosis of diabetes was first made in the two groups (those with and those without retinopathy). Differences in mean and median ages were not significant (P = 0.6031 and 0.4202 on two sample t - test and Mann-Whitney comparins means and medians respectively).

8.3.g. Degree of hyperglycaemia

Random blood sugar levels and HbA_{1c} levels in the 19 patients with retinopathy were compared with similar measurements in the 35 patients without retinopathy. Results are shown in Table 74. There were significant statistical differences between the two groups when values of random blood sugar were compared (P = 0.0355, t - test comparison of means; P = 0.0331, Mann-Whitney comparison of medians) but no significant differences were found when values of HbA_{1c} were compared (P = 0.0515, t - test comparison of means; P = 0.0572, Mann-Whitney comparison of medians).

These results were also used to determine whether measurements of levels of random blood sugar and glycosylated haemoglobin relate to the presence and severity of diabetic retinopathy. Patients were therefore divided into three groups: 1. Patients who had no retinopathy, 2. Patients with simple background retinopathy, and 3. those with "serious" retinopathy. Mean values of the two blood tests were compared, Table 75. It was found, again, that values of mean blood sugar were significantly different among the three groups. The group with no retinopathy had the lowest mean values (0.05 > P > 0.01 one way analysis of variance)

but mean values of glycosylated haemoglobin did not show significant differences between any two groups ($0.1 > p > 0.05$, one way anaylsis of variance).

The significance of these results is fully discussed in Chapter 12.

	No retinopathy	Background retinopathy	Serious retinopathy
Mean blood sugar (mmol/L)	8.86	12.98	10.33
Standard deviation	4.42	4.99	5.80
Mean HbAlc (per cent)	7.08	9.02	8.06
Standard deviation	2.56	3.30	1.99

Table 75. Mean values of random blood sugar and of glycoslated haemoglobin of patients who had no retinopathy on ophthalmoscopy, and of those who had different severity of retinopathy.

CHAPTER 9

BLINDNESS FROM DIABETIC RETINOPATHY IN THE WEST OF SCOTLAND

9.1 INTRODUCTION

One of the problems of surveys on blindness is the great variation in its definition adopted by studies from different countries. The World Health Organisation (1966) accepts 65 definitions of blindness.

In the United States, for example, a person is certified blind if the best obtainable visual acuity in the better eye is 20/200 (6/60), or less, whether or not associated with limitation of the visual field to 20° while in the United Kingdom blindness is broadly defined as a vision too poor to allow any work for which eyesight is essential and is generally accepted as a corrected visual acuity of 3/60 in the better eye and/or a field of vision of less than 10° in its widest diameter.

Causes of blindness have been studied in many countries of the world. In the Western world, however, few of the causes were found to interchange places as the leading ones. Thus glaucoma, cataract, atrophy of the optic nerve, senile degenerations of the macula, and diabetic retinopathy were always reported as the commonest blinding offenders.

Whatever the definition of blindness was, all studies on the causes of blindness have concluded that diabetes is the commonest blinding disease among all systemic disorders.

A study of the causes of legal blindness in the United States for the year 1978 (National Society to Prevent Blindness 1980) showed that glaucoma caused 12.5 per cent of the total number of new blind registrations, macular

degeneration 11.7 per cent, senile cataract 8.3 per cent, optic atrophy 7.0 per cent and diabetes 7.9 per cent. Diabetic retinopathy alone caused 6.6 per cent of all blind registrations and was, after glaucoma, the second leading cause of blindness among the 45-64 and 65-74 years old. It also was the fourth commonest cause of blindness in females but not among the first five causes in males. Its prevalence rate among the population was 4.8 per 100,000. A previous work (Kahn and Hiller 1974) estimated that about 10 per cent of new cases of blindness in the United States was due to diabetes and that this proportion was substantially higher in persons under 70 years of age. In persons 45-74 diabetes accounts for about 20 per cent. This study also suggested that American non-white women have very high rates of blindness from diabetic retinopathy and that the incidence of diabetes-related blindness in 1969-1970 based on registry data in States with reporting systems was about 1.5 cases per 100,000 per year. The prevalence rate of diabetes-related blindness among all the blind in the United States was about 2.4 per 100,000 population (Kahn and Hiller 1974) which is different from the rate reported recently (N.S.P.B. 1981).

In Canada a survey on the different epidemiological aspects of blindness is carried out annually by the Canadian National Institute for the Blind, CNIB. In the year 1979 the total number of cases registered with the Institute was 3142. Of these, 36.3 per cent were blind

from senile macular degeneration, 9.2 per cent from diabetic retinopathy, 8.1 per cent from glaucoma, 6.3 per cent from optic nerve atrophy, and 4.7 per cent from cataract. Diabetes caused 315 cases of blindness and of these 289 were blind from diabetic retinopathy alone. Diabetic retinopathy was also responsible for the highest number of registrations among the 40-49 and 50-64 years old. Some of the important causes of blindness in Canada are listed in Table 76 (CNIB 1981).

Chronic simple glaucoma, by causing 60 per cent of cases of blindness was found to be the commonest cause of blindness in Iceland (Bjornsson 1955); prevalence of diabetic retinopathy was zero per cent. In Denmark (Michaelson 1969) diabetic retinopathy accounts for 22.8 per cent of new blind registrations. It is the commonest blinding cause among adults at the age of 20-50 years (Rosenberg 1981, personal communication).

A study of 3557 adult Swedes with onset of blindness before age 60 showed that optic atrophy and retinal degeneration of genetic origin were the commonest causes, 16.1 per cent, and that diabetic retinopathy was the blinding cause in 412 instances, 11.6 per cent of the total blindness in that category of patients (Lindstedt 1969).

Damato (1960) from a study of 638 blind people of the Maltese Islands reported that myopia caused 18.6, cataract 18, glaucoma 17.2, diabetes 15.9 and trachoma 12.3 per cent of all blindness respectively. Damato also found that the majority of cases of diabetes-related blindness occurred in the age group above 50 and that diabetic blindness was 3

	No. of cases						
Age Group	SMD	DR	Glaucoma	Optic nerve atrophy	Cataract	Ret. pig.	Myopia
5 & under	3	0	0	27	8	0	2
6-15	11	0	2	39	21	12	11
16-19	2	1	1	16	2	6	2
20-29	11	38	1	22	15	21	5
30-39	11	22	3	13	4	31	2
40-49	10	29	5	6	7	23	10
50-64	62	94	34	28	9	41	25
65-80	502	95	115	36	32	10	30
81 & over	529	10	94	12	50	0	60
Totals	1,141	289	255	199	148	144	103
Incidence	36.3%	9.2%	8.1%	6.3%	4.7%	4.6%	3.3%

Table 76. Important causes of blindness in Canada. From CNIB 1981.

Cause	Prevalence
Cataract	22.2
Myopia	14.2
Senile macular degeneration	9.8
Glaucoma	9.2
External eye disease	7.4
Diabetic retinopathy	7.4
Optic atrophy	4.9

Table 77. Prevalence rates of blinding causes in England and Wales. From Sorsby (1966).

times greater in females than in males.

In Barbados diabetes is a common systemic disease although diabetic retinopathy is rarely seen among diabetics in this Island and is seldom a problem (Connell 1981, personal communication).

On the Island of Falster primary glaucoma was the most frequent cause of blindness, 29 per cent, followed by senile macular degeneration, 22 per cent. It was also noted that diabetic retinopathy and excessive myopia were among the relatively frequennt causes of blindness being represented by 10 and 9 per cent respectively (Norskov 1968).

In the United Kingdom results of many surveys have been reported, the best known of which is the comprehensive survey on the prevalence and incidence of causes of blindness in England and Wales reported by Sorsby (1966). Sorsby listed macular degeneration, cataract, glaucoma, myopia, and diabetic retinopathy as the most frequent causes in that order, see Table 77.

9.2. MATERIAL AND METHODS

The present study aims at the investigation of the common causes of blindness and visual handicap in the West of Scotland with a special reference to diabetic retinopathy. Such a survey would make possible as estimation of the number of diabetic blind persons in this part of Scotland and the approximate number of diabetics who could probably be saved through the application of the current preventative measures for example photocoagulation. It would also be of benefit in making recommendations as to the cost effectiveness of screening programmes for the detection of diabetes and diabetic retinopathy in the West of Scotland.

Blind registration is not compulsory in Britain. However a person registered blind is eligible for special services and certain opportunities offered through such organisations as the Society for the Blind in Glasgow and the West of Scotland like the availability of talking books and other teaching materials, the supply of guide dogs, free transport and certain tax exemptions.

In Scotland a special form, Form BP1, is completed by an Ophthalmologist to certify a person as blind or partially sighted , see Appendix 10.

Completed forms BP1 are returned to a central office in Edinburgh but a copy of all forms completed for persons resident in the West of Scotland goes to the Society for the Blind in Glasgow.

Forms BP1 held by the Society for the Blind in Glasgow and the West of Scotland were studied. These forms relate to people from the whole Strathclyde region. This area corresponds to that covered, before government reorganisation by the Area Health Boards of Greater Glasgow, Argyll and Clyde, Ayrshire and Arran, and Lanarkshire.

A total of 2118 forms were personally studied by the author. This number was composed of people who were registered with the Society as blind or partially sighted as shown in Table 78.

It is unfortunate that only 141 forms from the year 1960 were available for analysis. 619 forms of the total number of 760 registrations had earlier been destroyed or lost. However, the data studied are likely to be representative of all registrations because the forms were not selected by any specific criteria. Analysis of the available information also showed some expected results such

as the male:female ratio which gives some confirmation of the unselective destruction of forms.

The study is mainly concerned with the analysis of the 141 forms of 1960 and 772 forms of the year ended 31st December 1980. The other forms, which relate to the year 1970 and part of 1981, were studied in less detail, principally to see if the number of people registering with the Society every year was changing. Parameters were, however, similar to those reported for the year 1980.

Of the 772 forms completed till the end of the year 1980, 125 forms, 16 per cent, had to be excluded from further analysis because of lack of essential information. Some forms contained nothing other than the name of the Ophthalmologist and the person's name. It is believed that these exclusions do not invalidate the findings; all the rejected forms came from one general Ophthalmologist in an area with no apparent abnormal incidence of causes of blindness so that no particular cause should have been differentially excluded from the study.

Computer input was prepared , Appendix 10a,from the 788 141 of the year 1960 and 647 of 1980) forms, summarising the most important available data from the BPIs. The factors considered were the age and sex of the person, the visual acuity and visual field for each eye and the primary and secondary blinding cause in each eye. Two different ages for the same person were considered, the age at registration as visually handicapped and the age at onset of the visual impairment, i.e. the age at which the person first became severely visually handicapped. The data were analysed on the Edinburgh Regional Computer ICL 2980 using some of the standard data handling

Year	Number registered with the Society
1960	760
1970	786
1980	772
1981 (first 6 months)	419

Table 78. Number of visually handicapped people registered with the Society for the Blind in Glasgow and the West of Scotland.

Causes	All registered (141 persons, 282 eyes) No. of eyes.	Percent	Legally blind (81 persons, 162 eyes) No. of eyes.	Percent
Cataract	71	25.1	36	22.2
Myopia	45	15.9	23	14.2
Senile macular degeneration	25	8.8	16	9.8
External eye disease	19	6.7	12	7.4
Glaucoma	19	6.7	15	9.2
Diabetic retinopathy	17	6.0	11	6.8
Optic nerve atrophy	15	5.3	8	4.9
Uveitis	10	3.5	4	2.5

Table 79. Causes of visual handicap. The year 1960.

facilities of the MINITAB programme package.

In the analysis a distinction is drawn between the "registered" blind who are all those for whom a BP1 Form has been completed, and the "legally" blind who are those whose vision satisfied the United Kingdom criteria of legal blindness. Patients were also divided into the following age groups 0-4, 5-19, 20-44, 45-64, 65-74, 75-84, and 85 and over. This age grouping has been used in a previous study (NSPB 1980).

People who had visual handicap due to cerebrovascular accidents were also excluded from the category of "legal" blind but were included among the "all registered" because some Ophthalmologists had completed Forms BP1 for them classing them as "partially" sighted.

Additional information about the prevalence and causes of blindness in a number of overseas countries was obtained in response to a letter sent to Blind Societies, Welfare Authorities etc. as indicated in the introduction to Chapter 6. This information was used in making comparisons with the West of Scotland.

9.3. RESULTS AND DISCUSSION

9.3.a. The Year 1960

Among the 141 Forms studied there were 56 males, 40 per cent, and 85 females, 60 per cent; a male:female ratio of 1:1.5. Their ages at the time of registration with the Society ranged between 1 and 99 years with a median age of 72 years.

The highest incidence of registration occurred in age group 45-64, 34.7 per cent, followed by the 65-74 years old group, 27.6 per cent, and the lowest incidence of registration was among the 0-4 and the over 85, one case in each

Secondary cause	Per cent
No cause	42.9
Cataract	12.4
Myopia	6.7
Senile macular degeneration	5.7
Optic nerve atrophy	5.0

Table 80. Contributory causes of blindness. The year 1960.

Cause	No. of eyes.	Percent.
Congenital cataract	11	28.9
External eye disease	6	15.8
Optic atrophy	4	10.5
Congenital abnormality of the eye	4	10.5
Uveitis	3	7.9

Table 81. Important blinding causes among the 0-4 years old.

Cause	No. of eyes	Percent
Optic atrophy	8	44
Congenital cataract	6	33
Glaucoma	2	11
External eye disease	2	11

Table 82. Frequency of blinding causes among the 5-19 years old.

Cause	No. of eyes	Percent
Myopia	17	36.9
Cataract	10	21.7
External eye disease	4	8.7
Diabetic retinopathy	2	4.3
Glaucoma	2	4.3
Retinal detachment	2	4.3
Uveitis	2	4.3
Retinitis pigmentosa	2	4.3

Table 83. Causes of blindness among the 20-24 years old.

Cause	No. of eyes.	Percent
Cataract	16	57.1
Senile macular degeneration	8	28.6
Glaucoma	2	7.1
Myopia	2	7.1

Table 86. Causes of blindness among the 75-84 years old.

Patient	Age at onset	Sex
1	31	Male
2	45	Male
3	49	Female
4	50	Female
5	53	Female
6	62	Female
7	66	Female
8	70	Female
9	71	Female
10	72	Female
11	73	Female

Table 87. Age and sex distribution of the individual diabetics.

Cause	No. of eyes	Percent
Cataract	16	17.4
Myopia	16	17.4
Diabetic retinopathy	8	8.7
External eye disease	8	8.7
Glaucoma	7	7.6
Senile macular degeneration	7	7.6

Table 84. Causes of blindness among the 45-64 years old.

Cause	No. of eyes	Percent
Cataract	28	42.4
Senile macular degeneration	10	15.1
Diabetic retinopathy	7	10.6
Glaucoma	6	9.1

Table 85. Causes of blindness among the 65-74 years old.

category, but there were 19 cases in which the "onset" of blindness had occurred before 5 years of age, 13.5 per cent. Figure 36 (p. 237 seq) shows a histogram of the numbers of persons at onset of blindness and at registration for different age groups.

81 persons were legally blind, 57 per cent, and of these 32 were males and 49 females; again a male:female ratio of 1:1.5.

Analysis of the more common causes of blindness, all registered and legally blind, is presented in Table 79 which shows that, by far the commonest cause of visual handicap was cataract accounting for a quarter of the total number of all registered and more than a fifth of the legally blind. It was also the commonest secondary cause when other causes were the primary ones, see Table 80.

Blindness among different age groups

Age group 0-4 (38 eyes)

Nineteen people, 13.5 per cent, were found to have had their "onset" of blindness during this period of life; Table 81 shows the number and percentage of eyes blinded at this period by different causes.

Age group 5-19 (18 eyes)

Table 82 shows that only 9 people were registered at this age group in the sample studied and that optic atrophy was the leading cause of visual disability.

Age group 20-44 (46 eyes)

Myopia, cataract, and external eye disease lead the causes of legal blindness in this age group constituting 15.9, 21.7, and 8.7 per cent respectively, Table 83.

Age group 45-64 (92 eyes)

Cataract and myopia share the first place in this age group causing blindness in 16 eyes each. Diabetic retinopathy makes its first appearance as a major cause of blindness here forming 8.7 per cent of blind eyes, Table 84.

Age group 65-74 (66 eyes)

Once again cataract was the major cause of blindness in this age group.

Age group 85 years and over

Only one BP1 was found for this age. The person was blinded by corneal opacity in the right eye and by cataract in the left.

Diabetics 1960

Of the 141 people there were 11 diabetics, 7.8 per cent and of these 9 were females and 2 males; a male:female ratio of 1:5. They ranged in age between 31 and 78 years with a median age of 62 years. The two males were 31 and 45 years old.

The highest incidence of blindness in diabetics, whether by age at registration or at onset was among age 45-64.

Of the 11 diabetics registered with the Society, 6 (2 males and 4 females) had become visually handicapped before age 65. The other 5 were 66 to 73 years old and all were females. Table 87 shows the age at onset of visual impairment and sex of the diabetics in this sample.

Six of these diabetics, 1 male and 5 female, were legally blind and constitute 7.4 per cent of the legally blind in the whole sample. Diabetic retinopathy was the

Patient	Age at onset	Sex
1	31	Male
2	50	Female
3	53	Female
4	70	Female
5	71	Female
6	73	Female

Table 88. Age at onset of the legally blind diabetics. 1960.

Age (years)	All registered	Legally blind
Minimum	0	0
Maximum	93	93
Mean	64.5	65.5
Median	71.0	71.0
Standard deviation	22.8	21.9

Table 89. Age at onset parameters of blind persons registered during the year 1980.

aetiological factor of their blindness. The youngest was a 31 year old male and the oldest a 73 year old female. Sex and ages at onset of blindness of these six diabetics are shown in Table 88.

9.3.b. The year 1980

As discussed earlier, 773 people were registered with the Society during this year but only 647 forms, 84 per cent, were studied in detail because the others were so deficient in information.

The 647 comprised 253 males and 394 females; 357, 55 per cent, were legally blind and of this number 138 were males and 219 females. In either case the male:female ratio was 1:1.5 which is the same ratio found among people registered during the year 1960. Their ages at the onset of blindness ranged from birth to 93 years with a median age of 71 years. The oldest of the registered blind was 98, Table 89.

The age distribution of blindness among the legally blind is illustrated in Figure 37 (p. 237 seq). The histograms of age at registration and age at onset are similar but with the data for age at registration shifted a little to greater age. This is because registration usually occurs some time later than the onset of blindness. In fact the median time between onset and registration is one year. Some 64 per cent of registrations were made within two years of onset of blindness but there is a long tail in the distribution of times and a few registrations were actually made more than twenty years after the person became blind.

The peak incidence of onset of blindness can be seen in Figure 37 (p. 237 seq) to occur in the 65-74 years age group with 31 per cent of the legally blind falling within this bracket. Because of the delay noted above the peak in age at registration occurs later at 75-84 years and accounts for 32 per cent of the registrations.

When the data for age at onset are split to compare the ages of males with those of females, Figure 38, it is found that the highest incidence of onset for males is between 65 and 74 years of age while for females it is in the 75-84 years age group. However when the data are corrected for age on an actuarial basis using the mid-1980 population estimates for Strathclyde Region (Registrar General, Scotland 1981) the results show that, as expected, blindness becomes increasingly common with advancing age; the incidence rises sharply around 60 years of age. Figure 37 shows up another interesting point. Among the young, there were no registrations of children of up to four years of age, yet there were 23 instances of registration of those who had suffered the onset of blindness in this age range. Among the 23 legally blind children in this age group there were 19 males and 4 females.

BLINDNESS AMONG DIFFERENT AGE GROUPS

Data on the incidence of various primary blinding causes is presented in Figure 39 (p. 237 seq). The results are expressed in terms of the number of eyes blinded by a particular cause. A total of 1294 eyes of the registered blind including 714 eyes of the legally blind are considered. Some 10 per cent of blind people were found to have differing primary cause in their two eyes, but these conditions cover

the whole spectrum. Thus, the percentage affected by a particular cause is sufficiently nearly the same for the discussion below, whether eyes or people are considered. Figure 39 shows the overall incidence of blinding causes both for the registered blind and the legally blind. The pattern is the same for both categories. It is clear that senile macular degeneration, by causing legal blindness in 213 eyes, about 30 per cent, is by far the most common single cause of blindness in this sample. The other common causes in order of frequency, were: Glaucoma 104 eyes, 14.6 per cent; cataract 74 eyes, 10.4 per cent; diabetic retinopathy 61 eyes, 8.5 per cent; myopic degenerations 43 eyes, 6.0 per cent; and optic nerve atrophy 32 eyes, 4.5 per cent. Table 90 summarises the leading causes of legal blindness for all age groups and individual groups. It can be seen that optic nerve atrophy stands as the primary blinding cause for both age groups 0-4 and 5-19 years, while blindness from diabetic retinopathy and its complications heads the list in the age group 45-64 years, and senile degeneration of the macula constitutes the leading cause of blindness in all those above 65 years of age. It can also be seen that non-congenital glaucoma makes its first appearance as an important blinding cause in the age group 20-44 years and reaches its peak at 65-74 years, 20.5 per cent.

Sex variation

Table 91 shows the sex variation of incidence of the

common causes of blindness. It is noted that senility-related causes are more prominent in females than in males therefore senile macular degeneration caused around 35 per cent out of the legal blindness among females while it contributed to 22.5 per cent of blindness in males; and cataract furnished 13.2 per cent of cases in females while it constituted only 5.8 per cent in males; diabetic retinopathy does not appear at all among the five leading causes of legal blindness in males while it ranks third among females. There was also a sex variation in the incidence of glaucoma which forms about 20 per cent and 11.2 per cent in males and females respectively.

Diabetics 1980

Of the 647 individuals studied 59, 9.1 per cent, were diabetics; 13 males and 46 females. At the time of registration the oldest was an 83 year old female and the youngest a 20 year old male who had his onset of blindness at age 5 caused by optic atrophy. The youngest female to be registered was 21, Table 92.

Among the 357 legally blind people 32, 8.9 per cent, were diabetics; 5 males and 27 females, a ratio of 1:5 which is comparable to the male:female ratio of the year 1960. Their ages at the onset of blindness ranged from 21 to 83 with a median of 65 years. In Appendix 9 are listed the ages at registration and at onset, by sex, of the 32 legally blind diabetics. Table 93 compared the age at registration and at onset of blindness in diabetics and other blind persons with different primary blinding causes.

	Overall Total	No. of Eyes	Percent
1.	Sen. Mac. Deg.	213	29.8
2.	Glaucoma	104	14.6
3.	Cataract	74	10.4
4.	Diab. Ret.	61	8.5
5.	Myopic Deg.	43	6.0
6.	Optic Atrophy	32	4.5
7.	Corneal Opacity	20	2.8
	All Others	167	23.4
		714	100.0
	Under 5 years of age		
1.	Optic Atrophy	14	30.3
2.	Corneal and Other Postnatal Infections	12	26.1
3.	Prenatal Cataract	8	17.4
4.	Cong. glaucoma, microphthalmos	8	17.4
5.	Tumour	2	4.4
	All Others	2	4.4
		46	100.0
	Age Group 5-19		
1.	Ret. Pigmentosa	6	42.8
2.	Optic Atrophy - Cong.	2	14.3
3.	Myopia	2	14.3
4.	Injury	2	14.3
5.	Cong. Microphthal. Toxoplasmosis	2	14.3
		14	100.0
	Age Group 20-44		
.	Diab. Ret.	6	20.0
.	Myopia	6	20.0
.	Optic Atrophy	6	20.0
.	Uveitis	3	10.0
.	Glaucoma	2	6.7
	All Others	7	23.3
		30	100.0
	Age Group 45-64		
1.	Diab. Ret.	22	18.6
2.	Sen. Mac. Deg.	17	14.4
3.	Glaucoma	15	12.7
4.	Myopic Deg.	10	8.5
5.	Optic Atrophy	10	8.5
	All Others	44	37.3
		118	100.0
	Age Group 65-74		
1.	Sen. Mac. Deg.	56	26.2
2.	Glaucoma	44	20.5
3.	Cataract	24	11.2
4.	Diab. Ret.	19	8.9
5.	Myopia	10	4.7
	All Others	61	28.5
		214	100.0
	Age Group 75-84		
1.	Sen. Mac. Deg.	103	47.7
2.	Glaucoma	35	16.2
3.	Cataract	19	8.8
4.	Diab. Ret.	14	6.5
5.	Myopic Deg.	10	4.6
	All Others	35	16.2
		216	100.0
	85 years of age and over		
1.	Sen. Mac. Deg.	37	48.6
2.	Cataract	23	30.3
3.	Glaucoma	6	7.9
4.	Myopic Deg.	4	5.3
	All Others	6	7.9
		76	100.0
	65 years of age and over		
1.	Sen. Mac. Deg.	196	38.7
2.	Glaucoma	85	16.8
3.	Cataract	63	12.5
4.	Diab. Ret.	33	6.5
5.	Myopia	25	4.9
	All Others	104	20.6
		506	100.0

Table 90. Common causes of legal blindness in the West of Scotland. 1980.

	MALES	EYES	%		FEMALES	EYES	%
1.	Senile Macular Degeneration	62	22.5	1.	Senile Macular Degeneration	151	34.5
2.	Glaucoma	55	19.9	2.	Cataract	58	13.2
3.	Optic Nerve Atrophy	24	8.7	3.	Diabetic Retinopathy	51	11.6
4.	Cataract	16	5.8	4.	Glaucoma	49	11.2
5.	Myopic Degeneration	11	4.0	5.	Myopic Degeneration	32	7.3
	All other	108	39.1		All other	97	22.2
	Total	276	100.0		Total	438	100.0

Table 91. First five common causes of legal blindness in male and female. 1980.

	Age at registration	Age at onset of blindness
Minimum	21	21
Maximum	83	83
Mean	64.9	63.4
Median	67.5	65.0
Standard deviation	14.2	14.4

Table 92. Age parameters of blind diabetics, 1980.

Blinding cause	Median age at registration	Median age at onset
Diabetic retinopathy	67.5	65
Cataract	78	76
Optic atrophy	44	32
Glaucoma	76	72
All except diabetic retinopathy	76	72

Table 93. Median ages at onset and at registration of persons blinded by different causes, 1980.

COUNTRY	1ST CAUSE	2ND CAUSE	3RD CAUSE	4TH CAUSE	5TH CAUSE
Scotland	Senile Macular Degeneration	Glaucoma	Cataract	Diabetic Retinopathy	Myopia
England and Wales	Senile Macular Degeneration	Cataract	Glaucoma	Myopia	Diabetic Retinopathy
U.S.A.	Glaucoma	Senile Macular Degeneration	Cataract	Optic Nerve Atrophy	Diabetic Retinopathy
Canada	Senile Macular Degeneration	Diabetic Retinopathy	Glaucoma	Optic Nerve Atrophy	Cataract
Sweden	Tapetoretinal Degeneration of Genetic Origin	Diabetic Retinopathy	Optic Nerve Atrophy	Uveitis	Myopia
India	Cataract	Glaucoma	Staphyloma	Optic Nerve Atrophy	Anophthalmos

Table 94. Causes of blindness and visual handicap in some countries.

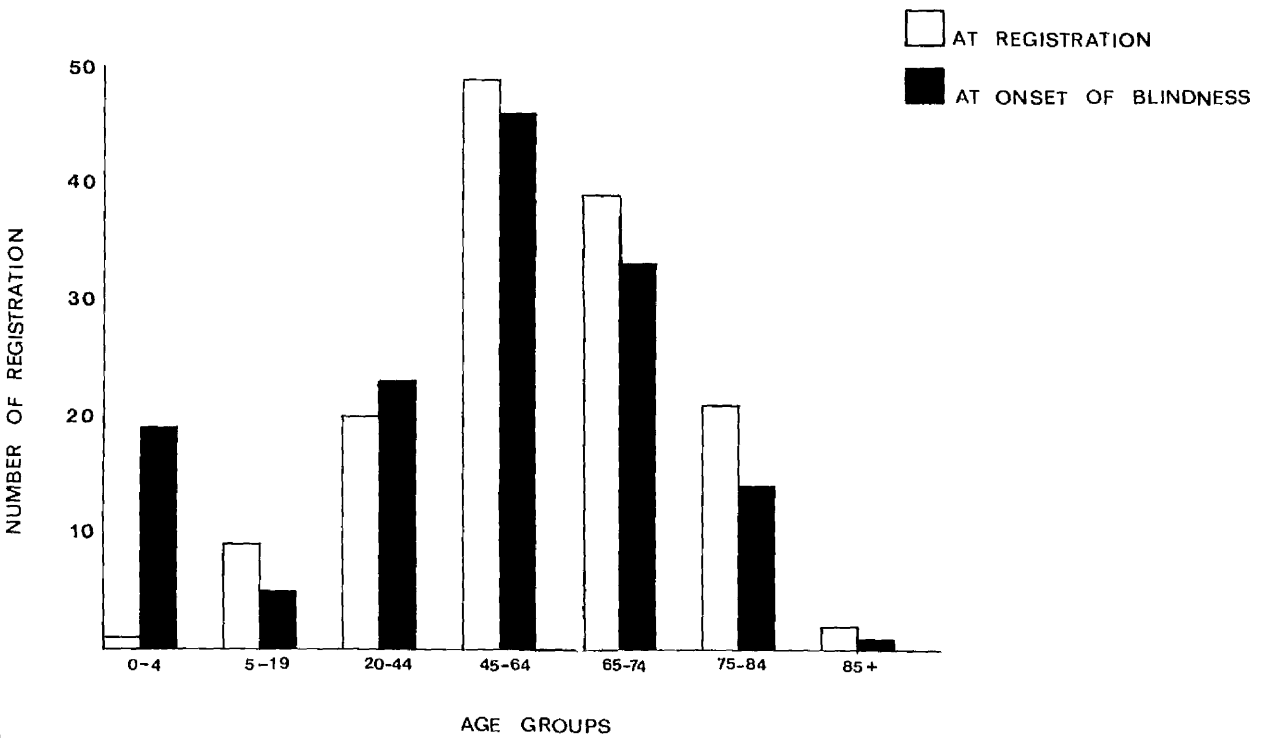

Figure 36. Age at registration and at onset of some people registered as visually handicapped in the year 1960.

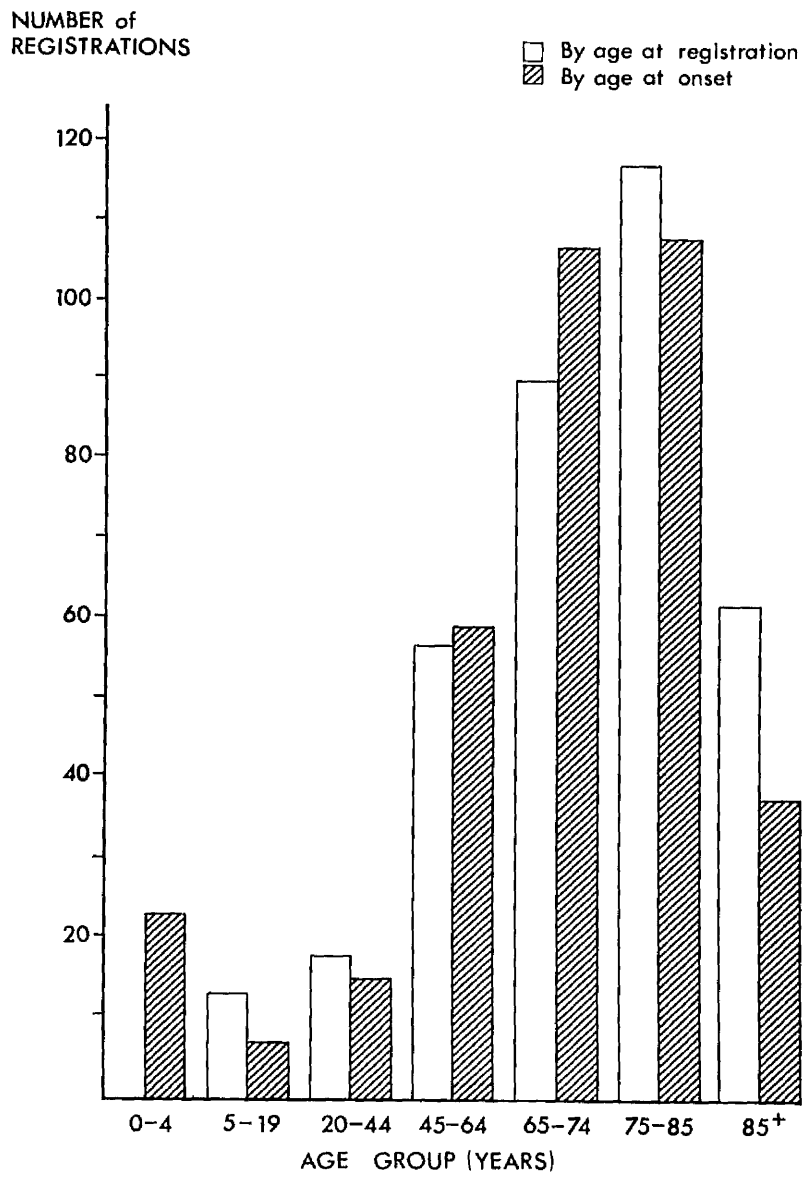

Figure 37. Age distribution, at onset and at registration, of legally blind persons registered with the Society of the Blind in the year 1980.

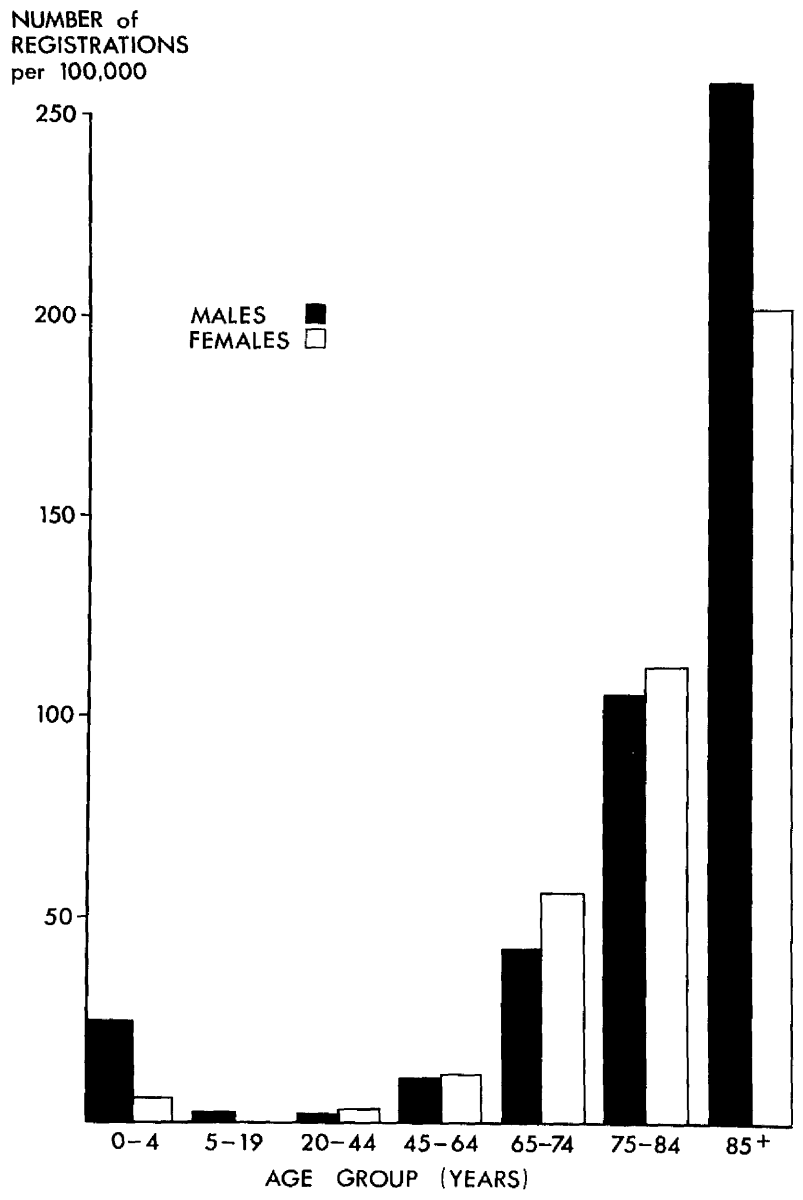

Figure 38. Age at onset of blindness in males and females, 1980.

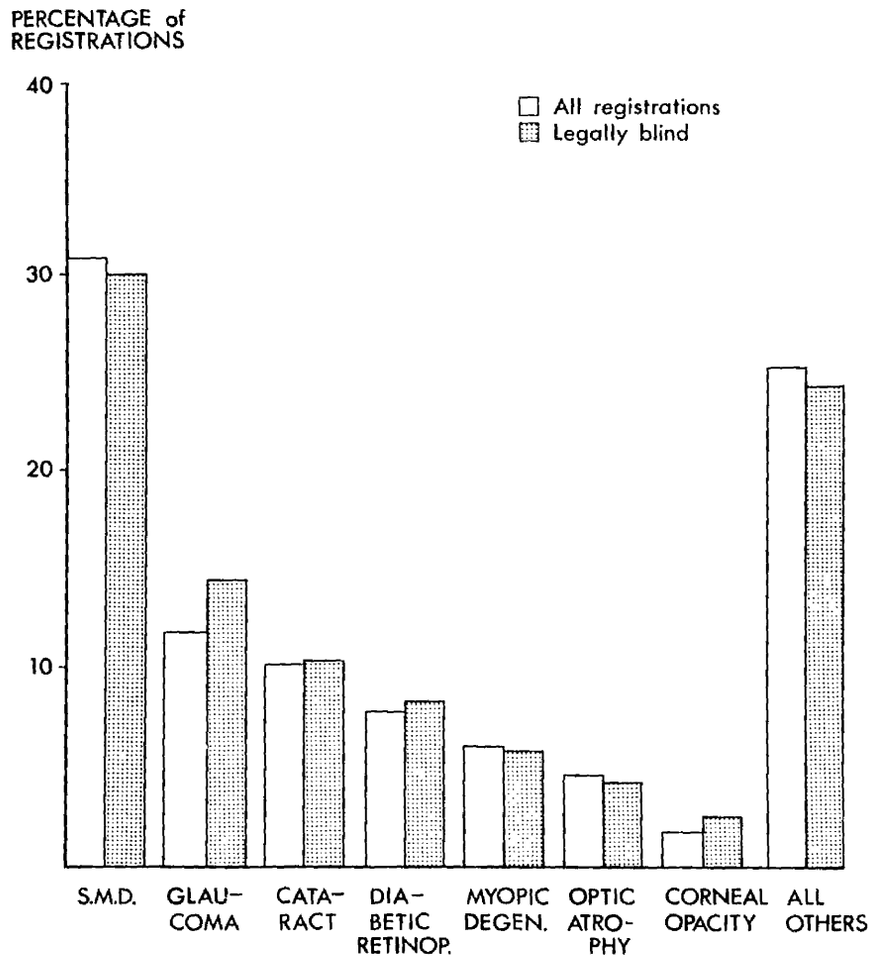

Figure 39. Leading causes of blindness among the legally blind persons (1980). No one cause of 'all others' contributes to more than 2.5 per cent of registrations.

It is clear that diabetics tend to be registered with the Society and certified as blind much earlier than other people blinded by other causes. They also have the onset of blindness about 7 years earlier than the rest. These differences of age at onset and at registration were found to be statistically significant ($P < 0.001$).

Of the 64 eyes affected by diabetes 61, 95.3 per cent, were blinded by retinopathy and its complications, 2 eyes by cataract and one eye by glaucoma and in these 3 eyes diabetic retinopathy was a contributory cause.

Among the 59 diabetics, registered with the Society 20, 5 males and 15 females, were less than 65 years old.

26 individuals, 44 per cent of visually handicapped diabetics, which included 6 males and 20 females, were registered with the Society after age 64 but they all had had the onset of blindness before this age. So about one half of the diabetics registered became legally blind while still within working age. In the year 1960, 6 out of 11, also about one half, were blinded by diabetic retiopathy.

Comment

The B P 1 registration forms are handled by only a few staff of the Society for the Blind in Glasgow and the West of Scotland thus ensuring precise recording and filing. Unfortunately an administrative decision was made to destroy all forms for registration prior to 1964. Fortunately the destruction of forms relating to 1960 was incomplete. This made interpretation of the available data

from the rest of the forms a rather uneasy task; caution is necessary in the process of concluding and commenting on the findings. However, most of the BP1 Forms for the year 1980 were available for analysis. The shortage of information in some of the BP1's might be due to a possible lack of interest, time, or evaluation on the part of the treating Ophthalmologist. Completing a BP1 Form and certifying a person as blind or partially sighted is a responsibility for which an Ophthalmologist is usually paid in England but not in Scotland! On the other hand some people might not be quite aware of the existance of such institutions as the Society for the Blind and would therefore not ask their treating Physician to put them on the blind register; this might be especially true if they happened to attend an Ophthalmologist who was reluctant to certify and label a patient as blind for social or other reasons as might happen with infants.

However, a few facts could be drawn from the present study. The number of people registering with the Society every year range between 700 and 800 of whom about 60 per cent are females. This might generally be due to longer longevity of females, a matter which is also indicated by the higher rate of age-related blinding causes such as senile macular degeneration and cataract among women. The same predominance of females among the blind has also been reported from other countries (Damato 1960; NSPB 1980). In the United States for example, after age 65, females exceed males at an increasing rate until among those age 85 and over there are 2 blind females for every blind male.

This predominance of females is noticed whether the whole group or the legally blind only are studied.

The figure for the frequency of blindness due to senile degeneration of the macula in the year 1960, about 30 per cent, is comparable to its incidence in England and Wales reported by Sorsby (1966), about 27 per cent.

It seems rather bizarre that more than 10 per cent of individuals registered with the Society in 1980 were blind from cataract since this condition is entirely treatable. Possible explanations for this would include long waiting operation lists, refusal of surgery, or general health being such as to prevent surgery. It is however encouraging that the finding shows an improvement since the time of Sorsby's survey (1966) when 23 per cent of registrations were due to cataract, Table 94, and from 1960 in this study when slightly less than a quarter of the registrations were due to this condition. In England and Wales the prevalence of cataract had also declined significantly over the last two decades (Sorsby 1972). Still, when the figures for cataract and glaucoma, 10.4 and 14.6 per cent, are added together it is found that a quarter of the current number of visually handicapped could be reduced since these conditions are treatable and preventable respectively.

The incidence of external eye diseases which included blinding conjunctival, corneal, and other ophthalmic infections has dropped sharply since 1960 and this drop, as might be expected is due to improvement of hygienic standards and preventive measures and improved therapy. It is possible that the increasing popularity of corneal grafting had contributed to this decline.

In both years studied it was interesting to note that retinitis pigmentosa, in spite of the relatively small number of cases involved was a major cause of blindness among the young and appeared, if at all, only low in the ranking for all other age groups. Retinitis pigmentosa is also a common cause of visual handicap in other countries especially among the young (CNIB 1981; Lindstedt 1969). See Appendix 11 for an overall comparison of the different major blinding causes in the two years 1960 and 1980.

The absence of registration for those in the 0-4 age group in both 1960 and 1980 might reflect a reluctance by Ophthalmologists to label an infant as blind from a very young age, and the rather difficult task of accurately assessing the visual acuity in this age category. Gross under-reporting of blind infants has also been recognised in the United States (NSPB 1980).

The incidence of diabetic retinopathy has not been found to have increased much. In Sorsby's survey (1966) diabetic retinopathy caused 7.1 per cent of blindness and there has been no clear evidence of any substantial increase in blindness from diabetic retinopathy in recent years (Sorsby 1972). These are somewhat similar figures for the years 1960 and 1980, 6.8 and 8.5 respectively. Kahn and Hiller (1974) reported that it was widely believed that in America blindness from diabetic retinopathy had been increasing in recent years, but they found little evidence to support this belief. However, diabetic retinopathy was found to be the fourth leading cause of blindness in the sample studied, the commonest in the 45-64 years age group and the third major cause among females although not among the first five causes among males.

The calculated prevalence of blindness from all causes in the general population is 19 per 100,000 while the calculated prevalence of blindness from diabetic retinopathy alone is 12 per 100,000 (Caird et al 1969). In the present series diabetics constituted about 9 per cent of all the legally blind and this is almost 9 times the prevalence of diabetes in the Community (Chapter 6) and is another confirmation that diabetes is the commonest systemic blinding disorder among all age groups especially the elderly (McWilliam 1975).

Finally, below is a calculation of the higher risk of blindness among diabetics compared to blindness from all other causes:

2,418,819 : Population of the West of Scotland - Mid 1980 (Registrar General 1981)

357 : Legally blind registered with the Society during 1980

32 : Legally blind from diabetic retinopathy 1980

325 : Legally blind from all other causes 1980

325/2418819 = 13.4 persons per 100,000 became legally blind every year from all causes

1 per cent : Prevalence of diabetes in the community chapter 6

24188 : Number of diabetics in the West of Scotland Mid 1980

32/24188 = 132 per 100,000 diabetics become legally blind from retinopathy every year

132/13.4 = 9.8

Diabetics are hence 9.8 times more susceptible to blindness from diabetic retinopathy than the rest of non-diabetic population from all other causes of blindness.

CHAPTER 10

PHOTOCOAGULATION IN THE TREATMENT OF DIABETIC RETINOPATHY

10.1. INTRODUCTION AND HISTORY

Photocoagulation is now the most commonly used procedure for the treatment of moderate and advanced forms of diabetic retinopathy (Dobree 1974).

With increasing experience the indications, limitations, and techniques have become well established and photocoagulators are now available in most of the well-equipped ophthalmic centres. Photocoagulation is more commonly used than pituitary ablation which carries serious risks to life and is therefore reserved for very few cases of advanced "florid" retinopathy especially in the young (Pyke 1976). It also has wider indications than vitrectomy, a procedure which is used only in the treatment of advanced cases of proliferative diabetic retinopathy especially those associated with unresolving vitreous haemorrhage and fibrosis (Machemer 1974).

Ocular photocoagulation was originally employed clinically in the spring of 1949 by Gerd Meyer-Schwickerath (L'Esperance and James 1981) although observations on the effect of light on coloured objects were described by Benjamin Franklin in the 18th century and the effect of unrays on the retina more precisely noted by Czerny in 1865 Raymond 1977).

The xenon arc photocoagulator was the first instrument be used for the treatment of retinal disease and reports its histopathological effects and advantages appeared re than two decades ago (Meyer-Schwickerath 1959).

The laser (Light Amplification by Stimulated Emission of Radiation) action was discovered in 1960 (Maiman 1960). A laser using a synthetic ruby crystal (chromium in corundum), was the first laser to be used for clinical purposes (Editorial, British Journal of Ophthalmology 1979), and since then many monochromatic systems became available (Thyagarajan and Ghatak 1981).

The argon laser (Zweng, Little, and Peabody 1971) gained more popularity due to its wavelength, 488 and 514.5 nm, which allowed direct photocoatulation of blood vessels since a large proportion of its energy is absorbed by blood. In addition was the relative ease with which it could be applied through a slit-lamp delivery system.

Krypton lasers with longer wavelengths (641 nm) became available later on. They possess greater penetration characteristics and are especially used in patients with mild and moderate vitreous haemorrhages (Schulenburg, Hamilton, and Blach 1979) because of the lack of absorption by blood thus avoiding the risk of accidental retinal blood vessel closure. This could, at the same time be a disadvantage since 85 per cent of the energy incident on the retinal pigment epithelium can pass into the choroid and cause undesirable damage.

0.2. BIOPHYSICS

In the xenon photocoagulator a xenon arc bulb is pulsed with current to cause a flash of white and infra red light. Xenon-arc radiation produces a more wide spread coagulation

and can be advantageous in seriously affected diabetic retinae. It is, however, limited as to the production of extremely small spot size, and the beam can be more highly absorbed by the ocular media due to the wide spectrum of wavelengths that have to pass through the cornea, lens, and vitreous.

The ruby laser delivers a 200 μ sec pulse of extremely intense red radiation which can be useful in performing retinal photocoagulation when multiple haemorrhages are present in the retina and when considerable retinal oedema is present but this instrument became obsolete with the introduction of the argon laser.

In the argon laser photocoagulator a laser tube is filled with argon gas at a precise pressure level; when current in the form of electrons passes across the tube, the argon molecules emit a blue/green light. This is collected by mirrors at either end of the tube and delivered to a slit-lamp through a fibre optic cable or an alternative optical system. A narrow laser beam is thus delivered to the eye. This creates a round burn on the retina, generally referred to as a burn or spot.

The effect of photocoagulation is produced entirely by the conversion of light energy to heat energy in absorbent substances (L'Esperance 1965).

The absorption bands of blood lie at approximately 430 μ and 500 to 600 mμ. Normally, blood pigments absorb approximately 10 per cent of the light incident on the

human cornea. In the eye, however, the amount of light absorbed by any stratum depends markedly upon the spectral distribution of the light incident on the cornea. The thermal effects of light absorption by the human eye are determined primarily by the energy-density gradient within a given stratum. The density gradient depends mainly upon 2 factors, the spectral quality of the light incident upon the cornea and the uniformity and density of pigmentation within a given layer (Geeraets, Williams, Ghan, and others 1962). The pigment epithelium or the choroid may absorb or scatter separately more energy than do the entire ocular media but absorption of energy by the pigment epithelium plays the primary if not the entire role in the production of mild burns; this is because of the concentration of pigment within a very thin layer, approximately 10 u in man. For equal energy absorption in pigment epithelium and choroid, the influence of pigment epithelium as the source of burn would be predominant because of the energy concentration within this very thin layer compared with the thicker choroid, approximately 100-200 μ in man. Absorption of radiant energy in pigment epithelium may, however, be greater than in the choroid or vice versa depending on the individual. Geeraets and co-workers (1962) found that in White individuals the pigment epithelium may absorb more energy than the choroid while in darker people, because the choroid was more densly pigmented than the pigment epithelium, much more energy was absorbed in the choroid. Retinal lesions from patients with blue irises were found to require considerably higher dose rates than comparable lesions in individuals with brown

irises (Tso, Wallow, and Elgin 1977). Geeraets and co-workers (1962) also found that energy absorption in the retinal pigment epithelium is the most important factor leading to the development of mild, so called "threshold" burns. High light energies can affect other structures and may easily rupture a retinal vessel by the destructive effect of heat generated in the pigment epithelium, by rapid expansion of the blood column or by coagulation and necrosis of the vessel wall from a direct, focused laser impact (L'Esperance 1965).

There are variations within the same eye as well as from eye to eye in both the distribution of granules and the concentration of pigment within granules. This variation and irregularity of pigment and granule distribution is pronounced in the pigment epithelium and in the choroid. The effect of this variation in both structures becomes more pronounced as the area of irradiation on the fundus is decreased. There is more energy density in a given area from a small laser spot, for example 50 or 100 micron, than in a larger spot if the power setting is equal (Constable and Lim 1981).

0.3. HISTOPATHOLOGY

The effect of photocoagulation on the structure of the retina and choroid depends ultimately on the amount of energy incident on these structures (Wallow and Davis 1979) thus the size of the spot, its duration, and intensity determine the histopathological appearance of the lesion produced.

Tso, Wallow, and Elgin (1977) correlated 4 grades of clinical and pathological lesions 1-2 days after application of xenon arc and argon laser spots. In grade 0 no lesion was seen on ophthalmoscopy and no change was noted on serial sections studied by light microscopy. Eyes with grade 1 burns showed a faint grayish-white disc on ophthalmoscopy; serial sections showed that the lesions were essentially confined to the choriocapillaris and retinal pigment epithelium. Occasional capillaries of the choriocapillaris occluded by thrombi and the retinal pigment epithelium cells were swollen with irregular displacement of melanin granules. In some of the lesions, some nuclei of photoreceptor cells were pyknotic but most of the nuclei of photoreceptor cells and all the internal layers of the retina were spared. Grade 2 lesions consisted of a grayish-white ring around a more dense whitish centre. Histologically the choriocapillaris was frequently occluded with thrombi; the pigment epithelial cells showed pyknotic nuclei, granular cytoplasm, and irregular arrangement of the pigment granules. Cytoplasmic vacuoles in the pigment epithelial cells were also seen. The photoreceptor outer and inner segments were necrotic, densly stained and shrunken with irregular outline. These burns also affected the external limiting membrane and macrophages laden with pigment granules clustered round the damaged photoreceptor cells. Most of the nuclei in the outer nuclear layers were pyknotic. The blood vessels in the nerve fibre layer overlying these lesions appeared intact. The damage in the retinal pigment epithelium extended beyond the area of necrosis of the outer nuclear layer.

Clinically the outer diameter of the grayish-white ring corresponded to the damage in the pigment epithelium while the diameter of the inner whitish centre corresponded to the damage in the outer nuclear layer. On ophthalmoscopy grade 3 lesions appeared to have 2 distinct grayish rings surrounding a white centre. The two rings corresponded to the necrosis of the outer nuclear layer and of the pigment epithelium respectively, while the white centre represented the damaged inner retinal layers. Light microscopy showed damage in the choriocapillaris, retinal pigment epithelium, outer nucleaur and inner layers of the retina. The choriocapillaris was occluded by thrombi. The cytoplasm and nuclei of the pigment epithelium and photoreceptor cells were necrotic, homogeneous and poorly stained although their outline appeared well preserved. The outer plexiform layer was vacuolated and the nuclei of the inner nuclear layers and of the ganglion cells in the nerve fibre layer were shrunken and pyknotic. The pigment epithelial cells in the periphery of the lesion were grossly vacuolated with dispersion of the pigment granules. Also in the periphery of the lesion the photoreceptor cells were pyknotic and their outline was grossly disrupted (Tso, Wallow, and Elgin 1977).

At a later stage photocoagulation burns acquire a black pigmented centre arranged as a ring or as a solid core and the centre of the burn is usually surrounded by a hypopigmented peripheral zone. This appearance is common to both xenon and argon laser burns although, due to the larger

size of the xenon burn, the area damaged by a single spot is wider (Wallow, and Davis 1979). Scar tissue formation in the full thickness burn is provided by proliferated retinal pigment epithelium and glial cells and numerous pigment-laden macrophages are also contained within the scar tissue. Wallow and Davis (1979) found that in all lesions, whether argon or xenon of long or short duration, Bruch's membrane remained a continuous structure but others (Gass 1972) listed rupture of Bruch's membrane as a possible complication of photocoagulation.

Lesions caused by lasers of different wavelengths show the same pattern of retinal damage especially with increasing intensity of the applied burn (Wieder, Pomerantzeff, and Schneider 1981). All burns caused by high intensity laser application showed damage to the inner as well as the receptor cell layers of the retina.

10.4. INDICATIONS AND TECHNIQUES

Photocoagulation with either the xenon coagulator or the argon laser is used in the treatment of both proliferative diabetic retinopathy and diabetic maculopathy.

The indications and techniques have been more clearly established for cases of proliferative diabetic retinopathy than for those with maculopathy.

It has long been recognised that diabetic patients' eyes with chorioretinal scars from old uveitis appeared to be protected from developing retinopathy. Random photocoagulation was used in the late 1950's in an attempt to influence the prognosis of established diabetic retinopathy of various types (Meyer-Schwickerath 1957; Wetzig and Arlton 1963).

Initially photocoagulation was directed at the various abnormalities present; microaneurysms, new vessels, areas of retinitis proliferans etc. Later it became apparent that photocoagulation might influence some lesions indirectly in particular that disc new vessels might regress following extensive photocoagulation applied to the peripheral fundus (panretinal coagulation). Indirect photocoagulation is thought to reduce the formation of the vasoproliferative factor by destroying hypoxic retina (see Chapter 4). Focal treatment of leaking capillaries or aneurysms may have a place in the management of diabetic maculopathy while in proliferative retinopathy focal treatment of new vessels has been replaced by indirect panretinal photocoagulation.

Since the introduction of photocoagulation into clinical use a large number of studies have been carried out to establish the indications, techniques, contra-indications, and complications of photocoagulation in the treatment of diabetic retinopathy and also to compare the efficacy and complications of the two most widely used photocoagulators namely the xenon arc and argon laser (Wetzig and Worlton 1963; Irvine and Norton 1971; Gass 1972; Ticho and Patz 1973; Kaback and Tanenbaum 1974; Rubenstein and Myska 1974; Cheng 1975; Little, Zweng, Jack, and Vassiliadis 1976; Dunnheim and Lullwitz 1977; Francois and Cambie 1977; Townsend, Bailey, and Kohner 1979; Blach 1980; Meyer-Schwickerath and Fried 1981; Plumb, Swan, Chignell, and Shilling 1982).

To establish the usefulness of a given therapeutic procedure it is necessary to conduct controlled randomised trials. In Ophthalmology this means treating one eye and leaving the other eye, of the same patient, without treatment

to serve as a control if the two eyes were similar or almost similar. Less satisfactorily one may treat one eye of a certain patient and compare the outcome of the treatment with an untreated eye of another patient provided that similar base line criteria in the two patients exist, for example initial visual acuity, age, level of control of diabetes etc.

10.4.a. Photocoagulation in proliferative diabetic retinopathy.

Focal photocoagulation

In the early years of the last decade focal photocoagulation of new vessels was the standard procedure. Many authors, however, failed to show any significance in visual acuity between treated and untreated eyes. In addition there was high risk of haemorrhage from treated new blood vessels. This was true whether xenon arc or argon laser was used.

Irvine and Norton (1971) followed up for three years patients whose disc vessels were directly treated and reported cases of identical regression of exudates and new vessels in the treated and untreated eyes. After direct xenon photocoagulation of proliferating vessels in 42 eyes Wetzig and Worlton (1963) found that vessels projecting into the vitreous continued to be active while flat retinitis proliferans could be completely obliterated. However, others (Zweng, Little, and Peabody 1971; Guinan 1967) reported more favourable results using direct photocoagulation to aneurysms and new vessels of the retina. Zetterstrom (1980) reported on 73 patients who were treated with the xenon arc photo-coagulator and followed up for 9 to 11 years; she noted that severe visual loss occured in 4 and 25 per cent of treated and untreated eyes respectively; only one patient had severe visual

loss in the treated group while 18 untreated eyes had severe visual loss. Of 15 untreated eyes with background retinopathy for which focal treatment was given to areas thought to be potentially subject to neovascularisation 2 had new vessels 9 to 11 years later; on the other hand of 15 untreated eyes 11 showed neovascularisation after the same period of follow-up (Zetterstrom 1980).

Little, Zweng, Jack, and Vassiliadis (1976) examined 4 techniques using the argon laser in the treatment of disc new vessels: (1) focal photocoagulation of new vessels on the disc and found that 65 per cent of their patients developed a decrease of visual acuity together with ischaemic papillitis and optic nerve pallor, (2) photocoagulation of the feeder vessel (arteriole) to the neovascular complex. This method caused deterioration of visual acuity in 46 per cent of the individuals and was hence abandoned, (3) feeder frond photocoagulation with panretinal photocoagulation; this procedure allowed for maintenance of visual acuity in 77 per cent of the treated eyes, and finally (4) panretinal photocoagulation alone, which gave the best results and was thus recommended as a preliminary procedure in the treatment of advanced ischaemic and moderate and severe proliferative diabetic retinopathy (Little, Zweng, Jack and Vassiliadis 1976; Dunnheim and Lullwitz 1977).

Focal photocoagulation may however still be indicated for certain cases of diabetic retinopathy (L'Esperance and James 1981); (1) as an adjunct to panretinal photocoagulation when this technique has failed to obliterate or reduce vitreo-retinal neovascularisation, (2) it can be employed in some cases of patchy neovascularisation less than 1 disc diameter in extent on the surface of the retina from which bleeding has

occured, particularly if the rest of the retinal structure appears to be intact. Neovascularisation extending from the retina or the optic nerve into the vitreous should be treated initially by panretinal photocoagulation and not by photocoagulation.

Panretinal photocoagulation

Multicentre randomised controlled studies on the use of xenon arc photocoagulation in the treatment of proliferative diabetic retinopathy were carried out in Britain in the 1970's (Multicentre Controlled Study 1977; Cheng 1979). The visual acuity was used as a measure of the outcome of the trial. In most of the centres which participated in the study the policy was to apply scatter photocoagulation in addition to focal treatment of areas of new blood vessel proliferation. 100 diabetic patients were followed up for 1 year, 58 for 2 years, and 23 for 3 years. Results of the study showed that the mean visual acuity was better in treated eyes than in untreated eyes 1, 2, and 3 years after the start of the treatment. The visual acuities of both treated and untreated eyes tended to deteriorate, but the deterioration was less marked among treated eyes and at 3 years the treated eyes had significantly better acuity than untreated eyes. There was no difference between treated and untreated eyes in those with neovascularisation at the disc, but more untreated developed new vessels at the disc later on than did treated eyes. The trial also showed that of the hundred patients followed up for year, 18 became blind among whom 13 had had no photocoagulation. Finally the study emphasised the need for early diagnosis of serious types of diabetic retinopathy.

One of the largest studies on proliferative diabetic retinopathy so far is that which started in the United States in 1971 and in which more than 1700 diabetic patients were randomly assigned to either a treatment or to a no treatment group; those in the treatment group were again assigned to either an argon laser or xenon arc therapy (Diabetic Retinopathy Study 1976, 1978). Treated eyes received extensive scatter photocoagulation plus focal photocoagulation of new vessels. Results of the study were in favour of treating cases of early proliferation at the disc and elsewhere but failed to show any indication for treating severe background retinopathy without evidence of proliferation. The cumulative incidence rate for a drop in visual acuity to 5/200 in two years was 15.9 per cent in untreated eyes but only 6.4 per cent in treated eyes; in three years the rates were 26.4 and 10.5 per cent among the two groups respectively. One year after inclusion in the study 78 per cent of eyes in the treatment group and 50 per cent of untreated eyes, initially without new vessels, remained free of neovascularisation. Only 7.5 per cent of treated eyes showed evidence of neovascularisation after one year, while 24 per cent of all untreated eyes developed new blood vessels one year after they were included in the study. In this study the visual results after argon laser treatment were better than with xenon coagulation. Xenon burns tend to be larger in size and full thickness and not confined to the outer retinal layers and pigment epithelium as is the case with properly applied argon laser burns.

A recent report of the study (Diabetic Retinopathy Study 1979) suggested that four conditions increase the 2-year risk of developing severe visual loss, which was defined by the DRS as a visual acuity less than 5/200 at 2 or more consecutively completed follow up visits scheduled at 4-month intervals; these factors are (1) presence of vitreous or preretinal haemorrhage, (2) presence of new vessels, (3) location of new vessels on or near the optic disc, and (4) severity of new vessels. The risk of visual loss grows progressively as more risk factors are added.

Like the British study, the need for close supervision of patients with advanced changes without vascular proliferation was stressed.

In panretinal photocoagulation the number of burns which it is recommended should be used varies but a minimum of 500 xenon burns or 2,000 argon laser burns size 500 u have been suggested (Davies, O'Connell, Murray, and Winter 1979). For a successful photocoagulation the treatment should be aggressive (Foulds 1978). Davies and co workers (1979) also suggested that peripheral application of the burns is less likely to cause visual discomfort or choroidal oedema with accompanying transient myopia.

In panretinal photocoagulation a topical anaesthetic is instilled and a contact lens is inserted. It has been recommended that retinal ablation procedure is conducted in -4 sessions approximately 2-7 days apart (L'Esperance and ames 1981). In xenon arc photocoagulation a retrobulbar naesthetic is administered. In laser photocoatulation sually small coagulations 100-200 u in diameter are laced around the disc; above, below, and nasally, but

avoiding the area temporal to the disc where the papillo-macular nerve bundle converges towards the optic nerve. Blood vessels are avoided as much as possible. This part of the procedure uses the central part of the Goldman 3-mirror contact lens. Peripheral coagulations of larger spot size, 500-1000 μ, are applied to the whole peripheral retina as far forward as possible using the mirrors of the contact lens (Figures 40 and 41).

During the course of this study the author personally used argon laser panretinal coagulation in the treatment of approximately 250 cases of proliferative diabetic retinopathy. A minimum of 2,500 burns of 500 μ size and of 0.2 sec duration at between 0.2-0.5 Watts were applied up to a maximum of 6,000 burns of similar duration and intensity. The treatment was given in 3-5 treatment sessions usually 1 week apart. In the majority of cases 2,500 burns were used and usually resulted in satisfactory regression of new blood vessels. Patients were seen again 6 weeks after the last treatment session. Further laser treatment was given if there was evidence of fresh neovascularisation or if there was a failure of the previous new vessels to regress satisfactorily. The additional laser treatment used in these cases was applied between the areas of earlier photocoagulation. In the initial therapy a space of approximately 2/3 of a burn size was left between burns.

Only a few cases of maculopathy were treated as another worker in the Tennent Institute of Ophthalmology was engaged in a study of laser photocoagulation on diabetic maculopathy.

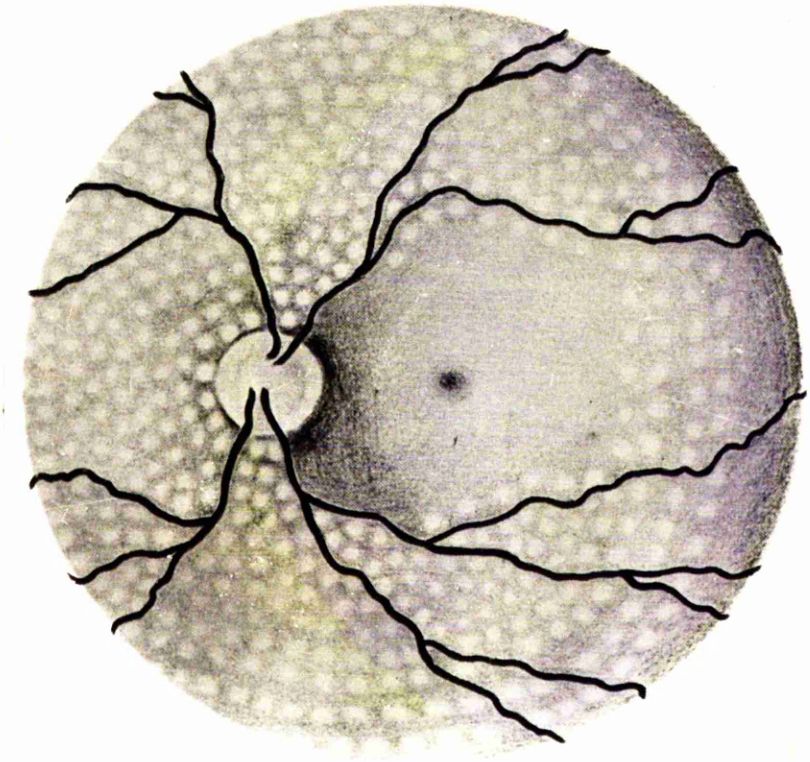

Figure 40. Pattern of panretinal photocoagulation treatment of proliferative diabetic retinopathy (from L'Esperance and James 1981).

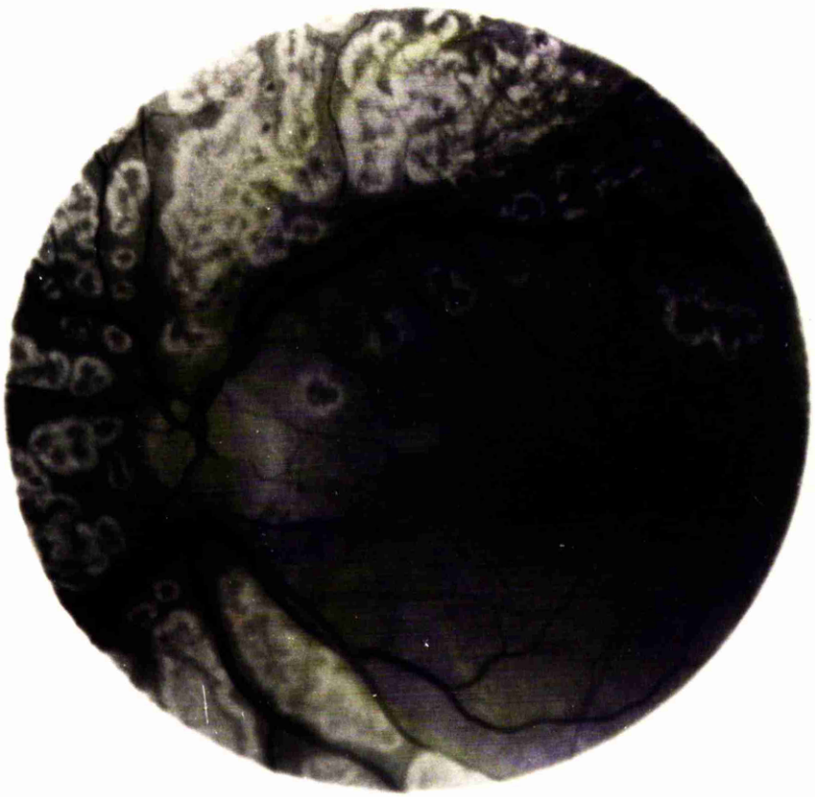

Figure 41. Fundus photograph. Pattern of panretinal photocoagulation treatment of proliferative diabetic retinopathy.

10.4.b. Photocoagulation in diabetic maculopathy

Visual loss from macular oedema is often less complete than from proliferative retinopathy, but nevertheless maculopathy is a significant cause of impaired vision in diabetics. The maculopathy shows two manifestations, oedema and ischaemia from capillary damage and closure.

Maculopathy has been divided into three types (Blach, Whitelocke, and Hamilton 1981). In focal maculopathy there are focal areas of increased capillary permeability with circinate exudates and good capillary perfusion. In the cystoid variety increased capillary permeability is more widespread and exudates are not a feature. In ischaemic maculopathy fluorescein angiography reveals paramacular capillary closure.

For focal maculopathy photocoagulation directed at areas of capillary leakage has been recommended (Blach et al 1981) while a "grid" pattern was used for the cystoid and ischaemic types. Focal photocoagulation is sometimes employed to obliterate microaneurysms which are leaking serum profusely and to treat other areas of retinal vessel leakage within the temporal vascular arcades. Differentiation of new vessels, shunt vessels, and other vascular complexes is necessary here (Henkind 1981). Macular oedema (Rubenstein and Myska 1972; Ticho and Katz 1973) with microcystic changes in the macular region can be treated provided that small segments of the macular region, usually indicated by fluorescein angiography as "hot spots" or zones of fluorescein accumulation, are treated preferentially with no more than 20 per cent of the macular region treated at any one session.

Alternative patterns of photocoagulation have been recommended for the treatment of diffuse (cystoid) maculopathy. A "horse shoe" pattern originally suggested by Rubinstein and Myska in 1972 and illustrated by L'Esperance and James (1981) is shown in Figure 42. These latter authors also mention the use of a circular distribution of photocoagulation burns around the nasal side of the disc and the posterior pole outside the vascular arcade, Figure 43.

Focal photocoagulation to obliterate areas of capillary leakage in cases of diabetic maculopathy has been instituted in a controlled randomised trial in the United Kingdom. 76 diabetic patients with maculopathy were seen after 1 year, 44 patients were seen after 2 years, and 25 patients after 3 years. Treated eyes retained significantly better visual acuity than non-treated eyes. In the treated eyes deterioration of visual acuity by 1-2 lines occurred less often than in the untreated eyes. Finally it was reported that the prognosis was better in those with initial visual acuity of 6/24 or better (Multicentre Controlled Study 1975; Cheng 1975).

Other patterns of photocoagulation such as the "horse shoe" pattern have not been tested in any formal manner.

The operation of photocoagulation should be explained to the patient, its disadvantages, and possible complications mentioned. It is even possible to show the patient some fundus photographs before the first treatment session (Hamilton 1978; Constable and Lim 1981). Guinan (1978) wrote "one must not only treat the eye but must give support and encouragement to a human being who is often in great need of both".

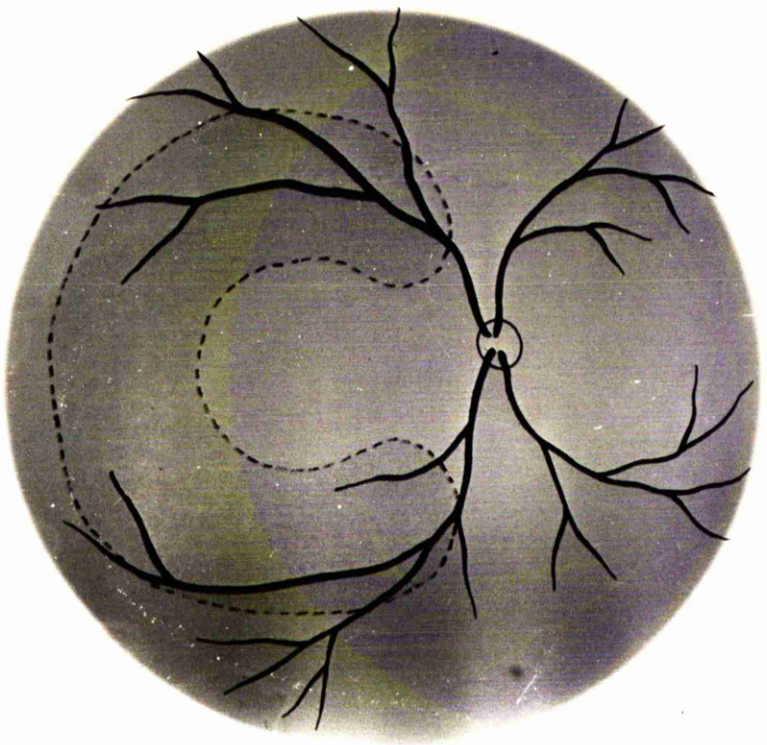

Figure 42. Horse-shoe pattern of photocoagulation treatment of macular oedema(from L'Esperance and James 1981).

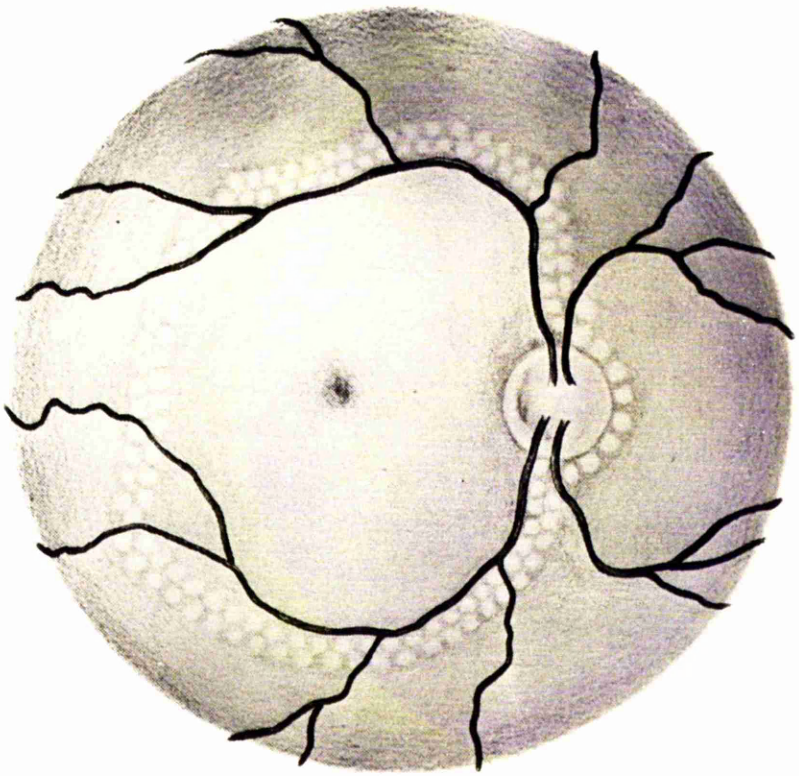

Figure 43. An alternative pattern of photocoagulation treatment of macular oedema(from L'Esperance and James 1981).

CHAPTER 11

COMPLICATIONS OF PHOTOCOAGULATION

11.1. INTRODUCTION

In the present state of knowledge of the pathophysiology of diabetes and the absence of an efficient method for the prevention and treatment of the basic changes that occur in diabetic retinopathy, photocoagulation is the most widely adopted procedure for the local management of the serious forms of diabetic retinopathy at the present time.

The favourable functional results obtained from photocoagulation have been documented by many authors (Chapter 10). Most of the publications on photocoagulation have been concerned with improvement or stabilisation of visual acuity in treated groups of patients (Cheng 1979; Diabetic Retinopathy Study 1976, 1978). There is in addition, however, a limited number of studies on the disadvantages of photocoagulation therapy for retinal disease.

Structural damage to the retina from light of varying intensities and from different sources is well recognised and many workers have, since the introduction of high intensity light sources for ophthalmic examination and therapy, reported that human and animal retinae are susceptible to structural damage when exposed to light from many sources including clinically used ophthalmic instruments, for example slit lamp microscopes, direct and indirect ophthalmoscopes and different types of photocoagulators.

Retinal damage is dependent on the amount of energy absorbed per unit mass or volume of tissue but when energy is absorbed mainly in a specific layer of tissue damage is more commonly measured as the energy absorbed, or incident, per unit surface area. The corneal epithelium for example,

absorbs most of the ultraviolet radiation up to 295 nm and visible radiation is absorbed mainly by the photoreceptor elements in the rods and cones and by the melanin in the pigment epithelium of the retina and in the choroid (Geeraetes and Berry 1968). Structural damage to the retina depends on the following variables (Lerman 1980).

1. The power density, measured in Watts per square centimetre at the corneal surface or the energy density measured in joules per square centimeter entering the eye.
2. The exposure time.
3. The wavelength or the spectral distribution of the beam at the corneal surface.
4. Transmission through ocular media as a function of the wavelength.
5. Pupillary diameter.
6. The diameter of the retinal image.
7. The absorption or transmission by the retinal pigment epithelium as a function of wavelength.
8. The absorption or transmission by the choroid as a function of wavelength.

In clinical practice lasers emitting between 300 and 1000 nm are used; these are the wavelengths that can penetrate the cornea. The cornea absorbs almost all of the ultraviolet radiation shorter than 295 nm. Energy that is transmitted by the cornea is absorbed by the lens. Thus all lasers that emit anywhere in the UV region are obviously hazardous if the cornea or lens is exposed for a sufficient period of time and to power densities above threshold levels (Mellerio 1966). Gerraets and Berry (1968) studied the transmission of light in the rabbit, human, and monkey eye and

demonstrated that well over 50 per cent of the light between 400 and 800 nm is transmitted through the ocular media and that the highest absorption of light at these wavelengths in the retinal pigment epithelium and choroid occurs in the 450 to 700 nm spectral region. At these wavelengths retinal damage is caused by the thermal effect of absorbed energy while at longer wavelengths a major part of the damage is caused by photochemical changes resulting from the absorbed energy. An irradiance of 24 Wcm^{-2} at a temperature of approximately 23°C above ambient produced a threshold lesion in a rhesus monkey retina in 1000 seconds with the Nd-YAG laser (1,064 nm), while the 441.6 nm line from the He:Cd laser required only 30 $mWcm^{-2}$ with negligible temperature rise to produce a threshold lesion in a 1000 second exposure. The ratio of the two irradiances on the retina is 800 (Ham, Mueller and Sliney 1976).

Structural damage to the retina has been demonstrated in a variety of experiments on animals subjected to varying intensities of light for varying periods of time, for example rhesus monkey (Lappin and Coogan 1970; Tso, Fine and Zimmerman 1972; Hochheimer, D'Anna and Calkins 1979; Sykes, Robinson, Waxler and Kuwabara 1981), dogs (Buyukmichi 1981), and rabbit (McKechnie and Foulds 1978). A few experiments have also been carried out on human retinae (Marshall, Hamilton and Bird 1975; Apple, Whinny, Goldberg, Polley and Bizzell 1976; Robertson and Erickson 1979; McKechnie and Ghafour 1982).

Clinically many complications of photocoagulation have been recognised. Some of these occur in the immediate

Figure 44. Accidental xenon arc burn to the fovea. From Constable and Lim (1981).

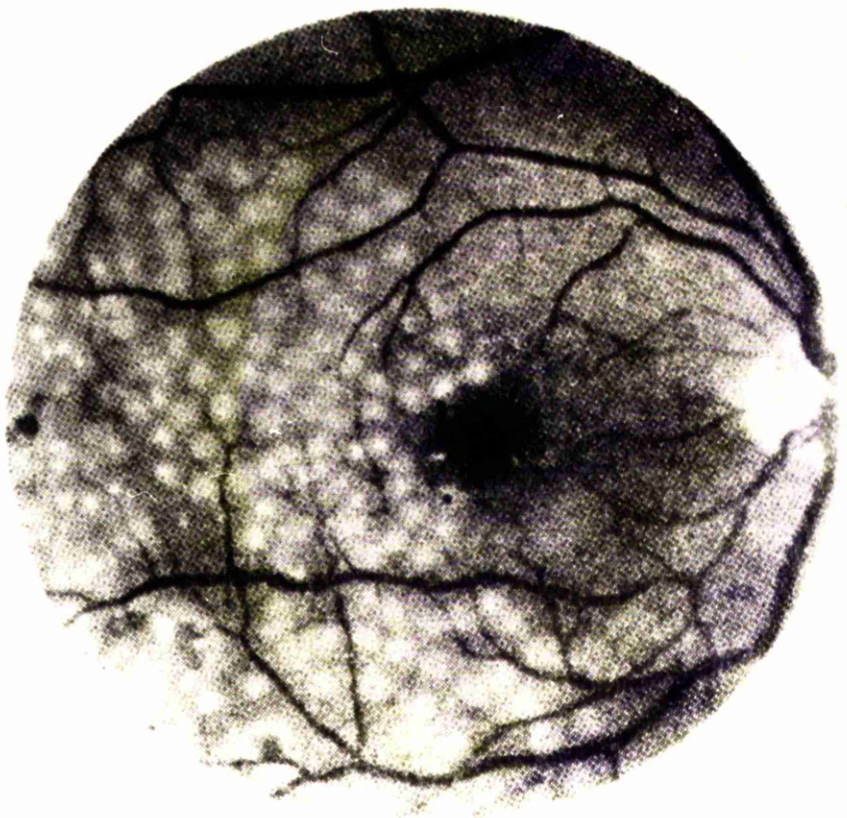

Figure 45. Accidental laser burn very close to the fovea.

From Constable and Lim (1981).

postoperative period and may be reversible (Apple et al 1976) but others may be delayed in onset. Changes can affect both the anterior and posterior segments of the eye.

In the anterior segment of the eye the following complications have been seen: Corneal oedema due to the contact lens, the anaesthetic, or possibly the light energy itself (Robertson and Erickson 1979), iritis which could result from overheating of the aqueous (Okun and Cibis 1966; Robertson and Erickson 1979), shallowing of the anterior chamber (Kanski 1975; Mensher 1977) with increase of intraocular pressure which may last for few hours or up to one or two days and might be attributable to congestion and hyperaemia in the area, (Diddie and Ernst 1977), swelling of ciliary body, or annular choroidal detachment with out-pouring of fluid from the choroid into the vitreous (Blondeau, Pavan and Phelps 1981), temporary myopia associated with a forward movement of the iris-lens diaphragm, and finally cataract (Kanski 1975; McCanna, Chandra, Stevens, Myers, de Venecia and Bresnick 1982; Lakhanpal, Schocket, Richards and Nirankari 1982).

In the posterior segment macular oedema or an increase of a pre-existing macular oedema is the commonest complication of light exposure (Francois and Cambie 1976; Okun and Cibis 1966; Meyers 1980). Other complications include accidental photocoagulation of the fovea with loss of central acuity (Figs. 44 and 45), vitreous and retinal haemorrhage; contraction of vitreous or preretinal membrane; subretinal neovascularisation; increase of pre-existing neovascularisation due to inadequate treatment; fibrous tissue formation; retinal detachment and optic

papillitis, a complication which was commonly induced when direct photocoagulation of optic nerve vessels was practised in the first half of the last decade (Francois, DeLaey, Cambie, Hanssens and Victoria Troncoso 1975; Gass 1972; Benson, Townsend and Pheasant 1979).

The effect of light, including photocoagulation, on the function of the retina has also been studied by many authors. Transient myopia due to forward movement of the lens - iris diaphragm is sometimes noted and takes only a few days to resolve (Kanski 1975). But as would be expected the main concern has been the visual acuity and to a certain degree the field of vision following photocoagulation treatment.

After photocoagulation with either laser or xenon arc deterioration of visual acuity of one or more lines on Snellen's test chart has been reported (Francois and Cambie 1976; Diabetic Retinopathy Study 1976, 1978) with or without restriction of the field of vision. Xenon arc phocoagulation therapy is especially prone to cause visual field loss although this may not be subjectively noted by the patient (Wetzig and Worlton 1963; Okun and Cibis 1966; Multicentre randomised trial 1975; Diabetic Retinopathy Study 1978; Crick, Chignell, and Shilling 1978; Boldrey, Little, Flocks and Vassiliadis 1981; Hamilton, Townsend, Khoury, Gould and Blach 1981). Changes in dark adaptation and electrophysiological behaviour of the retina after photocoagulation have been recorded (Francois, DeRouck, Cambie, and Castanheira 1978; Hamilton et al 1981).

The effects of light exposure on certain other visual functions such as contrast sensitivity or colour vision have not been studied thoroughly although some contradictory reports have appeared. Birch and Hamilton (1981) reported that diabetic patients treated with photocoagulation had higher total error scores on the Farnsworth-Munsell 100-Hue test 12 months after treatment than before it. Whether the deterioration of colour discrimination was due to the treatment or to worsening of the retinopathy is not clear. In diabetics worsening colour discrimination correlates with length of diabetic history (Aspinall 1974) and with the severity of diabetic retinopathy (Smith, Ernest and Pokorny 1976). On the other hand an improvement of colour vision after photocoagulation has been reported by other investigators (Crick, Chignell and Shilling 1978) and attributed to improvement in the retinopathy.

To assess the short term effects of light exposure during laser panretinal photocoagulation on retinal function in diabetic patients undergoing treatment for proliferative diabetic retinopathy a small study was carried out by the author. During laser coagulation the eye being treated is exposed for periods up to 20 minutes to a tungsten illuminating light projected on the retina through the central portion of a 3 mirror contact lens in addition to the intermittent focused and scattered laser light introduced into the eye for therapeutic purposes.

If light energy during this type of laser treatment effects retinal function either source of illumination might be involved and as both are used together clinically the combined effect of the tungsten light of the slit-lamp microscope and of the green-blue light of the argon laser

photocoagulator was studied. Visual acuity (Snellen's chart), contrast sensitivity (Arden grating test), and colour vision (Farnsworth-Munsell 100-Hue test) were measured before treatment, 20 minutes after exposure and 24 hours later.

11.2. SUBJECTS AND METHODS

The effects of combined tungsten and laser light were studied on diabetic patients who were admitted to hospital for panretinal photocoagulation for proliferative diabetic retinopathy (McKechnie and Ghafour 1982).

A stop was fitted to the rheostatic control of the tungsten light on the slit-lamp microscope so that the level of illumination was constant for each subject (217 mW/cm^2). Each session of photocoagulation was made to last 20 minutes and during this time an average of 750 (range 500-1000) burns size 500 μ of 2 msec. duration was given to the retinal periphery of one eye.

To assess the effects of light from the slit-lamp microscope alone, two other groups of individuals were also examined. The first consisted of nondiabetic normal volunteers who performed the tests before and then 20 minutes and 24 hours after being subjected to the slit-lamp illumination alone. The light was delivered through a Goldman 3-mirror contact lens and the pupil was dilated in a similar fashion to that used in the clinical situation. The second group consisted of diabetics who responded to written requests to attend for the test and underwent the same procedure. They were all informed of the nature of the study.

In all three groups of subjects the pupils were dilated prior to the start of the test and a pin-hole was used for visual acuity recording before and after exposure to the slit-lamp or laser light. For contrast sensitivity and colour vision testing a 3-dioptre convex lens was incorporated in a trial frame or clipped to the reading glasses of individuals who normally used a correction for near vision to counteract the effect of cycloplegia.

In the two control groups light from the slit-lamp was projected for 20 minutes onto different areas of the fundus to mimic clinical examination conditions. In the case of diabetics who were receiving laser treatment for their proliferative retinopathy the usual procedure of photocoagulation was followed, the laser beam being directed to the peripheral retina avoiding the area between the two temporal vascular arcades, blood vessels and the optic nerve head. As already noted each laser session lasted 20-30 minutes during which 500-1000 laser burns were applied. Each person, in all categories, was given a 20 minute rest before a test was repeated. Pupils were again dilated 24 hours later and the same test repeated.

One eye from each participant was used for a given test; the number of eyes, thus, represents the number of individuals tested each time. Shown in Table 95 is the number of eyes used in the various tests.

11.3. RESULTS

11.3.a. Visual acuity

Visual acuity of 6 normal individuals before, 20 minutes and 24 hours after exposure to slit-lamp tungsten light are shown in Table 96. All showed some reduction in acuity 20 minutes after light exposure, one showing a drop in acuity from 6/6 to 6/36 20 minutes after light exposure. The mean of the differences was - 1.8 Snellen lines. Non parametric two tailed paired test showed no significant difference when acuities within the group were compared (P = 0.0626). All visual acuities had returned to pre-exposure level 24 hours later. See Fig. 46.

Visual acuities in the diabetic group of patients who were subjected to slit-lamp light showed a significant deterioration 20 minutes after light exposure (P = 0.0156). In 5 of the 8 diabetics in this group the acuity returned to the initial level 24 hours later; in 3 there was a one-line drop in acuity. This, however, was found to be non-significant (P = 0.2500). See Fig. 47 and Table 97.

Seven patients received laser treatment and had their visual acuity tested before and after the treatment session. These are shown in Table 98. A significant deterioration was noted 20 minutes after treatment (P = 0.0312, non parametric paired test) but four out of seven had returned to pre-treatment levels at 24 hours and there was no significant change in acuities (P = 0.2500) at this time interval, Fig. 48. It is seen that in both diabetic categories there was a significant drop in visual acuity recorded 20 minutes after slit-lamp examination or laser therapy but that all had returned to within one line of the initial acuity 24 hours later.

	Visual acuity	Contrast sensitivity	Colour vision
Normal individuals subjected to slit-lamp light	6	10	10
Diabetics subjected to slit-lamp light	8	14	14
Diabetics subjected to laser (and slit-lamp)	7	8	8

Table 95. Number of individuals, normal and diabetic who participated in the study of the effect of light on some visual functions.

Subject	Initial visual acuity	20 minutes after light	24 hours later
1	6/6	6/36	6/6
2	6/6	6/9	6/6
3	6/5	6/9	6/5
4	6/6	6/12	6/6
5	6/6	6/6	6/6
6	6/6	6/9	6/6

Table 96. Initial and subsequent visual acuities of normal individuals subjected to tungsten slit-lamp light.

Subject	Initial visual acuity	20 minutes	24 hours later
1	6/12	6/36	6/12
2	6/9	6/12	6/12
3	6/6	6/6	6/6
4	6/9	6/12	6/9
5	6/6	6/12	6/9
6	6/6	6/9	6/6
7	6/18	6/36	6/18
8	6/24	6/60	6/36

Table 97. Effect of slit-lamp light on visual acuity of diabetic patients.

Patients	Initial visual acuity	20 minutes later	24 hours later
1	6/12	6/24	6/12
2	6/6	6/9	6/9
3	6/6	6/6	6/6
4	6/9	6/12	6/9
5	6/18	6/36	6/24
6	6/12	6/24	6/12
7	6/6	6/9	6/9

Table 98. Effect of laser photocoagulation on visual acuity of diabetics with proliferative retinopathy.

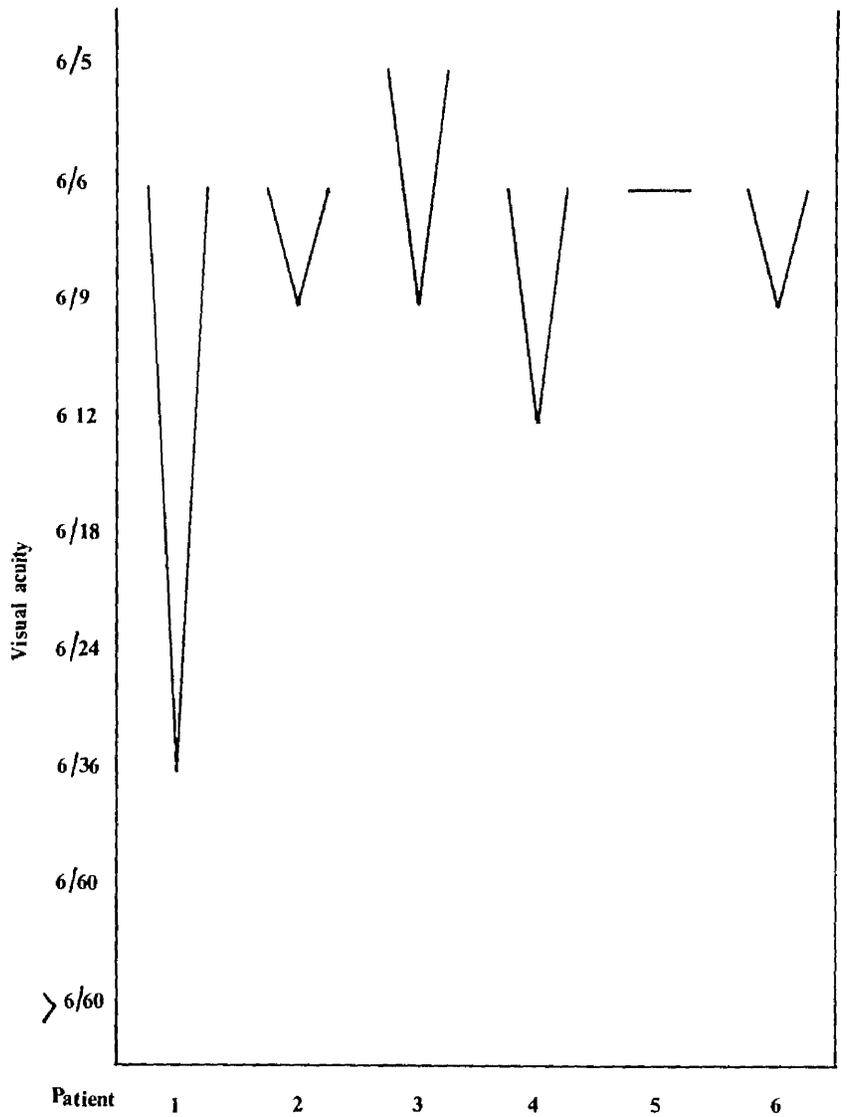

Figure 46. Visual acuities of six normal individuals subjected to the tungsten light of slit-lamp. Acuities are shown before, 20 minutes, and 24 hours after exposure.

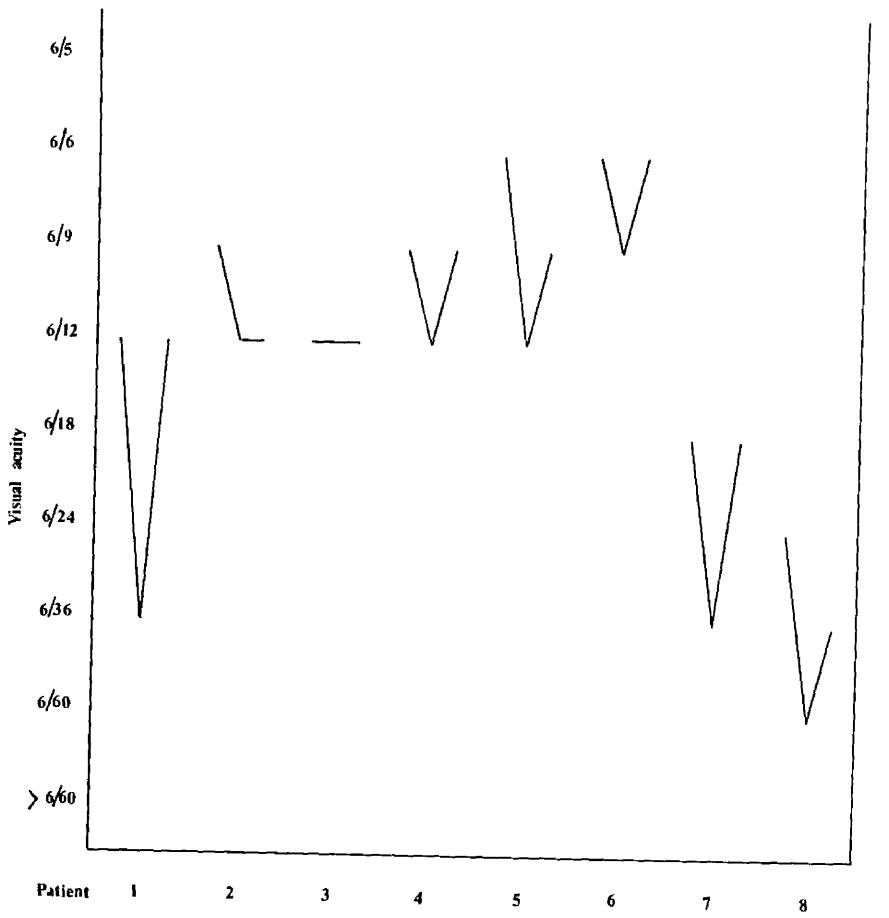

Figure 47. Visual acuities of 8 diabetic subjects before, 20 minutes, and 24 hours after exposure to the slit-lamp tungsten light.

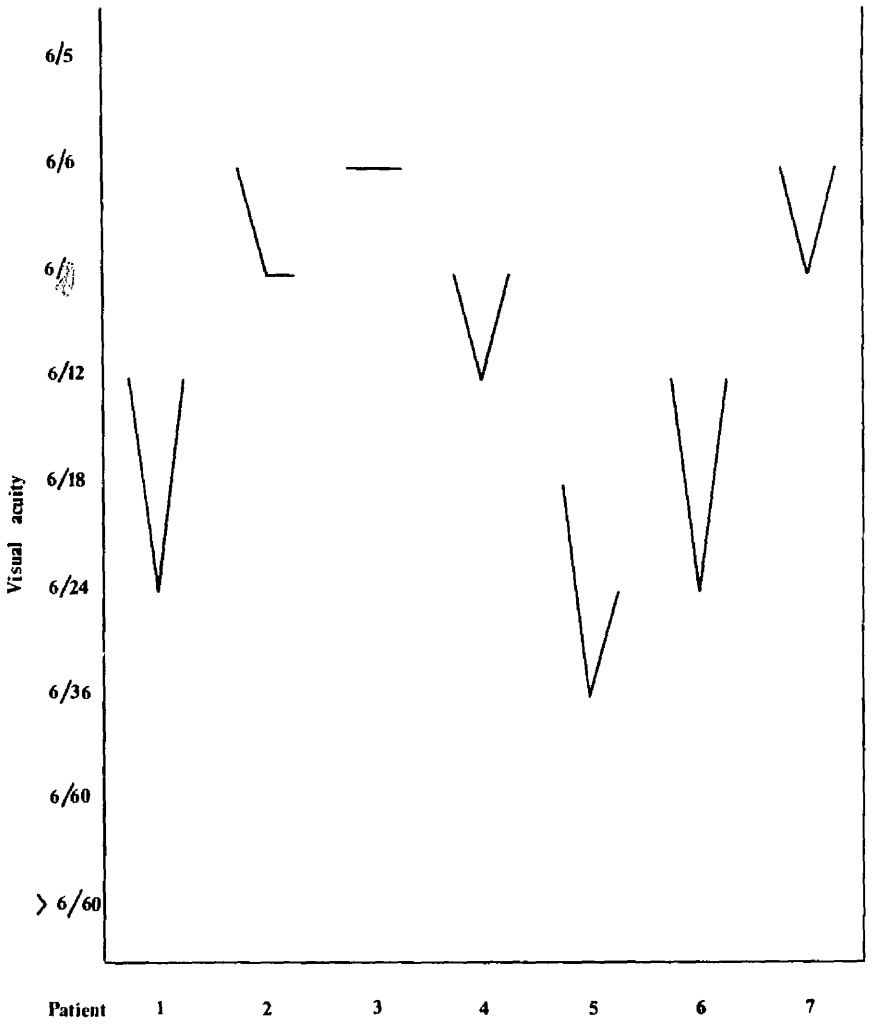

Figure 48. Visual acuities of 7 diabetic subjects before, 20 minutes, and 24 hours after a photocoagulation session for proliferative diabetic retinopathy.

11.3.b. Colour vision (Farnsworth-Munsell 100-Hue test)

The test was carried out as described in Chapter 5.

Table 99 shows the mean total error score of each group of individuals who performed the Farnsworth-Munsell 100-hue test before and after exposure to the two different sources of light.

Diabetics had higher mean total error scores than non diabetics and those receiving laser therapy had higher scores than the group of patients who received only slit-lamp light. This was expected since those with proliferative retinopathy had a more advanced retinopathy than the other group which consisted of diabetics who had no retinopathy or simple forms of it and were not specifically chosen on the basis of their retinopathy.

Colour discrimination, using the 100-Hue test, was not found to change significantly either 20 minutes or 24 hours after exposure to tungsten slit-lamp light or laser in any of the groups tested. Figs. 49 - 53. Probability figures using a non-parametric, two tailed paired test are shown in Table 100.

11.3.c. Contrast sensitivity (Arden grating test)

Diabetic patients with proliferative retinopathy generally have higher contrast thresholds than diabetics without retinopathy or with only simple retinopathy such as those who performed the contrast sensitivity test before and after tungsten light exposure. Diabetics in general have higher thresholds i.e. lower contrast sensitivity than normal individuals (Ghafour et al 1982).

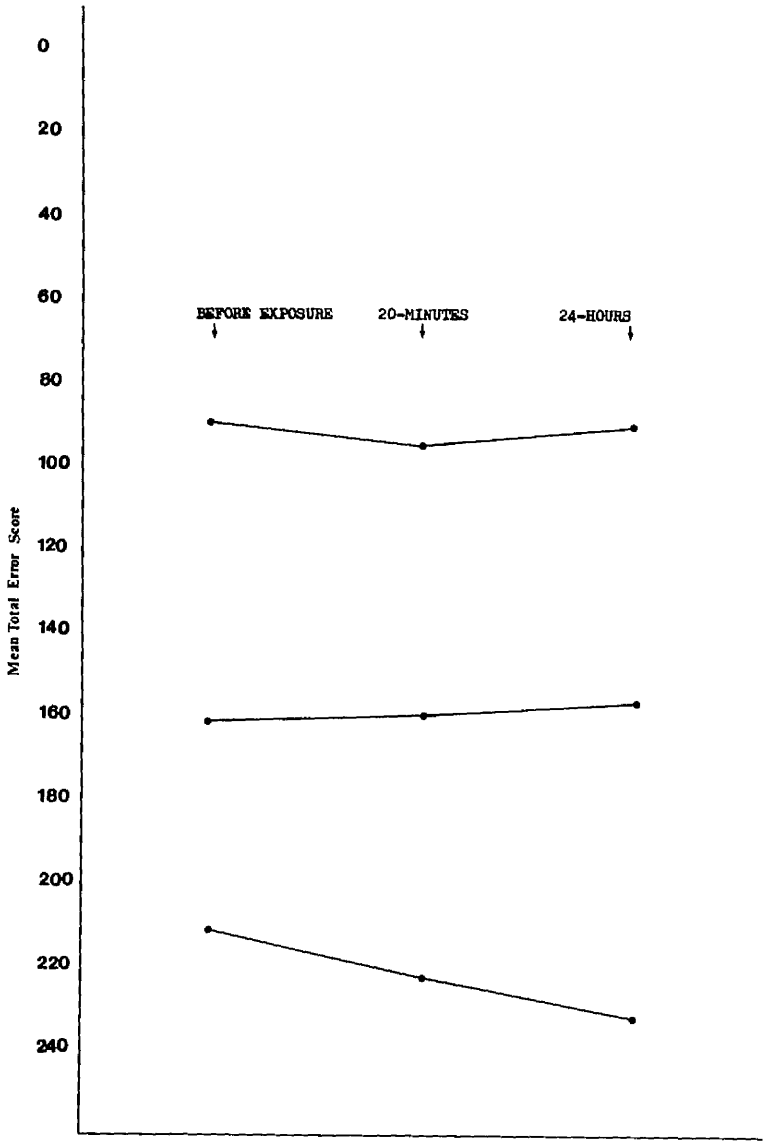

Figure 49. Mean total error scores on the Farnsworth-Munsell 100-Hue test of :

Top line : Normal subjects exposed to slit-lamp light.

Middle line : Diabetic subjects exposed to slit-lamp light.

Bottom line : Diabetic subjects exposed to argon laser light.

	Mean initial total score	20 minutes later	24 hours later
Normals; slit-lamp (10)	88.4	94.2	89.6
Diabetics; slit-lamp (14)	160.4	159.1	156.8
Diabetics; laser (8)	210.7	222.0	232.0

Table 99. Mean total error scores on the Farnsworth-Munsell 100-hue test of different groups of subjects exposed to light.

	Initial score Vs 20 minutes	Initial score Vs 24 hours
Normals; slit-lamp	P = 0.5078	P = 0.7540
Diabetics; slit-lamp	P = 0.5810	P = 1.0000
Diabetics; laser	P = 0.7266	P = 0.7266

Table 100. Comparison of total error scores on the 100-hue test of different groups of individuals exposed to slit-lamp with or without laser after varying periods. None of the probabilities is significant.

	PLATES					
Time of Test	2	3	4	5	6	7
Initial	12.75	10.75	12.50	12.75	10.12	9.62
20 minutes later	13.12	10.12	12.50	11.50	9.37	10.75
24 hours later	12.50	11.00	12.00	11.62	9.00	10.12

Table 101. Mean contrast thresholds on each plate of the Arden grating book of 8 normal individuals exposed to slit-lamp light.

	PLATES					
Time of Test	2	3	4	5	6	7
Initial	12.62	10.50	12.87	13.62	14.37	17.00
20 minutes later	12.37	11.50	14.75	14.25	15.00	17.00
24 hours later	12.12	10.75	12.50	13.12	14.00	16.87

Table 102. Mean contrast threshold on Arden grating book of 8 diabetics exposed to the slit-lamp light.

	PLATES					
Time of Test	2	3	4	5	6	7
Initial	11.66	9.44	13.22	15.88	16.33	17.55
20 minutes later	12.33	10.88	13.33	15.77	17.88	18.11
24 hours later	11.44	10.00	12.44	15.33	16.44	17.88

Table 103. Mean contrast threshold on Arden grating book of 9 diabetics exposed to laser for treatment.

Plate	Before Vs 20 minutes	Before Vs 24 hours	20 minutes Vs 24 hours
2	P = 0.1094	P = 1.0000	P = 0.6876
3	P = 0.0118 *	P = 0.2500	P = 0.3750
4	P = 0.7744	P = 0.2500	P = 0.2188
5	P = 0.3876	P = 1.0000	P = 0.6876
6	P = 1.0000	P = 1.0000	P = 1.0000
7	P = 0.7266	P = 1.0000	P = 0.5000
Total score	P = 0.1184	P = 0.5078	P = 0.0704

Table 104. Probability figures of mean contrast threshold of diabetics treated with the laser. Significant difference is marked with *.

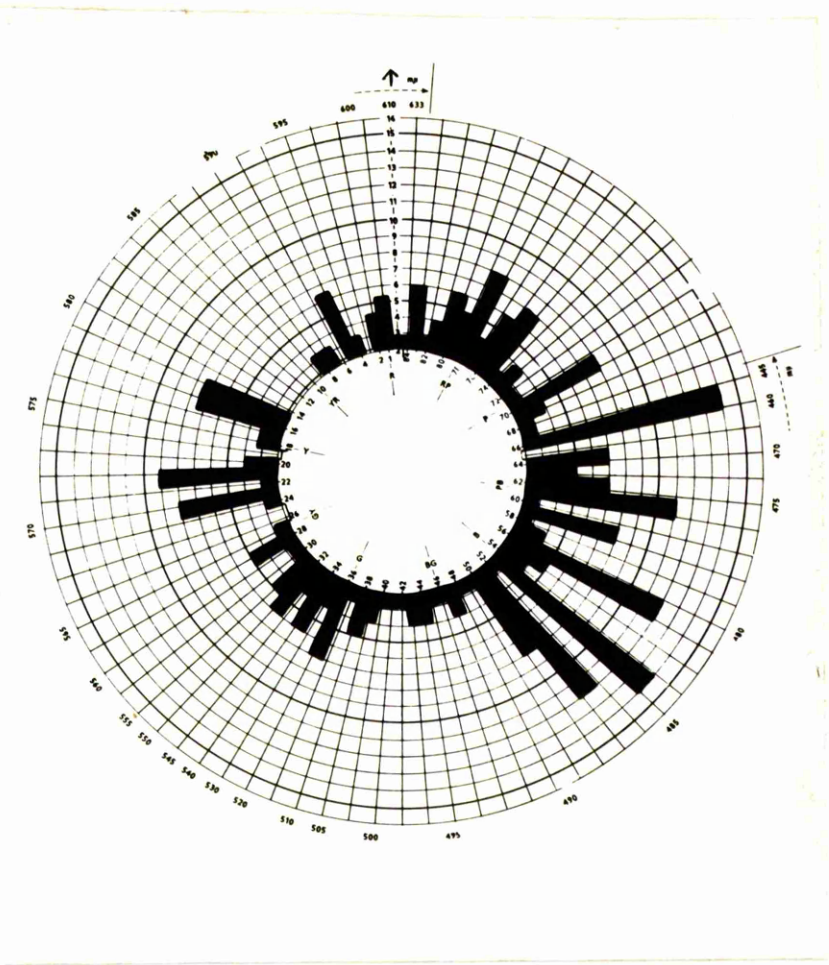

Figure 50. Farnsworth-Munsell 100-Hue test trace of a diabetic patient before exposure to slit-lamp tungsten light. Total error score 240.

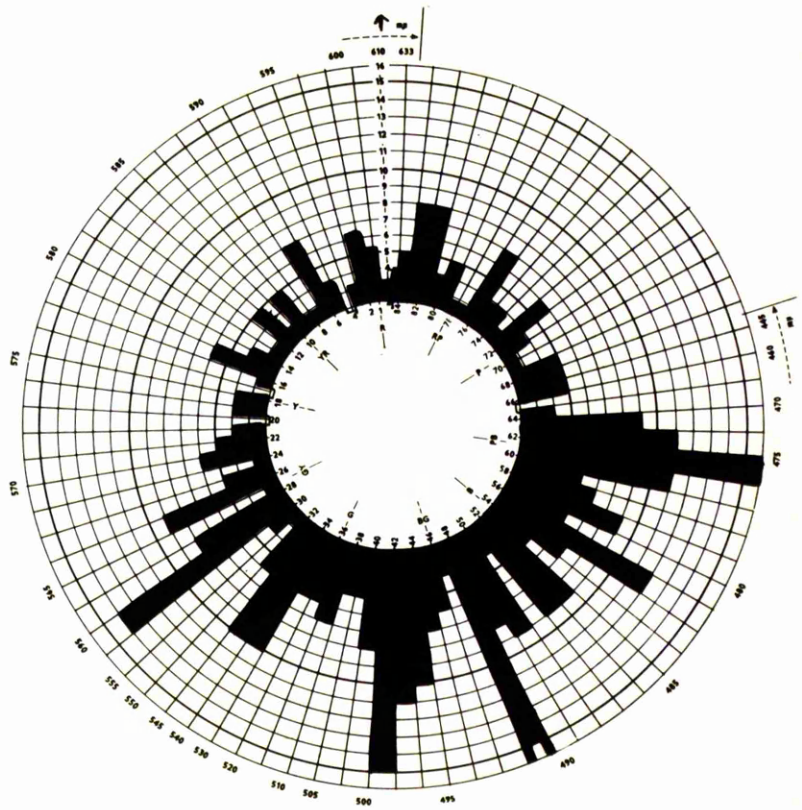

Figure 51. Farnsworth-Munsell 100-Hue test trace of the same patient as in Figure 50 after exposure to slit-lamp light. Total error score 344.

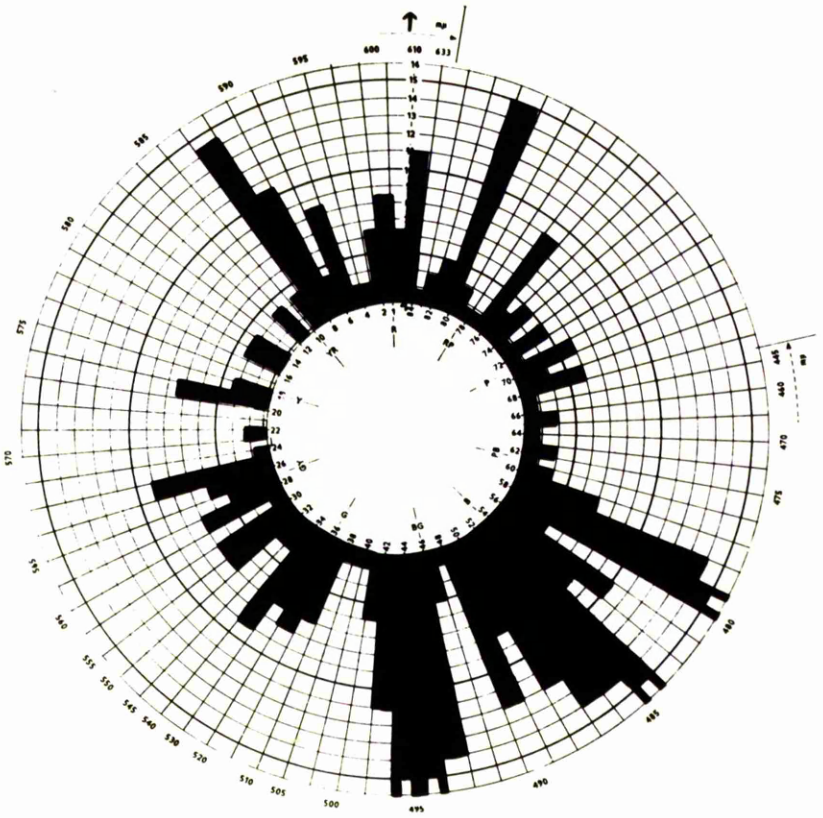

Figure 52. Farnsworth-Munsell 100-Hue test trace of a diabetic with proliferative retinopathy before a laser treatment session. Total error score 392.

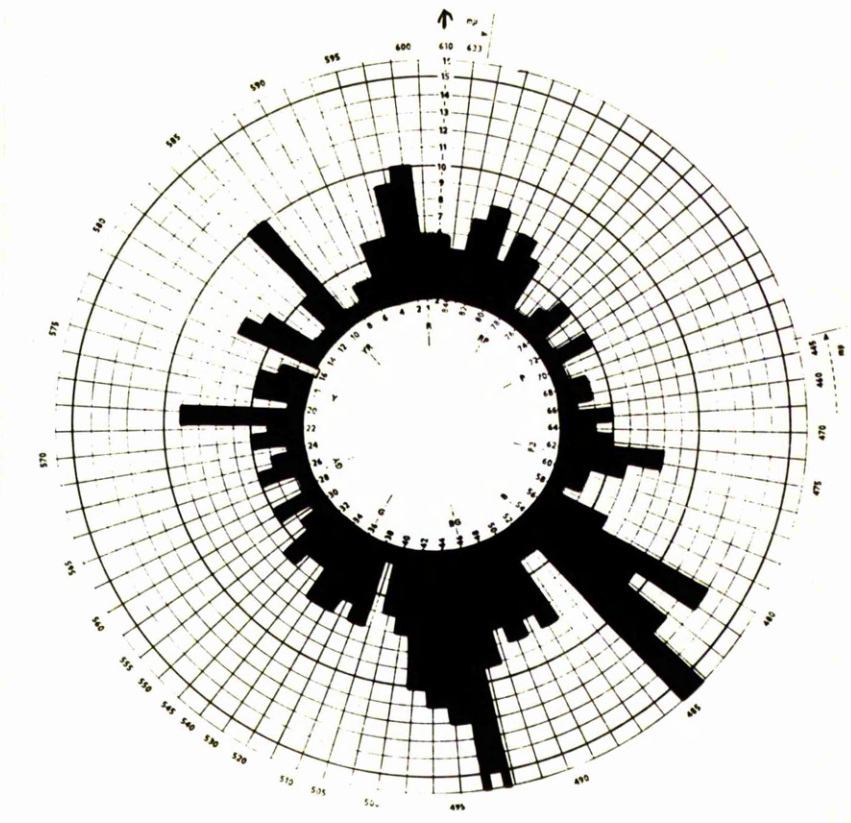

Figure 53. Farnsworth-Munsell 100-Hue test trace of the same patient as in Figure 52 after a laser treatment session. Total error score 322.

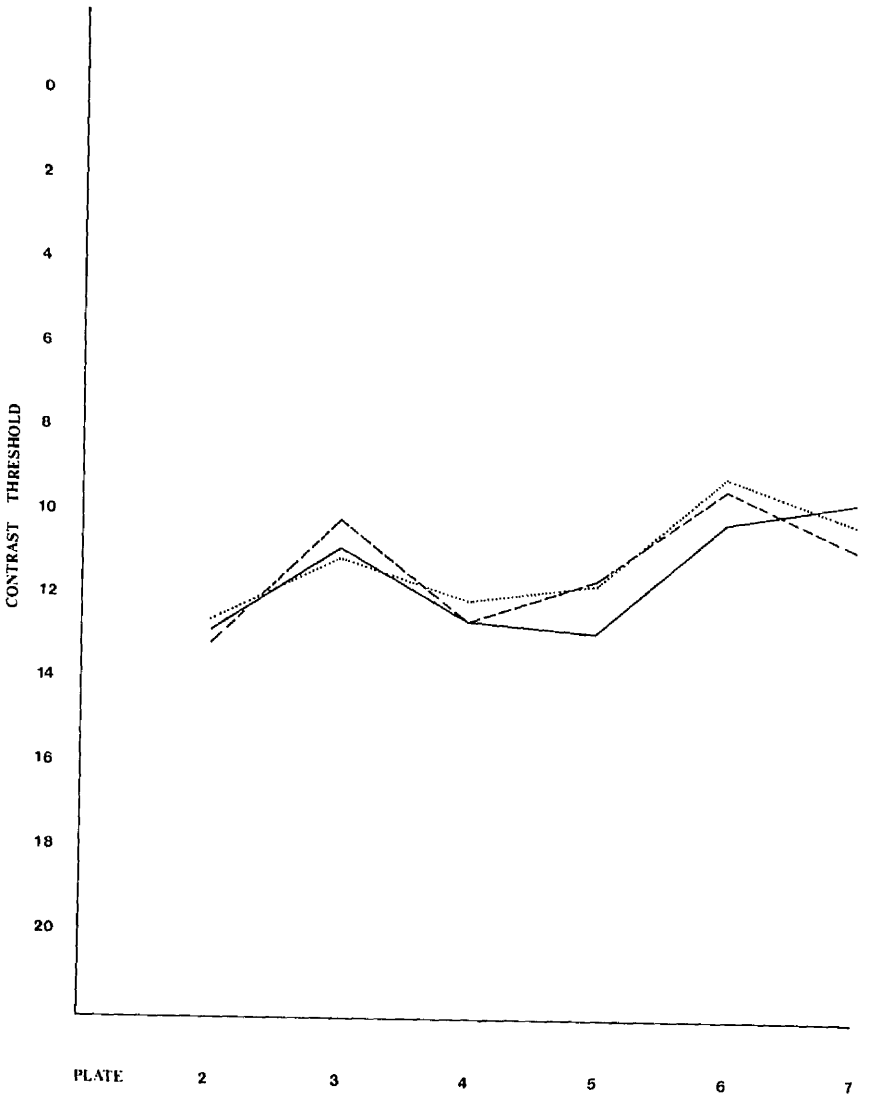

Figure 54. Mean cotrast threshold on the Arden grating book of normal individuals.

_____ Before exposure to slit-lamp.

----- 20 minutes after exposure.

..... 24 hours later.

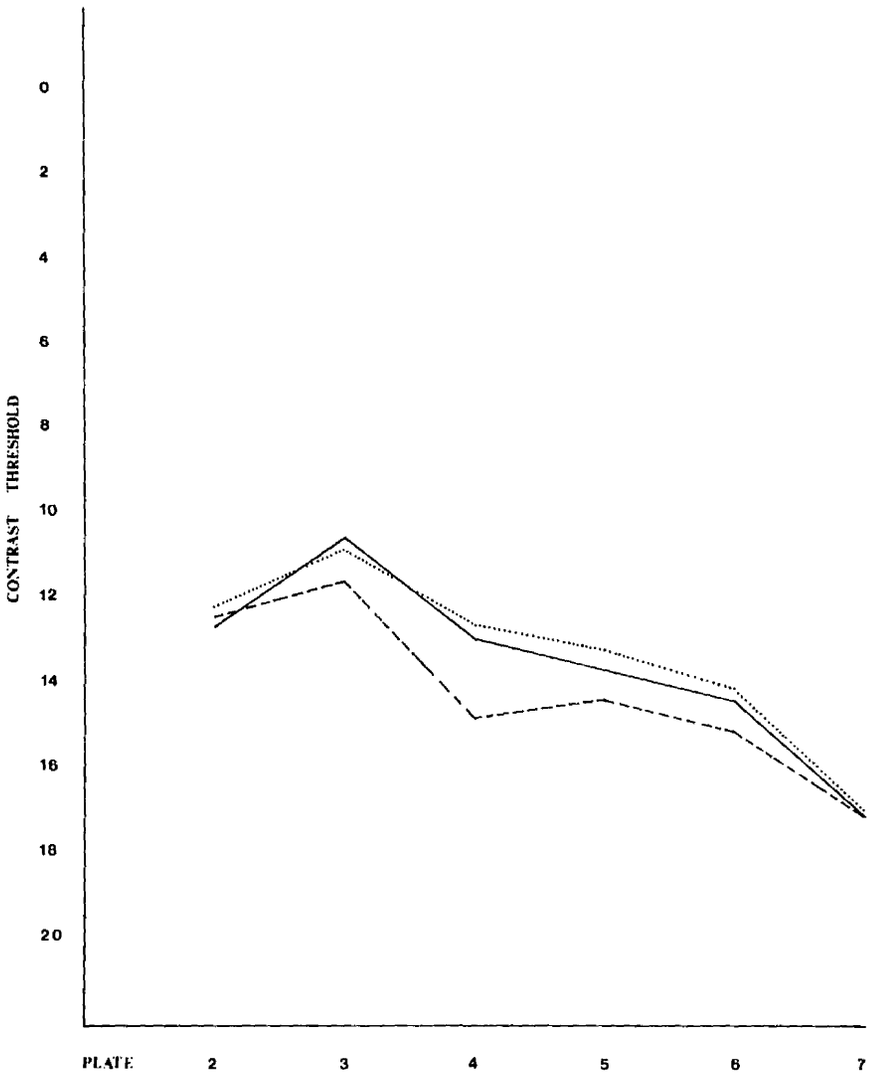

Figure 55. Mean contrast threshold on the Arden grating book of diabetics.

_____ Before exposure to slit-lamp.

------- 20 minutes after exposure.

..... 24 hours later.

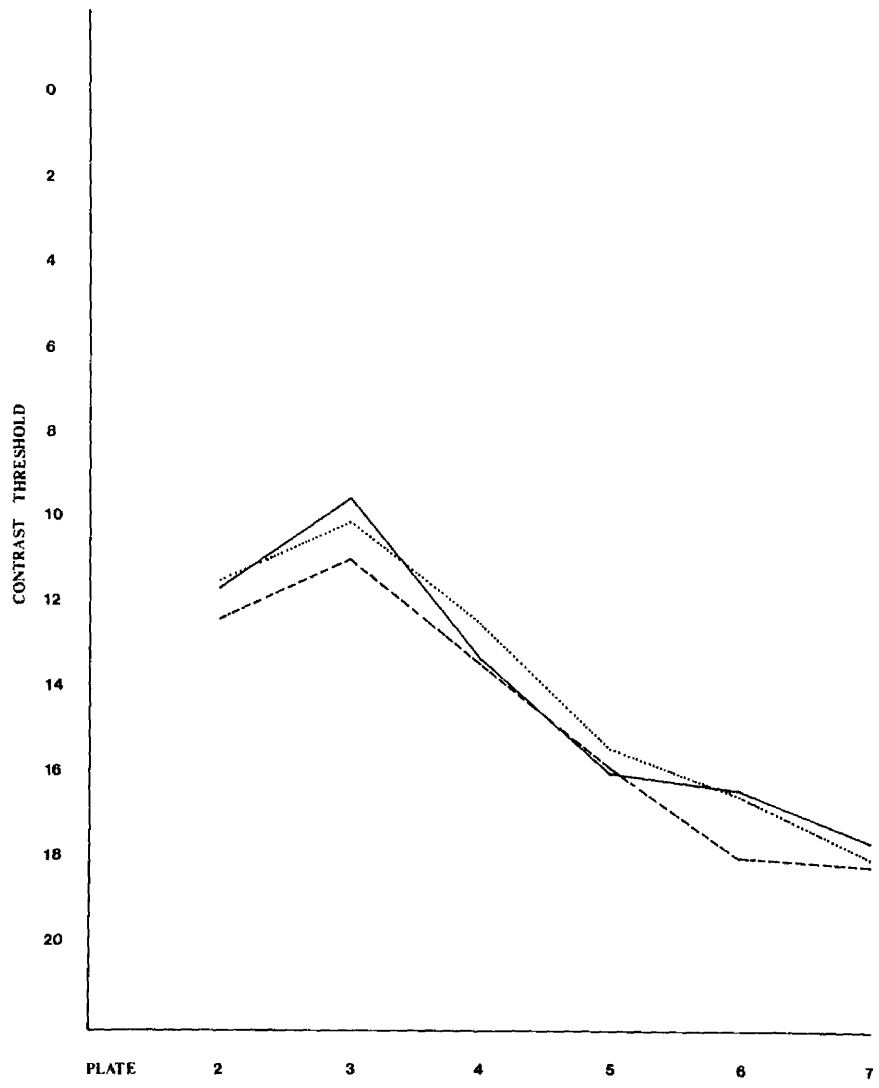

Figure 56. Mean contrast threshold on the Arden grating book of diabetics treated with argon laser.

_____ Before treatment.

----- 20 minutes after treatment.

..... 24 hours later.

No change of contrast threshold on any plate of the Arden grating book was found when the 8 normal individuals were re-tested 20 minutes or 24 hours after being exposed to the slit-lamp (Table 101). The same finding was obtained in the case of diabetics who were exposed to the tungsten light of the slit-lamp (Table 102). Diabetics treated with the laser showed no difference of contrast sensitivity on any plate whether tested 20 minutes or 24 hours after the treatment session; the only exception being on plate (3) 20 minutes after the treatment when a significant mean elevation of contrast threshold was noted ($P = 0.0118$), see Table 104. The mean threshold on this plate also had returned to pre-exposure level 24 hours later (Table 103). Figures 54-56 display the data of Tables 101-103.

On comparing the patterns of change for the different groups of patients it was found that the only statistically significant difference was between the normals and the lasered diabetics, 20 minutes after exposure and testing with plate 5 ($P < 0.0332$); all other differences were insignificant.

11.4. DISCUSSION

Ophthalmologists all over the world examine, treat, nd operate on patients using different sources of illumina- ion, yet hardly ever come across a patient who returns to he Ophthalmic Department to report a change in visual per- ormance. Many studies however have shown that a eterioration of visual acuity by one line, in many cases,

takes place after photocoagulation therapy for retinal disease, the most commonly treated of which is diabetic retinopathy (Francois and Cambie 1976; Diabetic Retinopathy Study 1978). Photocoagulation for diabetic retinopathy accounts for as much as 63 per cent of all laser treatment sessions (Zweng, Little and Vassiliadis 1977).

In this study normal and diabetic individuals were exposed to levels and durations of illumination similar to those encountered in everyday practice in ophthalmology.

Patients are very seldom exposed to the illumination of a slit-lamp for longer than 20 minutes. Indirect Ophthalmoscopy may take 15-20 minutes even when drawings are being made and a laser session usually lasts a maximum of 20-30 minutes. This contrasts with the "experimental" conditions under which structural damage to the retina has been produced. In these experiments very high energy levels have been used and the experimental animals exposed for much longer periods than those needed for examination of the fundus in humans or for photocoagulation treatment. In Table 105 some examples of these experiments are shown. It would not be surprising that such high luminances would damage animal and, perhaps, human retinae. Human retinae however might be more resistant than animal retinae to light damage and rhesus monkey, which is the commonly used animal for such experiments, may not be the most suitable for the study of such effects (Geeraets and Berry 1968; Boldrey et al 1981).

Boldrey and co workers (1981) reported the visual outcome in seven workers in laser industry who were accidentally subjected to very high intensities from different laser instruments where the conditions in which the accidents occured were thought to be similar to the conditions encountered in the clinical application of laser treatment. They found that, in spite of the persistence of minor field losses, most of the patients recovered excellent visual acuity a few weeks after the accident.

Even in monkeys, the retinal damage which was produced after 40 minutes of exposure to the highest possible intensity of light, from an indirect ophthalmoscope, disappeared in 4 weeks while exposures of 5, 10, or 20 minutes produced no photographically visible change (Hochheimer, D'Anna and Calkins 1979).

In the present study the drop of visual acuity 20 minutes after exposure of normals or diabetic patients to slit-lamp or laser light might be thought to be the result of incomplete adaptation; this is unlikely. The tests of function used here are all cone-mediated and cone adaptation is known to be rapid while human rods would require about 30 minutes to dark adapt after bleaching (Lerman 1980). In experimental light damage to the retina cones have been shown to be more sensitive to damage than rods (McKechnie and Johnson 1977) but the abnormalities in cone structure are rapidly reversible when light damage is moderate; even when the receptor outer segments are generally damaged regeneration is possible (Tso, Fine and Zimmermann 1972).

Animal Model	Source of light	Conditions of the experiment	Author
Rhesus monkey	Indirect Ophthalmoscope	Exposure of 1 hour. Light "continuously" directed on the fovea. Transformer set at 7.5 volts reading.	Tso et al 1972
Dutch rabbit	Tungsten light	Exposure for 1 hour to white light (67-235 mW/cm^2).	McKechnie & Foulds 1978
Rhesus monkey	Slit-lamp and operating microscope	Slit-lamp light set at maximum voltage. 5, 10, & 20 minutes produced no effect. Only 40 minutes exposure produced reversible changes.	Hochheimer et al 1979
Rhesus monkey	Fluorescent light	Exposure for 12 hours repeated for 4 days. Intensities as high as 24,700 lux were used.	Sykes et al 1981
Dog	Indirect Ophthalmoscope	Exposure for 1 hour. Eyelid opened by speculum. Position of light and eye maintained constantly. Light intensity control on Ophthalmoscope transformer turned up to maximum.	Buyukmichi 1981

Table 105. Experimental conditions in some studies which reported retinal damage from light.

In the present study, although the eye was moved about during light exposure and the macular area was not directly illuminated scattered light within the eye is likely to have affected all areas of the retina. It is probable that the temporary deterioration of visual acuity 20 minutes after exposure in all groups of subjects was the result of reversible and temporary damage to cone mediated vision. Tests of dark adaptation, electrophysiology and visual fields would be necessary to determine whether temporary reversible damage to rod mediated vision also occured.

Macular oedema or an increase in pre-existing macular oedema was found to follow extensive scatter retinal photocoagulation by Gass (1972) and it would be expected that a deterioration of colour vision and other aspects of cone mediated vision would result.

It is the policy in some centres to apply a large number of burns at the first treatment session. Hamilton et al (1981) put more than 500 Xenon burns or 2,000 laser burns size 500 μ during the first session and an average 711 xenon or 3459 argon laser burns overall. They reported that colour vision (Birch and Hamilton 1981) deteriorated in their patients together with some loss of visual fields and disturbance of night vision.

Apart from the study reported in this chapter occasional patients who appeared to have suffered adverse effects of photocoagulation have been seen by the author. These included a patient of Middle Eastern origin who developed temporary choroidal effusion following laser panretinal coagulation. In this patient two factors may have contributed to this effect. Firstly, pigmentation in the retinal pigment epithelium was heavier than in the European

patients usually treated and as a result the photocoagulation burns were more intense than usual. Secondly treatment sessions were separated by only 24 hours and the choroidal effusion developed after the third session. The effusion was accompanied by a temporary reduction in acuity from 6/9 to 6/36. Recovery to pre-treatment level with rapid regression of neovascularisation was noted 7 days later.

At the Tennent Institute of Ophthalmology, laser burns are usually applied up to an average maximum of 500 - 1000 at each treatment session. This limitation in the number of burns used per treatment session may explain the absence of significant short term deterioration in colour vision, visual acuity, and contrast sensitivity in the diabetics studied and was probably responsible for the low rate of complications seen among other patients treated. In another patient (McKechnie and Ghafour 1982) a calamitous fall in acuity from 6/36 to counting fingers occurred immediately after a single treatment session of 700 burns of 500 u size. None of the burns were near the macula and the poor acuity was associated with severe cystoid macular oedema. A gradual recovery of vision to 6/36 occurred over the succeeding 6 months. No other serious complications of panretinal coagulation were seen among the 250 patients treated.

In my opinion there is no justification for a treatment regimen which involves a total panretinal ablation in one treatment session.

CHAPTER 12

FINAL DISCUSSION AND SUGGESTIONS

Diabetes is the commonest systemic disorder causing blindness or visual disability among persons of working age (20-64 years). It is responsible for about 10 per cent of blind registration in the West of Scotland (Ghafour, Allan, and Foulds 1983). Here as in many other developed parts of the world diabetes affects about 1 per cent of the population. There are in addition likely to be a significant number of undiagnosed diabetics. The population in the West of Scotland is about 2.5 million (Registrar General, Scotland 1981), and consequently there are about 25,000 diagnosed diabetics in this part of the United Kingdom.

In the studies (Chapter 7 and 8) on diabetic patients attending a Hospital diabetic clinic or being cared for in General Practice, a prevalence of about 32 per cent of diabetic retinopathy was found. One third of patients with diabetic retinopathy had a serious sight threatening variety of eye disease. Applying these prevalence figures to the West of Scotland, 2,750 persons are likely to have serious retinopathy necessitating detailed ophthalmological assessment and laser or other appropriate treatment.

It has been estimated that at any one time up to one third of cases of diabetes are undetected (Amos 1974). As 60 per cent of diagnosed diabetics were symptom free at the time of diagnosis there is no evidence that those patients with undetected diabetes differ significantly from those with known diabetes. If this were true for the West of Scotland then the number of diabetics in this area might be as high as 37,500 while some 4,000 patients might have serious retinopathy.

In relation to the factors of importance in the development of retinopathy several aspects, some well known and others new have been identified in the present study.

It is well known that duration of diabetes is one of the most important factors in the development of diabetic eye disease and this is confirmed in the present work. Thus patients with retinopathy had had diabetes for 9 years on average while those without retinopathy had been recognised as diabetics for only 3 years on average.

There are some significant differences between the sexes both in the age of onset of diabetes and of retinopathy. Whether this is due to hormonal factors or related to other genetically determined parameters is controversial (Sabour et al 1962; Siperstein et al 1968). Conceivably environmental factors might play a role.

In the present study the mean age of diagnosis of diabetes in males was 7 years younger than in females (49 compared with 56 years). As a corollary males with diabetic retinopathy developed diabetes on average some 8 years earlier than females with retinopathy (median age at diagnosis of diabetes among males with retinopathy was 46 years and among females similarly affected 54). Thus males develop both diabetes and its complication, diabetic retinopathy at an earlier age than females. The earlier development of diabetic retinopathy among males may simply be an expression of the duration of the diabetes and its earlier onset among males but there are suggestions that males may be in addition more liable to the development of the complications of diabetes. These findings receive support from a recently reported study (Bodansky et al 1982).

Much interest has been shown over the years in the relationship between diabetic control and the development of retinopathy. Recently the measurement of glycosylated haemoglobin levels has been hailed as a better method of assessing control than the taking of random blood sugar levels as it is believed that the level of glycosylated haemoglobin is more closely related to the level of control over the previous few weeks. It is of interest therefore that in this study (Chapter 8) it was found that the severity of retinopathy among diabetic patients correlated much more with random blood sugar estimations than with levels of glycosylated haemoglobin, suggesting that short term fluctuations in blood sugar may be more important in the development of retinopathy than the average level of control as expressed by the measurement of glycosylated haemoglobin in the blood. Similar findings have been reported in another recent study (Dornan 1982).

It is a well held belief that coincident systemic hypertension in diabetes is a risk factor for the development of diabetic retinopathy and its severity. In the present study hypertensive diabetics were found not to show a higher prevalence of diabetic retinopathy than non hypertensive diabetics. Additionally it was found that in the West of Scotland diabetics are not more susceptible to hypertension than non diabetics (Beevers 1978). On general grounds it is obviously of benefit to a hypertensive diabetic patient to have his hypertension treated but the clinical impression that this may prevent the development of diabetic retinopathy or reduce its severity receives no support from the present study.

Another factor about which there are conflicting opinions is the influence of smoking on the development of diabetic retinopathy. Smoking is known to increase whole blood viscosity (Dintenfass 1975) and to be associated with arterial disease and increased platelet adhesiveness. Because it has been shown that increasing severity of diabetic retinopathy is associated with increasing whole blood viscosity (Lowe et al 1981; Trope et al 1983) there are theoretical grounds for recommending that patients at risk of developing diabetic retinopathy or indeed those who have already developed this complication should not smoke.

In spite of this the present study has failed to find any correlation between smoking and diabetic retinopathy. Thus the prevalence of retinopathy was similar in smokers and non smokers (Chapter 7). Other studies have reported similar results. Thus West et al (1980) in a survey of a large number of diabetic Pima Indians found no relationship between smoking and the prevalence of retinopathy. More recently Dornan, Mann and Turner (1982) compared 40 insulin dependent diabetics who remained free from diabetic retinopathy with 40 similar patients with background retinopathy and 47 with proliferative retinopathy. They reported that smoking did not appear to influence the development of diabetic retinopathy. The correlation of raised whole blood viscosity with severity of diabetic retinopathy and the lack of correlation with smoking which is known to be associated with raised whole blood viscosity suggests either that in additon to its effect on blood viscosity smoking may have some other effect on the eye which is protective as

regards retinopathy or alternatively that the association of raised blood viscosity and retinopathy may not be direct and that raised blood viscosity may only indicate the presence of some other factor which is itself causally related to the development of retinopathy.

Diabetics are known to be at risk of vascular complications in addition to retinopathy and smoking has been identified as a risk factor in many vascular diseases. It would appear reasonable on general grounds although not supported in relation to retinopathy, that diabetics should be strongly advised not to smoke. It is of interest that in the present study it was found that general vascular complications were commoner among diabetics with retinopathy than those without, indicating not only that all vascular complications in diabetes including retinopathy tend to be related to the duration of the disease and additionally that the state of the retina, while no guide to the severity of the diabetes is a good indication of other vascular complications such as coronary artery disease.

Blindness from any cause has social and economic aspects apart from the obvious deterioration in the quality of life that it may cause. Blindness from diabetes tends to occur at an earlier age than that from other causes (7 years earlier on average among blind patients registered with the Society for the Blind in Glasgow and the West of Scotland). It is also the commonest form of blindness among those of working age. Prevention of blindness from this cause, which has now become a real possibility with the

advent of laser treatment, would have obvious economic and other advantages for the community as well as the affected individual.

There is little doubt that to be effective laser therapy has to be employed at an early stage in the development of serious retinopathy. The detection of serious retinopathy at a suitable stage for therapy is therefore the most important step in the prevention of blindness from diabetes. Many diabetics regularly attend a Hospital diabetic clinic and it might seem reasonable that the detection of serious retinopathy would be part of the assessment of the diabetic patient at these units. Not all diabetics however, attend hospital clinics regularly. Sixty percent of diabetics in one practice studied were looked after in general practice.

In this study we have examined the various ways in which serious retinopathy might best be detected and it is clear (Chapter 5) that Ophthalmoscopy carried out by a trained observer is a reliable method.

More sophisticated tests of structure and function such as fluorescein angiography, quantitative visual field analysis, measurement of defects of colour vision or of spatial frequency contrast sensitivity were found not to be helpful in differentiating serious from non serious retinopathy, many patients with non serious background retinopathy and indeed some diabetic patients without retinopathy showed abnormal visual function. The results indicated that significant changes in retinal function were common among

patients with diabetes and that these tended to antedate the development of visible retinal pathology. Fluorescein angiography too detected unsuspected retinopathy in some 20 per cent of apparently normal diabetic eyes but once again this tended to be early background retinopathy of a non serious nature not requiring detailed ophthalmological investigation or treatment. Neither fluorescein angiography nor retinal photography were suited to the detection of serious retinopathy in screening programmes based in hospital or general practice. Fluorescein angiography was however of considerable value in assessing the severity of previously detected serious retinopathy. Fluorescein angiography was particularly useful in demonstrating the extent and degree of capillary under perfusion in cases of proliferative or ischaemic retinopathy and in detecting areas of microvascular abnormality and increased permeability in cases of exudative maculopathy.

The problem of screening for diabetic retinopathy is greater in general practice than in a hospital-based diabetic clinic. In the latter the screening personnel rapidly obtain expertise in the evaluation of retinal signs because of the large number of patients available for examination. In this study it was found (Chapter 5) that trained physicians became as accurate in the detection of serious retinopathy as experienced ophthalmologists although both observers missed 3-4 per cent of cases of serious retinopathy. The physicians involved in the study had spent time in the retina clinic of the Tennent Institute of Ophthalmology in Glasgow where they were trained in the detection of not only the signs of established serious retinopathy but

also the warning signs of impending serious retinopathy.

It would theoretically be possible for all patients attending a diabetic clinic to be screened for serious retinopathy on an annual basis by the physician responsible for the care of the patients. It has been calculated that such a screening programme would necessitate the appointment of one additional physician per million population but the increased costs would be likely to be offset by financial savings to the community of about three times the cost of the screening programme (Foulds et al 1983). Any such screening programme carried out by diabetic physicians would only be practical if the physicians concerned had been adequately trained in ophthalmoscopy and in the assessment of retinal abnormality. Such a screening programme would only be of value if backed up by an ophthalmology department having facilities for the further investigation and treatment of patients believed by the physician to have a serious retinopathy.

For patients cared for in general practice the problem is greater. Individual general practitioners have relatively few diabetic patients under their care and it would be impracticable to expect all such practitioners to develop and maintain skills in the early identification of established or potentially serious retinopathy. The British Diabetic Association may undertake the responsibility of including a course on the ophthalmoscopic evaluation of diabetic eye disease in the training programme for general practitioners and no doubt this would be a useful adjunct to the detection of diabetic eye disease among patients attending either hospital clinics or being cared for

in general practice (Thorn and Watkins 1982; Thorn and Russell 1973; Malins and Stewart 1971).

The role of Ophthalmic Opticians in the detection of diabetic eye disease is one that requires clarification. The use of opticians to conduct ophthalmological screening of diabetics is a possibility. Such personnel are suitably trained in their undergraduate and pre-registration years. Calculations show that the use of hospital based opticians for the screening of diabetics would show a cost benefit ratio of 1:6 (Foulds et al 1983). Recruitment of opticians to the hospital service may however prove financially unattractive. There seems little doubt that ophthalmic opticians outside hospital practice could play a role in diabetic screening particularly for those patients not attending hospital clinics but the cost benefit ratio based on the standard capitation fee paid by the General Ophthalmic Services would be reduced to at worst 1:1.

Doubtless some diabetic patients are more at risk of retinopathy than others. Unfortunately the younger symptomless patient is most at risk of the severest blinding form of the disease. In addition those with late onset diabetes may go many years without trouble but the gradual onset of this form of diabetes and the difficulty of exactly dating its onset results in many such patients presenting with established eye disease not long after their diabetes has been diagnosed.

For all those reasons a yearly screening of diabetics for eye disease has much to commend it.

Screening programmes need to be simple to be effective and as a matter of pragmatism a general ocular screening of all diabetics has much to commend it. On grounds of cost effectiveness alone it can be easily defended.

In this discussion the beneficial aspects of laser treatment in relation to the prevention of blindness have been stressed. Laser therapy is however a destructive form of treatment and will undoubtedly be replaced by more physiological forms of therapy in due course.

No one at present doubts the efficiency of laser therapy in preventing a significant (at least 60 percent) amount of blindness among diabetics (Diabetic Retinopathy Study 1976; Cheng 1979; Lawson et al 1983). Recently however the possible deleterious effects of light on retinal function and structure have raised doubts about the safety of laser therapy. Contrary to this the work reported in this thesis (Chapter 11) on the short term effects of laser or of slit lamp illumination on various aspects of visual function have been reassuring.

In clinical practice occasional instances of untoward reaction to laser photocoagulation are seen. These include temporary choroidal or retinal detachment, macular oedema, macular pucker, temporary myopia, shallowing of the anterior chamber, elevation of intraocular pressure and uveitis. In general these effects are short lived but permanent macular changes from oedema or pucker do occasionally occur. It is possible that suitable fractionation of the laser dose may reduce the incidence of these complications.

The inadvertent photocoagulation of the macular retina is an occasional accident and its occurance stresses the need for all ophthalmologists using the laser not only to be adequately trained in the use of this potentially dangerous instrument but to be conscious continually of fundal landmarks and to be ever watchful and attentive during its use.

We look forward to the day when more efficient and natural treatment of diabetes will obviate the development of retinopathy and render laser and similar treatments obsolete. Until that day, it behoves us to do all we can to detect retinopathy in its early treatable stage and to apply the treatment we have available in the most efficacious and efficient way that we can.

APPENDICES

COUNTRY	POPULATION (MILLIONS)	SEX	ALL AGES	0	1-4	5-14	15-24	25-34	35-44	45-54	55-64	65-74	75 +
ustralia 1973	13.16	T	13.6	0.4	0.1	0.1	0.3	1.0	2.5	5.8	24.9	81.3	198.5
		M	12.6	0.8	-	-	0.1	0.6	2.6	6.2	28.7	89.6	219.7
		F	14.7	-	0.2	0.3	0.5	1.4	2.6	5.3	21.2	74.4	186.7
ıstria 1973	7.46	T	15.8	-	-	-	0.3	0.9	2.3	3.4	18.3	64.1	138.0
		M	10.7	-	-	-	0.2	1.5	3.6	3.9	17.0	54.4	103.8
		F	20.3	-	-	-	0.4	0.2	1.0	3.0	19.2	70.6	154.3
lgaria 1973	8.58	T	7.4	-	0.4	0.2	0.1	0.8	1.4	4.6	15.7	42.3	57.1
		M	6.1	-	0.4	0.3	0.1	0.5	2.2	4.5	14.4	33.7	52.1
		F	8.1	-	0.4	0.2	0.1	1.0	0.6	4.7	16.9	50.0	60.8

OUNTRY	POPULATION (MILLIONS)	SEX	ALL AGES	0	1-4	5-14	15-24	25-34	35-44	45-54	55-64	65-74	75 +
anada 1973	22.10	T	14.8	-	0.2	0.1	0.3	1.3	3.0	7.3	26.5	83.2	221.3
		M	13.1	-	0.3	0.1	0.3	1.5	3.7	6.3	28.5	75.2	224.4
		F	16.5	-	0.1	0.2	0.3	1.2	2.2	6.3	24.7	90.1	219.3
ile 73	10.35	T	9.7	0.4	0.1	0.2	0.6	1.1	2.7	11.4	43.4	117.4	153.9
		M	9.3	-	0.2	0.1	0.4	1.3	3.3	12.4	47.7	112.3	158.7
		F	10.2	0.7	-	0.2	0.8	0.8	2.2	10.5	39.6	121.5	150.5
mark 73	4.99	T	12.7	-	-	0.3	-	0.8	4.2	5.7	17.1	48.2	118.5
		M	10.7	-	-	0.2	-	1.6	4.6	8.2	17.6	44.6	96.7
		F	14.6	-	-	0.3	-	-	3.9	3.3	16.5	51.2	133.6

COUNTRY	POPULATION (MILLIONS)	SEX	ALL AGES	0	1-4	5-14	15-24	25-34	35-44	45-54	55-64	65-74	75 +
Dominican Republic 1973	4.39	T	4.6	-	0.3	0.2	0.9	2.0	3.6	11.9	30.5	47.1	65.7
		M	3.8	-	0.3	0.3	0.7	2.9	4.2	10.5	24.8	37.8	30.6
		F	5.3	-	0.3	0.1	1.1	1.2	2.9	13.4	37.0	57.0	96.9
gypt * 972	34.98	T	6.5	0.8	0.2	0.5	1.7	2.4	4.7	13.7	39.9	63.3	58.5
		M	6.6	1.3	0.2	0.5	2.2	3.4	5.2	13.7	39.9	63.3	58.5
		F	6.5	0.3	0.2	0.4	1.2	1.5	4.1	13.6	32.4	69.4	82.1
:ance 1973	52.13	T	14.5	0.2	0.2	0.1	0.1	0.5	1.7	4.3	17.8	58.6	137.4
		M	10.9	-	0.3	-	0.1	0.4	2.0	5.0	19.0	55.7	125.9
		F	17.9	0.5	0.1	0.1	0.2	0.5	1.4	3.7	16.8	60.7	142.8

COUNTRY	POPULATION (MILLIONS)	SEX	ALL AGES	0	1-4	5-14	15-24	25-34	35-44	45-54	55-64	65-74	75 +
ermany 1973	61.90	T	34.8	0.8	-	0.1	0.5	0.9	2.9	8.6	42.3	147.3	332.7
		M	24.7	1.5	0.1	0.1	0.4	1.0	3.7	10.7	42.7	134.5	268.7
		F	44.0	-	-	0.1	0.6	0.8	2.1	7.0	42.1	156.1	364.0
eece 973	8.91	T	26.9	-	-	0.3	0.6	0.4	2.2	7.1	44.6	140.4	252.3
		M	22.2	-	-	0.4	0.4	0.4	3.1	6.9	40.3	117.9	245.3
		F	31.3	-	-	0.3	0.8	0.3	1.5	7.3	48.5	159.5	257.3
nduras 1973	2.80	T	3.1	0.8	0.2	0.1	0.4	0.9	2.1	7.2	17.8	39.4	194.7
		M	3.7	1.6	0.5	0.3	0.7	1.7	0.8	11.0	19.4	36.3	208.3
		F	2.6	-	-	-	-	-	3.2	3.5	16.2	42.3	105.3

COUNTRY	POPULATION (MILLIONS)	SEX	ALL AGES	0	1-4	5-14	15-24	25-34	35-44	45-54	55-64	65-74	75 +
Hong Kong 1973	4.18	T	4.8	1.2	-	0.1	0.1	0.5	1.4	3.4	20.7	48.9	70.7
		M	4.4	2.4	-	-	-	0.8	1.2	3.1	20.1	66.7	101.9
		F	5.3	-	-	0.2	0.2	-	1.8	3.8	21.2	38.1	59.9
Hungary 1973	10.48	T	6.2	-	0.2	0.1	0.3	0.2	0.4	3.3	11.8	31.4	46.9
		M	4.1	-	-	-	0.4	0.1	0.4	3.1	9.0	21.9	35.4
		F	8.2	-	0.3	0.3	0.1	0.3	0.3	3.6	14.1	38.7	53.6
Iceland 1973	0.21	T	4.7	-	-	-	-	-	8.8	-	-	25.1	64.9
		M	1.9	-	-	-	-	-	8.8	-	-	-	30.3
		F	7.6	-	-	-	-	-	9.0	-	-	50.0	93.0

COUNTRY	POPULATION (MILLIONS)	SEX	ALL AGES	0	1-4	5-14	15-24	25-34	35-44	45-54	55-64	65-74	75 +
		T	23.6	0.3	0.1	0.2	0.2	0.6	1.7	8.4	35.3	119.2	258.4
taly 973	54.63	M	16.9	0.2	0.1	0.2	0.2	0.7	2.1	9.0	33.2	98.0	200.6
		F	30.0	0.5	-	0.3	0.3	0.5	1.2	7.8	37.2	135.5	291.7
		T	7.7	0.1	0.1	0.1	0.4	0.7	2.3	5.3	19.3	56.2	89.1
apan 1973	108.36	M	7.6	0.2	0.1	0.1	0.4	0.6	2.9	6.3	21.1	58.7	103.7
		F	7.7	-	0.1	0.2	0.3	0.8	1.6	4.5	17.7	54.0	79.8
		T	4.3	1.2	-	0.2	1.5	0.5	1.9	10.9	18.2	84.8	
rdan 973	1.83	M	4.1	2.4	-	-	1.9	1.0	2.6	15.4	18.1	53.7	
		F	4.6	-	-	0.4	1.2	-	1.3	6.2	18.2	126.7	

COUNTRY	POPULATION (MILLIONS)	SEX	ALL AGES	0	1-4	5-14	15-24	25-34	35-44	45-54	55-64	65-74	75 +
lauritius 1973	0.83	T	14.0	-	1.3	0.9	1.6	2.0	9.0	30.8	67.6	160.9	162.8
		M	11.3	-	2.5	1.7	1.1	-	10.2	16.9	63.1	166.7	74.1
		F	16.8	-	-	-	2.2	3.9	7.8	45.9	72.1	157.5	203.4
exico 1973	54.36	T	14.3	1.5	0.3	0.3	0.9	2.7	9.9	33.3	86.7	178.8	230.2
		M	12.4	1.6	0.4	0.3	0.8	3.0	11.0	32.9	77.1	146.1	184.8
		F	16.2	1.4	0.2	0.2	1.0	2.3	8.7	33.6	96.0	210.6	267.8
ther-nds 73	13.42	T	10.5	0.5	0.1	0.1	0.4	0.6	1.8	3.8	14.2	42.9	144.0
		M	7.0	-	0.2	-	0.5	0.4	1.6	3.7	12.2	26.4	113.6
		F	14.0	1.0	-	0.3	0.4	0.8	2.0	3.9	16.1	55.9	165.4

OUNTRY	POPULATION (MILLIONS)	SEX	ALL AGES	0	1-4	5-14	15-24	25-34	35-44	45-54	55-64	65-74	75+
		T	10.6	0.6	-	0.1	1.1	1.5	2.5	6.6	22.9	58.5	91.8
ortugal 1973	8.54	M	8.8	1.1	-	-	0.9	1.5	4.0	6.3	21.3	53.8	83.5
		F	12.2	-	-	0.2	1.2	1.5	1.2	6.9	24.3	61.8	96.4
		T	11.3	-	-	-	-	0.3	3.0	22.3	60.7	160.0	
ngapore 1973	2.18	M	10.1	-	-	-	-	-	2.5	21.3	49.4	169.5	
		F	12.5	-	-	-	-	0.7	3.6	23.4	72.6	152.5	
		T	18.0	1.6	0.2	0.2	0.5	1.1	2.2	7.1	31.7	107.3	192.3
ain 73	34.67	M	12.7	2.0	0.3	0.2	0.4	1.3	2.4	7.7	28.1	81.6	148.2
		F	23.2	1.2	0.2	0.2	0.6	0.9	2.1	6.6	34.6	126.9	218.7

COUNTRY	POPULATION (MILLIONS)	SEX	ALL AGES	0	1-4	5-14	15-24	25-34	35-44	45-54	55-64	65-74	75 +
Sweden 1973	8.15	T	16.2	-	0.2	0.3	0.5	2.5	4.5	6.8	15.3	50.9	147.4
		M	14.2	-	-	-	0.7	2.9	5.4	9.8	14.7	51.1	131.0
		F	18.2	-	0.5	0.5	0.4	2.0	3.6	3.	15.9	50.7	158.7
U.K. England & Wales 1973	49.29	T	10.4	0.4	0.1	0.2	0.5	0.8	1.8	3.8	11.7	39.3	96.9
		M	8.3	0.3	0.1	0.1	0.5	0.7	2.5	4.6	12.3	37.9	91.6
		F	12.5	0.6	0.2	0.1	0.5	0.8	1.1	3.1	11.2	40.4	99.4
N. Ireland 1973	1.54	T	12.0	-	-	-	0.8	0.5	1.2	3.6	19.8	58.2	138.9
		M	8.0	-	-	-	1.6	1.0	-	3.7	15.9	51.3	96.2
		F	15.9	-	-	-	-	-	2.4	3.5	23.2	63.3	162.7

COUNTRY	POPULATION (MILLIONS)	SEX	ALL AGES	0	1-4	5-14	15-24	25-34	35-44	45-54	55-65	65-74	75 +
U.K. Scotland 1973	5.20	T	12.7	-	-	-	0.4	1.5	1.8	5.9	17.4	51.5	120.6
		M	9.5	-	-	-	0.8	1.9	2.1	5.3	19.8	39.4	118.5
		F	15.6	-	-	-	-	1.2	1.6	6.5	15.3	60.0	121.6
U.S.A. * 1972	207.92	T	18.6	0.5	0.2	0.2	0.6	2.4	4.9	12.3	33.8	87.9	195.9
		M	15.6	0.5	0.2	0.5	0.5	2.6	5.6	13.3	31.9	84.8	183.7
		F	21.4	0.5	0.1	0.2	0.7	2.3	4.2	11.4	35.5	93.7	203.4

Appendix 1. Death rate (per 100,000 deaths) for age and sex in different countries of the world. (Infant death per 100,000 live-born). * Statistics of the year 1972. The others are of 1973. Population is in millions.

	Error scores			
Normal subjects	No retinopathy	Background retinopathy	Exudative retinopathy	Proliferative retinopathy
96	96	106	334	58
104	84	142	288	68
80	152	136	440	336
	98	128		244
76	66	78	528	284
80	74		388	252
84	84	66	192	136
		64	222	112
76	104	58	164	502
	108			482
152	88	228	128	118
108		212	322	
102	68	104	144	228
104	94	88		192
72	88	98	344	78
66	102	102	298	56
68	164	178	402	60
78	132	200	384	
82	58	88		112
90	72			134
22	222	286		76
34	186			84
114	74	304		140
96	90	356		104
56	102	102		286
		140		262
134	100	68		248
152		94		270
	198	78		198
	162			
	112	114		184
		106		212

Number of eyes				
24	27	27	15	29
Number of subjects				
14	16	16	9	16

Appendix 2. Individual total error scores of diabetic and non-diabetic subjects tested for colour vision.

TENNENT INSTITUTE OF OPHTHALMOLOGY
UNIVERSITY OF GLASGOW

Department
SOR W. S. FOULDS

WESTERN INFIRMARY
GLASGOW G11 6NT.
TEL: 041-339 8822.
EXT. 640.

Date as post marked

Dear Sirs ,

I am currently preparing a Ph.D. Thesis on some aspects of diabetes-induced blindness and diabetic retinopathy in the west of Scotland under Professor W.S.Foulds' supervision .

To this end I wonder if you would be kind enough to send me any information relating to the common causes of blindness and the prevalence of diabetes and diabetic retinopathy in your Country/Province/Area or any other information that you might think helpful in relation to my work .

I should be very grateful for your cooperation in this matter .

Yours faithfully

Issam M.Ghafour

Appendix 3. The letter which was sent to different Societies and Authorities involved in the epidemiology of diabetes and blindness in some countries .

WOODSIDE HEALTH CENTRE

I.M.Ghafour

Name
Age
Sex
Duration of diabetes
Treatment
Family history
Smoking
Treating body
Blood pressure(Sitting)
V.A.R - Distant
Reading
V.A.L - Distant
Reading
Eye condition
Right
Left
Funduscopy
Right
Left
Random blood sugar
HbA_{1c}
Referral
Comment

Appendix 4. Form used for collection of data at Woodside Health Centre .

	0-4	5-15	16-44	45-64	65+	Total
	119	365	1975	838	549	3890
.9)	(47.4)	(50.4)	(55.4)	(47.4)	(35.2)	(49.0)
	132	359	1590	930	1010	4047
1)	(52.6)	(49.6)	(44.6)	(52.6)	(64.8)	(51.0)
70	251	724	3565	1768	1559	7937
.9)	(3.2)	(9.1)	(45.0)	(22.2)	(19.6)	

R 65 YEAR OLDS AT WOODSIDE HEALTH CENTRE ARE : 5366 OUT OF
(14.1 per cent).

Appendix 5. Age and sex distribution of patients on Woodside Health Centre practice list.

GLASGOW ROYAL INFIRMARY I.M.Ghafour

Name
Diabetic clinic number .
Age
Sex
Duration of diabetes
Treatment
Smoking habit
Blood pressure
Visual acuity
Right
Left
Eye abnormality
Right
Left
Funduscopy (Describe)
Right
Left
Referral
Comment

Appendix 6. Form used for collection of data at Glasgow Royal Infirmary .

Duration(years)	Male	Female	All
0-1	43	46	89
1^{+}-2	18	25	43
2^{+}-5	43	50	93
5^{+}-10	41	47	88
10^{+}-15	23	19	42
15^{+}-20	5	8	13
20^{+}	17	15	32
Total	190	210	400

Appendix 7. Known duration of diabetes (in years) and numbers of patients among 400 diabetic patients studied at Glasgow Royal Infirmary .

Duration(years)	Diet	O.H.A.	Insulin
0-1	43	39	7
1^{+}-2	18	20	5
2^{+}-5	24	52	17
5^{+}-10	9	44	35
10^{+}-15	3	12	27
15^{+}-20	1	2	10
20^{+}	3	4	25
Total	101	173	126

Appendix 8. Numbers of patients on different types of treatment . The total number is 400 patients studied at Glasgow Royal Infirmary .

Patient No.	Sex	Age at registration	Age at onset
1	M	68	65
2	M	72	71
3	M	58	58
4	M	82	82
5	M	29	29
6	F	67	63
7	F	79	79
8	F	78	78
9	F	50	48
10	F	69	69
11	F	78	77
12	F	70	65
13	F	21	21
14	F	39	39
15	F	66	65
16	F	57	57
17	F	75	75
18	F	64	64
19	F	73	73
20	F	64	64
21	F	61	60
22	F	67	62
23	F	59	47
24	F	75	73
25	F	66	66
26	F	57	53
27	F	59	59
28	F	78	78

29	F	68	68
30	F	83	83
31	F	70	69
32	F	75	74

Appendix 9. Sex, age at onset, and age at registration of 32 legally blind diabetics (1980).

CERTIFICATION OF PERSONS WHO ARE EITHER (1) SO BLIND AS TO BE UNABLE TO PERFORM ANY WORK FOR WHICH EYESIGHT IS ESSENTIAL,* OR (2) SUBSTANTIALLY AND PERMANENTLY HANDICAPPED BY DEFECTIVE VISION

PARTICULARS OF PERSON AND FORM OF MEDICAL CERTIFICATE

ithority..... *Date of application*.....

ie .....

ress .....

.....

ge of address.....

.....

.....

PART 1.—PARTICULARS OF PERSON

..... Date of Birth..... Sex.....

Aarried (ii) Single (iii) Widowed
category applicable)

ion in household—(i) Head (ii) Member of family (iii) Lodger
category applicable)

ber of dependants and their relationship person:—

a) adults .....

b) children under 16.....

ccupation before vision began to fail .....

e of any other occupation before vision

n to fail.....

) Nature of any work undertaken since

ision failed; .....

.....

) whether work is still being carried on.....

r willing to undergo a course of ical training:—

o, whether application already made to.....

local authority; .....

education authority; or .....

Department of Employment .....

receiving injury or disablement under National Insurance (Indus- njuries) Act, 1946 .....

er relevant information .....

.....

.....

.....

.....

ion of blindness contained in section 64(1) of the National Assistance Act, 1948.

EXAMINATION OF EYES

	RIGHT EYE	LEFT EYE
acuity—		
unaided	.....	.....
with correcting glasses	.....	.....
both eyes — best direct vision after correction	..... (also ring appropriate category—(1) less than 3/60; (2) less than 6/60; (3) less than 6/36; (4) less than 6/18; (5) 6/18 or more.)	
f vision		
g category applicable)	1. Nil 2. Less than 10° 3. Contracted 4. Central scotoma 5. Hemianopia 6. Good	1. Nil 2. Less than 10° 3. Contracted 4. Central scotoma 5. Hemianopia 6. Good
orbit, muscles, tension gmus, etc.	.....	.....
....	.....	.....
....	.....	.....
ciliary body	.....	.....
....	.....	.....
....	.....	.....
....	.....	.....
....	.....	.....
rve	.....	.....

DIAGNOSIS

lar disease producing ss / substantial and ent defect of vision	(1)	(1).....
ions and sequelae	(2)	(2).....
lar diseases	(3)	(3).....
ain ocular disease	(4)	(4).....
ye trouble	Age.....	Age .....
i) blindness*	Age.....	Age .....
substantial and perma- ct of vision*	Age.....	Age .....

PROGNOSIS (Ring category applicable)

remediable 2. Likely to deteriorate 3. Stationary 4. Likely to improve

HISTORY (Ring category applicable)

MIC TREATMENT—
ne
t amenable to treatment
atment refused (including refusal to complete full course of treatment)
4. Treatment accepted and still being given
5. Treatment completed—successful
6. Treatment completed—failed
7. Not known

EFECT IN PARENTS OR RELATIVES
known 2. No 3. Yes

INITY OF PARENTS
known 2. No 3. Yes (state relationship).....

LITIC TREATMENT
known 2. No 3. Yes

RECOMMENDATIONS (Ring category applicable)

NT OR CONTINUATION OF TREATMENT RECOMMENDED?
2. Medical 4. Optical
3. Surgical 5. Inadvisable on medical grounds

ATMENT PROBABLY CURE OR PREVENT *BLINDNESS/DEFECT OF VISION?
2. Yes 3. Doubtful

NATION NECESSARY, AND AFTER WHAT INTERVAL?
2. Yes Interval.....

of the applicant being employable, can you indicate—
tivity considered unsuitable (*e.g.*, stooping, the lifting of heavy weights) .....
tivity that is particularly suitable (*e.g.*, a sitting job, possibly handling material, for a glaucoma patient with small fields and good central vision) .....
nge of present occupation is desirable - - - - -

page of form.

(Ring category applicable)

	LEFT EYE
ls	000
lidia	001
ract	002
cated lens	003
ragmus	004
lyopia	005
thalmos	006
phthalmos	007
othalmos	008
rs	009
nism	010
nds of the eyeball	020
unctiva: Inflammatory diseases	030
unctiva: Essential shrinkage, etc.	031
and tear sac: Inflammatory diseases	040
paralysis	300
a: Inflammatory diseases	050
ea: Ulcerative keratitis	060
ea: Interstitial keratitis	070
ea: Other diseases	080
eal Dystrophies	081
ea: Keratoconus	082
cyclitis	090
	091
phthalmitis, panophthalmitis	100
pathetic ophthalmia	101
ental fibroplasia	102
opathy, exudative; Neuro-retinopathy	110
opathy, central exudative (disciform)	111
erative retinopathy: Retinitis pigmentosa, etc.	120
macular degeneration	121
ocular haemorrhage	250
ion retinal artery	251
ion retinal vein	252
sculitis retinae: Eales' disease	253
vascular diseases of the retina	254

	RIGHT EYE		LEFT EYE
	130	Detachment of retina	130
	140	Choroidal atrophy—not myopic	140
	141	Gyrate atrophy: Chorioderaemia	141
	142	Central (macular) atrophy	142
	150	Optic nerve atrophy and neuritis	150
	160	Retrobulbar neuritis and toxic amblyopia	160
	180	Tumour: ocular adnexa	180
	190	Tumour: intra-ocular, indeterminate	190
	191	Choroidal tumour, primary	191
	192	Choroidal tumour, secondary	192
	193	Retinal tumour	193
	200	Cataract—not congenital	200
	210	Aphakia (surgical)	210
	221	Dislocated lens	221
	220	Other lens anomalies	220
	230	Myopia	230
	240	Normal eye and refractive errors, not myopia	240
	260	Glaucoma, primary	260
	280	Nystagmus	280
	290	Cortical and tract lesions	290
	310	Amblyopia ex anopsia (Amblyopia from squint)	310
	311	Functional disturbances	311
	170	Indeterminate conditions	170
	320	Others	320

COMPLICATIONS

0	No complications	0
1	Corneal opacity or staphyloma	1
2	Occlusio, Seclusio	2
3	Secondary cataract	3
4	Detachment of the retina	4
5	Choroidal-retinal disease	5
6	Optic nerve atrophy	6
7	Enucleated eye: Phthisis Bulbi	7
8	Secondary glaucoma	8
9	Others, including conjunctivà and blepharitis	9

CAUSES OF EYE DEFECTS

NOTES.—(a) Ring category (categories) applicable, indicating major cause by (1) and other cause, if any, by (2).
(b) Where cause is not specified in appropriate category insert particulars in blank bracket provided.

		LEFT EYE
AL AND UNDETERMINED		
al anomalies		000
ies, etc.		010
f globe and orbit		020
		030
ors of refraction		040
, primary		050
primary		060
)		070
ed maternal infection		099
Rubella	091	
Toxoplasmosis	092	
Others (.....)	093	
AND TOXIC		
Neonatorum		100
Gonococcal	101	
Inclusion body	102	
Others (.....)	103	
		110
ther virus infections (.....)	111	
f outer coats of eye		120
Specify:		
.....		
.....)		130
		150
genital		160
cquired		170
ons		180
asles	181	
allpox	182	
us Meningitis	183	
encephalitis	184	
pes ophthalmicus	185	
pes febrilis	186	
ers (.....)	187	
tions		200
phtheria	201	
let fever	202	
lingococcal meningitis	203	
meningitis	204	
metazoal infections not specified.....		210
trumous, etc.		250
emia, etc.		270
.....)		200
CHEMICAL		
		300
rauma		310
hold accidents	311	
r sport	312	
or transportation	313	
al, surgical or radiational procedures	314	
flicted	315	
t	316	
.....)	317	
		320
	321	
ng	322	
al	323	
	324	
tural	325	
	326	
(.....)	327	
		330
e service: direct	331	
	332	
nal	333	
	334	
(.....)	335	

	RIGHT EYE		LEFT EYE
340	Trauma, category not ascertained		340
350	Sympathetic ophthalmia		350
360	Chemico-toxic		360
400	Scheduled industrial diseases		400
	B. SYSTEMIC DISEASES		
500	Anaemia and blood diseases		500
	501 Haemorrhage	501	
	502 Pernicious anaemia	502	
	503 Leukaemia	503	
	504 Polycythaemia	504	
	505 Others (.....)	505	
510	Diabetes		510
511	Hyperthyroidism		511
512	Lipoidosis		512
513	Other endocrine and metabolic diseases		513
	(.....)		
520	Nephritis		520
530	Disease of pregnancy and childbirth		530
540	Vascular diseases		540
	541 Essential hypertension	541	
	542 Arterio-sclerosis	542	
	543 Cerebral arterio-sclerosis	543	
	544 Others (.....)	544	
550	Intracranial neoplasm		550
560	Disease of central nervous system		560
	561 Disseminated sclerosis	561	
	562 Tabes	562	
	563 Other syphilis	563	
	564 Hydrocephalus	564	
	565 Friedreich's ataxia	565	
	566 Brain abcess	566	
	567 Others (.....)	567	
570	Functional Diseases		570
	571 Hysteria	571	
	572 Malingering	572	
	573 Others (.....)	573	
600	Arthritic affections		600
	601 Rheumatoid	601	
	602 Spondylitis	602	
	603 Others (.....)	603	
610	Disease of Bony System		610
	611 Oxycephaly	611	
	612 Leontiasis ossea	612	
	613 Others (.....)	613	
620	Nutritional deficiency		620
630	Diseases of skin		630
	631 Acne rosacea	631	
	632 Pemphigus	632	
	633 Scleroderma	633	
	634 Ichthyosis	634	
	635 Epidermolysis bullosa	635	
	636 Others (.....)	636	
640	Phakomatoses		640
650	Mesodermal syndromes		650
	651 Arachnodactyly	651	
	652 Elastosis dystrophica	652	
	653 Laurence Moon-Beidl	653	
	654 Others (.....)	654	
E 700	NOT CLASSIFIED OWING TO LACK OF DATA		700
F 800	NO DEFECT (Normal eye)		800
G 900	(If category is not sufficiently specific, state any other cause .....)		

1. None
2. Mental defect
3. Deafness
4. Deaf-mutism
5. Defects of hands and arms
6. Defects of lower limbs
7. Fits
8. General disease (specify further if possible)
9. Other

*See NOTE at foot of first page of form.

CERTIFICATE

IF AN ADULT, IS THE PERSON SO BLIND AS TO BE UNABLE TO PERFORM ANY WORK FOR WHICH EYESIGHT IS ESSENTIAL? (Write "Yes" or "No") .....

IF UNDER 16 YEARS, IS THE PERSON SO BLIND AS ONLY TO BE CAPABLE OF EDUCATION BY METHODS SUITABLE FOR CHILDREN WHO HAVE INSUFFICIENT VISION TO BENEFIT FROM EDUCATION AS PARTIALLY SIGHTED? (Write "Yes" or "No") ....

NOT SO BLIND AS TO BE UNABLE TO PERFORM ANY WORK FOR WHICH ESIGHT IS ESSENTIAL,

is the person substantially and permanently handicapped by defective vision? (Write "Yes" or "No") ....

if so, is the handicap due to—

1. Congenital defect? 2. Disease or injury? (Ring category applicable) ....

is the person, if under 16 years of age,

1. Likely to become, before reaching that age, so blind as to be unable to perform any work for which eyesight is essential? (Write "Yes" or "No") ....

2. Likely to benefit by class for visually handicapped? (Write "Yes" or "No") ....

or is the person, if 16 years of age or over, likely to become so blind as to be unable to perform any work for which eyesight is essential (Write "Yes" or "No") .....

f in the affirmative, is blindness likely to occur so soon, or is the nature of the visual defects such, that the person would benefit from training for employment or other services appropriate to blind people? (Write "Yes" or "No") ....

..... (1) *Signature* .....
Ophthalmic Surgeon

..... (2) *Signature* .....
Ophthalmic Surgeon

PART III.—FURTHER NOTES

SES OF EYE INJURY

defect is due to industrial or non-industrial trauma:—

Precise occupation at time of onset ....

Description of accident, including nature of object striking eye or cranium ....

ERMAN TEST

Date specimen taken .... No. of Specimen .....

Result ("Positive" or "Negative") ....

ction taken in positive cases ....

ACTION TAKEN ON RECOMMENDATIONS AND REGISTRATION FORM
(If no action necessary, write "Nil" across item)

MENT

.....

L EDUCATIONAL TREATMENT

when reported to education authority ....

R EDUCATION, TECHNICAL OR PROFESSIONAL

when reported to (a) local authority ....

(b) education authority ....

(c) Department of Employment and National Service .....

INATION

l duly noted ....

ANY OTHER RELEVANT INFORMATION

x 10. The Form BP1.

.....

.....

.....

.....

.....

.....

.....

SOCIETY FOR THE BLIND IN GLASGOW & THE WEST OF SCOTLAND I.M.Ghafour

Name	Age	Sex	Age at onset	Age at regist.	R.E. V.A.	R.E. Field	L.E. V.A.	L.E. Field	R.E. 1y. cause	R.E. 2y.	L.E. 1y. cause	L.E. 2y.	Comment

Appendix 10a. Contents of Form used for collection of data at the Society for the Blind in Gl

Cause	The year 1960	The year 1980
Cataract	22.2%	10.4%
Myopia	14.2%	6.0%
Senile macular degeneration	9.8%	29.8%
External eye disease	7.4%	2.8%
Glaucoma	9.2%	14.6%
Diabetic retinopathy	6.8%	8.5%
Optic nerve atrophy	4.9%	4.5%

Appendix 11. A comparison of the leading causes of legal blindness in the years 1960 and 1980(West of Scotland) .

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Contrast sensitivity in diabetic subjects with and without retinopathy

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SUMMARY The clinical usefulness of the Arden grating test in assessing early abnormalities in retinal function of diabetics has been explored. Although the test revealed significant differences in constrast sensitivities between diabetics and normal persons, the large variances in the test scores of diabetics limit its use as a clinical tool for the screening of diabetic patients.

Diabetes is said to be associated with detectable alterations in colour perception before the development of ophthalmoscopically detectable retinopathy.[1] The Arden grating test[2] is claimed to detect disturbances of retinal integrative function even when acuity is normal. The test was used to assess whether it was of clinical value in detecting early abnormality in retinal function in diabetic subjects without retinopathy or in those with established retinopathy and whether it was useful in differentiating serious from not serious retinopathy.

Materials and methods

The test was carried out as described by Arden and Jacobson[2] except that standard artificial daylight was used (Verivide Cabinet, Leslie Hubble Ltd). Plates were presented at a standard distance of 57 cm and each eye was tested separately. The test was used in 80 normal subjects (age range 24 to 68, mean age 46, median age 45 years) and in 99 diabetic subjects (age range 27 to 70, mean age 47, median age 49 years). The ages of the 2 groups of subjects were comparable ($p>0{\cdot}5$, Mann-Whitney nonparametric test). Forty-two of the diabetics had no detectable retinopathy on ophthalmoscopy. Twenty-two had background retinopathy, that is, scattered haemorrhages, microaneurysms, and a small number of hard exudates with retention of normal visual acuity. Twenty-nine patients had proliferative retinopathy as evidenced by disc or other new vessels. The visual acuities among patients with proliferative retinopathy ranged from 6/5 to 6/36 with a mean level of 6/9 and a median of 6/9. For analysis only one eye (the right) was used from each patient tested.

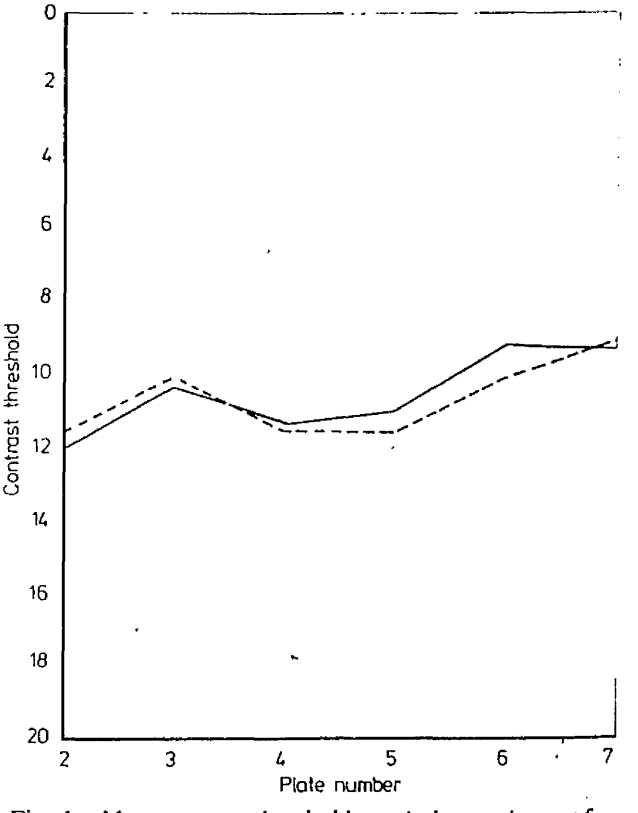

Fig. 1 *Mean contrast thresholds on Arden grating test for normal persons. (_____) Our controls. (_ _ _ _ _) Arden and Jacobson normal persons.*

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Table 1 *A comparison of mean contrast thresholds for Arden and Jacobson's normals, our controls, all diabetics, and different groups of diabetic patients. Standard deviations are shown in brackets*

Plate	*2*	*3*	*4*	*5*	*6*	*7*
Arden's figures (SD=2)	11·50	10·00	11·50	11·50	10·00	9·00
Mean readings of our normal subjects	11·96 (2·27)	10·26 (1·89)	11·33 (2·08)	10·90 (1·98)	9·08 (2·25)	9·19 (2·56)
Mean reading of normal subjects	11·96 (2·27)	10·26 (1·89)	11·33 (2·08)	10·90 (1·98)	9·08 (2·25)	9·19 (2·56)
Mean reading of 99 diabetics	13·42 (3·72)	11·17 (3·39)	13·37 (3·54)	13·73 (3·99)	13·91 (6·39)	15·80 (7·31)
Normal	11·96 (2·27)	10·26 (1·89)	11·33 (2·08)	10·90 (1·98)	9·08 (2·25)	9·19 (2·56)
'No retinopathy' diabetic group	12·86 (4·03)	9·53 (2·99)	11·73 (3·32)	11·60 (3·50)	12·40 (7·28)	13·26 (8·07)
Normal controls	11·96 (2·27)	10·26 (1·89)	11·33 (2·08)	10·90 (1·98)	9·08 (2·25)	9·19 (2·56)
'Background' retinopathy group	13·60 (2·87)	12·00 (2·23)	13·33 (3·06)	13·13 (2·64)	12·66 (4·33)	14·86 (5·20)
'Proliferative' retinopathy group	13·80 (4·31)	12·00 (4·22)	15·06 (3·65)	16·46 (4·18)	16·66 (6·65)	19·26 (7·43)

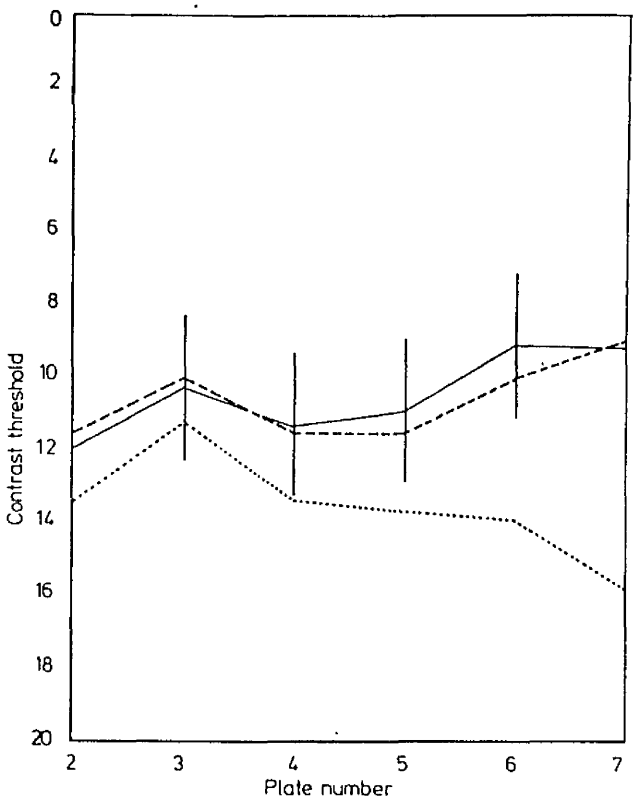

Fig. 2 *Mean contrast thresholds for: (_____) Our normals. (_ _ _ _ _) Arden and Jacobson's normals. (. . . . .) All diabetics. The vertical bars mark ±2 SD limits for our normals.*

Results

The mean contrast thresholds for normal and diabetic subjects for each of the 6 plates of differing spatial frequency used are shown in Table 1 together with the relevant standard deviations, as also are the mean normal values quoted by Arden and Jacobson.[2]

In general, for normal subjects our results for each plate were in agreement with those of Arden and Jacobson (Fig. 1) except for plates 5 and 6, where a significantly lower threshold was found for our normal subjects ($p<0·001$, each plate).

When the results for the 99 diabetic patients were compared with our normal results (or with those published by Arden and Jacobson), a significantly higher mean threshold was found for each plate (Fig. 2). When the results for our normal controls (Fig. 3) were compared with those from diabetic subjects without retinopathy, a significant increase in the threshold was found for the higher frequency plates 6 and 7 (whereas with Arden's control values a significant difference was also found with the low frequency plate number 2).

As would be expected, the results from our normal controls differed significantly from those obtained from patients with either background retinopathy or proliferative retinopathy (Fig. 4), as did the same results when Arden's control data were used.

When the various grades of retinopathy within the diabetic group were compared, the results were less clear-cut, though significant differences were found.

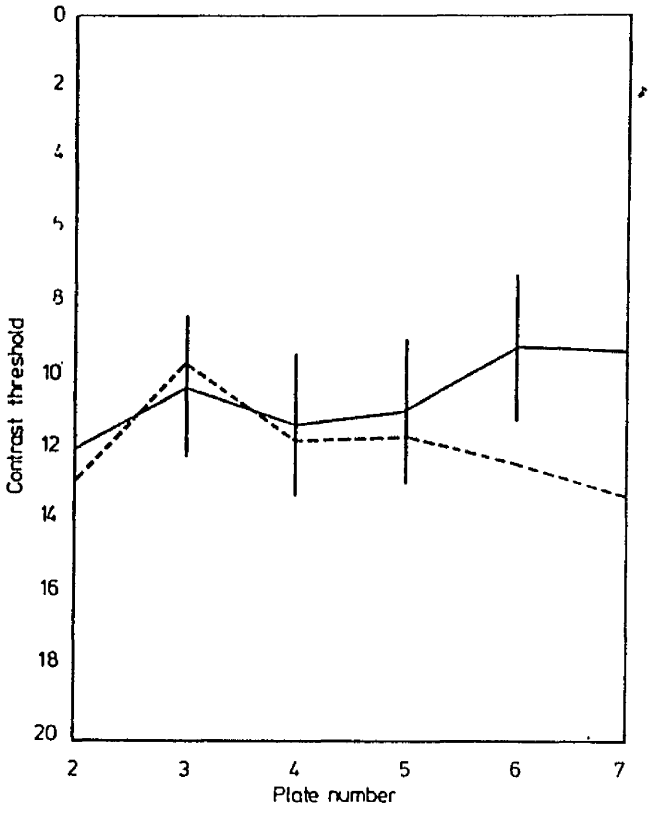

Fig. 3 *Mean contrast thresholds for: (_____) Our normals. (_ _ _ _ _) 'No retinopathy' group. ± 2 SD limits for the normals are shown.*

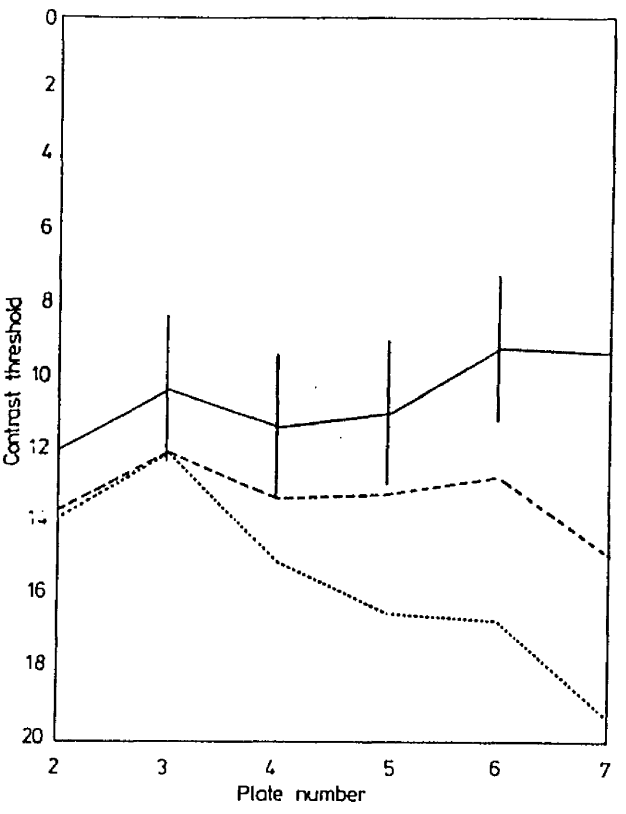

Fig. 4 *Mean contrast thresholds for: (_____) Our normals. (_ _ _ _ _) 'Background' retinopathy group. (. . . . .) 'Proliferative' retinopathy group. ± 2 SD limits for normals are shown.*

Thus the results for patients with diabetes but without retinopathy were significantly different in plates 3, 4, and 5 from those with background retinopathy and in all plates except plate 2 when compared with results from patients with proliferative retinopathy. Even when background retinopathy was compared with proliferative retinopathy, this latter group showed significantly increased thresholds for plates 5, 6, and 7 as compared with the former group. The results of the above comparisons are summarised in Fig. 5. The comparisons were made by a modified t test, applicable to cases with unequal variances.

It is worth noting that unlike the control group, in which the variance for each plate was similar (SD= 1·89 to 2·56), in all the diabetic groups the variances tended to be greater than in the controls, and particularly when higher frequency plates were used. An F test was used to assess whether the increased variance was significant, and significant values are marked with an asterisk in Fig. 6.

Discussion

Our results with the Arden grating test in normal subjects show a lower threshold for plates 5 and 6 (1·6 cycles/degree and 3·2 cycles/degree respectively) than those previously published by Arden and Jacobson[2] but are in agreement with figures recently published by Singh *et al.*[3] The results of the Arden grating test are to some degree age-related,[4] and the difference may reflect a different age composition in Arden and Jacobson's material and our own.

It is of interest that diabetic patients without retinopathy show increased thresholds at the higher spatial frequencies tested, which suggests that the functional deficit for these frequencies may precede ophthalmoscopically visible retinopathy.

Even within the group of diabetic patients increasing severity of retinopathy (background versus proliferative) was, as might be expected, associated with a decreased contrast sensitivity to grating patterns and an increasing variability in results, especially for plates of high frequency content.

Unfortunately the relatively large standard deviations in the groups affected by retinopathy resulted in considerable overlap between groups, so that the test was not found to be clinically useful in separating individual diabetic patients into serious or not serious

Plate	2	3	4	5	6	7	Comparison
				*	*		Normal Controls v. Arden Normals
	*	*	*	*	*	*	Arden Normals v. All Diabetics
	*				*	*	Arden Normals v. No Retinopathy
	*	*	*	*	*	*	Arden Normals v. Background Retinopathy
	*	*	*	*	*	*	Arden Normals v. Proliferative Retinopathy
	*	*	*	*	*	*	Normal Controls v. All Diabetics
					*	*	Normal Controls v. No Retinopathy
	*	*	*	*	*	*	Normal Controls v. Background Retinopathy
	*	*	*	*	*	*	Normal Controls v. Proliferative Retinopathy
		*	*	*			No Retinopathy v. Background Retinopathy
		*	*	*	*	*	No Retinopathy v. Proliferative Retinopathy
				*	*	*	Background Retinopathy v. Proliferative Retinopathy

Fig. 5 *Summary of the comparison of mean contrast thresholds. Differences significant at the level of at least p=0·05 are indicated by*.*

Plate	2	3	4	5	6	7	Comparison
						*	Normal Controls v. Arden Normals
	*	*	*	*	*	*	Arden Normals v. All Diabetics
	*	*	*	*	*	*	Arden Normals v. No Retinopathy
	*		*	*	*	*	Arden Normals v. Background Retinopathy
	*	*	*	*	*	*	Arden Normals v. Proliferative Retinopathy
	*	*	*	*	*	*	Normal Controls v. All Diabetics
	*	*	*	*	*	*	Normal Controls v. No Retinopathy
			*	*	*	*	Normal Controls v. Background Retinopathy
	*	*	*	*	*	*	Normal Controls v. Proliferative Retinopathy
					*	*	No Retinopathy v. Background Retinopathy
		*					No Retinopathy v. Proliferative Retinopathy
	*	*		*	*		Background Retinopathy v. Proliferative Retinopathy

Fig. 6 *Summary of the comparisons of the variances in contrast thresholds. Differences significant at the level of at least p=0·05 are indicated by*.*

categories of retinopathy. The test is, however, easily carried out and in conjunction with other findings may be useful in the assessment of the functional status of the eye in diabetic patients.

We thank Miss F. Maitland for secretarial assistance and Mr F. Addison for the preparation of the illustrations.

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Common causes of blindness and visual handicap in the west of Scotland

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SUMMARY An analysis of blind registration forms was made to determine the commonest causes of blindness in the west of Scotland. It was found that the leading causes of blindness in order of frequency of incidence were senile macular degeneration, glaucoma, cataract, diabetic retinopathy, and myopic degeneration. Diabetic retinopathy was the leading cause of blindness among persons of working age.

In the UK all persons with legal blindness—that is, those whose vision is too poor to allow work for which eyesight is necessary (in general a corrected visual acuity of less than 3/60 in the better eye or a visual field of less than 10°)—may be placed on the blind register by having a certificate of blind registration completed by an ophthalmologist (Form BP1 in Scotland and Form BD8 in England). Persons who have a permanent and significant visual handicap as the result of a congenital defect, an injury, or disease (in general a vision of 3/60–6/60) may be similarly registered as partially sighted.

Analyses of the predominant causes of blindness have been performed for a number of countries, including England and Wales,[1] Sweden,[2] and the United States of America.[3] In this paper a comparison is made between the causes of blindness in the west of Scotland and those reported from other parts of the world.

Materials and methods

Forms BP1 for the year ended 31 December 1980 and returned to the Society for the Blind in Glasgow and the West of Scotland were studied. These forms relate to people resident in Strathclyde Region. This is the area covered by the area health boards of Greater Glasgow, Argyll and Clyde, Ayrshire and Arran, and Lanarkshire.

Seven hundred and seventy two visually handicapped people were registered with the society during the year 1980. Of this number 125 forms, 16% of the total, had to be excluded from further analysis because of lack of essential information. These rejected forms contained nothing other than the name of the ophthalmologist and person being registered. We believe that the exclusions do not invalidate our findings; all the rejected forms came from one ophthalmologist in an area with no apparent abnormal incidence of causes of blindness, as assessed from a study of forms returned by other ophthalmologists working in the same area.

Patients with visual loss from cerebrovascular accident where visual loss was a homonymous field defect were classed as partially sighted for the purpose of the study. In some instances ophthalmologists registered such patients as legally blind and in others as partially sighted. Because these patients in general retained a useful field of vision, it was thought that the partially sighted category was the more appropriate.

Computer input was prepared from the remaining 647 fully completed forms, summarising the most important data on the Forms BP1. The facts considered were the age and sex of the person, the visual acuity and the visual field for each eye, and the primary cause of blindness for each eye. Both the age of the person at the time of examination for registration and that at which the visual handicap developed were noted. The data were analysed on the Edinburgh Regional Computer Centre ICL 2980 by means of some of the standard data handling facilities of the MINITAB program package.

For the purpose of analysis patients were divided into the following age groups 0–4, 5–19, 20–44, 45–64, 65–74, 75–84, and 85+. This age grouping has been used in a previous study.[3]

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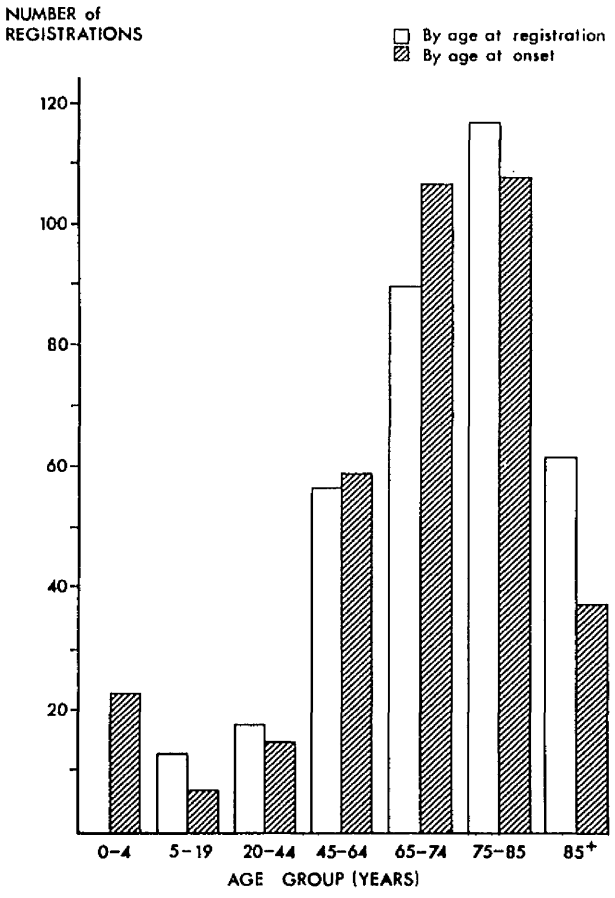

Fig. 1 *Numbers of eyes registered blind classified by age: ☐ by age of registration; ▨ by age at onset of blindness.*

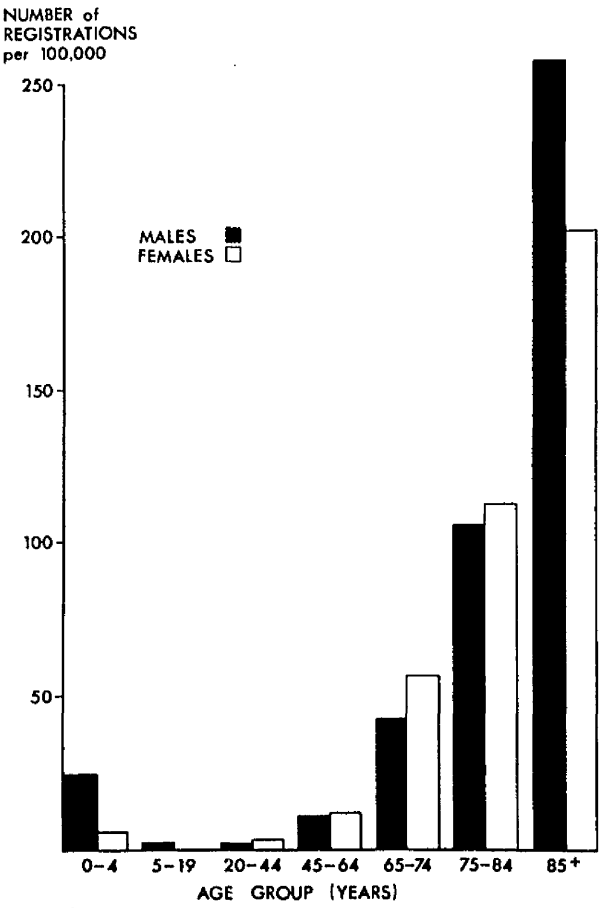

Fig. 2 *Numbers of eyes registered blind per 100 000 population: ■ for males; ☐ for females.*

Results

The 647 completed Forms BP1 were in respect of 253 males and 394 females. Of these, 138 males and 219 females were legally blind (total 357 or 55%). The male-to-female ratio was 2:3 both for the total registration and for the legally blind. The male-to-female ratio in the population as a whole is 1:1·1 in the west of Scotland.[4]

Fig. 1 depicts the age distribution of the legally blind. Because registration usually takes place some time after the onset of blindness, the distribution for 'age at registration' tended to be shifted to an older age than that for 'age at onset.' In fact the median time between the onset of the visual defect and registration was one year. Some 64% of registrations were made within 2 years of the onset of blindness, but owing to the long tail of the distribution times a few registrations were made more than 20 years after the person became blind.

The peak incidence of onset of blindness occurred in the 75–84 year age group, but there were almost as many whose onset of visual loss was between 65 and 74 years of age. 30% of all registrations fell within each of these 2 age groups. The incidence of registration reached a peak in the 75–84 year group with 33% of all legally blind registrations.

The data have been corrected for age on an actuarial basis by using the mid-1980 population estimates for Strathclyde Region.[4] The results are shown in Fig. 2, and it was found that, as expected, blindness became increasingly common with advancing age, and the incidence rose sharply around 60 years of age. The corrected incidences are comparable for males and females, given the limits on interpretation set by the small numbers of registra-

Table 1 *Leading causes of legal blindness for all ages and individual age groups, west of Scotland, 1980*

		No. of eyes	%
	Overall total		
1.	Sen. mac. deg	213	29·8
2.	Glaucoma	104	14·6
3.	Cataract	74	10·4
4.	Diab. ret.	61	8·5
5.	Myopic deg.	43	6·0
6.	Optic atrophy	32	4·5
7.	Corneal opacity	20	2·8
	All others	167	23·4
	Total	714	100·0
	Under 5 years of age		
1.	Optic atrophy	14	30·3
2.	Corneal and other postnatal infections	12	26·1
3.	Prenatal cataract	8	17·4
4.	Cong. glaucoma, microphthalmos	8	17·4
5.	Tumour	2	4·4
	All others	2	4·4
	Total	46	100·0
	Age group 5–19		
1.	Ret. pigmentosa	6	42·8
2.	Optic atrophy—cong.	2	14·3
3.	Myopia	2	14·3
4.	Injury	2	14·3
5.	Cong. microphthal. toxoplasmosis	2	14·3
	Total	14	100·0
	Age group 20–44		
1.	Diab. ret.	6	20·0
2.	Myopia	6	20·0
3.	Optic atrophy	6	20·0
4.	Uveitis	3	10·0
5.	Glaucoma	2	6·7
	All others	7	23·3
	Total	30	100·0
	Age group 45–64		
1.	Diab. ret.	22	18·6
2.	Sen. mac. deg.	17	14·4
3.	Glaucoma	15	12·7
4.	Myopic deg.	10	8·5
5.	Optic atrophy	10	8·5
	All others	44	37·3
	Total	118	100·0
	Age group 65–74		
1.	Sen. mac. deg.	56	26·2
2.	Glaucoma	44	20·5
3.	Cataract	24	11·2
4.	Diab. ret.	19	8·9
5.	Myopia	10	4·7
	All others	61	28·5
	Total	214	100·0
	Age group 75–84		
1.	Sen. mac. deg.	103	47·7
2.	Glaucoma	35	16·2
3.	Cataract	19	8·8
4.	Diab. ret.	14	6·5
5.	Myopic deg.	10	4·6
	All others	35	16·2
	Total	216	100·0
	85 years of age and over		
1.	Sen. mac. deg.	37	48·6
2.	Cataract	23	30·3
3.	Glaucoma	6	7·9
4.	Myopic deg.	4	5·3
	All others	6	7·9
	Total	76	100·0
	65 years of age and over		
1.	Sen. mac. deg.	196	38·7
2.	Glaucoma	85	16·8
3.	Cataract	63	12·5
4.	Diab. ret.	33	6·5
5.	Myopia	25	4·9
	All others	104	20·6
	Total	506	100·0

tions in some of the age groups. When the raw data for age at onset of visual defect for males is compared with that for females, it is seen that the recorded age of onset for females was about one decade later than for males.

Although no children in the age group 0–4 were registered, subsequent registration revealed that in 23 instances (19 males and 4 females) the onset of blindness was prior to age 5.

Data on the incidence of various primary blinding causes are presented in Fig. 3. The results are expressed in terms of the number of eyes blinded by a particular cause. A total of 1240 eyes were considered of which 714 eyes were legally blind. Fig. 3 shows the overall incidence of causes of blindess both for total registrations and the legally blind. The pattern is the same for both categories. It is clear that senile macular degeneration, accounting for about 30% of the registrations, was by far the commonest single cause of blindness in our sample.

In Table 1 the incidence of various causes of blindness among the legally blind is broken down by age of the person at onset of blindness. It is seen that retinitis pigmentosa was the main cause of blindness among the 5–19 year olds, but it appeared, if at all, only low in the ranking for all other age groups.

Diabetic retinopathy was one of the 3 first equal causes in the 20–44 year olds, the principal cause for the 45–64 years age group, the fourth most frequent cause for 65–74 and 75–84 year olds, but it did not occur at all as the blinding cause for any of the 78 eyes of the legally blind in the age group 85 years and over.

Senile macular degeneration first appeared among the 45–64 year olds and was the leading blinding cause in later years. It is interesting that of the 17 eyes blinded by senile degeneration of the macula in the

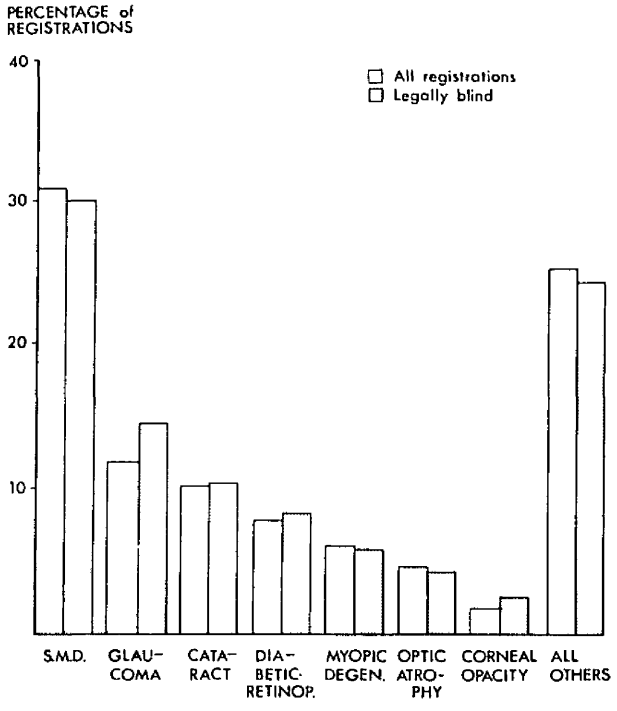

Fig. 3 *Proportion of registrations attributable to various blinding causes. In 'All Others' no one cause contributes more than 2·5%. Data are shown for:* ☐ *all registrations; and* ▨ *the legally blind alone. SMD=senile macular degeneration.*

45–64 year olds 12 eyes were in men and 5 in women.

Several differences in the pattern of blindness in the 2 sexes have already been mentioned, but others show up in the data. Table 2 shows the incidence of the different leading causes of blindness in males and females.

Discussion

The homogeneity of the population of the west of Scotland is greater than in some countries, and both environment and level of health care are uniform over this region. The moderate number of registration forms is handled by only a few staff of the Society for the Blind in Glasgow and the West of Scotland, which helps to ensure precise recording and filing of the Forms BP1, and information can be extracted easily by one person, which again assists uniform interpretation.

Although guidelines are provided to aid the the ophthalmologist in deciding whether a patient should be registered 'blind' or 'partially sighted,' some subjectivity evidently enters into the decision. To minimise this problem the registered blind who satisfied the United Kingdom criteria for legal blindness were considered here. In some previous analyses[1] no distinction was drawn between age at registration and age at onset of visual defect. In the present study the age of onset was considered the more useful of these 2 alternatives.

There are problems in comparing surveys of the blind. Even when objective criteria for blindness are used, comparison with other studies is difficult, because many different definitions of blindness are in use throughout the world; the World Health Organisation accepts some 65 definitions of blindness.[5] To give one example of the differences, the legally blind in the USA are those whose corrected visual acuity for distance is 20/200 (6/60) or poorer in the better eye or with a field of vision not greater than 20° at its maximum. Such differences may differentially exclude or include particular conditions, and so comparison must again be made cautiously.

However, the data from the present study shows some points which are worthy of comment. The male-to-female ratio of 2:3 among all those registered and among the legally blind is to be expected because of the longer average life span of women and the demonstrated relationship between aging and incidence of blindness. The absence of registration for those in the 0–4 age group reflects not only a reluctance of ophthalmologists to register as blind a young infant whose visual function may be difficult to assess, but also a more recently introduced policy of delaying registration in infancy.

Some 10% of blind people were found to have differing primary causes of blindness in their 2 eyes, but these conditions cover the whole range. Thus the percentage affected by a particular cause is about the same whether eyes or people are considered.

Table 2 *Common causes of blindness in males and females, west of Scotland, 1980*

Males	*Eyes*	*%*	*Females*	*Eyes*	*%*
1. Senile macular degeneration	62	22·5	1. Senile macular degeneration	151	34·5
2. Glaucoma	55	19·9	2. Cataract	58	13·2
3. Optic nerve atrophy	24	8·7	3. Diabetic retinopathy	51	11·6
4. Cataract	16	5·8	4. Glaucoma	49	11·2
5. Myopic degeneration	11	4·0	5. Myopic degeneration	32	7·3
All other	108	39·1	All other	97	22·2
Total	276	100·0	Total	438	100·0

Table 3 *Comparison of the important causes of blindness in some countries*

Country	*1st cause*	*2nd cause*	*3rd cause*	*4th cause*	*5th cause*
Scotland	Senile macular degeneration	Glaucoma	Cataract	Diabetic retinopathy	Myopia
England and Wales	Senile macular degeneration	Cataract	Glaucoma	Myopia	Diabetic retinopathy
USA	Glaucoma	Senile macular degeneration	Cataract	Optic nerve atrophy	Diabetic retinopathy
Canada	Senile macular degeneration	Diabetic retinopathy	Glaucoma	Optic nerve atrophy	Cataract
Sweden	Tapetoretinal degeneration of genetic origin	Diabetic retinopathy	Optic nerve atrophy	Uveitis	Myopia
India	Cataract	Glaucoma	Staphyloma	Optic nerve atrophy	Anophthalmos

If the figures for cataract and glaucoma are combined, one finds that about a quarter of all legal blindness or severe visual handicap results from these 2 conditions, the effects of which are largely treatable or preventable respectively. It is encouraging to note that the figure of 10% of the registrations attributable to senile cataract signifies an improvement since the time of Sorsby's survey,[1] when 23% of registrations were for this reason. The percentage for glaucoma has shown little change (14·6% for our data and 13% in Sorsby's results).

It has been suggested that a tight control of the diabetic state together with early treatment of proliferative retinopathy with laser or xenon arc photocoagulation might prevent 60% of blindness from diabetes.[6] If this was achieved, some 8% of the blind registrations in the west of Scotland would be eliminated.

Thus about 30% of current registrations might be prevented by rigorous application of current treatment techniques for cataract, glaucoma, and diabetic retinopathy. But a proportion of those whose sight was saved would subsequently lose vision from an as yet untreatable cause of blindness such as senile macular degeneration.

It has already been noted that diabetes is the commonest systemic disorder causing blindness, yet it does not figure as a major cause of blindness among the 85 year olds. This evidently reflects the shorter life expectancy of diabetics, and in addition many are blinded while still relatively young and so do not contribute to registrations in the older age groups.

Cataract is a more important cause of blindness for women than for men, again reflecting the longer life span for females. Diabetic retinopathy ranks as the third cause of blindness for females, yet it does not show among the first 5 conditions for men. This again might be a phenomenon related to life expectancy (Table 2).

COMPARISON WITH OTHER COUNTRIES

As remarked earlier, there are many obstacles to comparing the results of surveys such as this. With these reservations in mind, the pattern of incidence of common causes of blindness is shown for several countries in Table 3. It is apparent that at least for developed countries[1–3 7] the same causes tend to appear among the leading 5, although the order changes.

As an example of the problems of detailed comparison, one might speculate that the interchange of the order of glaucoma and senile macular degeneration for the USA in comparison with the UK might be due to the different visual field criteria for blindness used in each. There is not sufficient information about visual fields on the Form BP1 to analyse blind population data for the west of Scotland by the USA criteria.

The contrast between India (Venkataswamy 1981, personal communication) and the other nations is marked, but it is much what the differing social and medical care conditions would lead one to expect.

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Potential retinal light damage from the use of therapeutic instruments

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Summary

The question of light damage to the retina occurring as a direct consequence of the use of therapeutic or diagnostic procedures is posed. It would appear from theoretical and experimental considerations that, in some instances, light damage may occur. This possibility is discussed with reference to the available literature and experimental work undertaken by the authors.

There exists in the literature a vast amount of evidence attesting to the damaging effects of light on the retina (Table I). The aim of this paper is to relate some of this experimental work to the clinical situation. Are, for instance, slit-lamp biomicroscopy of the retina or indirect ophthalmoscopy liable to produce retinal damage?

(1) Possible causes of light damage

Light can produce an effect on the retina in three ways:

(*i*) Mechanically,
(*ii*) Thermally,
(*iii*) Photochemically.

These types of damage are not mutually exclusive and areas of overlap exist between them. However, both mechanical damage and thermal damage are produced by irradiance levels and short exposure times which are beyond the scope of this paper. The type of damage which may result from the use of diagnostic instruments clinically is photochemical and perhaps also thermally enhanced photochemical damage. The probable sites of photochemical damage are shown in Fig. 1.

The most obvious group of photosensitive molecules are the visual pigments. Experimental work on rhesus monkeys by Harwerth and Sperling (1971) has shown that particular classes of cone cells can be damaged by light of the appropriate wavelength, appropriate in this context being wavelengths which are close to the peak absorbance of the visual pigment of the damaged receptor cell type. Noell (1980) has postulated that light damage produced in rats exposed to low levels of fluorescent illumination is also mediated by a visual pigment, in this case rhodopsin. The mechanisms postulated include structural instability of the outer segment due to loss of rhodopsin (Noell, Walker, Kang, and Berman, 1966), or to a retinotoxic membranolytic action of free retinol (Noell and Albrecht, 1971). This type of damage would be mostly restricted to the outer segment. A third suggestion (Noell, 1980) is that light could initiate destructive oxidizing reactions in the retina. Photoreceptor discs are mostly composed of unsaturated fatty acids. Noell suggests that the action of light on the photopigments begins a series of reactions which result in the production of free radicals. These free radicals could initiate a chain reaction, which is unchecked by the presence of antioxidants such as vitamin E and could proceed to the oxidization of the lipid membranes (Feeney and Berman, 1976). Hayes (1974) has shown that cone outer segment damage occurs in vitamin E deficient monkeys.

In addition to the photopigments, there are various other molecules which are photolabile and capable of producing free radicals. These include nucleic acids, specifically those containing adenine and guanine, some amino-acids, namely histadine, tryptophan, and tyrosine (Fowlks, 1959; Gallo and Santa Maria, 1972). It is also thought that melanin is capable of free radical production and electron transfer to other molecules (Mason, Ingram, and Allan, 1960; Proctor, McGinnes, and Corry, 1974). Some photosensitizing drugs (phenothiazines, psoralens, and tetracyclines) can bind to uveal melanin (Potts, 1964a, b). This may enhance the damage produced by photochemical mechanisms.

(2) Appearance of light damage

The appearance of light-damaged retinal tissue varies with species and exposure regime. However, when relating experimental work to the clinical situation, it is exposure times, in the range of seconds to hours and retinal irradiances from milliwatts to hundreds of milliwatts per square centimetre, which are of consequence.

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Table I *Summary of some of the major damage studies, 1966 to 1981*

Authors	*Species*	*Source*	*Estimated retinal irradiance* ($\times 10^{-3}$ *W cm*$^{-2}$)	*Duration*	*Maximum damage*
Noell and others (1966)	Rat	Fluorescent	3.3*	1 hr–2 days	Receptor cells and retinal pigment epithelium gone
Friedman and Kuwabara (1968)	Rhesus monkey	Indirect ophthalmoscope	270*	5–60 min	Degeneration of outer segment and retinal pigment epithelium
Grignolo and others (1969)	Rat	Fluorescent	0.2–3.0*	8–100 hrs	Receptor cells and retinal pigment epithelium gone
Radnot and others (1969)	Human	Incandescent	7.5*	43 min	Outer segment disintegration Müller and horizontal cell damage
Marshall and others (1972)	Pigeon	Fluorescent	0.09*	6–24 hrs	Cone outer segment damage
Tso and others (1972)	Rhesus monkey	Indirect ophthalmoscope	50–100 approx.	1 hr	Outer segment loss Retinal pigment epithelium depigmentation
Tso (1973)	Rhesus monkey	Indirect ophthalmoscope	50–100 approx.	1 hr	Outer segment loss Retinal pigment epithelium depigmentation
Lawwill (1973)	Rabbit	Argon laser	17–47*	4 hrs	Receptor cells and retinal pigment epithelium gone
		Xenon arc	150–1600*	4 hrs	Patchy severe outer retina damage
Sperling and others (1980)	Rhesus monkey	436 nm	0.1	80 min/day for 7–21 days	Cone cell death Loss of blue sensitivity
		520 nm	0.1	80 min/day for 7–21 days	Loss of green sensitivity 18 days
Sykes and others (1981)	Rhesus monkey Pigtail macaque	Fluorescent	0.36–0.61	12 hrs	Rod outer segment damage

* Estimates of retinal irradiance from Lanum (1978)

The average retinal irradiance produced by such procedures as indirect ophthalmoscopy and slit-lamp biomicroscopy has been estimated (Hochheimer, D'Anna, and Calkins, 1979; Calkins and Hochheimer, 1980) (Fig. 2). In general, light damage produced by retinal irradiances in the range of 10^{-3} to 10^{-1} mW cm^{-2}, with exposure durations of seconds to hours, usually results in damage to the outer retina. With higher irradiances other retinal layers may be involved (McKechnie and Foulds, 1981) (Fig. 3).

If damage is restricted to the photoreceptor outer segment it seems likely that the outer segment will regenerate (Wyse, 1980), presumably as a result of the outer segment renewal process (Young, 1978).

If the damage to the outer retina is severe, for example with destruction of both the receptor cell outer segments and the RPE, there is usually a macrophagic response within 24 to 48 hours. These cells rapidly remove any remaining cellular debris. Recovery of severely damaged retina is only partial, gliosis of the outer retina being a common result (Fig. 4) (McKechnie and Foulds, 1980).

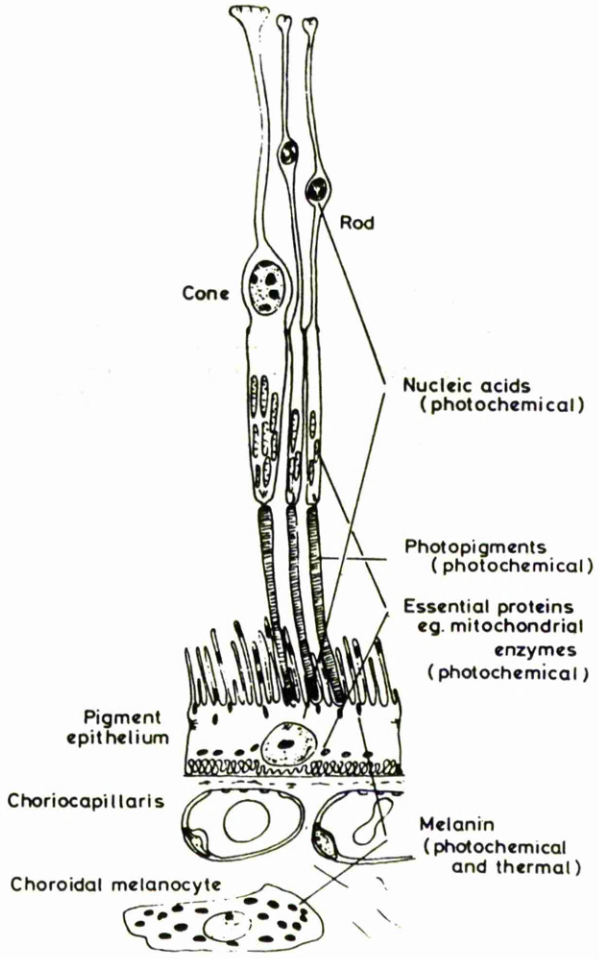

FIG. 1 *Some possible sites of light damage*

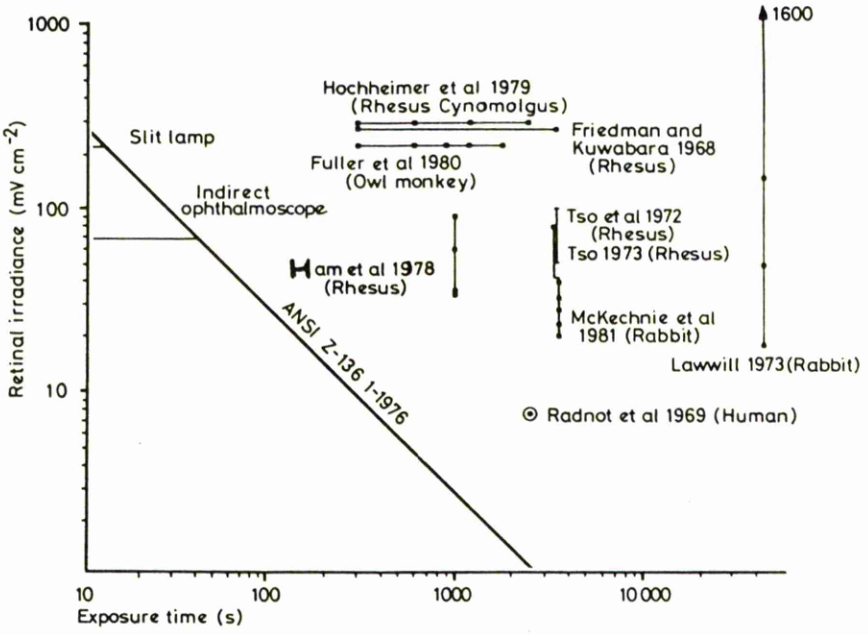

FIG. 2 *ANSI (1976) guideline for safe use of lasers compared to selected light damage studies. Estimates of retinal irradiance (Calkins and Hochheimer, 1980) for slit-lamp biomicroscopy and indirect ophthalmoscopy also shown.*

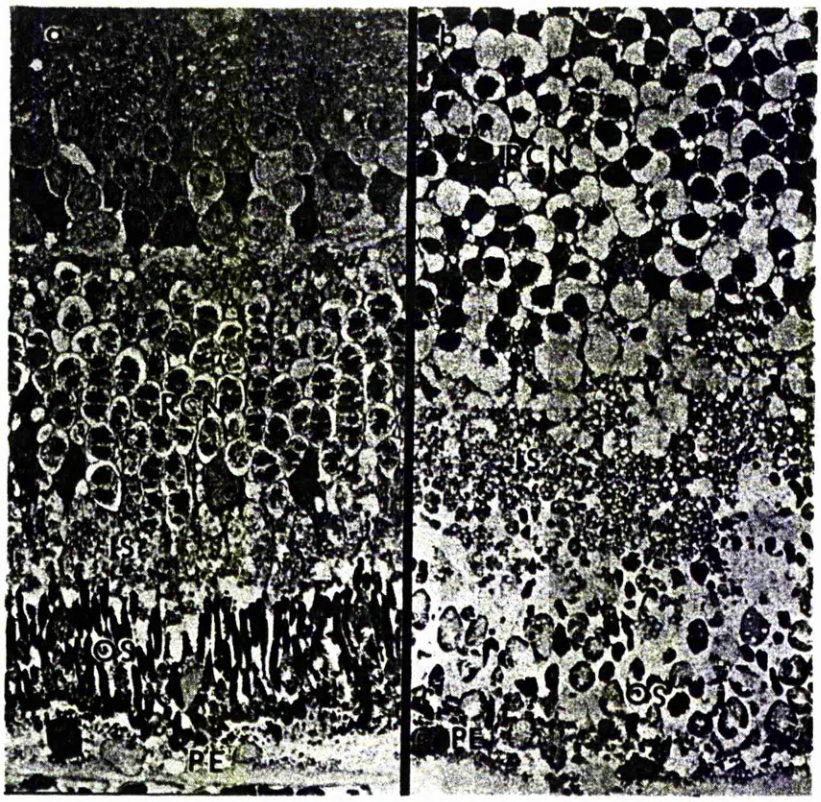

FIG. 3 *Low-power electron micrographs showing appearance of rabbit retina. Estimated retinal irradiances: (a) 39 mW cm^{-2}; (b) 84 mW cm^{-2}. In both the outer retina has suffered considerable damage. PE: pigment epithelium; OS: outer segments; IS: inner segments; RCN: receptor cell nuclei.* ×700

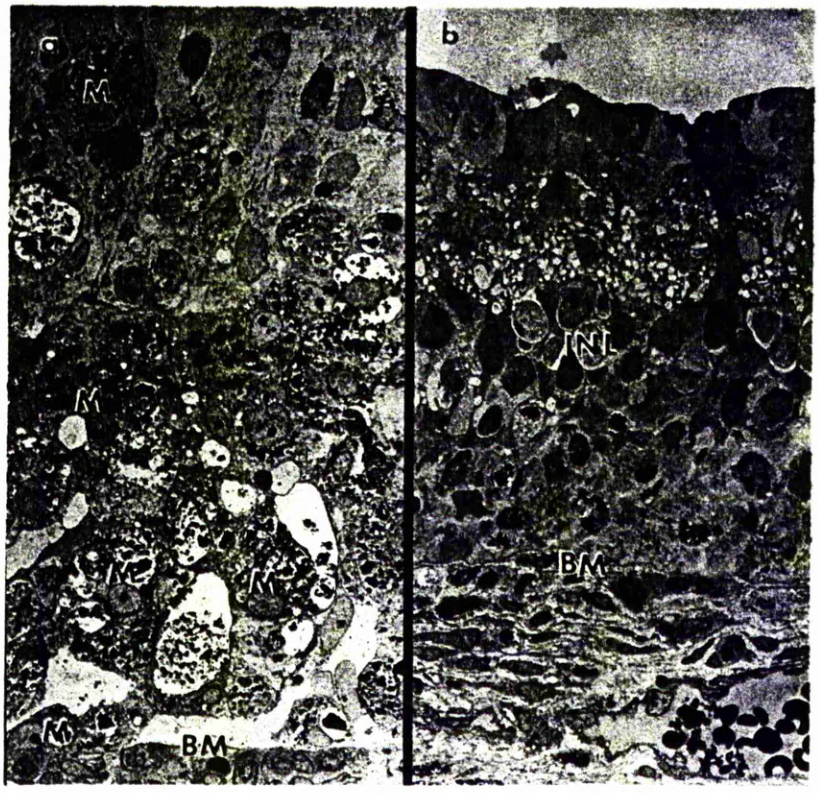

FIG. 4 *(a) Electron micrograph showing appearance of rabbit retina 4 days after a 1-hour exposure to light with an estimated retinal irradiance of 84 mW cm^{-2}. Numerous macrophages present within retinal tissue.*
(b) Similar to (a), but after 2 weeks' recovery. Little remains of outer retina, both the receptor cells and the retinal pigment epithelium having been destroyed. BM: Bruch's membrane; M: macrophage; INL: inner nuclear layer. ×560.

(3) Effect of pre-existing pathology

Some authors have questioned the effect of light exposure when coupled with a pre-existing pathology (Pomerantzoff, Govignon, and Schepens, 1969). To investigate this problem we have conducted a series of experiments in which rabbit eyes were exposed to a combined insult of pressure-induced ischaemia and light exposure. The rabbit eyes were exposed to a retinal irradiance of approximately 20 mW cm^{-2} for 1 hour, which produced only minor disturbances of outer segments of the receptor cells. The 1 hour's light exposures were coupled with various periods of ischaemia (15, 30, 45, or 60 min). The morphology of light-exposed ischaemic eyes was compared to that of eyes which had been subjected to acute ischaemia in total darkness (Johnson and Foulds, 1978). It was found that the light-exposed ischaemic eyes suffered considerably more damage, a unique feature of the combined insult being focal detachments of the RPE (Fig. 5) (McKechnie, Johnson, and Foulds, 1982). From these results it would seem that a pre-existing pathology may increase the susceptibility of the retina to light damage.

(4) Possible light damage in humans

Given that both indirect ophthalmoscopy and slit-lamp biomicroscopy can produce retinal irradiances sufficient to cause retinal damage in rhesus monkeys (Fig. 2), why is light damage not observed in human subjects? There are probably two parts to the answer:

(*a*) The exposure times may not be sufficiently long. Examination of different regions of the fundus and eye movements during examination will tend to diminish the total exposure of any one area.

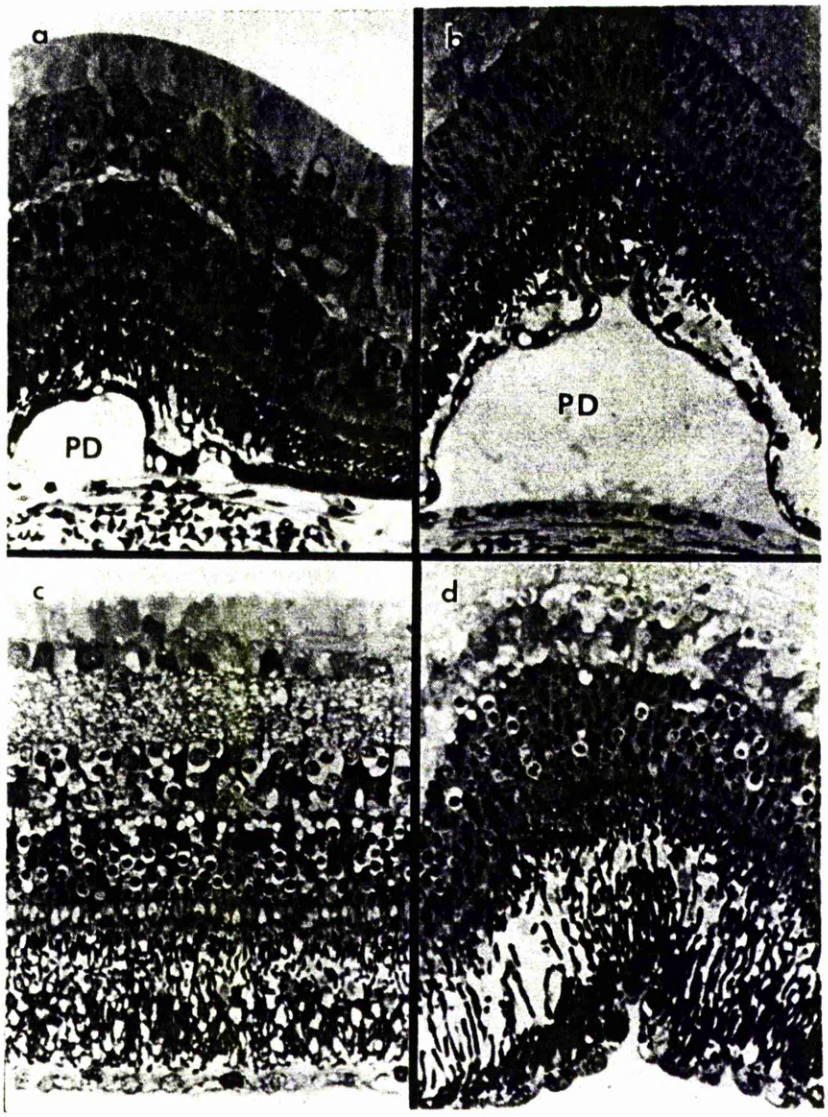

FIG. 5 *Light macrograph showing effect on retinal structure of combining light exposure and ischaemia. Eyes were exposed to light for 1 hour (estimated retinal irradiance 23 mW cm^{-2}) and made ischaemic for periods of 15, 30, 45, or 60 min. In all instances the resulting retinal damage was more severe than that produced by ischaemia or light separately. (a) Light plus 15 min ischaemia. (b) Light plus 30 min ischaemia. (c) Light plus 45 min ischaemia. (d) Light plus 60 min ischaemia. A unique feature of the insult is the production of a proteinaceous detachment (PD) of the retinal pigment epithelium.* ×280

(*b*) Any harmful effect of the exposure may be ascribed to the further development of a pre-existing pathology.

A loss of blue sensitivity after argon laser and xenon arc panretinal ablation has been described by Birch and Hamilton (1981). They suggest that the loss of blue sensitivity may be related to the suggestion that rods share a neural pathway with blue-sensitive cones (Trezona, 1970). Birch and Hamilton (1981) also suggest that the loss in hue sensitivity may result from light scatter occurring during photocoagulation. The experimental work of Harwerth and Sperling (1971) and Sperling, Johnson, and Harwerth (1980) suggests that particular classes of cones can be selectively damaged by light of the appropriate wavelength. In this respect blue cones appear to be the most sensitive, showing little or no recovery (Sperling and others, 1980).

As part of a larger study assessing visual function in diabetics before and after panretinal coagulation, normal subjects were exposed to the viewing light of a Carl Zeiss 95021 slit-lamp. The subjects were asked to move their eyes during the exposure and not to fix the light. On subsequent testing of visual acuity (Table II) and contrast sensitivity, there was no significant finding. Assuming the retinal irradiance of the slit-lamp to be 217 mW cm^{-2} (Calkins and Hochheimer, 1980), an exposure of 15 min results in a total energy input of 195.3 J cm^{-2}. This represents an exposure 67 times greater than the maximum permissible exposure of 2.92 J cm^{-2} recommended by the American National Standards Institute (ANSI Z-136. 1–1976). However, the effect of eye movements during the exposure period is unknown, but movement must reduce the time during which any one area of retina is exposed.

Table II *Visual acuity of six normal subjects 15 min and 24 hrs after exposure to slit-lamp biomicroscopy for 15 min*

Subject no.	*Visual acuity before exposure*	*Assessment after biomicroscopy*	
		15 min	*24 hrs*
1	6/6	6/36	6/6
2	6/6	6/9	6/6
3	6/5	6/9	6/5
4	6/6	6/12	6/6
5	6/6	6/6	6/6
6	6/6	6/9	6/6

Conclusion

Although light damage would appear to be an unlikely consequence of therapeutic or diagnostic procedures, the effects of pre-existing pathology, extended viewing times, and photosensitizing agents should be borne in mind.

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'DIABETIC RETINOPATHY IN THE WEST OF SCOTLAND : ITS DETECTION AND PREVALENCE, AND THE COST-EFFECTIVENESS OF A PROPOSED SCREENING PROGRAMME'

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INTRODUCTION

Diabetes is one of the four commonest causes of blindness in the United Kingdom and the commonest cause of blindness in the working population (1). A recent investigation of blind registration statistics in the West of Scotland (2) established that diabetes was responsible for 10% of the 1000 persons registered as blind or partially sighted during the year ended December 1980, and was the commonest cause of blindness in the age groups 45-54 and 55-64.

The main blinding complication of diabetes is diabetic retinopathy. It is known that, diabetic retinopathy is a complication of long-standing diabetes (3) but estimates of its prevalence among the diabetic population are inexact.

Diabetic retinopathy is thought to evolve through the following stages:

NO RETINOPATHY

BACKGROUND OR "SIMPLE" RETINOPATHY

EXUDATIVE MACULOPATHY <--------> PROLIFERATIVE RETINOPATHY

Many patients with diabetes will develop retinopathy within 5 years of onset of the disease (4). Initially this is of the background or simple variety characterised by retinal haemorrhages, microaneurysms and hard exudates with the retention of good vision. A proportion of patients will develop more serious sight-threatening retinopathy of either an exudative or proliferative variety. Exudative maculopathy secondary to increased capillary permeability is characteristic of late onset diabetes. The resulting visual loss affects central vision only and is incomplete. Proliferative retinopathy in which new formed

blood vessels develop in the fundus of the eye is characteristic of early onset insulin dependent diabetes. This form of retinopathy may lead to recurrent vitreous haemorrhage, intraocular fibrosis, retinal detachment and complete blindness. Mixed forms occur and occasionally patients with exudative maculopathy subsequently develop proliferative retinopathy.

Until recently no useful therapy for diabetic retinopathy was available. With the advent of xenon arc and laser photocoagulation, it has been established beyond doubt that suitable treatment may halt or reverse the development of diabetic retinopathy (5, 6).

During the years 1979 to 1982 (inclusive) a study of the prevalence of diabetic retinopathy and the cost-effectiveness of its detection and treatment was given financial support by the SHHD (Grant K/MRS/C186).

This study was conducted jointly by members of the staff of the Tennent Institute of Ophthalmology at the Western Infirmary, Glasgow and the staff of the Diabetic Clinic at the Glasgow Royal Infirmary. A pilot study of patients attending one general practice at Woodside Health Centre was also undertaken.

The aims of the study were to assess the prevalence of diabetic retinopathy as diagnosed by ophthalmoscopy, to assess the incidence of fresh retinopathy arising annually, to compare the effectiveness of ophthalmoscopic screening by Diabetic Physicians with that conducted by Ophthalmologists, to categorise the relative prevalences of the different stages and types of retinopathy found and to assess the financial and staffing implications

of mounting a screening programme for diabetic retinopathy in the West of Scotland.

MATERIAL AND METHODS

Arrangements were made for all patients attending the diabetic out-patient clinic of the Glasgow Royal Infirmary to have an annual ocular examination. This examination was carried out in a darkened room with the patients pupils dilated. Patients were seen either by a Physician who had received training in the classification of diabetic eye disease in the Retina Clinics of the Tennent Institute of Ophthalmology, or by an experienced Ophthalmologist. On the basis of this examination, the patient was classified as either having no retinopathy, background retinopathy or serious retinopathy.

Serious retinopathy was sub-divided into three categories.

1. Exudative maculopathy: Exudates or oedema affecting the macular retina and usually accompanied by symptoms of visual impairment.
2. Proliferative retinopathy: The presence of new formed blood vessels on the optic disc or elsewhere in the fundus.
3. Ischaemic retinopathy: A pre-proliferative stage of which the ophthalmoscopic signs are of background retinopathy with additional soft exudates in the absence of overt hypertension.

The total number of ophthalmoscopic examinations by either an Ophthalmologist or a Physician was 2115. This total included a preliminary examination of 1212 patients and 903 re-examinations. 132 patients were seen yearly on 3 occasions, 421

patients were seen on two occasions in successive years and 38 patients were examined in year 1 and year 3 of the study.

All patients categorised as having some form of serious retinopathy were referred for full ophthalmological investigation in the Tennent Institute of Ophthalmology. This further investigation included a battery of tests of visual function [quantitative visual field analysis, quantitative and qualitative assessment of colour vision (a sensitive test of visual function), determination of spatial contrast sensitivity (a measure of retinal integrative function) and fluorescein angiography].

Detailed results of this part of the study have been or are being published elsewhere (7).

On the basis of this further investigation a final categorisation of stage or type of retinopathy was made and the accuracy of the original classification determined. A decision was also made as to whether treatment was indicated. If laser therapy were considered appropriate this was carried out.

In addition to patients undergoing regular yearly ophthalmoscopic examination, a group of 93 patients chosen at random underwent full ophthalmological investigation even if on ophthalmoscopy there was no evidence of retinopathy.

In a parallel pilot study, 76 patients with diabetes were identified from perusal of all 7189 case records of one general practice at Woodside Health Centre. These patients were called for ophthalmoscopic examination and categorised according to the state of the fundi. Those with ophthalmoscopically diagnosed

serious retinopathy were referred for full ophthalmological investigation to the Tennent Institute of Ophthalmology.

RESULTS

1. IDENTIFICATION OF DIABETIC RETINOPATHY

Prevalence of diabetic retinopathy.

From the first 1000 patients serially examined by either a Physician or an Ophthalmologist (8) the prevalence of retinopathy was found to be 26.7%, and of serious retinopathy 9.5%. This group of patients was representative of diabetics in general in terms of age, insulin requirements, blood pressure etc.

From the 93 patients selected at random, 181 eyes were available for study, and from examination of these eyes the prevalence of retinopathy was found to be 28% and of serious retinopathy 11%.

Of the 76 patients identified as having diabetes from among 7139 patients making up one general practice (1.06% of the total practice population) 54 responded to a request for ophthalmoscopic examination. Of these 35% had retinopathy and 11% serious retinopathy. Some bias may have been introduced in this group of patients as those presenting for ocular examination might have been expected to be those with some ocular complaint.

Nevertheless the prevalence figures for patients attending Woodside Health Centre are comparable with those for patients attending the Diabetic Clinic of the Glasgow Royal Infirmary, and the prevalence of retinopathy in the diabetic population appears to lie between 26 and 35%, and of serious retinopathy between 9.5 and 11%.

Incidence of diabetic retinopathy.

Figures for the yearly incidence of fresh retinopathy were obtained from patients examined on 2 or 3 occasions. It was found that the annual overall incidence of fresh retinopathy was 5% per annum and of serious retinopathy 1.2% per annum.

Accuracy of diagnosis by Physician or Ophthalmologist.

182 patients were examined by both a Physician and an Ophthalmologist separately without the diagnosis made by one being available to the other. A further 349 patients were seen only by a Physician and 635 only by an Ophthalmologist. The prevalences of retinopathy diagnosed by the Physicians in these two categories were 22% and 26% respectively. Similarly the prevalences of retinopathy diagnosed by Ophthalmologists were 25% and 20%. The prevalences of serious retinopathy diagnosed by Physicians in the two categories were 4% and 10% respectively and Ophthalmologists 10% and 6%. Overall Physicians and Ophthalmologists detected similar numbers of patients with serious retinopathy (see Table 1) although some variation in individual assessments was apparent. In general there was more variance in the diagnosis of serious retinopathy by Physicians as compared with Ophthalmologists but the differences are unlikely to be significant.

On the basis of further ophthalmalogical investigation the number of patients thought initially to have serious retinopathy and who subsequently proved to have non serious retinopathy was determined and from this the accuracy of the initial ophthalmoscopic diagnosis was compared between Physician and Ophthalmologist. 24% of referred cases fell into this false positive category in both the Ophthalmologists and Physicians referral figures. The

Table 1. Relative prevalences of Diabetic Retinopathy

	Ophthalmoscopic Assessment		
	No Retinopathy	Background Retinopathy	Serious Retinopath
Prevalence of Diabetic retinopathy in random sample	72%	17%	11%
Prevalence diagnosed by Physicians	75%	17%	8%
Prevalence diagnosed by Ophthalmologists	79%	14%	7%

Both the Physicians and Ophthalmologists may have under-diagnosed serious retinopathy.

Tests of Visual Function

It is not thought appropriate that a detailed presentation of the result of the various tests of visual function should be presented here. In general many of the tests of function showed evidence of abnormality before ophthalmoscopically visible changes were evident. While interesting in relation to the development of diabetic retinopathy the tests were found not to be useful in separating patients requiring laser treatment from those not requiring treatment.

Fluorescein Angiography

In the case of fluorescein angiography some 20% of eyes which appeared normal on ophthalmoscopy revealed evidence of early retinopathy on fluorescein angiography. Unsuspected serious retinopathy was rarely encountered. The main value of fluorescein angiography was in relation to which form of laser therapy (if any) was appropriate for an already identified case of serious retinopathy.

Conclusion

Annual ophthalmoscopy carried out either by a suitably trained Physician or an Ophthalmologist in a darkened room with the patients pupils dilated is a highly effective way of detecting retinopathy and in particular in detecting sight threatening retinopathy among diabetic patients. Referral of all patients with ophthalmoscopically classified serious retinopathy for further ophthalmological investigation including fluorescein angiography will identify virtually all of those at risk of blindness from diabetic retinopathy, and allow treatment with photocoagulation to be undertaken at an appropriate stage in the evolution of the disease. About a quarter of those so referred will have retinopathy which is not sight-threatening.

Such a screening programme could certainly be justified purely on the basis of the reduction in blindness which would result from earlier identification and treatment of those with sight-threatening retinopathy. The question of whether such an exercise would be cost-effective is however important.

2. COST-EFFECTIVENESS OF SCREENING FOR DIABETIC RETINOPATHY.

The results presented in this section are based on a projected annual ophthalmoscopic examination of all diabetic patients in the West of Scotland. It may be argued that some patients are more at risk than others and that a less frequent examination of low risk patients might be appropriate. Unfortunately, many patients with serious retinopathy are symptom-free and not infrequently serious retinopathy is found at or shortly after the

diagnosis of diabetes has been made. From the figures of annual incidence derived from the present study, an annual examination of all diabetic patients would appear to be justified.

Cost analysis of proposed screening programme.

In order to cost the identification and treatment of patients with sight-threatening retinopathy each stage in the process was timed and the staff requirements identified.

The time required for consultation including full ophthalmoscopic examination of both eyes of each patient was found to be 8 minutes approximately. The staff involved was a Diabetic Physician or Ophthalmologist aided by a nurse.

The time required for ophthalmological examination including fluorescein angiography was approximately 30 minutes. The staff involved was an Ophthalmologist and Technician.

The time required for laser therapy was on average 40 minutes per eye treated (20 minutes for exudative maculopathy, 60 minutes for proliferative retinopathy). The staff involved was an Ophthalmologist.

Projected Workload

The population of the West of Scotland is approximately 2.5 million (10). The prevalence of diagnosed diabetes is 1% so that in the West of Scotland there should be 25,000 diagnosed diabetics. As 25 patients can reasonably be examined ophthalmoscopically in one clinic session, provided patient preparation, including dilatation of the pupils is carried out by a nurse, examination of 25,000 patients would require 1,000 working sessions annually. On the assumption that 10 sessions per week are available, and that 45

working weeks are available in the calendar year, this workload would occupy the equivalent of 2.2 fulltime Physicians' or Ophthalmologists' sessions plus an additional 2.2 fulltime nurses' and in total would cost £51,800 per annum.

The incidence of fresh serious retinopathy is 1.2% per annum and 300 patients per annum would be expected to come into this category in the West of Scotland and require full ophthalmological investigation. This workload would require 0.1 of an Ophthalmologists' time per annum and 0.1 of a Technicians' time. The annual cost of this ophthalmological investigation including photographic film etc., at £1 per patient would be £3,500.

The total annual cost to identify patients with serious retinopathy would therefore be £55,300 or £183 per patient with serious retinopathy identified. To these costs must be added the costs of treatment of 150 patients per annum * which on the same basis of calculation as before would amount to £2,730 per annum or £18 per patient treated. The total cost per annum of identifying and treating patients at risk of blindness is therefore £387 per patient <u>treated</u>.

In the first year because of the backlog of some 2,500 patients with serious retinopathy of whom 1,250 might need laser therapy, the cost of identification and treatment would be increased by the time required for full investigation and treatment of those identified as having serious retinopathy, while the initial screening costs would remain unaltered. The total cost in the first year to identify and investigate the backlog of 2,500 patients with serious retinopathy in the West of Scotland and to

treat approximately 1,250 of these by laser would amount to £108,000 or £86 per patient treated.

* It has been our experience that 50% of patients referred with suspected serious retinopathy require laser treatment. As already noted 25% of referred cases prove not to have sight-threatening retinopathy, but 75% of the remainder require laser treatment.

Economic benefit of screening for diabetic retinopathy.

The staffing costs of the Blind Welfare Service in the Strathclyde Region for 1981-82 are estimated at £420,794. There are 5,048 registered blind, and most of the cost of the service is related to these persons. A smaller proportion of the costs relates to 1,707 patients registered as partially sighted. The staffing costs are therefore approximately £75 per blind patient.

The average patient going blind from diabetic retinopathy is in the forties and likely to have a family commitment. Most will be unable to continue in employment and require support from the state. The average cost per patient is difficult to determine, but from discussions with the Blind Welfare Services and the Department of Employment, a reasonable estimate would be £3,500 per patient per annum.

The average savings per person prevented from going blind would therefore be -

1.	Proportion of costs of Blind Welfare Services	£ 75
2.	State benefits	£3,500
	TOTAL	£3,575

It has been estimated that appropriate laser therapy will prevent 60% of blindness from diabetic retinopathy (9). In rela-

tion to the estimated 150 patients per annum requiring laser therapy (after the backlog has been dealt with), adequate laser treatment should prevent 90 of these 150 patients from going blind with an annual saving per patient treated of £2,145. The annual saving per patient identified as having serious retinopathy would be £1,073, and per patient screened would be £12.87p. The total savings to the State per annum in treating and preventing 60% of patients threatened with blindness from going blind would be £193,050. In the case of the backlog of 2,500 patients with serious retinopathy of whom 1,250 will require treatment and of whom 750 may be prevented from going blind, the total once only saving would be £1,612,500.

Thus the annual cost per annum for screening and treating diabetic patients in the West of Scotland would be £58,030, and the total annual saving in preventing 90 patients from going blind from diabetic retinopathy would be £193,050 with a net saving of £135,025 per annum. (In addition there would be a net once only saving of £1,504,500 in identifying and treating the backlog of patients at present requiring laser therapy). The cost benefit ratio of using Consultant Physicians or Consultant Ophthalmologists to conduct the initial screening would be 1 : 3.3.

In addition to direct savings identified above, additional account should be taken of the likely earnings of such patients. The average income in the United Kingdom is at present £6,292 per annum. The 90 patients prevented from going blind in the West of Scotland per year by adequate identification and laser treatment would be expected to earn per annum a total sum of £5,666,280.

From further enquiries it appears that a small proportion of blind patients are not in receipt of state benefit. The savings from prevention of blindness from diabetes could therefore be reduced proportionately but would still be significant.

Apart entirely from economic considerations there are obvious social and physcological losses in blindness which cannot be assess in economic terms.

There are implications in terms of staffing and facilities of any projected screening programme for diabetic retinopathy. In order to institute an annual screening programme such as outlined above would require in the first year and subsequent years the appointment of an additional 2.2 whole time equivalent Consultant Physicians or Ophthalmologists in the West of Scotland. In addition the temporary appointment in the first year of the equivalant of one full time Ophthalmologist and one full time Technician for the ophthalmological investigation and treatment of the backlog of diabetic patients with serious retinopathy identified by the initial screening would be required. In subsequent years it is believed that the annual incidence of fresh retinopathy is such that the numbers requiring ophthalmological investigation and laser therapy could be accommodated within existing staffing levels, although return visits of patients with serious retinopathy identified and treated would add to the return out-patient load and might as a result justify additional ophthalmic staffing. As far as equipment is concerned, in the West of Scotland at present there are at least six lasers suitable for the treatment of diabetic patients. The treatment of the backlog of patients with serious diabetic

retinopathy identified in the proposed screening programme would fully utilise the equivalent of one laser for a year. Subsequently the relatively small number of patients requiring treatment annually could easily be accommodated without any increase in facilities. Laser installations are of course used in the treatment of a wide variety of ophthalmic conditions and geographic considerations have to be taken into account in their provision.

It would thus appear both on grounds of cost-effectiveness and on social need, a screening programme for the early detection of serious diabetic retinopathy is desirable.

For patients attending a hospital diabetic clinic this screening could reasonably carried out by the Physician who has overall responsibility for the patients health providing he were suitably trained in the recognition of sight-threatening retinopathy. For patients being cared for in general practice, the problem is more difficult, and for these patients the Optician or Ophthalmic Medical Practitioner working in the General Ophthalmic Services may well have a role. If patients were being seen by an Optician or Ophthalmic Medical Practitioner purely for ophthmoscopic screening rather than for full refraction and ocular assesssment, it may be that a reduced fee for this service would be appropriate.

There is no doubt that many patients with diabetic eye disease are referred tragically too late for laser treatment to be effective in the prevention of blindness, and some mechanism for the earlier detection of such patients is undoubtedly required.

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BLOOD VISCOSITY IN PROLIFERATIVE DIABETIC RETINOPATHY AND COMPLICATED RETINAL VEIN THROMBOSIS

by

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SUMMARY:

42 patients with longstanding retinal vein thrombosis and 36 patients with diabetes had their blood viscosity levels measured. In both conditions blood viscosity, plasma viscosity, and serum fibrinogen levels were significantly higher in those patients with capillary non-perfusion and/or new vessels on Fluorescein Angiography, compared to those patients without these complications. The possible role of abnormal blood viscosity in producing capillary non-perfusion and its sequelae in both conditions is discussed.

INTRODUCTION:

Blood viscosity is a major determinant of blood flow (1). Raised blood viscosity is known to decrease retinal blood flow (2). Raised blood viscosity has been shown to exist in patients with retinal vein thrombosis (3) and diabetic retinopathy (4).

Capillary non-perfusion on fluorescein angiography is believed to herald the onset of new vessels in both conditions (5, 6). The aetiology of capillary non-perfusion remains uncertain, but it is presently believed that poor retinal circulation is responsible for this angiographic feature and for its sequelae, neovascularisation (7, 8).

The purpose of this study was to measure blood viscosity and its determinants in patients with retinal vein thrombosis and diabetic retinopathy. We wished to determine whether patients with capillary non-perfusion or new vessels from these diseases have higher blood viscosity levels than those patients without these complications. In view of the relationship between blood viscosity and retinal blood flow, it was felt that such a study would provide insight into the mechanism of production of capillary non-perfusion and its complications - iris and posterior segment new vessels.

METHODS AND MATERIAL:

2 groups of patients were studied. Group I had longstanding retinal vein thrombosis while Group 2 had Diabetes. Both groups contained patients with capillary non-perfusion and or new vessels on fluorescein angiography.

Group 1: 42 patients with longstanding retinal vein thrombosis were studied (9). These patients were examined from three months to three years since their onset of symptoms to rule out an acute - phase increase of their blood viscosity. All underwent full ophthalmological and medical assessment including fluorescein angiography. All patients were ambulant, and none had any acute illnesses. The mean age was 67 years. 20 of the patients had capillary non-perfusion or new vessels. 24 patients had central retinal vein occlusion, 16 had branch vein occlusion, and two had both.

Group 2: 36 patients with diabetes were studied. 18 patients had proliferative retinopathy confirmed on fluorerscein angiography and the other 18 had background or nil retinopathy. Both the proliferative and non-proliferative groups were matched for age, sex, smoking, duration, and type of diabetic treatment. The mean age was 53.3 years and mean duration of diabetes 17 years.

Both groups had viscosity measured in the same manner. A mid-morning, non-fasting forearm venous sample was taken. Blood was anticoagulated with edetic acid (EDTA, 1.5 mg/ml) for blood viscosity studies at low ($0.94s^{-1}$) and high ($94s^{-1}$) shear rates using a CONTRAVES LS30 rotational viscometer at 37oC.

Haematocrit was measured using a Hawksley microhaematocrit, centrifuge (13,000g x 5 mins.) Plasma viscosity was measured using a Coulter-Harkness capillary viscometer, (25°C) Plasma fibrinogen was measured using a Dode fibrometer and standards. Blood viscosity is presented as measured at native haematocrit, and also after correction to a standard haematocrit of 0.45 using regression equations. Corrected viscosity allows studies of factors other than haematocrit which affect blood viscosity.

Statistical analyses of the retinal vein thrombosis group was performed using the 2 Tailed Students t-test, and Mann-Whitney U test as appropriate. Statistical analysis on the diabetic group included the use of the 2 Tailed Students t-test and Wilcoxon's rank sum test.

RESULTS:

Table I shows the results of blood viscosity measurements (both uncorrected and corrected) in patients with retinal vein thrombosis. The group of patients with capillary non-perfusion or new vessel formation have statistically significant increases in mean values of their blood viscosity, plasma viscosity, and plasma fibrinogen. Haematocrit was also higher but the difference between the 2 groups was not statistically significant.

Table II compares blood viscosity and its determinants in the two types of diabetic patients. Blood viscosity at both uncorrected and corrected levels are noted to be higher in the proliferative group of patients. This raised blood viscosity is associated with an increase in plasma viscosity and plasma fibrinogen levels.

RESULTS:

TABLE I

	Capillary non-perfusion/ new vessels	Uncomplicated retinal vein thrombosis	P value
Blood Viscosity (m Pa.s)			
$0.94s^{-1}$	23.2 (1.6)	17.2 (.6)	$P < 0.01$
$94s^{-1}$	6.54 (0.30)	5.37 (0.17)	$P < 0.01$
Corrected Blood Viscosity (m Pa.s)			
$0.94s^{-1}$	22.8 (0.8)	19.3 (0.4)	$P < 0.01$
$94s^{-1}$	6.48 (0.17)	6.05 (0.12)	$P < 0.01$
Plasma Viscosity (m Pa.s)	1.88 (0.03)	1.79 (0.03)	$P < 0.05$
Fibrinogen (g/L)	3.67 (0.20)	2.79 (0.15)	$P < 0.01$
Haematocrit	0.450(0.010)	0.425(0.008)	N.S.

RETINAL VEIN THROMBOSIS GROUP.

Blood viscosity and its determinants in patients with capillary non-perfusion/new vessels, and in patients without these complications. Levels expressed as mean values (SEM in brackets)

m Pa.s = Millipascal seconds

N.S. = Not significant

TABLE II

	Proliferative Retinopathy	Uncomplicated diabetes	P value
Blood Viscosity (m Pa.s)			
$0.94s^{-1}$	20.8 (1.2)	17.8 (0.9)	P< 0.05
$94s^{-1}$	6.12 (0.18)	5.35 (0.21)	P< 0.01
Corrected Blood Viscosity (m Pa.s)			
$0.94s^{-1}$	21.7 (0.8)	19.3 (0.6)	P< 0.02
$94s^{-1}$	6.25 (0.15)	5.57 (0.15)	P< 0.00
Plasma Viscosity (m Pa.s)	1.89 (0.03)	1.71 (0.02)	P< 0.00
Fibrinogen (g/L)	3.69 (0.25)	3.19 (0.16)	P< 0.05
Haematocrit	0.437 (0.009)	0.433 (0.005)	N.S.

Viscosity measurements in proliferative and non-proliferative diabe groups.

m Pa.s = Millipascal seconds. N.S. = not significant.

DISCUSSION:

This study clearly shows that patients with capillary non-perfusion or new vessel formation from diabetes or retinal vein thrombosis have significantly higher blood viscosity levels than patients without these complications. It is interesting to note that the complicated retinal vein thrombosis group have higher viscosity levels than the uncomplicated diabetic group. The low shear rate levels in the retinal vein thrombosis group were increased by 35%, while high shear rate levels were increased by 22% compared to the uncomplicated group. The proliferative diabetics had a 17% increase in their high shear rate viscosity levels and a 14% increase in their low shear rate levels compared to diabetics without these complications. The blood viscosity difference could in part be due to the older age of the retinal vein thrombosis patients, and in part to their higher haematocrit.

Both the complicated retinal vein thrombosis group and proliferative diabetic group had increases in their plasma viscosity levels. These were due to increased fibrinogen levels. Capillary circulation is thought to depend at least in part on plasma viscosity (10). It is therefore possible that capillary non-perfusion as detected on fluorescein angiography may be due to increases in plasma viscosity secondary to hyperfibrinogenaemia. Red cell deformability also influences capillary circulation (10). A study of red cell deformability is indicated in patients with capillary non-perfusion or new vessel formation from retinal vein thrombosis or diabetic retinopathy.

As indicated above, blood viscosity is increased in patients with proliferative diabetic retinopathy and complicated retinal vein thrombosis. This suggests that abnormal blood viscosity may play an etiological role in the formation of capillary non-perfusion and/or new vessel formation. If these rheological factors do predispose to capillary non-perfusion and new vessel formation, reduction ofblood viscosity could have a place in preventing the ischaemic complications of both conditions.

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