FACTORS INFLUENCING THE NATURAL HISTORY OF DIABETIC RETINOPATHY

M. R. W. ULBIG and A. M. P. HAMILTON
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SUMMARY

Despite recent improvements in the management of blood glucose control and in modern technology such as laser treatment and vitreoretinal surgery, diabetes mellitus is the major systemic cause of blindness in the Western world. The study of the natural history of diabetic retinopathy is difficult because of the variability of the disease, and the numerous factors that may influence its course and outcome. In the many studies available of the natural history of diabetic retinopathy, there is a failure to identify these factors. This article tries to identify and to classify the influences that may modify the outcome and the natural course of diabetic retinopathy, and gives some advice on how to deal with them. They can be subdivided into external, internal and ocular factors. Any future studies of the natural history of diabetic retinopathy are marred by the fact that effective treatment is now established and the guidelines for when to commence treatment and the techniques of treatment are well documented.

Diabetes mellitus is the major systemic cause of blindness in the Western world. In the United Kingdom diabetic eye disease results in approximately 1000 registrations per year. In total 2% of the diabetic population are blind (8000–10 000 persons in the United Kingdom), accounting for 7–8% of all blind registrations. A diabetic is 10–20 times more likely to go blind than a non-diabetic and indeed diabetes is the commonest cause of blindness in the 30–60-year-old age group. Of the registered blind diabetics 44% are over the age of 70 and 92% are over the age of 50; 75% are women. The rising incidence is due to increased longevity and procreativity and relative inability to prevent vascular complications.[1,2]

The study of the natural history of diabetic retinopathy is complicated by the variability of the disease and the numerous factors that may influence its course and outcome. This article tries to identify and to classify these factors that may modify the outcome and the natural course of diabetic retinopathy, gives advice on how to deal with them and shows what treatment may be beneficial.

Correspondence to: A. M. Peter Hamilton, FRCS, Moorfields Eye Hospital, City Road, London EC1V 2PD, UK.

CLASSIFICATION OF DIABETIC RETINOPATHY

Today's classification of diabetic retinopathy is a modified Airlie-House classification.[3] Diabetic retinopathy can be divided into various stages. First, there is pre-retinopathy, when there are changes in haemodynamics and vascular permeability but no obvious retinopathy. Second, there is mild non-proliferative retinopathy characterised by microaneurysms, which develops into either maculopathy and/or more severe non-proliferative retinopathy including intraretinal microvascular anomalies (IRMA), cotton wool spots and intraretinal haemorrhages. Finally, there is proliferative retinopathy characterised by epiretinal outgrowth of new vessels and membrane formation, and a cross-linkage to maculopathy. Those with non-proliferative retinopathy are very likely to develop proliferative retinopathy if they live long enough.

THE NATURAL HISTORY OF DIABETIC RETINOPATHY

The natural history of diabetic retinopathy can be assessed in terms of the type of diabetes mellitus, change in retinopathy appearance, effect of retinopathy on visual outcome, and the final outcome, that is the chances of going blind.

The Type of Diabetes

In terms of types of diabetes mellitus, insulin-dependent (type 1) diabetics have predominantly proliferative retinopathy, and non-insulin-dependent (type 2) diabetics tend to have maculopathy. Fifty per cent of those with proliferative retinopathy had the onset of diabetes mellitus before the age of 20, while 75% of those with diabetic macular oedema had the onset of diabetes after the age of 40.

The Change in Retinopathy

As regards the change in retinopathy appearance the best data are those of Kohner,[4] who showed that 58% of cases of mild non-proliferative retinopathy were unchanged

Table I. Chances of going blind from diabetic retinopathy within 5 years

Fundus lesions	% blind patients
Age under 29 years	
Microaneurysms	0
Haemorrhages and exudates	4
Age 30–59 years	
Microaneurysms	12
Haemorrhages and exudates	24

Table II. ETDRS guidelines for laser treatment of diabetic retinopathy

Panretinal photocoagulation should not be carried out in eyes with mild or moderate non-proliferative retinopathy
Panretinal photocoagulation should be considered for severe non-proliferative retinopathy
Panretinal photocoagulation should not be delayed in the high-risk proliferative stage
Focal or grid treatment should be carried out for macular oedema that involves or threatens the centre of the macula

after 4 years of follow-up whereas 42% had progressed after 4 years. Among cases of severe non-proliferative diabetic retinopathy followed for 4 years 35% were changed, 65% had progressed and 14% had developed proliferative retinopathy. The presence of IRMA and the amount of intraretinal haemorrhage are indicators for the progression of retinopathy. Once macular oedema is present, then an increase in oedema will inevitably occur; this is associated with further deterioration of vision.

The Chances of Going Blind

Table I shows the chances of going blind within 5 years depending on age and the retinal changes. It clearly demonstrates that the risk of going blind increases with age and the severity of retinal changes.

Any future studies of the natural history of diabetic retinopathy are marred by the fact that effective treatment is now established[3,5] and that guidelines on when to commence treatment and the techniques of treatment are well documented. Table II is a short summary of the well-known treatment guidelines of the Early Treatment Diabetic Retinopathy Study Group (ETDRS).[3]

Table III. Oslo study: severity of diabetic retinopathy at baseline and after 7 years in patients grouped according to mean blood glucose concentrations (HbA_1)

Mean no. of microaneurysms and retinal haemorrhages	HbA_1		
	Below 9%	9.1–10%	Over 10%
At baseline	11.8	24.7	17.6
After 7 years	25.5	41.1	80.5
Change	+13.8	+16.4	+62.8

Table IV. The influence of good and poor glycaemic control on the development of diabetic retinopathy in dogs

30 months of poor control followed by 30 months of good control = retinopathy
30 months of poor control followed by 30 months of poor control = retinopathy
30 months of good control followed by 30 months of poor control = no retinopathy

FACTORS INFLUENCING THE NATURAL HISTORY OF DIABETIC RETINOPATHY

In those studies available on the natural history of diabetic retinopathy, there is a failure to identify factors other than those mentioned above that may modify the outcome and, of course, the effect of treatment. These other factors can be subdivided into external factors, internal factors and ocular factors.

External Factors

The external factors that are under discussion as possibly interfering with the course of diabetic retinopathy are diabetic control and diet, cigarette smoking, alcohol consumption, the contraceptive pill and aspirin.

Control of Diabetes. A considerable amount has been published on the effect of improved blood glucose control on diabetic retinopathy. Early reports such as the KROC Study[6] showed rapid deterioration of diabetic retinopathy associated with rapid improvement in blood glucose concentrations. But it is only with the publication in 1992 of a study by the Oslo group[7] that the beneficial effect of better control has been proved. The Oslo study assessed the severity of retinopathy at baseline and after 7 years in patients grouped according to mean blood glucose concentrations measured as HbA_1 (Table III). Another recent publication from Stockholm[8] supports those findings and stresses the advantages of intensified conventional insulin treatment over conventional insulin treatment.

There seems to be a point of no return once more severe diabetic retinopathy has become established. In the presence of large areas of non-perfused retina, even perfect normoglycaemia as achieved by pancreatic transplantation is unable to protect against the development of proliferative diabetic retinopathy.[9] The Engerman dog studies[10] showed that good control of blood glucose concentration is important at the onset of the disease, while improvements in control achieved later are of questionable value (Table IV). However, the Oslo study[7] comes to the conclusion that even secondary intervention by long-term lowering of glycated haemoglobin has a beneficial impact on non-proliferative diabetic retinopathy.

Alcohol. There is a controversy about the influence of drinking habits on the development of diabetic retinopathy. There has been a suggestion from a Scottish study[11] that alcohol has an adverse effect on diabetic retinopathy, particularly in the advancement of macular oedema and the development of proliferative retinopathy. However, two other studies, one from the Veneto region in Italy,[12] and the other from Wisconsin,[13] have shown that alcohol intake is not associated with deterioration, and indeed in the younger patients may well have a beneficial effect. These controversial results may be explained by the different drinking habits and the preferred typical alcoholic

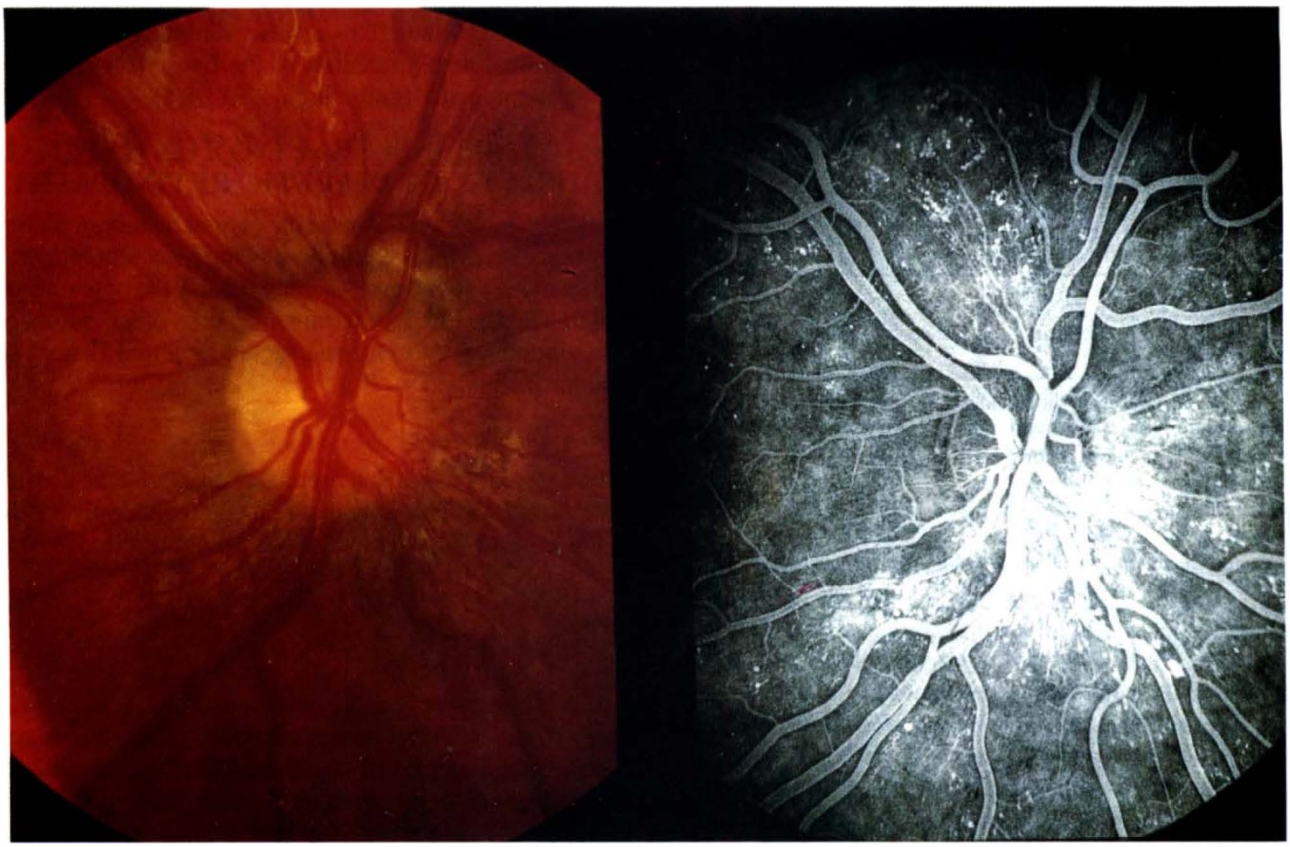

Fig. 1. *Fundus photograph (left) and fluorescein angiogram (right) of a young diabetic woman taking the contraceptive pill.*

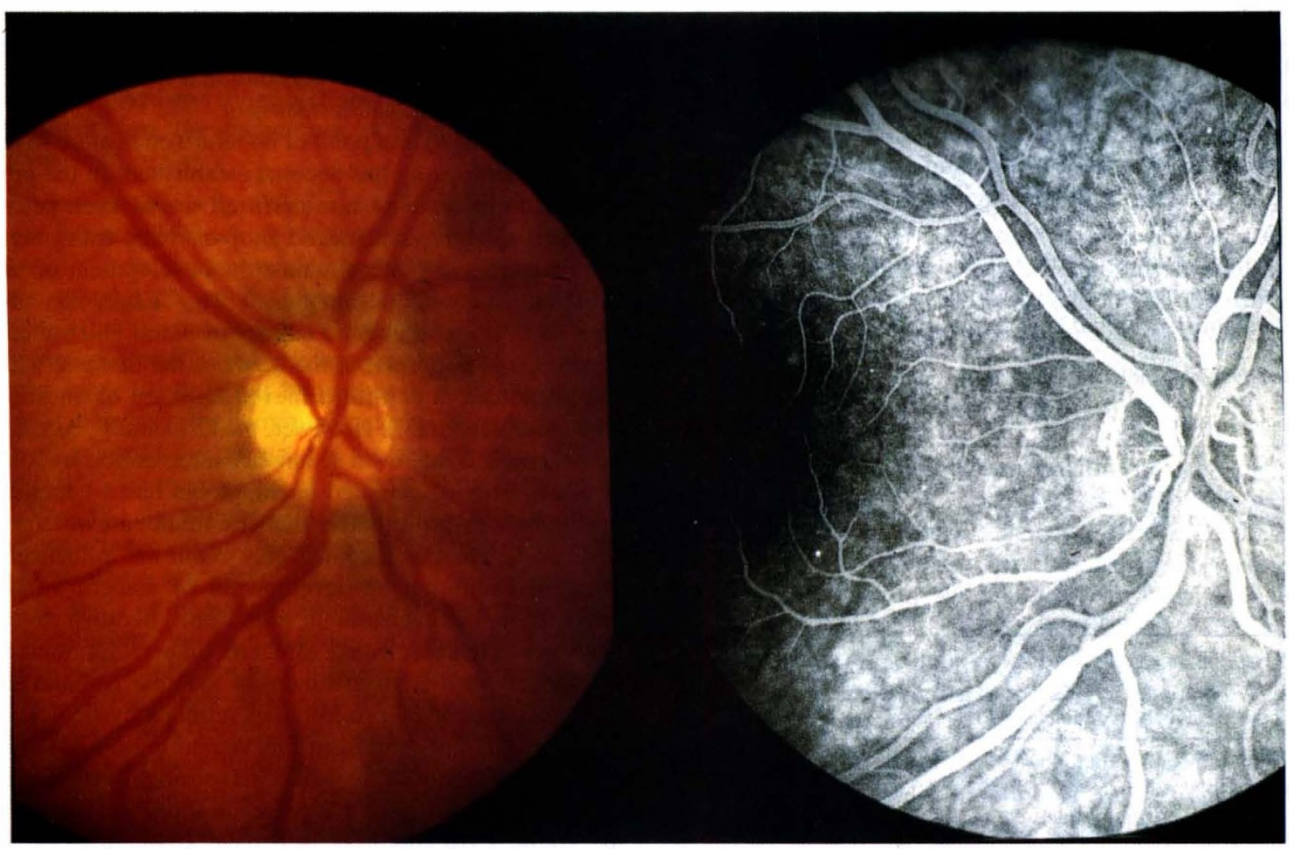

Fig. 2. *Fundus photograph (left) and fluorescein angiogram (right) of the same woman as in Fig. 1, 12 months after stopping the contraceptive pill. The retinal vascular changes have resolved.*

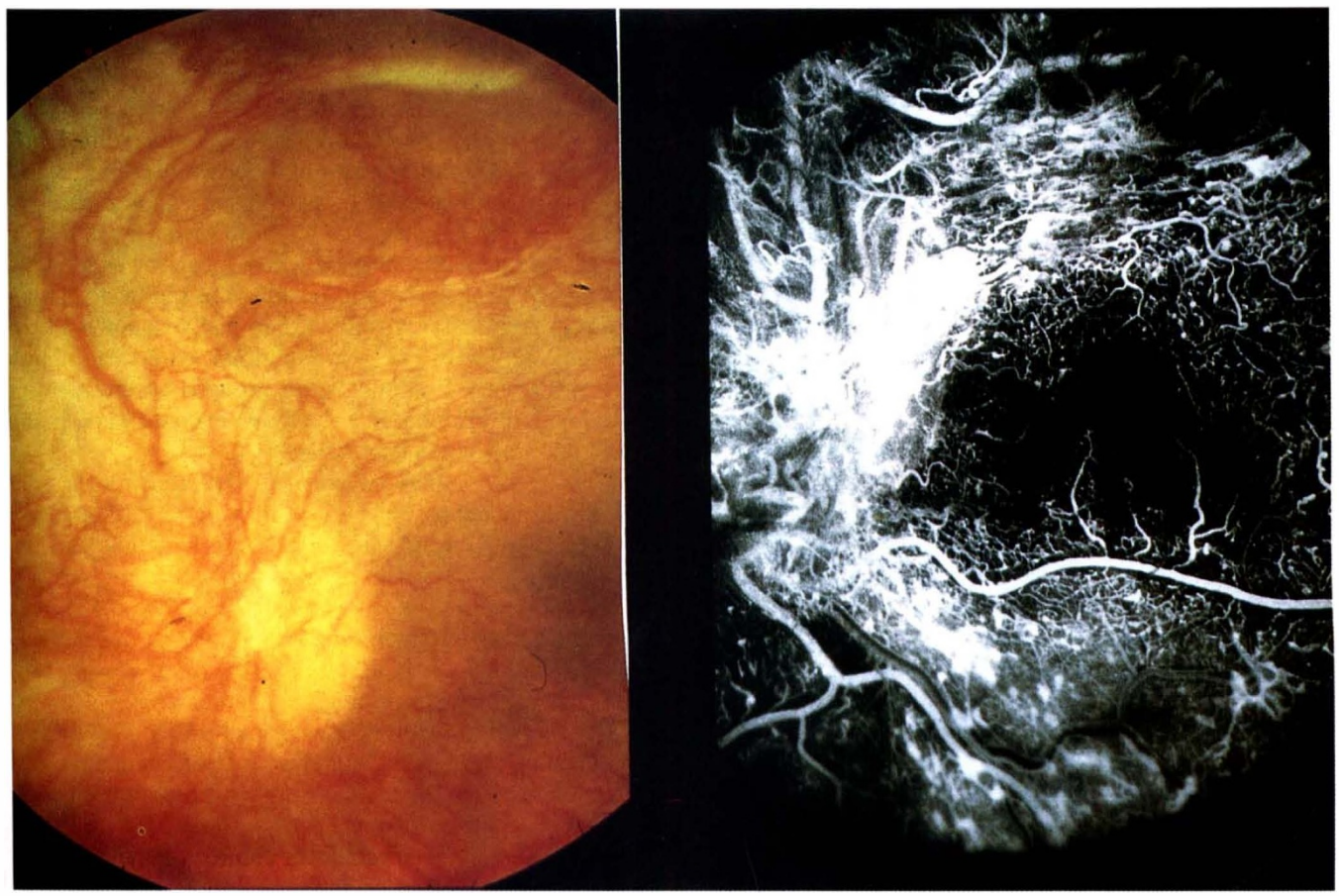

Fig. 3. *Fundus photograph (left) and fluorescein angiogram (right) of a young insulin-dependent diabetic with florid proliferative retinopathy. There is massive neovascularisation from the optic disc.*

drinks in these countries. The patients reported in the Scottish study may have been more excessive drinkers, whereas the Italian study observed the effects in a typical wine-drinking population.

Smoking. The effect of cigarette smoking is even more difficult to assess. The devastating effect of smoking on macrovascular disease is well recognised but its impact on microvascular disease is not so well documented and evidence has not always been consistent. Chase and co-workers[14] found that smoking increases the risk of albuminuria and thus almost certainly causes microvascular changes in the retina as well, whereas Moss and Klein[15] have shown recently that smoking cigarettes has no adverse effect and caused progression of retinopathy only in younger persons. This is consistent with the findings of Reichard and co-workers[8] who found no correlation

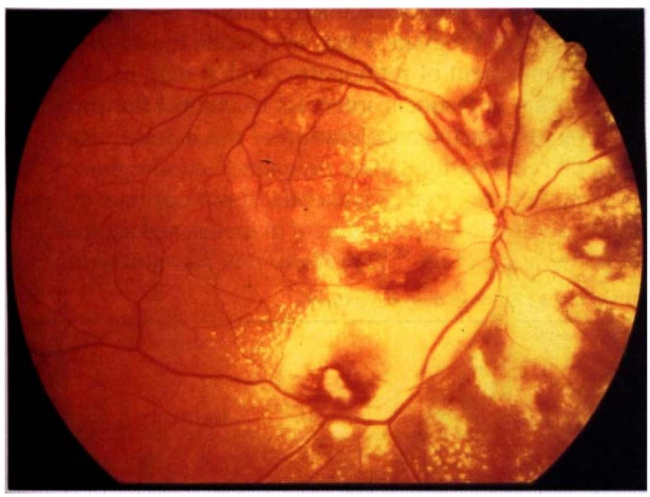

Fig. 4. *Fundus photograph of a diabetic patient with massive hypertension. Note that the exudates and leakage are located around the optic nerve.*

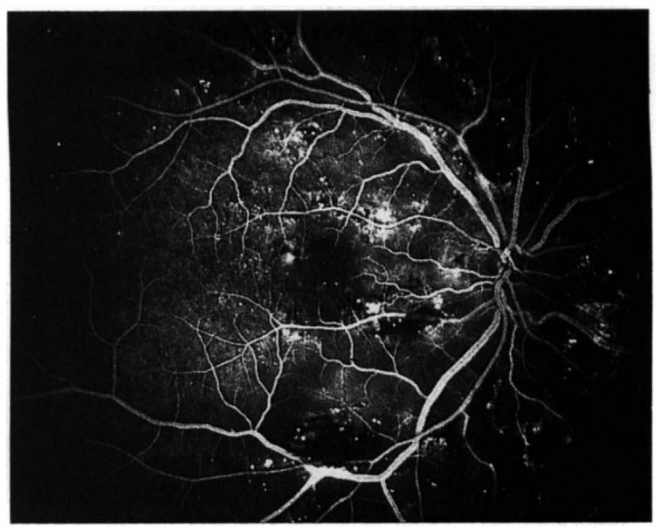

Fig. 5. *Fluorescein angiogram of the same eye as in Fig. 4.*

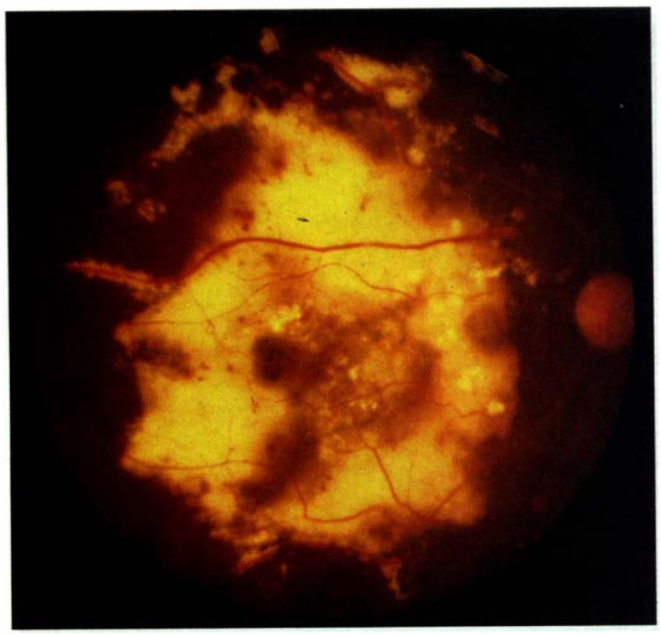

Fig. 6. *Fundus photograph showing extensive exudative maculopathy in a diabetic patient with hyperlipidaemia and hypertension.*

between smoking habits and the progression of diabetic retinopathy. By contrast Dodson[16] showed that progression from background retinopathy to proliferative retinopathy was more likely in older women who smoked.

The Contraceptive Pill. The contraceptive pill also has been incriminated in causing advancement of retinopathy. Our group has seen several cases, all of which have been with the high-dose progesterone pill. In one patient with mild retinopathy (Fig. 1), stopping the pill resulted within several months in improvement of retinopathy and reduction in the leakage seen on the fluorescein angiogram (Fig. 2). It is unclear whether the modern low-level hormone pill has enough thrombogenic activity to cause such advancement of retinopathy. The effect of hormone replacement therapy is as yet uncertain.

Aspirin. Drugs such as aspirin or dobesilate calcium are known to decrease thrombogenic activity, but whether this is of any benefit in the prevention of diabetic retinopathy is still under discussion. The ETDRS study[3] that investigated the effect of aspirin intake on the formation and advancement of existing diabetic retinopathy concluded that there was no beneficial effect from aspirin.

Internal Factors

Internal factors to be discussed are age, hypertension, lipids, control of nephropathy, pregnancy and pituitary abnormalities.

Age. Age dictates to a large extent the type of retinopathy. The younger group are usually insulin-dependent diabetics and develop proliferative retinopathy, while the older group are non-insulin-dependent diabetics and develop maculopathy. The rate of progression differs. In the younger group there is a subgroup with what is known as florid retinopathy (Fig. 3) whose course was so aptly described by Beaumont and Hollows[17] as rapid and bloody and blinding, and it was this group that was amenable to pituitary ablation[18] before panretinal photocoagulation was established. Fortunately this group is becoming rarer with the improvement in early diabetic control and in the techniques of photocoagulation.[3,5]

Cholesterol and Hypertension. Hypertension is well known as a factor that worsens diabetic retinopathy.[19] Dodson and Gibson[16] in 1991 listed hypercholesterolaemia as a risk factor in non-insulin-dependent diabetes mellitus in addition to hypertension (Figs. 4–6). Hyperlipidaemia and hypertension are well recognised associated problems of kidney disease. Both factors are associated with deteriorating macular oedema.

Nephropathy. Diabetic nephropathy also aggravates retinopathy, especially maculopathy, an effect that may be mediated through the increase in blood pressure, fibrinogen levels and raised lipoproteins, as pointed out by Kostraba.[20] The early and adequate control of hypertension has a favourable effect on the progression of retinopathy. The effect of various methods of control of renal failure on the course of visual acuity is illustrated in Table V. As shown by Ulbig and Khauli[9,21] the most effective method is renal transplantation, with or without a pancreatic graft, while the least effective method is haemodialysis. This is explained by the effect of good control of nephropathy on the development of macular oedema. Fig. 7 illustrates the aggravation of diabetic maculopathy within 1 year after the onset of renal failure. Photocoagulation in those severe cases can barely do more than control the situation and not until a renal graft has succeeded will the retina dry out and the response to photocoagulation improve.

Pregnancy. Pregnancy may accelerate the development and advancement of retinopathy, which may need photocoagulation at frequent intervals to control the progress. Risk factors for the acceleration of the natural history of diabetic retinopathy during pregnancy are pregnancy *per se*, hypertension, hyperglycaemia, rapid normalisation of blood glucose levels, duration of diabetes, and stage of retinopathy at baseline.[22] Therefore, it is recommended that

Table V. Course of visual acuity associated with different modes of treatment for renal failure in diabetic patients

	Visual acuity		
Treatment	Impoved or stable (%)	Worse (%)	Reference
Haemodialysis (n = 29)	38	62	Khauli *et al.*[21]
Peritoneal dialysis (n = 18)	83	17	Khauli *et al.*[21]
Renal graft (n = 45)	89	11	Khauli *et al.*[21]
Renal + pancreatic graft (n = 34)	88	12	Ulbig *et al.*[9]

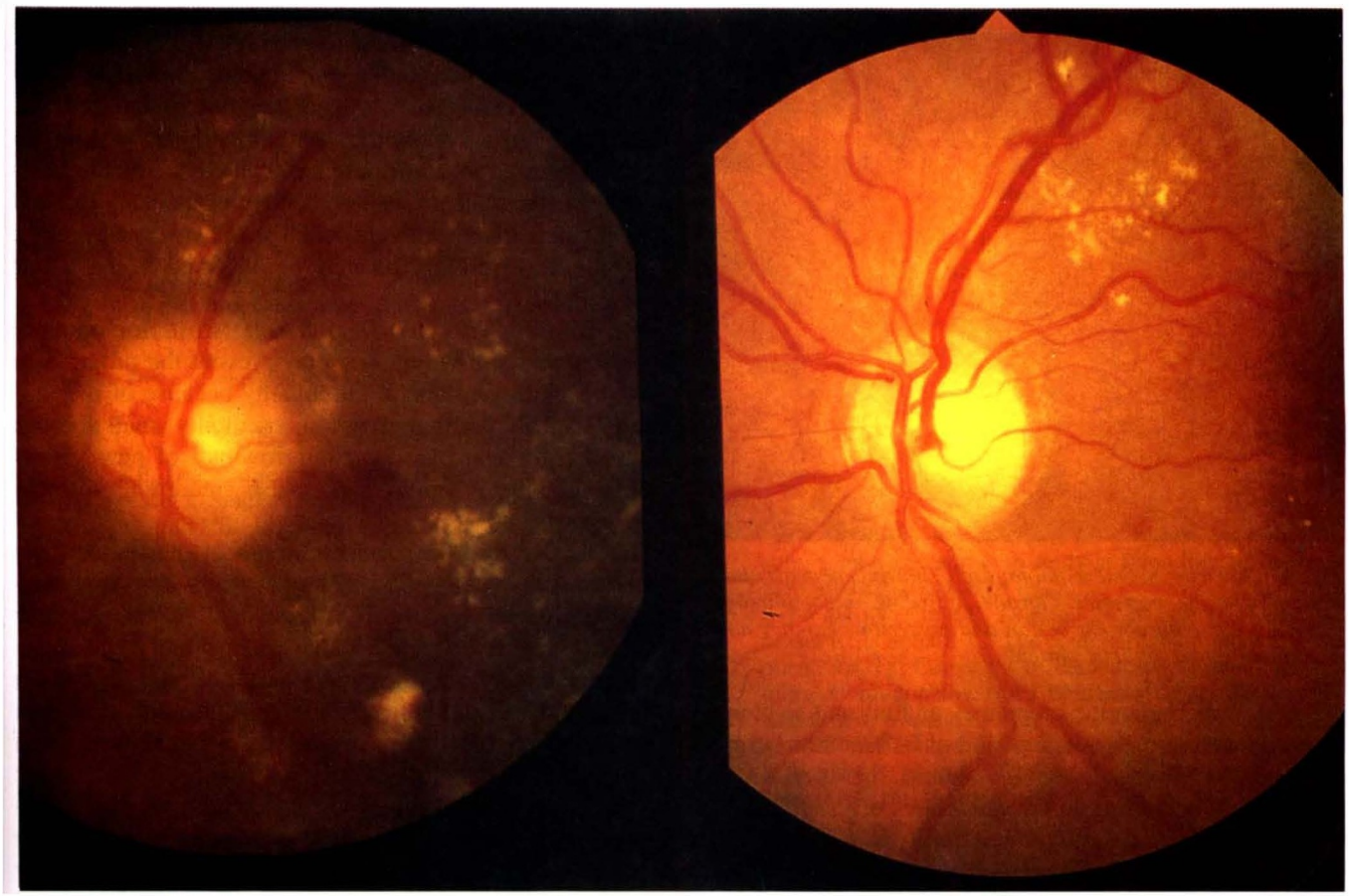

Fig. 7. *Right: Fundus photograph showing mild to moderate non-proliferative diabetic retinopathy. Left: Fundus photograph of the same patient 1 year after the onset of renal failure, showing massive exudative macular oedema.*

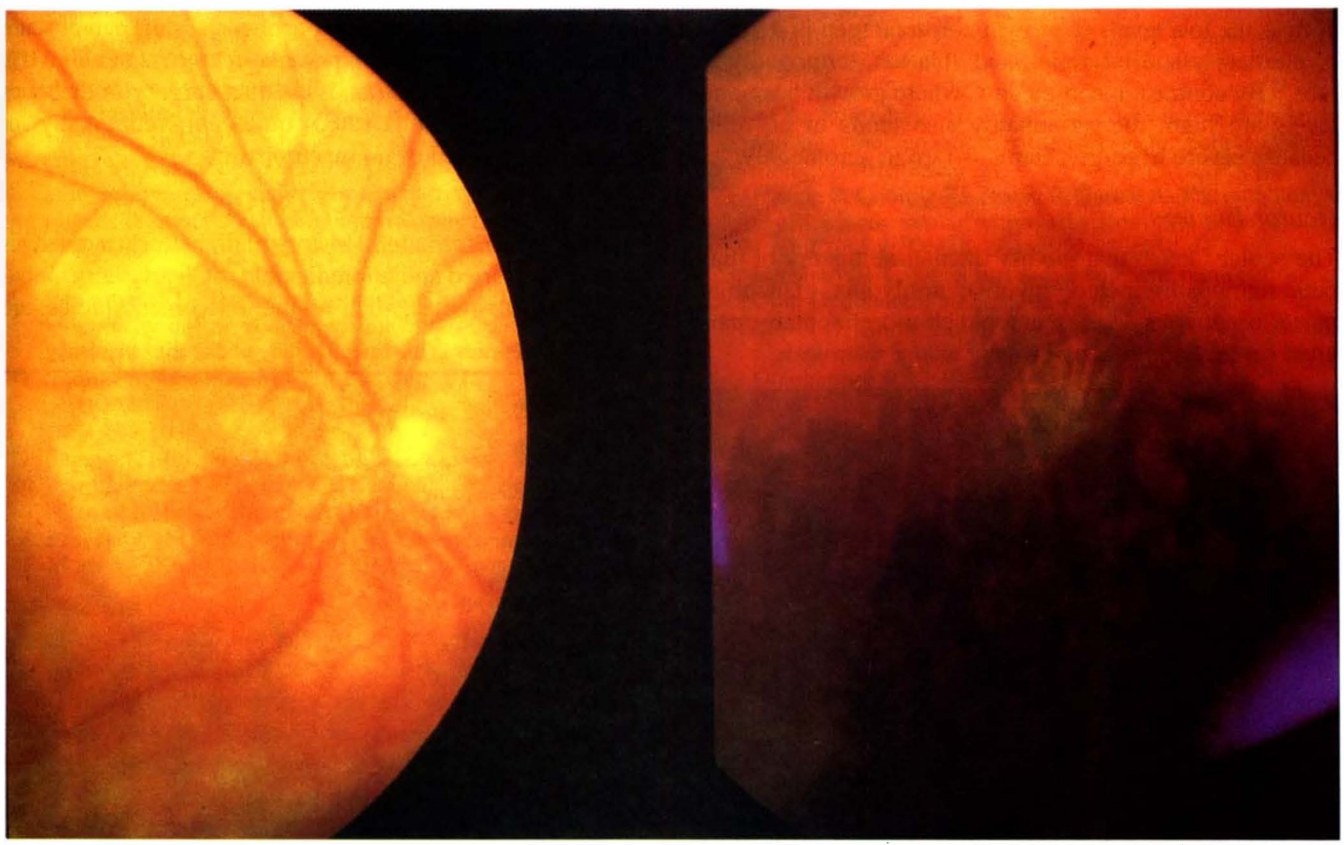

Fig. 8. *Left: Fundus photograph of the right eye showing neovascularisation on the disc and fresh panretinal photocoagulation burns. Right: Fundus photograph of the left eye of the same patient showing no signs of diabetic retinopathy but a large area of choroidal scarring.*

Fig. 9. *Anterior segment photograph showing neovascularisation near the posterior capsule following uncomplicated extracapsular cataract extraction and posterior chamber lens implantation in a diabetic patient.*

diabetic women plan the pregnancy and normalise blood glucose levels slowly over a period of 6–8 months before conception. Photocoagulation should be performed aggressively according to the guidelines of the ETDRS[3] during pregnancy, despite the possibility of regression of vascular changes *post partum*. If the patient is already pregnant normalisation of blood glucose is important and intensive surveillance of retinopathy is needed.

Pituitary Abnormalities. With pituitary abnormalities such as the low levels of growth hormone seen in dwarfs, or pituitary gland infarction and ablation, retinopathy is rare.[23] By contrast in acromegaly, where growth hormone levels are high, the retinopathy also tends to be mild because severe hyperglycaemia is rare in acromegaly.[24]

Ocular Factors

The ocular factors that modify the natural history of diabetic retinopathy include myopia, amblyopia, glaucoma, posterior vitreous detachment, old chorioretinopathy, cataract surgery and rubeosis iridis.

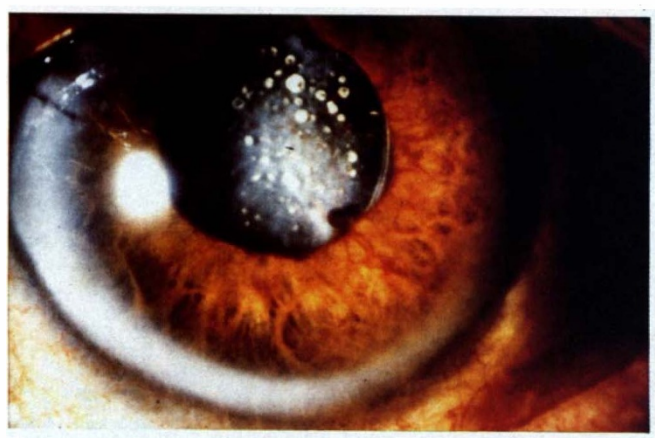

Fig. 10. *Anterior segment photograph showing iris neovascularisation, an opaque posterior capsule, and deposits on the lens implant in a diabetic patient.*

Myopia, Glaucoma and Choroidal Atrophy. Extensive myopia with choroidal degeneration, amblyopia, glaucoma and extensive old chorioretinopathy all protect against diabetic retinopathy and probably act in the same way as panretinal photocoagulation by reducing the metabolic needs of the retina, as recently discussed by Boulton *et al.*[25] In patients with choroidal atrophy in one eye only, proliferative retinopathy may be observed in the fellow eye (Fig. 8).

Posterior Vitreous Detachment. Posterior vitreous detachment and vitrectomy may prevent the progression of proliferative diabetic retinopathy because of the missing scaffold,[26] although not uncommonly small abortive raspberry-like neovascular outgrowths[27] of new vessels may develop which can cause recurrent vitreous haemorrhages.

Cataract Surgery. The development of cataract may obscure developing treatable retinopathy and thus seriously alter the prognosis. Removal of a cataract may aggravate both existing macular oedema and proliferative retinopathy and may hasten the onset of rubeosis.[28] Even anterior hyaloidal fibrovascular proliferation, which is common in vitrectomised phacic diabetic eyes,[29] can occur after uncomplicated cataract surgery in diabetic eyes as shown by Ulbig (Fig. 9).[30] Therefore, if the cataract is not too dense retinopathy should be treated properly prior to cataract surgery. The intention to perform early photocoagulation after cataract surgery is often prevented by poor view or post-operative fibrinous uveitis. It is too easy to end up in a situation where anterior fibrinous deposits, an opaque capsule or rubeosis iridis can obscure the view and prevent adequate laser treatment (Fig. 10). However, the best results of cataract surgery in diabetics are in those with treated quiescent retinopathy or adequately treated or no maculopathy.[28]

CONCLUSION

In conclusion, the natural history of diabetic retinopathy is extremely varied and unpredictable.[31] Clearly large population-based studies, such as the Wisconsin studies, are

Table VI. Factors in the natural history of diabetic retinopathy

Internal factors
Age
Hypertension
Lipids
Control of nephropathy
Pregnancy
Pituitary abnormalities
External factors
Diabetic control and diet
Smoking
Alcohol
Contraceptive pill
Ocular factors
Myopia
Amblyopia
Glaucoma
Posterior vitreous detachment
Old chorioretinopathy
Cataract surgery
Rubeosis iridis

useful in giving a general aspect to the likely prognosis. However, there are many other factors, both external, internal and ocular, that may have a role to play in the development and progression of retinopathy (Table VI. These factors must always be borne in mind when considering treatment and follow-up in diabetic retinopathy.

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Key words: Diabetic retinopathy, Natural history.

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