The Prevalence of Blindness in Diabetics

HARRY KEEN, MD, FRCP, Professor of Human Metabolism, Guy's Hospital Medical School, London, and Physician, Guy's Group of Hospitals

The Committee on Blindness of the British Diabetic Association (1967–69) estimated recently (1970) that there were 8,000–9,000 blind diabetics in the British Isles. Cataract accounted for about one-fifth of these; almost all the rest were described by the rubric 'diabetic retinopathy'. Between 5 per cent and 10 per cent of diabetics surviving twenty years of the disease will be blind, and more will suffer a degree of visual disturbance short of blindness. Which of our new patients are destined to become visually disabled? What factors govern this process? What measures can be taken to avoid this catastrophe?

Despite the familiarity of physicians dealing with diabetics with the ophthalmoscopic progression from a normal fundal appearance through the stage of 'background retinopathy'—the scattered small dots, blots and exudates of which the patient is often totally unaware—to the grossly disorganised, sightless eye, it remains impossible to predict either the individuals who will be affected or the rate of progression of the retinopathy in particular cases. One gains little indication from study of the blind eyes themselves. Myers *et al.* (1968) analysed the causes of visual loss in 217 blind eyes of diabetics. Vitreous haemorrhage accounted for 30 per cent, macular traction and detachment for 28 per cent, macular oedema, exudate or pigmentation for 24 per cent, with haemorrhagic glaucoma and rarer causes accounting for the rest. Presumably, these groupings include those seemingly numerous patients in whom vision is obstructed by the skein of new vessels and connective tissue that hangs apparently in the substance of the vitreous body. While caution must be exercised in interpreting these figures—the authors are ophthalmologists and may enjoy a rather selective experience—it is at least clear that a variety of mechanisms can be responsible for visual loss in the diabetic and these may be the consequence of differing provocative factors.

Although prediction in the individual diabetic is restricted, some broad correlations and indications of likely visual damage can be made out in groups of patients. Of these predictive factors, age at diagnosis and the known duration of diabetes are generally accepted, while the question of the influence of metabolic control is still hotly debated. Despite the clinical impression that retinopathy is more striking in young insulin-treated diabetics (Bradley and Ramos, 1971), Caird *et al.* (1969) computed from the eye examination records

of diabetics at the Radcliffe Infirmary, Oxford, that when 'background' retinopathy only was present, the chance of serious visual deterioration in patients diagnosed as diabetic under the age of sixty years was of the order of 1 per cent p.a. compared with 4 per cent p.a. when the diagnosis was made after that age. Miki *et al.* (1969) echoed his comment that the advance of retinopathy is more rapid in patients diagnosed late in life, but this must be interpreted in the light of the uncertainty of dating the true onset of the metabolic disorder in older patients. This interaction of age and apparent duration is further illustrated by the data of Soler *et al.* (1969), represented in Fig. 1, which shows the frequency with which diabetic retinopathy was found

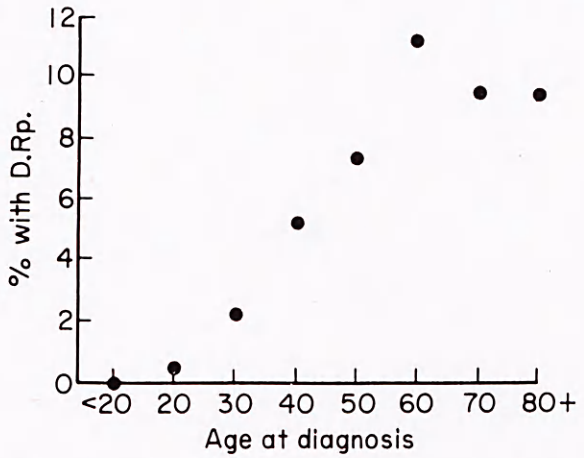

Fig. 1. Frequency of diabetic retinopathy (% with D.Rp.) found ophthalmoscopically in 5,157 newly diagnosed diabetics, by age at diagnosis (*from* Soler *et al.*, 1969).

at the time of initial diagnosis of diabetes. The virtually linear increase in frequency between 20 and 60 years of age suggests strongly that diabetes is discovered further and further along its road to retinopathy as the age of diagnosis increases. There is also an age change in the retinal pathology associated with blindness. In the younger diabetic new vessel formation is of grave significance for vision; 50 per cent of eyes so affected are blind in five years (British Diabetic Association, 1967–1969; Caird *et al.*, 1969; Patz and Berkow, 1968; Deckert *et al.*, 1967). Early neovascularisation in the retina is often localised and easy to miss. Its import is particularly grave when it occurs at or near the optic disc. The technique of retinal fluorescein angiography has rendered new vessels much more readily identifiable, for they usually show abnormal permeability to the dye (Scott *et al.*, 1964). In contrast, new vessel

formation is rare in diabetics diagnosed later in life. Bradley and Ramos (1971) considered that, in the Joslin clinic, proliferative retinopathy was virtually never found in diabetics with a true onset at sixty years of age or later. The key to this difference may be the long duration of diabetic metabolic abnormality that usually precedes new vessel formation. Unlike ordinary 'background' retinopathy, which may appear after 5 to 10 years, a further 10 years of diabetes usually elapses before proliferative changes occur. This is indicated graphically from the composite figures published by Caird *et al.* (1969) which emphasise the importance of increasing duration of known diabetes as a determining factor in both. The literature is replete with collections of data showing the clear relationship of frequency of retinopathy with duration of diabetes but it is an interesting and curious fact that almost all of these show a levelling off of the frequency curve at about 80 to 85 per cent among patients surviving twenty years or so of diabetes (Bryfogle and Bradley, 1957; Whittington, 1969).

The influence of metabolic control of diabetes upon development of retinopathy and hence of blindness, remains an open question. Knowles (1968) reviewed over 300 papers on this subject and concluded that, largely for methodological reasons, the relationship was neither established nor refuted. On the basis of retrospective clinical studies, Constam (1965) and Burditt *et al.* (1968) have adduced evidence that patients with lower levels of blood sugar and less glycosuria (i.e. better control) in the early years of their diabetes are less likely to develop retinopathy than those with early 'poor control', regardless of the level of metabolic disturbance displayed later. They are unable to exclude the possibility that early ease of 'control' simply denotes an earlier stage in the evolution of diabetes and it is to this that freedom from retinopathy is attributable. However, the closely observed prospective study of Kohner *et al.* (1968) suggested that certain elements of even established retinopathy might be decelerated by improved metabolic control. Miki *et al.* (1969) also showed, in Japanese diabetics, that, as judged by frequent estimates of the fasting blood sugar, those in whom the levels were lowest showed least appearance of new retinopathy or worsening of existing retinopathy. This was true despite a clear association between the initial diagnostic fasting blood sugar level and the frequency of retinopathy at diagnosis. Our own experience (Keen and Jarrett, 1971) in the Bedford study also provides some evidence supporting the apparent association between retinopathy and blood sugar level. Figure 2 illustrates the proportions showing 'microaneurysms' in the newly discovered borderline diabetics (B/L) and diabetics (Q 1–4) at the time of the population survey in 1962 and on re-examination approximately five years later. The new-found diabetics are separated into 'quartiles' of the

distribution of their capillary blood sugar levels at 2 hours after 50g glucose by mouth. Not only is there, as shown, a trend to increasing retinopathy with increasing glucose intolerance, but the degree of involvement was very

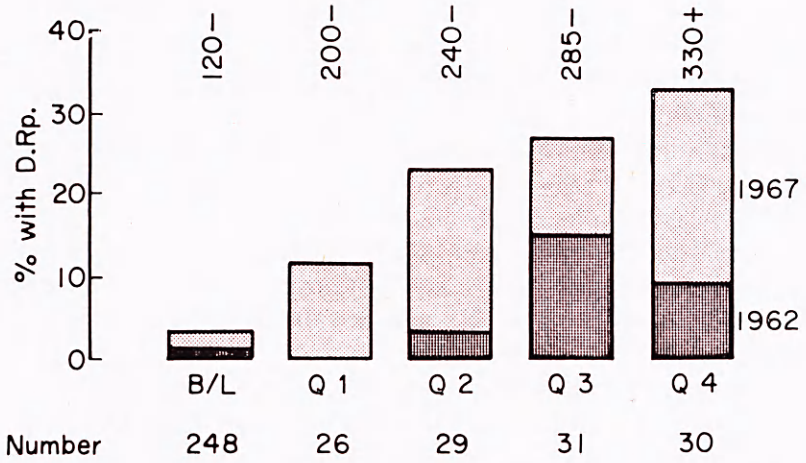

Fig. 2. Frequency of diabetic retinopathy (% with D.Rp.) found in newly-diagnosed borderline diabetics (B/L) and diabetics (Q1–Q4) in Bedford in 1962 and on re-examination in 1967. Numbers in each group shown below columns. Numbers above columns represent capillary blood sugar categories measured in the Survey 2 hours after 50 g oral glucose. Q1–Q4 represent quartiles of the 2-hour blood-sugar distribution in diabetics (2-hour blood-sugar 200 mg/100 ml or more).

different. None of the few affected borderline diabetics showed more than 3 microaneurysms, while the five-year follow-up showed visual deterioration due to retinopathy in three of the diabetics and florid changes in many others.

The effect of raised arterial pressure on the development of retinopathy has been referred to and Kornerup (1958) presented evidence to support the view that it might play some part in pathogenesis. In a systematic study of blood pressure in an unselected group of 674 clinic diabetics (Keen *et al.*, 1972), there was a suggestion of higher mean pressures in patients with retinal micro-aneurysms than in those without (Fig. 3). The differences were small and inconstant, however, and using methods of statistical analysis which allowed for the 'normal' influence of age and sex on blood pressure levels, no association could be found between blood pressure and arcus senilis, conjunctival vascular abnormalities, dilatation of retinal veins, blot haemorrhages, hard retinal exudates or lenticular opacities. With some of the more advanced and severe manifestations of retinopathy, however, clearly raised mean pressures

and scores were found (Table 1) but in evaluating the significance of these one must take account of the probability of accompanying renal disease. The importance of renal disease is supported by Table 1 which shows that pressure

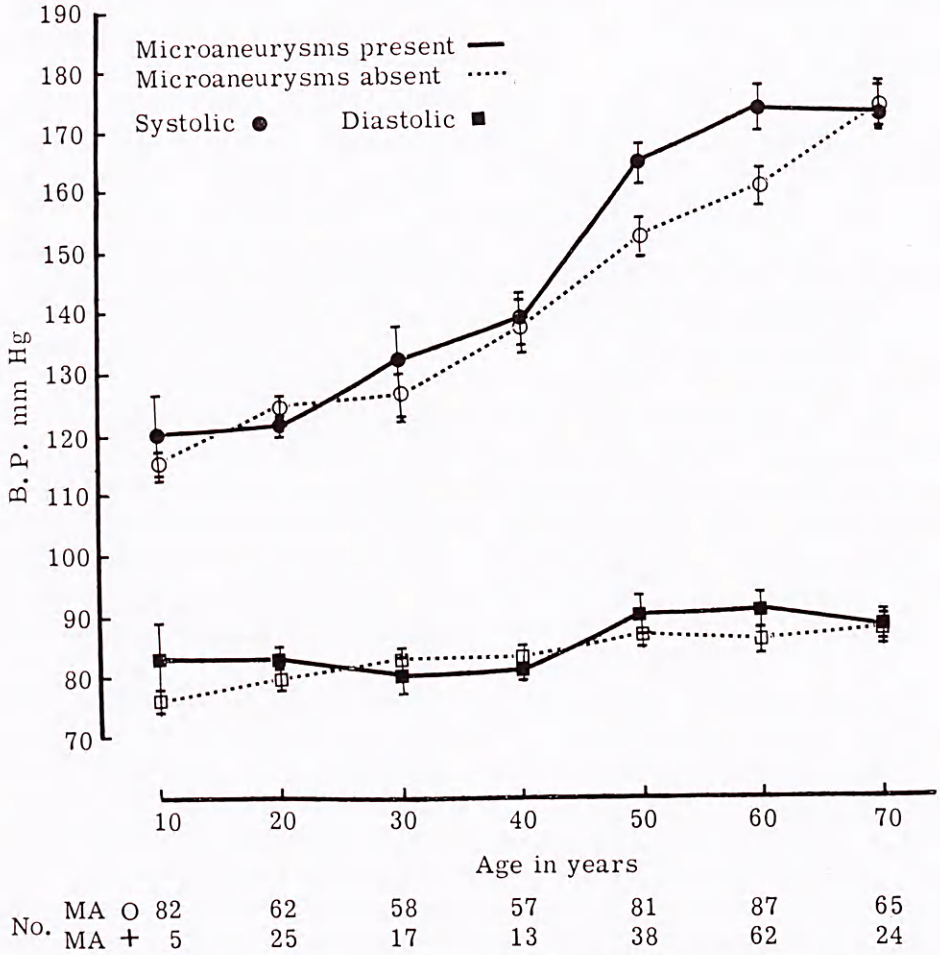

Fig. 3. Mean blood pressure (systolic and diastolic) by age in 676 unselected clinic diabetics calculated separately for those with and those without microaneurysms detected on direct ophthalmoscopic examination of the fundi. Vertical lines represent standard errors of the means. Ages are the lower limits of class intervals.

elevation was greatest in these selected categories of retinal abnormality when clinical proteinuria was present. Clinical tests for proteinuria are insensitive indicators of renal damage (Keen *et al.*, 1969) and substantial changes may well have been present in those with urine tests negative for protein. While it

TABLE 1. Mean BP and 'scores' in diabetics with specified retinal changes.

Abnormality	P/u	No.	Mean age	Blood pressure		Age/Sex 'Score'	
				Systolic	Diastolic	Systolic	Diastolic
Vitreous haemorrhage	0	16	56·9	167·3	91·3	+18·0	+ 5·3
	+	13	52·6	169·2	95·0	+30·8	+13·8
'Flame' haemorrhages	0	21	62·0	173·8	93·1	+19·5	+ 4·8
	+	15	57·5	181·7	94·0	+38·3	+12·0
Retinitis proliferans	0	9	56·7	158·3	89·4	+ 8·3	+ 3·9
	+	8	39·7	162·5	96·2	+51·2	+25·0
Rubeosis of iris	0	5	63·0	171·0	101·0	+18·0	+13·0
	+	2	51·0	190·0	107·5	+57·5	+25·0

Mean blood pressure and age/sex adjusted 'score' (systolic and diastolic) in diabetics found to have particular specified retinal abnormalities. P/u=clinical proteinuria (positive to sulphosalicylic acid). 'Scores' represent the mean deviation of pressures from the mean of that sex and age group in a non-diabetic sample, adjusted to take account of the increasing variation of pressures with age and the difference between the sexes (Hamilton *et al.*, 1954).

may be, therefore, that the apparent association of retinopathy and raised blood pressure levels is simply a reflection of the accompanying renal disease, one cannot exclude the possibility that diabetics who chance to have higher levels of systemic pressure may be more vulnerable to the microvascular sequelae, both retinal and renal, of diabetes. Reduction of diastolic pressures to below 100mm Hg has been recommended in the management of diabetic retinopathy (Bradley and Ramos, 1971), but there is no good evidence that this affects the progress of the condition.

Other local factors may influence the appearance or rate of progression of retinopathy. A raised intraocular tension may slow its development (Mooney, 1963; Becker, 1967) and a fluctuating tension enhance it (Poos, 1930). Retinopathy occurs less frequently in the myopic eye (Oakley, 1951) and impairment of the retinal circulation secondary to choroido-retinal degeneration (Okun and Johnston, 1968) or retinal artery occlusion (Becker, 1967) may even be associated with the regression of vasoproliferative changes. It may be that the restriction of local blood supply is responsible for the 'burning-out' of a previously inexorably progressive retinopathy with visual damage that stops short of complete blindness; change of this sort in the local vascular/metabolic balance may explain the regression of lesions distant from an area of therapeutic light coagulation. Atherosclerosis of large arteries is unlikely to play an important pathogenic role in retinopathy for, in Japan, where atherosclerotic disease is much less common than in Western diabetics, microvascular disease occurs with at least comparable frequency and intensity. The evidence bearing on the importance of genetic factors in retinopathy is conflicting. It has been stated that there is no greater resemblance in retinopathy between diabetic

siblings than between unrelated diabetics (Bradley and Ramos, 1971; Caird *et al.*, 1969). Pyke and Tattersall (1972), however, showed striking similarity in 'the development and pattern of retinopathy' between 12 pairs of identical twins when both had had diabetes for 15 years or more. In 10 discordant pairs of identical twins (when only one had diabetes), even after 15 years of the disease, retinopathy was less frequent and less severe in the diabetic twins compared with the concordant pairs. Although the numbers are small, the elegant structure of this study compels the conclusion that genetic factors play some part in determining the advent and degree of diabetic retinopathy.

For the national estimates of the incidence of diabetic retinopathy as a cause of blindness, we are greatly indebted to Sorsby's analysis (1966) of blindness registration figures in England and Wales. He found that diabetic retinopathy accounted for about 7 per cent of all new blind registrations, but this average figure varied considerably from age group to age group. In the period 1955–1962 diabetic retinopathy was second only to myopic chorio-retinal atrophy as a cause of registration in middle-aged people. Information made available by the Department of Health and Social Security to the Blindness Committee of the British Diabetic Association (1967–69) suggests that registrations for diabetic retinopathy under the age of 60 years increased by about 50 per cent in the period 1963–1966, with little change in the total number of registrations. Hence, diabetic retinopathy now almost certainly enjoys the dubious distinction of being the single commonest cause of blind registration among the middle-aged in the United Kingdom.

Among the blind in general, diabetes may be the most important single category in middle age but numerically it is the older diabetics who bear the brunt of blindness, the numbers involved outrunning the natural increase of frequency of diabetes with age. In addition, there is reason to suspect considerable under-registration of elderly blind diabetics; a pilot clinic enquiry (British Diabetic Association, 1967–1969) revealed that about half the men and a third of the women with severe visual disability were unregistered. Although diabetic macular haemorrhage, exudate and oedema are major causes of visual disability in the elderly diabetic, diabetes may occasionally be unfairly blamed for visual loss due, in fact, to senile maculopathy.

The Seeing Eye Inc. (Berkow *et al.*, 1965) is an American institution dedicated to the provision of guide dogs for the blind. The staff of this organisation, impressed by the rarity with which blind diabetics returned for a second dog, discovered by way of explanation that although the useful life of a guide dog was 7 to 10 years, the period from blindness to death in diabetics was only 5·8 years. This gross average curtailment of life expectation in the blind diabetic has been confirmed by others (Deckert *et al.*, 1967; Root *et al.*, 1959)

and is the same at all ages (Rogot, 1965). This striking statistic is a reminder of the importance of the associated 'complications' of diabetes that are responsible for much morbidity and mortality—nephropathy and renal failure in younger diabetics and coronary artery disease in older patients. To achieve worthwhile results, an attack upon blindness in the diabetic must also take these other problems into consideration.

Blindness is far from being an inevitable end to long-term diabetes. Those of us who had the privilege of knowing the late Dr R. D. Lawrence will recall that, even after 35 years of diabetes, very little missed his good eye; the other was injured in an accident earlier in life. In 1963, he published an account of 90 of his very long-term insulin-treated diabetics (Lawrence, 1963), many of whom had escaped visual disturbance. Recently, Chazan *et al.* (1970) published details of 24 Joslin Clinic Medal winners with 37 to 40 years of treated diabetes without visual complications, and in a group of about 100 long-term diabetics currently being assembled at the Diabetic Department of King's College Hospital (Oakley, 1971), visual disturbance is frequently absent.

With survivor groups of this sort one must ask what proportion they represent of those who started the race. They presumably constitute the 10 per cent or so of diabetics who, even after prolonged exposure to the disease, show few or none of the ophthalmoscopically evident retinal changes referred to earlier. Do they have a different kind of diabetes? Were they in some way identifiable as a group at the time of diagnosis? Does anything distinguish their regime of treatment or their response to it? We must, of course, press on with our investigations of the mechanisms and management of manifest retinopathy, but surely we should give more attention to those anomalies that may enable us to find an answer to the question posed some years ago by the late Elliott P. Joslin: 'Who are the exceptional happy warriors? Who is he, who is she, who have won out in the 25-year diabetic battle?'

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Oral Therapy in Diabetes

ARNOLD BLOOM, MD, FRCP, Physician, Whittington Hospital, London

Oral therapy for diabetes came into general use in 1956 and tolbutamide was one of the first drugs used. Since then, this type of treatment has been extended by the use of other compounds in the sulphonylurea group and by the introduction of the biguanides (see Table 1).

There is convincing clinical and experimental evidence that the administration of the sulphonylureas in the short term leads to an increased output of endogenous insulin and so reduces blood sugar levels. However, this may not be the only action. It can be demonstrated in animals (Madsen, 1967) that the