PAPERS AND SHORT REPORTS

Factors protective against retinopathy in insulin-dependent diabetics free of retinopathy for 30 years

TIMOTHY DORNAN, J I MANN, ROBERT TURNER

Abstract

To investigate which factors might protect against the development of retinopathy 40 insulin-dependent diabetics who had remained free from retinopathy despite diabetes of long duration (mean $\pm$ 1 SD 30 ± 10 years) were compared with 40 patients who had background and 47 who had proliferative retinopathy (mean durations of disease 16 ± 5 and 19 ± 5 years respectively). The three groups had had similar mean ages at onset of diabetes. The mean of all postprandial blood glucose measurements at hospital clinics from diagnosis of diabetes to detection of retinopathy, or to the most recent negative eye examination, was 9.9 ± 2.1 mmol/l (178 ± 38 mg/100 ml) in the group with no retinopathy, 11.8 ± 2.1 mmol/l (213 ± 38 mg/100 ml) in those with background retinopathy, and 12.4 ± 2.1 mmol/l (223 ± 38 mg/100 ml) in those with proliferative retinopathy ($p < 0.0001$). This difference was not reflected in present concentrations of haemoglobin A_{1C}, probably because glycaemic control had been improved after the development of retinopathy. In the groups with background and proliferative retinopathy there were significant negative correlations between mean blood glucose concentrations and the number of years that had elapsed from diagnosis of diabetes to detection of retinopathy, suggesting that the development of both grades of retinopathy depends on the degree and duration of glycaemic exposure.

The patients with no retinopathy had attended clinic more frequently ($p < 0.025$), more of them had required

emergency hospital treatment for hypoglycaemia ($p < 0.0025$), and they tended to have had a lower prevalence of hyperglycaemic coma than the other groups. Although mean percentage ideal body weight and diastolic blood pressure were lower in the patients with no retinopathy at the time of study, mean body weight, blood pressure, and the prevalence of smoking in the years before the development of retinopathy had been similar in all groups, suggesting that these did not influence the development of retinopathy.

Introduction

Retinopathy is a major cause of disability in diabetics. Overall, its prevalence increases with duration of diabetes,¹ but there are remarkable differences between individual patients: some become blind early in the course of the disease¹ while others retain normal vision for 40 years or longer.²⁻⁴ Investigation of the pathogenesis of retinopathy is complicated by its long natural history. Case-control comparisons between diabetics with and without retinopathy after similar durations of diabetes have been made in an attempt to solve this problem. The results of cross-sectional studies, however, may be misleading in several ways, since the development of retinopathy often prompts a change in the attitudes of patients and physicians towards glycaemic control.⁵ Nephropathy, which commonly accompanies severe retinopathy,¹ may raise blood pressure and cause other metabolic changes. The large prospective study of Pirart⁶ evaluated the contribution of factors such as glycaemic control and obesity towards the development of retinopathy, but few prospective data are available concerning other potential risk factors in insulin-dependent diabetics.

Many diabetics attend hospitals regularly from diagnosis, and their case notes contain much information recorded in the years before the development of retinopathy. We used this source of information to investigate how insulin-dependent diabetics who remained free from retinopathy after exceptionally long durations of diabetes differed from patients who had developed background or proliferative retinopathy. Evidence that genetic type (the presence of HLA-DR4) increased the risk of retinopathy has been presented elsewhere.⁷ We now report our evaluation of other factors in these same patients.

Diabetes Research Laboratories and Department of Community Medicine, Radcliffe Infirmary, Oxford OX2 6HE

TIMOTHY DORNAN, DM, MRCP, research fellow (present appointment: senior registrar in medicine, City Hospital, Nottingham)

J I MANN, PHD, DM, university lecturer in social and community medicine and honorary consultant physician

ROBERT TURNER, MD, FRCP, clinical reader in medicine

Patients and methods

RECRUITMENT OF PATIENTS

Insulin-dependent diabetics were recruited to the study through retinopathy screening programmes in three adult diabetic clinics in the Oxford Region. Fundi were examined carefully with a direct ophthalmoscope through widely dilated pupils by ophthalmologists and physicians experienced in fundoscopy for diabetic retinopathy. If there was doubt about the retinal appearances patients were referred for more detailed examination by indirect ophthalmoscopy, fundus photography, and fluorescein angiography.

Forty patients with diabetes of long duration with no or minimal retinopathy were recruited to the study; 37 yielded normal results on ophthalmoscopy while three, each of whom had been diabetic for 40 years or longer, had fewer than five red dots visible in both eyes with no other features of diabetic retinopathy. Thirty-two of the 40 patients had been diabetic for over 20 years, 16 for 30 years or more, and seven for 40 years or more. Ten underwent fundus photography or fluorescein angiography, or both.

Forty patients had background retinopathy, 32 of whom had developed retinopathy within 20 years after diagnosis. They were all recruited to a prospective clinical trial of "optimised glycaemic control" in addition to the present study and underwent fundus photography and fluorescein angiography; none had disc or peripheral new vessels.

Out of 47 patients with proliferative retinopathy, 24 had developed retinal new vessels within 20 years after diagnosis. Forty-four had required photocoagulation, two had become blind before photocoagulation was available, and one had peripheral new vessels that did not require treatment.

All patients were dependent on insulin to prevent severe hyperglycaemia or ketosis or both. One hundred and eleven had required insulin treatment within one year of diagnosis, and the remaining 16 had required insulin within a mean of eight years. All had developed diabetes by the age of 55 years.

SURVEY OF CASE NOTES

If patients had not attended solely their present hospital since diagnosis case notes were sought from other hospitals or general practitioners. Records covering part or all of their diabetic careers were available for 37 patients without retinopathy and for 33 with background and 44 with proliferative retinopathy. The date of diagnosis of diabetes was checked, all measurements of blood glucose concentration, blood pressure, and body weight were noted, and hospital attendances were counted. The date when retinopathy had first been detected was sought in the notes, and no information after this date was included in the survey; thus all the information analysed had been recorded before retinopathy was detected. Duration of disease was expressed as years from diagnosis of diabetes to detection of retinopathy, or to the most recent negative eye examination for patients with no retinopathy.

The mean of all measurements of blood glucose concentration made at afternoon clinics was calculated for each patient. Glucose measurements made at presentation with diabetes or during hospital admissions were excluded as repeated measurements during brief periods of uncontrolled diabetes might have affected the mean value disproportionately. A mean of 27 measurements (range 4-138) was available for the 114 patients. To obtain an estimate of the frequency of clinic attendance the total number of clinic attendances was divided by the time for which the patient had been registered with the hospital(s). The number of times patients were admitted to hospital with hypoglycaemic or hyperglycaemic coma was counted. The mean percentage ideal body weight was calculated,⁸ but measurements made before the age of 20 or during pregnancies were excluded. No previous record of blood pressure could be found for seven patients; for the remaining 107 patients a mean of three previous measurements was available (range 1-13). Mean systolic and diastolic pressures were calculated.

INTERVIEW AND CLINICAL EXAMINATION

All patients were questioned about present and previous smoking habits, current insulin doses, and previous emergency attendances at hospital with hypoglycaemia or hyperglycaemia. Blood was taken for assay of haemoglobin A_{1C} concentration by isoelectric focusing,⁹ for assay of creatinine concentration by multichannel analyser (Vickers M300), and for HLA typing. HLA results are given elsewhere.⁷ Blood pressure was recorded and height and weight measured.

STATISTICAL ANALYSIS

Trend tests were used to take into account both the differences between patients with and without retinopathy and the differences between those with background and proliferative retinopathy. A permutational test for trend (R Peto, unpublished method; see appendix) was used for continuous variables and the χ^2 test for trend¹⁰ for discontinuous variables. Standard linear correlation analysis was also used. The terms "previous" and "present" are used to distinguish between results of the case-notes survey and measurements made at the time of the interview. Results are expressed as means $\pm$ 1 SD, and two-tailed probability values are given throughout.

Results

The mean age at onset of diabetes was similar in the three groups—namely, 22 ± 12 years in the patients without retinopathy, 23 ± 11 years in those with background retinopathy, and 19 ± 9 years in those with proliferative retinopathy ($p > 0.1$). The mean duration of diabetes was 30 ± 10 years in the group with no retinopathy, due to preferential recruitment of patients whose disease was of long duration, compared with 16 ± 5 and 19 ± 5 years in the patients with background and proliferative retinopathy respectively. Men constituted 50% (20/40) and 55% (22/40) of the groups with no retinopathy and background retinopathy but 72% (34/47) of those with proliferative retinopathy. This reflects an excess of proliferative retinopathy among men in the screening programme as a whole.¹¹

Previous blood glucose concentrations—Figure 1 shows individual mean blood glucose concentrations in the patients in the three groups.

FIG 1—Mean blood glucose concentrations in 37 patients with no retinopathy and in 33 with background and 44 with proliferative retinopathy, with group means $\pm$ 1 SD. Permutational test for trend through the three groups: $p < 0.0001$.

Conversion: SI to traditional units—Glucose: 1 mmol/l $\approx$ 18 mg/100 ml.

Mean concentrations were substantially lower in the patients with no retinopathy (9.9 ± 2.1 mmol/l (178 ± 38 mg/100 ml)) than in those who subsequently developed background (11.8 ± 2.1 mmol/l (213 ± 38 mg/100 ml)) or proliferative retinopathy (12.4 ± 2.1 mmol/l (223 ± 38 mg/100 ml)) ($p < 0.0001$, permutational trend test). Within the groups with background and proliferative retinopathy there were significant inverse correlations between mean blood glucose concentration and the

number of years that elapsed from the diagnosis of diabetes to the detection of retinopathy (fig 2).

Mean haemoglobin A_{1c} concentration at the time of study was similar in the three groups—namely, $11.4 \pm 2.0\%$, $11.6 \pm 1.4\%$, and $11.5 \pm 1.9\%$ respectively for patients with no retinopathy and with background and proliferative retinopathy.

Insulin dose—The mean insulin dose, expressed as units/kg body weight, was 0.70 ± 0.29 in patients with no retinopathy, 0.85 ± 0.30 in those with background retinopathy, and 0.86 ± 0.37 in those with proliferative retinopathy ($p < 0.04$, permutational trend test). The

FIG 2—Mean blood glucose concentrations plotted against duration of diabetes before detection of retinopathy in 33 patients who developed background and 44 who developed proliferative retinopathy. Two-tailed p values are shown.

TABLE 1—Details of hospital emergency treatment and clinic attendance†

	n	Hospital emergency treatment		Clinic attendance	
		No (%) who received hospital treatment for hypoglycaemia	No (%) who received hospital treatment for hyperglycaemic coma	n	Mean interval between hospital clinic attendances (months)
No retinopathy	38	22 (58)*	8 (21)**	32	3.8 ± 1.3 †
Background retinopathy	40	17 (43)*	11 (28)**	31	4.2 ± 1.7 †
Proliferative retinopathy	47	12 (26)*	14 (30)**	43	4.7 ± 2.5 †

* $p < 0.0025$, ** $p > 0.1$, χ^2 trend test. † $p < 0.025$, permutational trend test.
‡Prevalences of hypoglycaemia and hyperglycaemic coma are shown as numbers of patients who gave histories of hospital treatment on one or more occasions for these conditions, confirmed whenever possible in hospital records. Data were unavailable for two patients with no retinopathy. The mean interval between clinic attendances was unavailable for 21 patients due to incomplete records.

TABLE II—Mean (± 1 SD) body weight, blood pressure, and plasma creatinine concentration, and proportions of patients requiring antihypertensive treatment and smokers

	Percentage of ideal body weight		Systolic blood pressure (mm Hg)		Diastolic blood pressure (mm Hg)		No (%) of patients who required antihypertensive treatment	Mean plasma creatinine (μ mol/l)	No (%) of smokers
	Previous	Present	Previous	Present	Previous	Present			
No retinopathy	107 ± 10	106 ± 10 *	135 ± 16	135 ± 16	80 ± 8	81 ± 10 †	3 (8)‡	99 ± 24 *	24 (60)
Background retinopathy	109 ± 13	112 ± 17 *	129 ± 13	133 ± 19	82 ± 7	80 ± 9 †	1 (3)‡	83 ± 15 *	22 (55)
Proliferative retinopathy	108 ± 18	112 ± 20 *	129 ± 12	141 ± 23	80 ± 6	86 ± 12 †	10 (21)‡	128 ± 131 *	22 (47)

* $0.1 > p > 0.05$, † $p < 0.03$, permutational trend test. ‡ $\chi^2 = 4.57$, $df = 1$, $p < 0.04$, χ^2 trend test.
Conversion: SI to traditional units—Creatinine: $1 \mu\text{mol/l} \approx 11.3 \mu\text{g/100 ml}$.

proportion of patients treated with highly purified insulin, however, was slightly higher in the group with no retinopathy (53% (21/40)) than in those with background and proliferative retinopathy (38% (15/40) and 49% (23/47) respectively).

Hospital emergency treatment and clinic attendances (table I)—Patients with no retinopathy had most frequently, and those with proliferative retinopathy had least frequently, required hospital treatment for hypoglycaemia on one or more occasions ($p < 0.0025$, χ^2 trend test). The opposite trend was found with hyperglycaemic coma but was not significant. Patients without retinopathy had attended clinics most frequently and those with proliferative retinopathy least frequently ($p < 0.025$, permutational trend test).

Body weight (table II)—Although the present percentage of ideal body weight in patients with no retinopathy tended to be lower ($0.1 > p > 0.05$, permutational trend test), the previous percentage of ideal body weight was similar in all groups.

Blood pressure and plasma creatinine concentration (table II)—Present mean diastolic blood pressure was significantly raised in diabetics with proliferative retinopathy, but previous mean diastolic blood pressure and both present and previous mean systolic blood pressures were similar in all groups. Ten (21%) patients with proliferative retinopathy required antihypertensive treatment compared with one (3%) and three (8%) of those with background and no retinopathy respectively ($p < 0.04$, χ^2 trend test). Mean plasma creatinine concentration at the time of study was highest in patients with proliferative retinopathy ($0.1 > p > 0.05$, permutational trend test), but the results were skewed by several patients with very high concentrations. There was a significant positive correlation between present diastolic blood pressure and plasma creatinine concentration ($r = 0.353$; $p < 0.001$).

Smoking (table II)—Patients were defined as smokers if they had smoked tobacco in appreciable amounts (more than one cigarette a day or an equivalent amount of pipe or cigar tobacco) for more than half of the time for which they had been diabetic. There was no significant difference between groups in the proportion of smokers.

Family history of diabetes (table III)—Insulin-dependent diabetes in first-degree relatives was least common among patients with background retinopathy but equally common among those with proliferative retinopathy and those with no retinopathy. There were no differences in family history of non-insulin-dependent diabetes.

TABLE III—Proportions of patients with family history of diabetes in first-degree relatives

	n	No (%) of patients with family history of:		No (%) with no family history
		Insulin-dependent diabetes	Non-insulin-dependent diabetes	
No retinopathy	40	11 (28)*	5 (13)	24 (60)
Background retinopathy	38†	3 (8)*	5 (13)	30 (79)
Proliferative retinopathy	47	14 (30)*	4 (9)	29 (62)

* $\chi^2 = 6.67$, $df = 2$, $p < 0.04$.

†Two patients with background retinopathy were adopted and did not know their family histories.

Discussion

Patients were recruited to this study and then data analysed retrospectively, but the results of the case-notes survey could not have been influenced by the presence of retinopathy since the measurements had been recorded before retinopathy was first detected. The discrepancy between previous and present

mean diastolic blood pressures in the patients with proliferative retinopathy shows how late changes may affect the evaluation of risk factors. The study had the inevitable shortcoming that recruitment was restricted to "survivors." Deckert *et al*¹ reported that only 40% of patients who developed diabetes before the age of 30 survived 40 years from diagnosis. Of those who did survive, 17% had impaired vision or were blind. Severe microangiopathy is associated with early death in diabetics,¹² and some risk factors for retinopathy might be obscured if they also increased the risk of early death. Smoking may contribute to the development of nephropathy,¹³ and obesity and hypertension may increase cardiovascular mortality.^{14 15} Thus selective mortality might, unavoidably, affect results. There was no other selection bias, however, since patients were recruited consecutively from a retinopathy screening programme and from ophthalmic clinics.

MEAN BLOOD GLUCOSE AND HAEMOGLOBIN A_{1C} CONCENTRATIONS AND INSULIN DOSES

Mean blood glucose concentrations were significantly lower in the patients who remained free from retinopathy than in those who went on to develop retinopathy. This is consistent with the findings of Pirart⁶ and of many other studies reviewed by him. Furthermore, the significant inverse correlations between mean blood glucose concentration and duration of diabetes before retinopathy was detected (fig 2) suggest that the development of both background and proliferative retinopathy is a function of the degree and duration of glycaemic exposure. There has been much controversy about the assessment of control in insulin-dependent diabetics. Single random measurements of blood glucose concentration are an imprecise index of overall glycaemic control because the concentration is subject to rapid fluctuations. The mean glucose concentrations used in this study, however, had the advantage that they were calculated from large numbers of measurements spanning the years when retinopathy was developing. Burditt *et al*¹⁶ emphasised that use of imprecise observations is more likely to diminish than to inflate differences between study groups. The considerable overlap of mean glucose concentrations in patients with and without retinopathy may be partly due to this imprecision but also reflects genetically determined differences in susceptibility to the effects of hyperglycaemia.⁷

The similarity of present mean haemoglobin A_{1C} concentrations in the three groups appears to conflict with the difference in mean glucose concentrations and with the results of other studies that have shown raised haemoglobin A_{1C} concentrations in diabetics with retinopathy.^{5 17} This apparent discrepancy could be explained by the policy of clinics of making more strenuous efforts to lower glucose concentrations when retinopathy is detected. It is also consistent with the observation¹ that glycaemic control in the early years of diabetes may exert a particularly strong influence on the later development of retinopathy.

The mean insulin dose was slightly lower in the patients without retinopathy. This may have been due to their higher mean age at the time of study¹⁸ and to the higher proportion of patients treated with highly purified insulins. Seven of the patients without retinopathy also underwent measurement of diurnal C-peptide profiles: none had preserved B-cell function.¹¹ This subgroup was not preselected and included many of those with the shortest durations of diabetes. It seems unlikely, therefore, that the lower insulin doses and lower glucose concentrations in the whole group without retinopathy could be explained by preserved B-cell function ("less severe diabetes").

HYPOGLYCAEMIA, HYPERGLYCAEMIC COMA, AND CLINIC ATTENDANCE

Patients with no retinopathy had most often required hospital emergency treatment for hypoglycaemia and least often for

hyperglycaemic coma. The reverse was seen in patients with proliferative retinopathy. This bears out the difference in glycaemic control between the groups, since hypoglycaemia might be expected to occur more often in patients with low mean glucose concentrations and hyperglycaemic coma in patients with high mean glucose concentrations. The high prevalence of hypoglycaemia in patients with no retinopathy might be attributed to their long mean duration of diabetes, but this would not explain the difference between patients with background and proliferative retinopathy. Previous studies have found a high prevalence of hypoglycaemia in diabetics who had survived 30 years or more from diagnosis² and in patients with diabetes of long duration who remained free from retinopathy.¹⁹⁻²¹ The more frequent clinic attendance in patients with no retinopathy might suggest a beneficial effect of attending a clinic or simply that these patients were the most conscientious in all respects. It has been reported that frequent contact with a specialised diabetic clinic has a favourable effect on survival²² and on the incidence of disabling late complications.^{22 23}

SMOKING

Our findings appear to conflict with those of a previous study, which concluded that smoking increased the risk of proliferative retinopathy.²⁴ This relation, however, was found only in a subgroup of patients who had been diabetic for over 20 years, after pipe smokers and patients with maculopathy (few of whom smoked) had been excluded. No control group without retinopathy was studied, and smokers and non-smokers may have differed in other important respects such as age and type of diabetes. Other workers have found no overall relation between smoking habit and retinopathy,^{13 25-27} although the prevalence of nephropathy may be increased in smokers.¹³ An association between smoking habit and retinopathy cannot be excluded since selective mortality might have affected all of these studies, but it does not appear to be a major factor.

OBESITY

Many cross-sectional studies have found that diabetics with retinopathy tend to be more obese than those without.^{17 28-30} On the other hand, prospective⁶ and retrospective³¹ investigations have found no relation between obesity and the development of retinopathy in patients with insulin-dependent diabetes. The same discrepancy was found in this study. The late rise in body weight may have been caused by attempts to improve glycaemic control after the development of retinopathy.¹¹

BLOOD PRESSURE

As with body weight, a raised mean diastolic blood pressure was found only after the development of proliferative retinopathy. This may suggest that the raised blood pressure was an effect of accompanying nephropathy rather than a factor contributing to the development of retinopathy. Many cross-sectional studies have found that blood pressure is higher in diabetics with retinopathy than in those without^{28 29 31-36}; another did not.³⁰ The findings of prospective studies in diabetics with established retinopathy have also been conflicting.^{37 38} Knowler *et al*³⁹ followed up diabetic Pima Indians without retinopathy for six years prospectively; the development of retinal exudates, but not haemorrhages, was significantly related to the mean of the initial and final systolic pressures. Even this finding might have been influenced by changes secondary to microangiopathy.

FAMILY HISTORY OF DIABETES, AND SEX

Several previous studies have found no association between family history of diabetes and susceptibility to retinopathy.^{3 6 32}

³⁶⁻⁴⁰ and no clear effect was found in this study. Men appeared to be more susceptible to proliferative retinopathy,¹¹ but this finding might have been due to attendance patterns at the hospital clinics.⁴¹ More complete identification of patients who do not attend hospital clinics would be required to provide firmer evidence that male sex is a risk factor for retinopathy.

CONCLUSIONS

In conclusion, low mean blood glucose concentrations appear to be the main factor that protects some insulin-dependent diabetics from retinopathy. Genetically determined factors may also influence susceptibility.⁷⁻⁴² Blood pressure, body weight, and smoking habit do not appear to be major factors, although this does not lessen their relevance to other forms of vascular disease. Improved glycaemic control seems to have the best chance of reducing the incidence of diabetic blindness, but its efficacy has yet to be proved in a prospective study.

We thank Dr Valerie Mayon-White, Dr Charles Fox, Mr Lyn Jenkins, and Mr Clive Peckar for recruiting patients, and Dr Derek Hockaday, Dr Anthony Knight, Mr Hung Cheng, Mr Philip Awdry, and Mr Anthony Bron for allowing us to study patients under their care. We thank the many other physicians who gave us access to case notes, supplied us with clinical information, or allowed us to study patients under their care. Mrs Leora Hoffman helped us to trace records, and Mrs Caroline Plowright and Mrs Jill Steemson gave excellent nursing help. We thank Mr Richard Peto and Dr Klim McPherson for advice over statistical analysis, Ms Cathy Whittle and Mr Philip Poon for assaying haemoglobin A_{1C} concentrations, Dr Jerry Palmer for helpful discussion of the results, and Ms Sylvia MacMillan for preparing the manuscript. TLD was supported by the Wellcome Trust, and the study received support from the Oxford area research committee.

Appendix

In the permutational test for trend observations from the three groups (mild, moderate, and severe) are pooled and their overall mean and standard error estimated by the usual formulae. If the numbers of observations in groups 1, 2, and 3 are n_1 , n_2 , and n_3 respectively and the totals of the observations in groups 1, 2, and 3 are t_1 , t_2 , and t_3 then the trend statistic T is $T = 1(t_1 - n_1\bar{x}) + 2(t_2 - n_2\bar{x}) + 3(t_3 - n_3\bar{x})$. By standard permutational arguments, if there were no systematic differences between the three groups T would be distributed approximately normally with expectation exactly zero and variance V exactly $S^2(n_1 + n_2 + n_3 - (n_1 + n_2)^2/(n_1 + n_2 + n_3))$; p -value estimation follows direct from examination of $T/\sqrt{V}$.

References

- Caird FI, Pirie A, Ramsell TG. *Diabetes and the eye*. Oxford: Blackwell, 1969:30-1,72-7,85,88-91.
- Chazan BI, Balodimos MC, Ryan JR, Marble A. Twenty-five to forty-five years of diabetes with and without vascular complications. *Diabetologia* 1970;6:565-9.
- Oakley WG, Pyke DA, Tattersall RB, Watkins PJ. Long-term diabetes, a clinical study of 92 patients after 40 years. *Q J Med* 1974;43:145-56.
- Deckert T, Poulsen JE, Larsen M. Prognosis of diabetics with diabetes onset before the age of thirty-one. I. Survival, causes of death and complications. *Diabetologia* 1978;14:363-70.
- Davis RE, Constable IJ, Nicol DJ, McCann VJ, Welborn TA. Association of retinopathy and glycosylated haemoglobin levels in diabetes mellitus. *Med J Aust* 1980;2:558-60.
- Pirart J. Diabetes mellitus and its degenerative complications. A prospective study of 4,400 patients observed between 1947 and 1973. *Diabetes Care* 1978;1:168-88.
- Dornan TL, Ting A, McPherson CK, et al. Genetic susceptibility to the development of retinopathy in insulin-dependent diabetics. *Diabetes* 1982;31:226-31.
- Metropolitan Life Assurance Company. New weight standards for men and women. *Statistical Bulletin of the Metropolitan Life Insurance Company* 1959;40:1-4.
- Jeppsson JO, Franzen B, Nilsson KO. Determination of the glycosylated hemoglobin fraction HbA_{1c} in diabetes mellitus by thin-layer electrofocusing. *Science Tools* 1978;25:69-72.
- Armitage P. *Statistical methods in medical research*. Oxford: Blackwell, 1971:363-5.
- Dornan TL. Diabetic retinopathy—a study of risk factors. Oxford: Oxford University, 1982. DM thesis.
- Root HF, Mirsky S, Ditzel J. Proliferative retinopathy in diabetes mellitus. Review of 847 cases. *JAMA* 1959;169:903-9.
- Christiansen JS. Cigarette smoking and prevalence of microangiopathy in juvenile-onset insulin-dependent diabetes mellitus. *Diabetes Care* 1978;1:146-9.
- Pell S, D'Alonzo CA. Factors associated with long-term survival of diabetics. *JAMA* 1970;214:1833-40.
- Goodkin G. Mortality factors in diabetes. A 20-year mortality study. *Journal of Occupational Medicine* 1975;17:716-21.
- Burditt AF, Caird FI, Draper GJ. The natural history of diabetic retinopathy. *Q J Med* 1968;37:303-17.
- Schanzlin DJ, Jay WM, Fritz KJ, Tripathi RC, Gonen B. Hemoglobin A₁ and diabetic retinopathy. *Am J Ophthalmol* 1979;88:1032-8.
- Gale EAM, Tattersall RB. Unrecognised nocturnal hypoglycaemia in insulin-treated diabetics. *Lancet* 1979;i:1049-52.
- Johnsson S. Retinopathy and nephropathy in diabetes mellitus. Comparison of the effects of two forms of treatment. *Diabetes* 1960;9:1-8.
- Lawrence RD. Treatment of 90 severe diabetics with soluble insulin for 20-40 years. Effect of diabetic control on complications. *Br Med J* 1963;ii:1624-5.
- Dornan TL, Peckar CO, Mayon-White VA, et al. Unsuspected hypoglycaemia, haemoglobin A₁ and diabetic control. *Q J Med* 1981;50:31-8.
- Deckert T, Poulsen JE, Larsen M. Prognosis of diabetics with diabetes onset before the age of thirty-one. II. Factors influencing the prognosis. *Diabetologia* 1978;14:371-7.
- Keiding NR, Root HF, Marble A. Importance of control of diabetes in prevention of microvascular complications. *JAMA* 1952;150:964-9.
- Paetkau ME, Boyd TAS, Winship B, Grace M. Cigarette smoking and diabetic retinopathy. *Diabetes* 1977;26:46-9.
- Nielsen MM, Hjollund E. Smoking and diabetic microangiopathy. *Lancet* 1978;ii:533-4.
- Jarrett RJ, Keen H. The WHO multinational study of vascular disease in diabetes. 3. Microvascular disease. *Diabetes Care* 1979;2:196-201.
- West KM, Erdreich LS, Stober JA. Absence of a relationship between smoking and diabetic microangiopathy. *Diabetes Care* 1980;3:250-2.
- Nilsson SE, Nilsson JE, Frostberg N, Emilsson T. The Kristianstad survey. II. Studies in a representative adult diabetic population with special reference to comparison with an adequate control group. *Acta Med Scand [Suppl]* 1967;469:1-42.
- Job D, Eschwege E, Tchobroutsky G, Guyot-Argeon C, Aubry J-P, Derot M. Diabetic retinopathy, duration of diabetes and risk factors of atherosclerotic cardiovascular disease. *Acta Diabetol Lat* 1975;12:1-8.
- Hunter PR, Heath H, Bloom A. A clinical comparison between diabetics with no retinopathy after 15 years and severe, deteriorating retinopathy. *Diabetologia* 1977;13:403.
- Szabo AJ, Stewart AG, Joron GE. Factors associated with increased prevalence of diabetic retinopathy; a clinical survey. *Can Med Assoc J* 1967;97:286-92.
- Kornerup T. Blood pressure and diabetic retinopathy. *Acta Ophthalmol (Copenh)* 1957;35:163-74.
- Balodimos MC, Aiello LM, Gleason RE, Marble A. Retinopathy in mild diabetes of long duration. *Arch Ophthalmol* 1969;81:660-6.
- Keen H. The prevalence of blindness in diabetics. *J R Coll Physicians Lond* 1972;7:53-60.
- Adler R, Freedman J, Kukar N, Gombos GM. Various parameters of diabetic retinopathy among clinic populations. *Ann Ophthalmol* 1975;7:1447-54.
- West KM, Erdreich LJ, Stober JA. A detailed study of risk factors for retinopathy and nephropathy in diabetes. *Diabetes* 1980;29:501-8.
- Kohner EM, Fraser TR, Joplin GF, Oakley NW. The effect of diabetic control on diabetic retinopathy. In: Goldberg MF, Fine SL, eds. *Symposium on the treatment of diabetic retinopathy*. Washington, DC: US Government Printing Office, 1968:119-28. (PHS publication No 1890.)
- Freyler H, Nichorlis ST, Arnfelder H, Egerer I. Welche Faktoren beeinflussen die Progredienz der diabetischen Retinopathie? *Wien Klin Wochenschr* 1974;86:621-4.
- Knowler WC, Bennett PH, Ballantine EJ. Increased incidence of retinopathy in diabetics with elevated blood pressure. *N Engl J Med* 1980;302:645-50.
- Kojima K, Niimi K, Watanabe I. Diabetic retinopathy. In: Tsuji S, Wada M, eds. *Diabetes mellitus in Asia*. Amsterdam: Excerpta Medica, 1971:183-92.
- Danowski TS, Limaye NR, Cohn RE, Grimes BJ, Nardozi JV, Shelkrot JW. Sex distribution and frequency of diabetic concomitants or complications. *Diabetes* 1966;15:507-10.
- Pyke DA, Tattersall RB. Diabetic retinopathy in identical twins. *Diabetes* 1973;22:613-8.

(Accepted 29 July 1982)