COMMUNICATIONS

NATURAL HISTORY OF LENS OPACITIES IN DIABETICS*†

BY

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IT IS uncertain whether senile lens opacities are more frequent in diabetics than in non-diabetics (Andersen, 1925; Waite and Beetham, 1935; Heinsius and Arndt, 1950; Dollfus, 1954; Kato, Amaha, Hagai, and Matui, 1960; Tulloch, 1962), yet cataract extraction is undoubtedly commoner, by a factor of five times or so, in known diabetics than in non-diabetics (Caird, Hutchinson, and Pirie, 1964). The visual indications for cataract extraction do not differ in diabetics and non-diabetics (Caird, Hutchinson, and Pirie, 1965a). The simplest explanation for this disparity would be that maturation, which may be defined as the progression of opacities to the point where cataract extraction is indicated (Caird, Hutchinson, and Pirie, 1965b), is more rapid in diabetics.

The present study is an attempt to define in quantitative terms some of the factors involved in the natural history of lens opacities in diabetics by an analysis of over 2,800 observations by ophthalmologists on the eyes of over 1,800 diabetics who have attended one clinic in the past 15 years.

Material and Methods

The patients studied were those attending the Radcliffe Infirmary Diabetic Clinic with a definite diagnosis of diabetes (Burditt, Caird, and Draper, 1968). Since 1949, ophthalmologists have regularly examined these patients, though only by ophthalmoscopy, no slit-lamp examinations having been made. The examinations are largely random, and the interval between them is usually between 2 and 5 years. An observation was considered valid for the purposes of the present study if there was a clear statement about both lenses. Patients with lens opacities thought to be congenital or traumatic in origin were excluded, but all other lens opacities of whatever nature were considered together. There were 2,820 valid observations on 1,827 patients, of whom 687 had more than one valid observation. The observations were classified as follows:

- Group 1.* Both lenses normal;
- Group 2.* Unilateral lens opacity with a view of both fundi;
- Group 3.* Bilateral lens opacity with a view of both fundi;
- Group 4.* Unilateral or bilateral lens opacity with no view of one or both fundi;
- Group 5.* Unilateral or bilateral aphakia.

Groups 2, 3, 4, and 5 are referred to together as "lens opacities", and Groups 4 and 5 together as "cataract".

Control of diabetes was assessed from the "glycosuria percentage", that is, the proportion of routine urine tests at clinic attendances showing 2 per cent. or more glycosuria (Caird, 1967). Only patients with five or more attendances were considered; they were divided into those with a "glycosuria percentage" over the period in question of 19 per cent. or less, and those with 20 per cent. or more.

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Results

Table I shows the frequency of lens opacities and of cataract as defined, in relation to age and sex. In both sexes the frequency of lens opacities is low under the age of 40 years but rises sharply after that age. In women the increase begins earlier, and the frequency is significantly greater than in men between the ages of 30 and 70 years. The frequency of cataract begins to rise at age 60, and again is greater in women than men at all ages over 40.

TABLE I
FREQUENCY OF LENS OPACITIES AND CATARACT IN DIABETICS RELATED TO AGE AND SEX

Sex	Age (yrs)	0-19	20-9	30-9	40-9	50-9	60-9	70-9	80+	Total
M F	No. of Observations	40 33	84 53	108 104	155 143	251 352	268 576	160 402	21 70	1,087 1,733
M F	Per cent. with Lens Opacities	5 0	5 9	4 14	9 29	32 53	55 73	80 84	86 88	37 63
	Difference*	N.S.	N.S.	1%	1%	1%	1%	N.S.	N.S.	
M F	Per cent. with Cataract	3 0	1 2	0 3	1 4	4 7	7 15	13 18	32 40	55 13
	Difference*	N.S.	N.S.	N.S.	N.S.	N.S.	5%	N.S.	N.S.	

* Significance level of difference between percentages for men and women; here and throughout, Fisher's exact test (Bailey, 1959) has been used to test the significance of differences.

Tables II and III show the frequency of lens opacities and of cataract in relation to age at diagnosis and to duration of diabetes. Both increase in frequency with increasing duration of diabetes, and both are significantly more common in women, except at the youngest ages.

TABLE II
FREQUENCY OF LENS OPACITIES

Age at Diagnosis of Diabetes (yrs)	Sex	Duration of Diabetes (yrs)		
		0-9	10-19	20+
0-19	Male	3/61 (5%)	2/42 (5%)	8/35 (23%)
	Female	0/41 (0%)	3/27 (11%)	6/19 (32%)
20-39	Male	6/128 (5%)	10/68 (15%)	12/29 (41%)
	Female	15/112 (13%)*	28/81 (35%)**	24/33 (72%)*
40-59	Male	99/332 (29%)	50/95 (53%)	9/14 (64%)
	Female	262/507 (52%)**	154/205 (75%)**	41/44 (93%)*
60+	Male	175/245 (71%)	26/29 (90%)	1/1 (100%)
	Female	479/584 (82%)**	78/89 (88%)	4/4 (100%)

Difference from frequency for corresponding group of men { *Significant at 5 per cent. level.
**Significant at 1 per cent. level.

The chance of developing lens opacities, as determined from patients with initially normal lenses and more than one observation, is shown in Table IV. It increases significantly with age, and again is greater in women than in men. The chance of lens opacities progressing from Group 3 to Group 4, that is of the development of an opacity obscuring fundus view in patients with bilateral opacities, is shown in Table V; it increases significantly with age in both sexes. The chance of regression, that is the disappearance of bilateral opacities

TABLE III
FREQUENCY OF CATARACT

Age at Diagnosis of Diabetes (yrs)	Sex	Duration of Diabetes (yrs)		
		0-9	10-19	20+
0-19	Male	2/61 (3%)	0/32 (0%)	0/19 (0%)
	Female	0/38 (0%)	0/27 (0%)	1/19 (5%)
20-39	Male	0/128 (0%)	3/68 (4%)	0/47 (0%)
	Female	2/112 (2%)	3/81 (4%)	8/33 (24%)
40-59	Male	13/332 (4%)	6/95 (6%)	2/14 (14%)
	Female	44/407 (9%)**	40/205 (20%)**	18/44 (41%)
60+	Male	27/245 (11%)	6/29 (21%)	0/1
	Female	94/584 (16%)	25/89 (28%)	2/4

** Difference significant at 1 per cent. level from frequency in corresponding group of men.

TABLE IV
DEVELOPMENT OF LENS OPACITIES IN PATIENTS WITH NORMAL LENSES

Age at Diagnosis of Diabetes (yrs)	Sex	Interval since First Observation (yrs)		
		0-4	5-9	All
0-39 40+	Male	5/36 (14%)	2/35 (6%)	8/81 (10%)
		13/29 (45%)*	11/42 (26%)*	26/82 (32%)**
0-39 40+	Female	1/20 (5%)	6/34 (18%)	8/63 (13%)
		27/53 (51%)**	24/54 (45%)*	53/113 (47%)**

In this and Tables V, IX, and X, numerators are the numbers of patients observed within the interval to have shown the change in question and denominators are the total numbers of patients with their last observation in the interval.

Difference from frequency for younger age group { *Significant at 5 per cent. level.
**Significant at 1 per cent. level.

TABLE V
PROGRESSION AND REGRESSION OF BILATERAL LENS OPACITIES (GROUP 3)

Change	Sex	Age at Diagnosis of Diabetes (yrs)	Interval since First Observation (yrs)		
			0-4	5-9	All
Progression to Group 4	Male	40+	1/23 (4%)	7/30 (23%)	8/57 (14%)
	Female	40-59	8/44 (18%)	11/53 (21%)	22/109 (20%)
		60+	16/58 (28%)	11/43 (26%)	30/110 (27%)
Regression to Group 1	Male	40+	8/23 (35%)	4/30 (13%)	13/57 (23%)
	Female	40-59	11/44 (25%)	13/53 (25%)	26/109 (24%)
		60+	5/58 (9%)*	5/43 (12%)	10/110 (9%)**

Difference from frequency for age 40-59 at diagnosis { *Significant at 5 per cent. level.
**Significant at 1 per cent. level.

leaving normal lenses, is shown to be about 25 per cent. in 5 years, except in women over 60 years old at the time of diagnosis of diabetes, in whom it is less than half this figure (Table V). The chance of progression of lens opacities in Group 4, that is, the chance of having a cataract extraction, is 40 to 50 per cent. in 5 years (Table VI, overleaf).

TABLE VI
PROGRESSION OF CATARACT: PROGRESSION FROM GROUP 4
TO GROUP 5 (ALL PATIENTS)
Interval since First Observation (yrs)

0-4	5-9	All
8/21 (38%)	8/17 (47%)	17/39 (44%)

The relationship between the frequency of lens opacity and cataract and "glycosuria percentage" is shown in Tables VII and VIII.

TABLE VII
"GLYCOSURIA PERCENTAGE" AND FREQUENCY OF LENS OPACITIES

Sex	Age at Diagnosis of Diabetes (yrs)	"Glycosuria Percentage"	Duration of Diabetes (yrs)		
			0-9	10-19	20+
Male	0-39	≤ 19 ≥ 20	1/54 (2%) 4/102 (4%)	7/38 (18%) 5/66 (8%)	8/18 (45%)** 2/35 (6%)
	40-59	≤ 19 ≥ 20	48/175 (27%)* 43/106 (40%)	21/49 (43%)** 33/39 (87%)	9/12 (75%) 3/4 (75%)
	60+	≤ 19 ≥ 20	82/119 (69%) 65/85 (75%)	19/22 (87%) 5/5	1/1
Female	0-39	≤ 19 ≥ 20	5/46 (11%) 9/88 (10%)	11/34 (32%) 19/67 (28%)	10/22 (46%) 12/22 (55%)
	40-59	≤ 19 ≥ 20	126/249 (51%) 109/192 (57%)	64/85 (76%) 90/118 (76%)	22/22 18/21 (86%)
	60+	≤ 19 ≥ 20	264/322 (82%) 141/168 (84%)	46/50 (92%) 30/34 (88%)	4/4

Difference within pair { *Significant at 5 per cent. level.
**Significant at 1 per cent. level.

Lens opacities are significantly more frequent in association with the higher "glycosuria percentage" in men aged 40 to 59 at the time of diagnosis of diabetes, but not in women. In younger men, the reverse relationship holds after 20 years of diabetes. There are no significant differences in respect of cataract (Table VIII, opposite). Lens opacities develop more commonly in older patients, especially women, with the higher "glycosuria percentage" (Table IX, opposite), but there is no systematic difference in the chances of progression and regression of opacities in Group 3 (Table X, overleaf).

Discussion

There is little doubt that the patients in this study are broadly representative of all diabetics attending clinics, and that because the ophthalmological observations are not seriously biased by the examination of patients solely because of new visual symptoms, these patients represent reasonably accurately the true natural history of lens opacities in diabetics

TABLE VIII
 "GLYCOSURIA PERCENTAGE" AND FREQUENCY OF CATARACT

Sex	Age at Diagnosis of Diabetes (yrs)	"Glycosuria Percentage"	Duration of Diabetes (yrs)		
			0-9	10-19	20+
Male	0-39	≤ 19 ≥ 20	0/54 (0%) 2/102 (2%)	2/38 (5%) 1/66 (2%)	0/18 (0%) 0/35 (0%)
	40-59	≤ 19 ≥ 20	7/175 (4%) 6/106 (6%)	5/49 (10%) 0/39 (0%)	0/12 (0%) 0/4 (0%)
	60+	≤ 19 ≥ 20	17/119 (15%) 7/85 (8%)	3/22 (15%) 0/5 (0%)	
Female	0-39	≤ 19 ≥ 20	0/46 (0%) 2/88 (2%)	0/34 (0%) 3/67 (4%)	2/22 (9%) 5/22 (23%)
	40-59	≤ 19 ≥ 20	25/249 (10%) 16/192 (8%)	16/85 (19%) 22/118 (19%)	7/22 (32%) 10/21 (48%)
	60+	≤ 19 ≥ 20	63/322 (20%) 24/168 (14%)	16/50 (32%) 10/34 (30%)	2/4 (50%)

TABLE IX
 "GLYCOSURIA PERCENTAGE" AND DEVELOPMENT OF LENS OPACITIES

Sex	Age at Diagnosis of Diabetes (yrs)	"Glycosuria Percentage"	Interval since First Observation (yrs)		
			0-4	5-9	All
Male	0-39	≤ 19 ≥ 20	2/17 (12%) 3/17 (18%)	2/15 (13%) 1/19 (5%)	5/37 (14%) 4/40 (10%)
	40+	≤ 19 ≥ 20	10/20 (50%) 2/7 (28%)	8/32 (25%) 3/10 (30%)	20/63 (32%) 10/17 (59%)
Female	0-39	≤ 19 ≥ 20	0/5 (0%) 0/11 (0%)	3/20 (15%) 3/10 (30%)	4/28 (14%) 5/17 (29%)
	40+	≤ 19 ≥ 20	18/39 (46%) 7/11 (64%)	10/32 (31%) 14/22 (63%)*	28/74 (38%) 23/35 (66%)**

Difference from frequency for lower glycosuria percentage { *Significant at 5 per cent. level.
 **Significant at 1 per cent. level.

(Burditt and others, 1968). Since the observations were made by several observers over a period of years, questions of observer error must enter in. In a retrospective study these cannot of course be directly solved, but if, as seems reasonable, observer error is assumed to be unaffected by, say, the sex of the patient, then comparisons between groups of men and women should not be seriously affected by its existence.

It is not possible from the observations as recorded to determine the precise configuration of the lens opacities in many cases, nor to define the frequency of opacities which might be considered more or less specific to diabetes. The inclusion of all opacities together conforms to the customary current view that opacities in older diabetics cannot be distinguished from those in non-diabetics. The simple classification used seems not unreason-

TABLE X
 "GLYCOSURIA PERCENTAGE" AND PROGRESSION AND REGRESSION OF LENS OPACITIES (GROUP 3)

Change	Sex	Age at Diagnosis of Diabetes (yrs)	"Glycosuria Percentage"	Interval since First Observation (yrs)		
				0-4	5-9	All
Progression to Group 4	Male	40+	≤ 19 ≥ 20	1/22 (5%) 0/5 (0%)	5/23 (22%) 1/7 (14%)	6/47 (13%) 1/14 (7%)
	Female	40-59	≤ 19 ≥ 20	3/19 (16%) 4/20 (20%)	6/28 (21%) 5/22 (23%)	11/54 (20%) 10/47 (21%)
		60+	≤ 19 ≥ 20	8/36 (22%) 5/15 (33%)	8/33 (24%) 3/9 (33%)	19/74 (26%) 8/27 (30%)
Regression to Group 1	Male	40+	≤ 19 ≥ 20	7/22 (32%) 1/5 (20%)	3/23 (13%) 1/7 (14%)	10/47 (21%) 3/14 (21%)
	Female	40-59	≤ 19 ≥ 20	5/19 (26%) 5/20 (25%)	6/28 (21%) 6/22 (27%)	12/54 (22%) 12/47 (26%)
		60+	≤ 19 ≥ 20	5/36 (14%) 0/15 (0%)	5/33 (15%) 0/9 (0%)	10/74 (14%) 0/27 (0%)

able, and the use of obscuration of fundus view as a criterion of "cataract" may be justified by the fact that patients with this degree of opacity have almost a 50 per cent. chance of coming to cataract extraction within the period of observation.

The frequency of lens opacities found in any one investigation will depend principally on definitions and methods of examination. Thus comparison between investigations are likely to be hazardous, but comparisons between groups within the same investigation should be possible. Little can therefore be inferred from the fact that the frequency of opacities found in this study of diabetics is greater in relation to age than that found by Gjessing (1936) among non-diabetics, or less than that found by Anthonisen (1936) or Fischer (1948), although it is possible that the much higher frequency of opacities found by O'Brien, Molsberry, and Allen (1934) and O'Brien and Allen (1942) among young diabetics (13 to 14 per cent. under age 30) is due to the fact that many of their patients were evidently extremely poorly controlled by present-day standards. Much more reliance can be placed on the substantial and consistent sex difference demonstrated throughout this study. Lens opacities are significantly commoner and tend to be more advanced in diabetic women between the ages of 30 and 70 (Table I), are commoner in women in relation to age at diagnosis and duration of diabetes (Tables II and III), and develop more frequently (Table IV) and tend to progress more rapidly in women (Table V). Gjessing (1936) found a small but consistent excess of lens opacities in non-diabetic women under the age of 75 years. Cataract extraction is more frequent in women than in men (Caïrd and others, 1965b), though differences between the sexes in the visual indications for operation make comparisons difficult. Some studies of diabetics show an excess of opacities in women (Martensson and Palm, 1950; Janert, Mohnike, and Günther, 1956) but some do not (Kornerup, 1955). Cataract extraction is relatively commoner in diabetic women (Caïrd and others, 1964; Ramsell, 1968). However, the excess frequency of lens opacities in diabetic women in this study seems to be of a higher order and greater consistency than that

shown among non-diabetics by others. It may be that women have a greater tendency to develop lens opacities and for the opacities to progress, and that diabetes accentuates and accelerates this tendency.

The degree and duration of hyperglycaemia affects the rate of development of lens opacities in experimental animal diabetes (Patterson, 1951). There is some evidence that the same is true in human diabetes (Caird and others, 1964). O'Brien and Allen (1942) considered that periods of poor diabetic control might precede the occurrence of snow-flake cataracts in young diabetics, and thought that better control might arrest their progress. Tables VII and IX show that the frequency of lens opacities in men, and the chance of their development in older patients of both sexes, are greater in those patients with the higher "glycosuria percentage", and thus presumably with the higher blood sugar levels (Caird, 1967). There is, however, no such difference in progression of established opacities, nor in the frequency of cataract as defined (Tables VIII and X). This study thus provides support for the general thesis that poor control of diabetes may be associated with a greater tendency to the formation of lens opacities, though it does not directly confirm the idea that it accelerates their progress.

Reversal of established lens opacities is usually considered not to occur, although there are in the literature a considerable number of well-documented examples in diabetics (Alt, 1906; Fischer, 1925; Braun, 1935; Granström, 1937; Bücklers, 1939; Lawrence, 1946; Schlosshardt, 1950; Jackson, 1955; Neuberg, Griscom, and Burns, 1958; Turtz and Turtz, 1958); most have occurred soon after the diagnosis of diabetes. The present study suggests that this process may be more common than is thought (Table V). The crucial problem is clearly that of observer error. There is no reason to believe that observer error is affected by the age of the patient. Thus the finding of a significantly lower chance of regression of lens opacities in women over the age of 60 at diagnosis of diabetes is of great importance, since, if all the apparent regression in this group is attributed to observer error, then at least part of the difference between the chance of regression in this group and that for younger women (and for men) is arguably attributable to true regression. If this is so, the chance of regression of bilateral lens opacities in younger diabetics may be as high as 10 per cent.

Summary

2,820 observations by ophthalmologists on the eyes of 1,827 diabetics have been analysed.

The frequency of lens opacities increases with age, and with age at diagnosis, and with duration of diabetes, and is significantly greater in women than in men. The chances of development of lens opacities and of progression of opacities to the point where fundus view is obscured are similarly related to age and sex.

A higher frequency of glycosuria is associated with a greater frequency of lens opacities in middle-aged men, and with greater chances of their development in both sexes, but not with a greater chance of their progression.

Evidence is presented that bilateral lens opacities may disappear in as many as 10 per cent. of younger diabetics.

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