Diabetologia (1987) 30: 199-207

Diabetologia

Originals

Long-term follow-up of patients who underwent yttrium-90 pituitary implantation for treatment of proliferative diabetic retinopathy

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Summary. Between 1960 and 1976 117 patients underwent pituitary implantation with yttrium-90 (^{90}Y) for treatment of proliferative retinopathy at the Hammersmith Hospital, London. Mean age at operation was 35 ± 11 years (mean $\pm$ SD), and mean duration of diabetes 18.6 ± 10.0 years. Mean insulin dosage prior to implant was 67.2 ± 24 units, falling to 30.4 ± 14.9 units post-implant. Thirty-two per cent of patients are still living, 60% are deceased and 8% are lost to follow-up. The 5-year survival rate was 82%. Of the causes of death, 21% died of infection, adrenal insufficiency or hypoglycaemia, 12% of renal failure, and 47% of myocardial or cerebral vascular disease. Ophthalmological follow-up was carried out on the 100 patients operated on between 1965 and 1976. The mean age of this group at implant was 35 ± 10.5 years, and mean duration of diabetes 17.2 ± 8.7 years. Visual acuity in the better eye at operation was 6/12 or better in 84% of patients, and this percentage remained similar at the time of the 5 and 10 year follow-up. Blindness (6/60 or worse) in both eyes was present in 12% of patients at the time of 5 and 10 year assessments. By 5 years new vessels on the disc had improved from a mean grading of 2.7 ± 1.6 to 0.8 ± 1.2 ($p < 0.001$), and by 10 years there was no disc neovascularisation in any eye. There was a similar improvement in the grading of hard exudates, microaneurysms and haemorrhages, but there was an increase in fibrous retinitis proliferans. It is concluded that pituitary ablation was an effective method of treating proliferative retinopathy, and may have had a beneficial effect on other microvascular complications.

Key words: Pituitary ablation, yttrium-90, renal function, survival, proliferative retinopathy.

Following a report in 1953 of regression of diabetic retinopathy after post-partum pituitary necrosis [1], destruction of the pituitary gland was quickly assessed as a therapeutic manoevre in the treatment of retinopathy. The first results of the effect of hypophysectomy were reported in 1955 [2], but the operation was not without its problems. An alternative method, destruction of the pituitary gland by implantation with ^{90}Y, was used successfully at the Hammersmith Hospital in the late 1950s in patients with breast carcinoma [3]. This method was subsequently used in patients with diabetic retinopathy. In 1962 the first tentative but encouraging results of destruction of the pituitary gland by ^{90}Y implantation on the course of diabetic retinopathy in 10 patients were reported [4], with the series later being enlarged [5].

Between 1960 and 1964 ^{90}Y pituitary implantation as a treatment for diabetic retinopathy remained a largely experimental procedure, since neither the optimum radiation dosage nor the retinal features likely to respond were known. For example, patients with plaques of hard exudate at the macula and irreversible fibrous retinitis proliferans and retinal detachment were initially treated by this means. Further, the radiation dose at the gland periphery was varied from 50,000 rad to 300,000 rad in order to ascertain the optimum level. By 1965 it was established that 150,000 rad achieved complete ablation in the majority of patients, and side effects such as diabetes insipidus and CSF rhinorrhoea were of acceptably low frequency.

Pituitary implantation with ^{90}Y for proliferative retinopathy was carried out in a large series of patients at the Hammersmith Hospital between 1960 and 1976, with use of the procedure for this indication being discontinued with the advent of photocoagulation. The short-term results on retinal features and visual acuity have been reported in various groups of these patients [4-11]. We report here on the medical aspects of long-term follow-up of all patients operated on between 1960 and 1976; the ophthalmological outcome in a group of these patients describes only those operated on after 1965, when the retinal indications for pituitary implantation were known.

Subjects and methods

The medical selection criteria for consideration of pituitary ablation for diabetic retinopathy at the Hammersmith Hospital were: (1) good general health (2) blood urea below 12.5 mmol/l (3) ability to manage diabetes under difficult circumstances. One hundred seventeen patients who underwent pituitary implantation with ^{90}Y for diabetic retinopathy at the Hammersmith Hospital between 1960 and 1976 have been followed. This number does not include the one patient who died immediately post-operatively. The mean age of the patients was 35 ± 11 years (mean ± SD), with a range of 16–62 years. The mean duration of diabetes prior to implantation was 18.6 ± 10.0 years. All but one had proliferative retinopathy. Before operation, 13 patients were being treated with diet alone or diet plus oral hypoglycaemic agents; the remainder were on insulin therapy. After implantation, all but one were treated with insulin. The irradiation dose was 300 krad or more in 54% of subjects, 150 krad in 40% and 50 krad in 6%. Of the total, 22% had more than one implant in an attempt to achieve complete ablation.

Patients attended the Hammersmith Hospital for review at least once a year. If this was not possible due to difficulties with traveling, a medical report was obtained from the patient's local diabetic clinic. Where neither of these possibilities was available, the patient was considered to be lost to follow-up. Cause of death was taken from the death certificate. Where possible, clinical details were also obtained from the attending physician at the time of death. Results of post-mortem examination were taken into consideration when available.

Assessment of pituitary function in the early patients consisted of an insulin tolerance test with measurement of growth hormone (GH), metyrapone test with measurement of 17-oxogenic steroids, 48 h ^{131}I neck uptake and steroid withdrawal with assessment of symptoms. These tests have been changed and superseded over the years to the present methods of pituitary function testing outlined below. For this report, assessment of pituitary function at any time depends on the tests then available.

Patients for re-assessment of pituitary function underwent an insulin tolerance test, where there were no contraindications, with simultaneous administration of luteinising hormone/follicle stimulating hormone releasing hormone (LH/FSH-RH) and thyrotrophin releasing hormone (TRH) [12]. In view of the fact that the patients were diabetic and hypopituitary, the dose of insulin given was 0.15 units/kg body weight (Actrapid, Novo). If there was no significant fall in the blood glucose within 30 min, a further dose was given as considered appropriate. In all subjects the plasma glucose fell below 2.5 mmol/l, and symptomatic hypoglycaemia was obtained. Blood samples were taken at 30 min intervals for measurement of GH, cortisol and prolactin; these measurements continued for at least 60 min after symptomatic hypoglycaemia was achieved. Patients in whom insulin tolerance testing was contraindicated were given, in addition to LH/FSH-RH and TRH as above, an intravenous bolus of 100 μg growth hormone releasing factor (GRF, Peninsula Laboratories, Calif., USA) with measurement of serum GH at 15 min intervals for 90 min. The maximum serum GH was taken as a measure of the patient's somatotroph function. Glycosylated haemoglobin A1 was measured by ion exchange chromatography (Bio Rad Kit).

One hundred patients who underwent ^{90}Y pituitary implantation for proliferative diabetic retinopathy between 1965 and 1976 were included in the ophthalmological follow-up. Patients were carefully assessed prior to being offered pituitary ablation. They were considered eligible for this treatment if, in addition to the medical criteria quoted above, they had at least one 'treatable' eye defined as visual acuity of 6/24 or better, the macula not threatened by fibrous retinitis proliferans (RP) and/or detachment, and RP on the disc not exceeding grade 3 out of 5 on the Hammersmith grading system [13]. If complete ablation was not achieved with one operation, and an eye remained treatable, a second operation was offered. Twenty-three patients had two pituitary implants.

Patients admitted to the study were assessed at regular intervals, and once a year underwent a full ophthalmic examination including measurement of best corrected visual acuity and intraocular pressure. Anterior segment examination and retinal evaluation including colour photography of the fundus and fluorescein angiography were also performed. Colour photographs were assessed using the Hammersmith system, which separately grades microaneurysms and haemorrhages (MA), new vessels elsewhere (NVE), retinitis proliferans (RP) and hard exudates (HE) on a numerical system between 0 (absent) and 5 (most severe), based on comparison with standard photographs [13]. New vessels arising from the disc (NVD) were graded according to the method of Kohner et al. [14] by assessing the number of quadrants of the optic disc crossed by the new vessels and the distance the vessels extend beyond the disc margin, again assigning a value of 0 to 5. Photocoagulation had been carried out on 15 patients before they entered the study, and pituitary ablation was performed in these cases because of failure of response.

Ophthalmic records of each patient were recently reviewed. Retinopathy grading and visual acuity immediately prior to implant ('initial') and at 1, 3, 5, 10 and 15 years post-implant, had been recorded and were available for consideration. Original photographs were examined in 15% to verify the original gradings, which were done by different observers over the years. In the sample tested, no changes in grading had to be made. For the purposes of this study 'blindness' is defined as visual acuity of 6/60 or worse. For the purposes of data analysis, time of entry into the study in the 23 patients who had a second implant was immediately prior to the first operation. Visual acuity results were converted from Snellen-chart values to numerical scoring to facilitate statistical analysis (Table 1).

Statistical analysis

Data are quoted as mean ± SD throughout. The significance of differences between groups was assessed using a paired Student's t-test.

Results

Medical follow-up

Of the 117 patients, 108 (92%) have been successfully followed (84% at the Hammersmith Hospital) and 9 (8%) lost to follow-up (8 of whom were resident abroad). All patients were followed for at least 6 months post-implant; the longest has now been followed for 21 years. The mean follow-up period is 10.0 ± 4.9 years (i.e. time from implant to death or to the present time if still alive).

Pituitary function. Of the total number of patients, the mean insulin dose pre-implant was 62.7 ± 24 units, falling 6 months post-implant to 30.4 ± 14.9 units. On evidence available at the time, 90 patients (77%) were thought to have complete pituitary ablation, 22 (19%) to be partially ablated [which number includes all

Table 1. Numerical scoring of visual acuity

6/ 6 = 1	6/60 = 7
6/ 9 = 2	3/60 = 8
6/12 = 3	CF = 9
6/18 = 4	HM = 10
6/24 = 5	PL = 11
6/36 = 6	NPL = 12

CF = counting fingers; HM = hand movements; PL = perception of light; NPL = no perception of light

Table 2. Pituitary function tests in 7 patients thought to have partial ablation on original assessment (maximum values during combined pituitary function testing)

Patient	Sex	Irradiation dosage (krad)	Plasma GH (mU/l)	Plasma cortisol (nmol/l)	Thyrotrophin (TSH) (mU/l)	Luteinising hormone (U/l)	Follicle stimulating hormone (U/l)
JM-S	F	50	11.0	660	13.5	19.4	8.0
TH	M	150	4.2	305	<1	1.8	<1
PS	F	50	2.6	750	9.3	17.0	16.6
AJ	F	300	1.6	176	<1	14.3	8.6
SB	F	300	<1	526	2.9	7.5	4.5
RC	M	300	<1	<55	<1	1.2	<1
DB	F	300	1.7	<55	<1	<1	<1
Normal:			>20	>550	>4.5	>16	>2

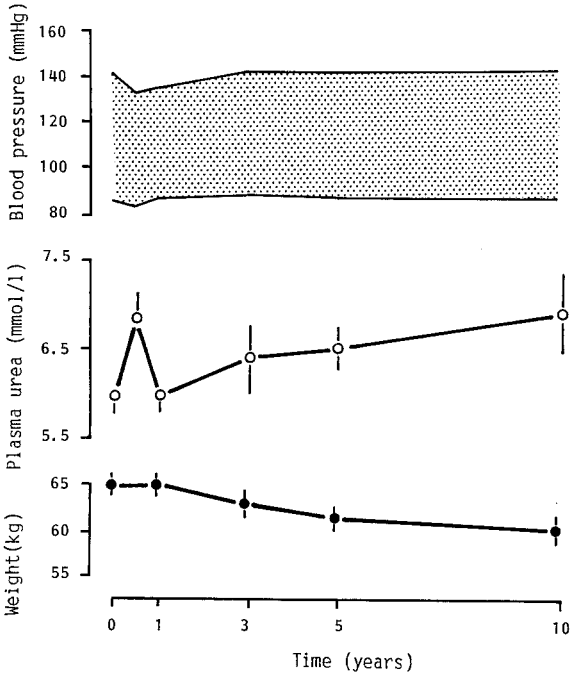

Fig. 1. Changes in blood pressure, plasma urea and body weight with time in all patients followed

7 patients who had the 50 krad radiation dosage, 2 of whom are still surviving (Table 2)], leaving 5 (4%) in whom insufficient evidence was available. Of the currently surviving 38 patients, 23 were admitted to hospital for reassessment of their pituitary function as above. This number included 7 of the 8 surviving patients who had been thought to have some residual pituitary function. Results from these 7 patients are shown in Table 2, where it is seen that one had no detectable pituitary function and the remainder had reduced reserve secretion. The other 16 patients who were tested and had been thought to be completely ablated were all confirmed to be so with no response to any of the stimulatory tests performed.

Replacement therapy. Of the 108 patients followed, 96% were taking replacement therapy with prednisone or hydrocortisone and thyroxine. Only 6 (6%) have been replaced with fludrocortisone. The males were all taking intramuscular depot injections of testosterone at 3 to 6 weekly intervals. Amongst the females, it is difficult to persuade them of the need to take oestrogen replacement; at present, only one of the surviving women is doing so. No subject required any form of therapy for diabetes insipidus beyond 6 months post-implant.

Glycaemic control. Amongst the survivors, glycaemic control is difficult. The mean glycosylated HbA_1 is $10.5 \pm 1.5\%$ (normal range 5-8%). The principal problem is hypoglycaemia, since in the majority of patients this is asymptomatic until it results in loss of consciousness. Many patients complain that addition of 1 unit of insulin to their daily dosage leads to troublesome hypoglycaemia, and all are advised not to take long-acting preparations of insulin in the evening to avoid nocturnal hypoglycaemia.

Morbidity. At the time of implantation, 8% of the patients had a history suggestive of autonomic neuropathy (impotence, diarrhoea, postural hypotension or gustatory sweating) and 8% had some electrocardiographic abnormality. During the follow-up period, a further 18% developed autonomic neuropathy and 34% an abnormality on ECG. There was a tendency to lose weight post-implant. At the time of operation, the mean weight was 64.8 ± 8.8 kg, falling to 60.3 ± 9.1 at 10 years ($p < 0.01$) (Fig. 1). There was a drop in blood pressure at 6 months, but only the drop in systolic pressure reached significance (from a mean value of 141/85 to 133/83, the fall in systolic pressure being significant at $p < 0.02$) (Fig. 1).

Apart from the general problems associated with hypopituitarism, there have been a number of problems peculiar to these patients with diabetes. In one patient postural hypotension has been so severe that, despite treatment with mineralocorticoids, she has been confined to a wheelchair. Osteoporosis with bone fractures has been a problem in a number of cases, and in one patient non-union of a fractured shaft of femur

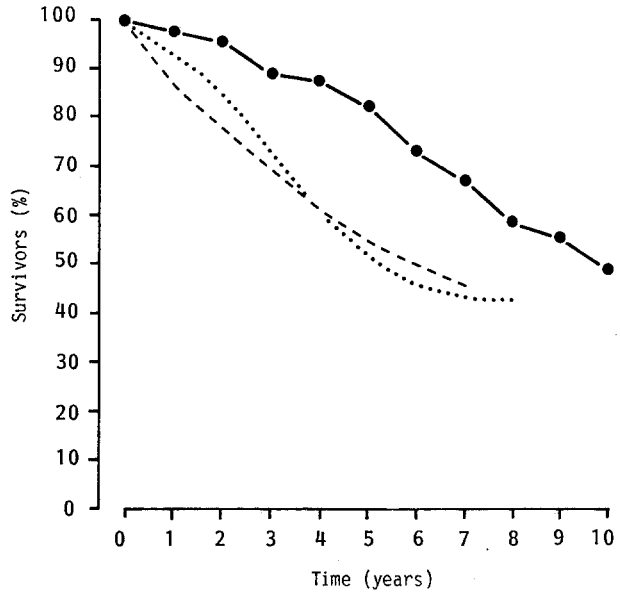

Fig. 2. Cumulative mortality for the 108 patients followed. Survival curves for the studies of Caird et al. [19] (dotted line) and Davis et al. [20] (dashed line) are shown for comparison

Table 3. Details of patients who died as a result of hypopituitarism

Patient	Age at time of death	Years post-implant	Cause of death
BB	33	7	Hypoglycaemia
JB	31	3	Hypoglycaemia
AB	43	0.5	Meningitis, adrenocortical insufficiency
DC	33	7	Hypoglycaemia
RC	47	2	Meningitis, adrenocortical insufficiency
BD	32	8	Asphyxia secondary to hypoglycaemia
TD	38	8	Status epilepticus secondary to hypoglycaemia
EG	47	8	Meningitis
DH	49	4	Pneumonia, adrenocortical insufficiency
GK	34	10	Pneumonia, hypoglycaemia
RN	29	6	Hypoglycaemia
JP	35	11	Hypoglycaemia
WR	61	3	Meningitis, hydrocephalus
WR	46	6	Pneumonia, adrenocortical insufficiency
MW	45	9	Influenza

required pinning and 2 years to allow return to full mobility. Avascular necrosis of the femoral head on a dose of 5 mg of prednisone has been reported in one case. Problems with hypopituitarism and diabetes are illustrated in the following 2 case histories, which are not atypical.

Patient GD, female with diabetes since the age of 14 years, was found to have 'florid' proliferative retinopathy in both eyes at the age of 31 years. Her visual acuity at the time was 6/9 in the right eye, with repeated vitreous haemorrhages, and 6/60 in the left eye due to retinal detachment. She was treated with a 300 krad ^{90}Y pituitary implant, and at 6 month assessment was thought to be completely ablated. Her daily insulin dosage had fallen from 40 to 24 units daily. She was on replacement therapy with prednisone, thyroxine and oestrogens, although she discontinued the latter since she said they upset her diabetic control and made her feel unwell. Glycaemic control proved difficult, and she suffered from repeated hypoglycaemia. She was commenced on thrice daily Actrapid insulin, to a total of 20 units daily, and began monitoring her home blood glucose 4 times daily. Nevertheless, she is frequently found unconscious due to hypoglycaemia at home. She lives alone and is unmarried. Friends have frequently had to administer intramuscular glucagon, and she has had frequent hospital admissions with hypoglycaemia. Her renal function is normal, with a serum creatinine of 62 μmol/l, and she has no proteinuria. She maintains 6/6 vision in her right eye.

Patient MP, female with diabetes since the age of 2 years, was found to have bilateral proliferative retinopathy at the age of 27 years, and treated with a 150 krad ^{90}Y pituitary implant. On assessment at 6 months she was found to be completely ablated, and her daily insulin dosage had fallen from 60 to 30 units daily. She was on replacement therapy with prednisone and thyroxine. She developed pulmonary tuberculosis 3 years post-implant and was kept on prophylactic isoniazid in view of her steroid therapy. She had photocoagulation to the left eye in South Africa, and subsequently lost vision in that eye due to retinal detachment. When seen 12 years post-implant, age 39 years, her daily insulin dosage had dropped to 18 units daily, in spite of which she continued to have frequent hypoglycaemic attacks. Despite treatment with oestrogens and calciferol, she complained of back ache, and had sustained several fractures of ribs and fingers. On X-ray examination, she was found to have osteoporosis with collapse of T12 and wedge fractures of L3-4 in addition to 2 fractured ribs. When seen 16 years post-implant, her general health was poor. She was 5 kg less than her pre-implant weight. Her daily insulin dosage was down to 16 units daily, but she continued to suffer from repeated debilitating hypoglycaemic attacks, resulting in a fractured ankle on one occasion. She had never married and had no children. Her plasma creatinine was normal at 86 μmol/l, and she had no proteinuria. She maintained 6/6 vision in the right eye with no active retinopathy.

Mortality rate. Of the patients followed, 38 (35%) are still alive at the time of writing and 70 (65%) deceased. The 5-year mortality was 18% and the 10-year mortality 51% (Fig. 2).

Causes of death. Causes of death were confirmed by the attending physician or by postmortem examination in 49% of patients and taken from the death certificate in 51%. Of the 70 patients who had died, 15 (21%) died of the consequences of hypoglycaemia, infection or adrenal steroid deficiency. The mean survival time in this group was 6.2 ± 3.1 years. These patients are detailed in Table 3. Subjects BD and TD both suffered from epilepsy and, although treated with anticonvulsant agents, had grand mal seizures secondary to hypoglycaemia which resulted in their deaths. Eight patients (12%) died of unequivocal renal failure (see below). The mean survival time of this group was 6.5 ± 3.4 years. Thirty-three patients (47%) died of ischaemic heart disease or cerebral vascular disease, mean survival in this group being 8.2 ± 3.5 years. Fourteen patients (20%) died of miscellaneous causes, including cancer, gastric haemorrhage and pancreatitis. This group also includes those in whom the death certificate states only bronchopneumonia, since this is often quoted as the cause of death where the exact cause

Table 4. Patients who died with an elevated plasma urea

Patient	Age at implant (years)	Age at death (years)	Urea at implant (mmol/l)	Urea at death (mmol/l)	Proteinuria (Y/N)	Cause of death
DB	34	40	10.8	34.6	Y	Myocarditis
MD	48	60	5.8	13.0	N	Cardiac failure, IHD
DF	30	38	5.5	Not known	Not known	Renal failure
WF	48	54	6.0	17.0	Y	Cardiac failure, IHD
EH	27	39	7.8	41.5	Y	Renal failure
MH	30	33	8.8	30.6	Y	Renal failure
CJ	23	28	7.6	31.3	Y	MI, renal failure
AP	42	52	10.7	44.7	Y	Renal failure
SP	20	23	6.5	Not known	Y	Renal failure
FS	36	39	9.0	Not known	Y	Renal failure
RT	28	35	7.2	45.0	Y	Renal failure
AV	55	64	7.1	17.2	N	Cardiac failure, IHD

MI myocardial infarction; IHD ischaemic heart disease

of death is unknown. Of all patients, both living and deceased, there had been no episodes of ketoacidosis.

Renal function. Assessment of renal function is difficult, since the only marker of renal function available consistently in all patients is plasma urea. While it is known that 16 patients (14%) had proteinuria at the time of implant, the presence or absence of proteinuria during follow-up is not known in all patients. Table 4 gives details of all 12 patients who died with an elevated plasma urea (>13 mmol/l). One surviving patient has developed rapidly progressive renal failure 14 years post implant, and another has early renal failure, with a plasma creatinine of 154 μmol/l and poorly controlled hypertension. Thus, 13% of patients followed apparently developed some degree of renal failure. This figure is likely to be an overestimate, since on examination of the details in Table 4 some patients had medical conditions which could have contributed to an elevated plasma urea. Subjects MD, WF and AV had cardiac failure and were on diuretic therapy. Subject CV had a myocardial infarction following which her plasma urea was elevated. In addition, two patients had evidence of renal failure prior to implant with plasma urea greater than 10 mmol/l and proteinuria. Thus, only 8 patients (7.4%) could truly be said to have developed renal failure post pituitary ablation. A plot of plasma urea against time (Fig. 1) shows a brief rise above basal (6.1 ± 1.6 versus 7.3 ± 2.6 $p < 0.05$) within 6 months of operation followed by a swift return to normal and subsequent slow progressive rise. This is apparent even when the 12 patients who died with an elevated plasma urea are excluded.

Ophthalmological follow-up

Sixty-seven male and 33 female patients underwent pituitary ablation between 1965 and 1976. Mean age at entry was 35 ± 10.5 years (range 16–62 years) and mean duration of diabetes at entry was 17.2 ± 8.7 years (range 1–40 years). Fifteen patients who had previously had photocoagulation and were 'treatment failures' were included in the pituitary ablation series. At 10 years, a further 14 subjects had had photocoagulation.

Table 5. Mean visual acuity of right eyes

Year	Mean grading	SD	No. of patients
Right eyes			
Initial	3.2	2.8	100
One	3.6	3.4	97[a]
Three	4.3	3.8	83[b]
Five	4.7	4.2	68[b]
Ten	4.6	4.4	49[b]
Fifteen	4.8	4.5	19[a]
Left eyes			
Initial	4.1	3.4	100
One	4.5	3.6	97[a]
Three	4.8	4.0	83[b]
Five	4.6	4.2	68[a]
Ten	4.7	4.4	49[b]
Fifteen	5.1	4.7	19

[a] $p < 0.05$; [b] $p < 0.01$ comparing the same eye at initial and subsequent visits

Visual acuity. At the initial assessment there was a significant difference in the mean visual acuities between right and left eyes: right 3.2 ± 2.8, left 4.1 ± 3.4, $p < 0.05$ (Table 5). Thirty-eight patients were blind in one eye, 14 in the right and 24 in the left. The cause of blindness was usually vitreous haemorrhage or RP causing traction detachment.

Sixty-eight patients were assessed at the five-year follow-up. Mean visual acuity had deteriorated to 4.7 ± 4.2 in the right eye ($p < 0.001$) and 4.6 ± 4.2 in the left eye ($p < 0.02$). At this stage eight patients were blind in both eyes, secondary to RP/detachment, vitreous haemorrhage or rubeotic glaucoma. Forty-nine patients were analysed at the 10-year follow-up. Com-

Table 6. Grading of better eye from initial to the 15-year visit

	6/6	6/9	6/12	6/18	6/24	6/36	6/60	3/60	CF	HM	PL	NPL	Total
Initial	55	20	9	10	5	1	0	0	0	0	0	0	100
One	54	21	8	5	2	4	1	0	1	1	0	0	97
Three	44	16	11	0	0	3	3	1	2	2	1	0	83
Five	38	14	3	3	1	1	2	0	1	2	1	2	68
Ten	33	3	3	1	1	2	0	0	1	1	3	1	49
Fifteen	12	2	0	1	0	0	2	0	0	0	0	2	19

CF = counting fingers; HM = hand movements; PL = perception of light; NPL = no perception of light

pared with the 5-year result, mean visual acuity was almost unchanged at 4.6 ± 4.4 in the right eye and 4.7 ± 4.4 in the left eye. Six patients were blind in both eyes, secondary to RP/detachment or rubeotic glaucoma.

Analysing the data by best eye only, 84% of patients had vision of 6/12 or better at the time of initial assessment, declining after 5 years to 81% and by 10 years to 80% (Table 6).

Disc and peripheral new vessels. There was a significant improvement in both disc and peripheral neovascularisation. After 5 years, disc new vessels in both eyes had improved from a mean of 2.7 ± 1.6 to 0.8 ± 1.2 ($p < 0.001$). By 10 years there was almost no evidence of neovascularisation in any eye (Fig. 3). The 19 patients who have reached the 15-year follow-up have no evidence of disc neovascularisation, though 4 still have evidence of peripheral new vessels. The improvement in neovascularisation was matched with a reduction in the incidence of vitreous haemorrhage. At 1 year, 14 (14.4%) patients had one eye that was unassessable because of haemorrhage (2 being unassessable in either eye), while by 10 years only 4 (8.5%) had this complication. There was a tendency for patients who had undergone photocoagulation in addition to pituitary ablation to lose neovascularisation more rapidly than those who had undergone pituitary ablation alone. For instance, at 5 years the mean grading of disc new vessels in the right eye in those who had photocoagulation had fallen from an initial grading of 2.7 ± 1.9 to 0.3 ± 0.7, whereas in those treated by pituitary ablation alone it had fallen from 2.7 ± 1.4 to 1.1 ± 1.4. By 10 years, there was no difference between the two groups.

Retinitis proliferans. The mean grading for RP increased from 1.0 ± 1.3 to 1.8 ± 1.3 at 10 years. The increase in RP does not mean that new vessels invariably progressed to RP, as some disc vessels resolved without residual fibrous tissue. In general, the more severe the neovascularisation at the initial assessment, the more likely RP was to develop. RP was the other major cause of eyes becoming unassessable.

Hard exudates, microaneurysms and haemorrhages. There was a significant reduction in the level of exudates from initial to ten years (0.68 ± 0.73 versus 0.15 ± 0.28, $p < 0.001$). Those who underwent photocoagulation after implant reduced their level of exudates more rapidly than those who underwent implantation alone. Thus, at 15 years grading in the right eye was 0.4 ± 0.6 in those who had not undergone photocoagulation but 0.1 ± 0.2 in those who had (NS).

Microaneurysms and haemorrhages declined significantly during the first year whether the patients had undergone photocoagulation or not (2.3 ± 1.1 versus 1.3 ± 0.7, $p < 0.01$).

Discussion

The initial assessment of the proportion of patients thought to be completely ablated was probably accurate as assessed by contemporary methods, but with the passage of time may have become an underestimate. All patients studied who were thought to be completely ablated were confirmed to be so. In addition, two of those thought to be partially ablated were now found to have no residual pituitary function. This may have resulted from fibrosis of the pituitary gland. Those thought to be partially ablated had variable residual pituitary function. In all of these, GH production is disproportionately reduced compared with other pituitary modalities, in keeping with the findings of Shalet et al. [15], who found that irradiation of the hypothalamic-pituitary axis resulted in a greater reduction in GH than other pituitary hormones. If indeed GH is the important pituitary hormone in the pathogenesis of diabetic microvascular disease [16], then ^{90}Y implantation was theoretically successful in nearly all patients in whom the procedure was carried out.

In some situations, the combination of hypopituitarism and diabetes would appear to have an additive effect in terms of complications. Thus, hypotension can be aggravated by diabetic autonomic neuropathy; osteoporosis, which is reported to be more common in diabetic patients [17], has been a significant problem despite treatment with sex steroids. While most patients have managed to lead a normal life, the effects on the life of a sizeable minority have been devastating. Impotence and inability to produce children led to several episodes of depression requiring psychiatric help, and suicide in at least one case. Lethargy was a common complaint despite full replacement therapy.

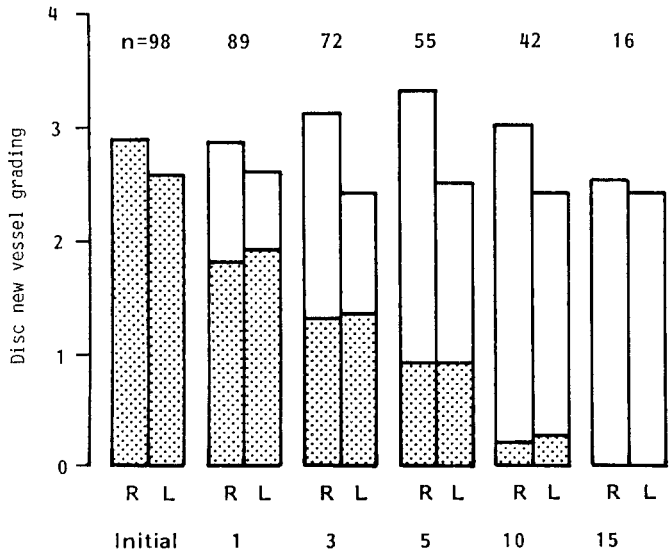

Fig. 3. Mean grading of new vessels with time in the 100 patients included in the ophthalmological follow-up. The shaded area represents the actual grading at that time point, and the open area the grading in that group of patients at the time of operation. The figures represent the number of patients included in each group

Interestingly, while men are happy to take replacement therapy with androgens, the women are reluctant to take oestrogens, despite a full explanation of the reasons for doing so. Fear of hypoglycaemia dominates the lives of many patients, and the advent of home blood glucose monitoring has been a help in this direction. Asymptomatic hypoglycaemia has become a major problem in the surviving patients, but is most likely due to long duration of diabetes and associated autonomic neuropathy rather than hypopituitarism, since lack of hypoglycaemic symptoms is also seen in non-ablated diabetic subjects. It is surprising that there have been no episodes of ketoacidosis. It has, however, been previously reported [18] that hypopituitary diabetic patients are surprisingly slow to demonstrate a rise in plasma glucose and ketone bodies following insulin withdrawal, especially in association with steroid deficiency.

Mortality rates reported for patients with proliferative retinopathy vary. Two studies have reported figures of approximately 50% at 5 years [19, 20] and rather more among the diabetic blind [21]. A further study, selecting patients with 'a good prognosis for survival', reported a 5-year mortality of 25% amongst the patients with proliferative retinopathy [22]. Thus, the 5-year mortality of 17.9% found in the present study is seen to be very low. This is presumably in part because the patients were a selected group with no significant evidence of renal dysfunction at the time of implant. A small clinical study of 51 patients with proliferative retinopathy who were selected to exclude patients with renal failure at the outset found a mortality rate of approximately 10–15% over a mean follow-up time of 6 years [23]. This seems to confirm that the low mortality rate found in this study is largely due to the selection criteria. Nevertheless, the figure is still remarkably low when one considers that the combination of diabetes and hypopituitarism carries its own risks. Although the question is open to debate, it could be argued that those patients who died of hypoglycaemia died as a consequence of their hypopituitary state, as it is not common for diabetic patients to die of hypoglycaemia. In addition, there are a number of patients in whom clinical details suggest that they were admitted to hospitals where they were not known, and the dose of adrenal steroid was omitted or not increased to cover the intercurrent illness.

The large proportion of patients who died from myocardial or cerebral vascular disease is in keeping with the figures of other studies in diabetic patients [24, 25]. It is now accepted that diabetes predisposes to atheromatous disease. Pituitary ablation would be unlikely to have any effect on this.

The reports of Ireland et al. [26] and Greenwood et al. [27] of thinning of the glomerular basement membrane after pituitary destruction suggests that pituitary implantation may have beneficial effects on microvascular disease in kidney in the long-term, although there may have been early deterioration. Arriving at a figure indicating the numbers in this study who developed renal failure has been difficult. Taking all patients who had an elevated plasma urea is likely to be an overestimate, but including only those patients who developed renal failure secondary to diabetes is perhaps making too fine a point. However, in this group of 108 patients followed for a mean of 10 years, between 7 and 13% developed renal failure. It is difficult to find data with which to compare this figure. In two large series from the Joslin Clinic looking at all diabetic patients [24] and those with proliferative retinopathy [28], some 50% of patients of comparable age and duration of diabetes died of renal failure. In a study by Deckert et al. [29] of patients diagnosed as diabetic before the age of 31 years, 31% died of renal failure. Even in the small study of patients with proliferative retinopathy in whom patients with renal failure were excluded, 24% of patients died of or developed uraemia over the mean follow-up period of 6 years [23]. This is approximately double the figure found in the present report. However, a study examining the prognosis for renal function in otherwise fit patients with proliferative retinopathy is needed.

The fall in plasma creatinine with time following pituitary ablation reported by Lundbaek et al. [30] has not been confirmed. In addition, there was a pronounced rise in plasma urea at 6 months post implant which subsequently returned to normal. Although previously reported [31], the cause of this is not clear. Presumably by 6 months all patients had recovered from the acute effects of the procedure. Possible causes are a sudden fall in glomerular filtration rate, loss of muscle mass or possibly dehydration due to diabetes insipi-

dus, which occurred in a number of patients as an early complication.

The ophthalmological results presented here are in accord with the findings of short-term assessments of pituitary ablation in the treatment of diabetic retinopathy [10, 32], confirming it as an effective method of treatment. To find suitable control series, it is necessary to examine the literature prior to the use of photocoagulation, as it is would now be considered unethical to withold this treatment in a patient with neovascularisation. The first important point to note is that spontaneous regression of untreated proliferative retinopathy is uncommon, being less than 10% in one early study [33]. Since the new vessels regressed in all patients in the present study, the benefit of pituitary ablation can be readily appreciated. In fact, as late as 1978 the results of pituitary ablation in the treatment of 'florid' retinopathy were being compared favourably with those of photocoagulation [11, 34]. The benefit of pituitary ablation is also apparent on assessment of visual outcome. Three studies of untreated proliferative retinopathy put the progression to blindness at 27–50% [23, 29, 35], whereas in the present study group the percentage of patients blind in both eyes remained at 12% from 3 to 15 years. The difference in visual acuity between the right and left eyes has been previously noted [36], and it has been postulated that this is due to differences in blood supply between the two eyes. In the analysis of this data the role of photocoagulation is a complicating factor, as it played an increasing part in treatment as the benefits of the xenon, and later the argon, photocoagulators became obvious. However, when photocoagulation was first introduced in 1970, the exact indications for its use were not clearly established, nor was the treatment given adequate in the light of later experience. The precise impact on the present results, therefore, is difficult to assess. For example, two patients had retinal detachment and blindness precipitated by xenon treatment, and some of the 15 patients in whom photocoagulation failed to cause regression of new vessels had inadequate treatment. Nevertheless, its influence cannot be ignored, since by the 10-year follow-up more than 50% of the surviving 49 patients had received photocoagulation. The main influence seems to have been on the rapidity of resolution of neovascularisation. However, even if the photocoagulated group is removed from the analysis a significant improvement is still apparent in those who had undergone pituitary ablation alone. There was no difference in final visual acuity between the two groups. In conclusion, the present results indicate that destruction of the pituitary gland may have had a beneficial effect on the microvascular complications of diabetes.

Acknowledgements. We wish to acknowledge the contributions of Professors R. Fraser and F. Doyle, and the substantial contributions of Dr. N. Oakley, Dr. D. Scott, Professor D. Hill, Mr. R. Blach, Mr. A. M. Hamilton and Mr. H. Cheng. This work was supported by the British Diabetic Association.

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Received: 26 August 1986
and in revised form: 19 February 1987

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