Communications

Pituitary gland ablation by $^{90}\text{yttrium}$ implantation for advancing diabetic retinopathy

A further report

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The early results of treatment by $^{90}\text{yttrium}$ pituitary ablation in ten diabetics with advancing retinopathy were previously presented in this Journal in 1965 (Cullen, Harris, Turner, Donaldson, Munro, and Duncan, 1965a). The present report reviews the later results in these patients and in ten more recently treated diabetics.

Materials and method

All twenty subjects were selected according to the ophthalmological and, except for three, the medical criteria suggested by Field, Schepens, Sweet, and Appels (1962) and detailed by us previously (Cullen, Harris, Munro, and Duncan, 1965b). About two-thirds of all patients referred to us for treatment were rejected because the retinal changes were already too far advanced, or because of ischaemic heart disease, significant impairment of renal function, or their being considered unsuitable or otherwise unreliable in controlling their diabetes and taking the prescribed endocrine replacement therapy. Patients 1, 2, and 10 were, however, subjected to surgery despite significant renal involvement revealed by examination of biopsy material, a blood urea exceeding 60 mg./100 ml., and creatinine clearance of less than 60 ml./min.

Preoperatively all subjects were carefully assessed ophthalmologically, medically, and endocrinologically. The two $^{90}\text{yttrium}$ rods were placed in the pituitary fossa under television monitoring by image intensifier, the dose of radiation being calculated to deliver 100,000 r to the periphery of the gland (Cullen and others, 1965a).

Patients were reassessed 4 weeks postoperatively for evidence of reduced pituitary function, in particular:

(a) Decrease in severity of the diabetes as indicated by a fall in insulin requirement to 40 per cent. or less of the preoperative dose or control by diet alone in those previously requiring an oral hypoglycaemic drug.

(b) Reduction of the serum P.B.I. to less than 3/ μg . per cent. and the thyroid 48-hour ^{131}I uptake to less than 10 per cent.

(c) Absent response to the Metyrapone test, after postoperative steroid cover had been withdrawn or, if this had not been provided, a fall in plasma cortisol (11-OHCS) to a dangerously low level (Mattingly, 1962).

(d) Significant decrease or disappearance of the pituitary gonadotrophin levels, measured in the urine with reference to the 2nd International Reference Preparation and using the normal figures as previously defined (Loraine and Bell, 1966).

(e) The temporary occurrence of diabetes insipidus.

On the basis of these results patients were divided into three groups according to the estimated degree of pituitary gland destruction.

(1) COMPLETE ABLATION: These patients showed no residual pituitary function, as evidenced by criteria (a), (b), (c), and (d) above, and had developed diabetes insipidus lasting up to 40 weeks.

Table I Preoperative data on twenty patients

Case no.	Age (yrs)	Sex	Duration of diabetes (yrs)	Hypoglycaemic therapy	Diabetic control
1	50	M	11	26 i.u. lente	Good
2	54	M	14	14 i.u. Sol/22 PZI	Fair
3	22	F	10	16 i.u. Sol/32 PZI	Good
4	40	F	20	16 i.u. Sol/36 PZI	Fair
5	26	F	22	32 i.u. Sol/40 PZI	Fair
6	35	F	14	20 i.u. Sol/40 PZI	Good
7	49	F	19	24 i.u. Sol/48 PZI	Fair
8	32	M	18	68 i.u. PZI	Fair
9	62	F	1	Diet only	Good
10	44	F	20	16 i.u. Sol/24 PZI	Good
11	48	F	38	16 i.u. Sol/16 PZI	Fair
12	52	M	12	125 mg. chlorpropamide	Good
13	43	M	21	16 i.u. Sol/32 PZI	Fair
14	34	M	15	32 i.u. Globin/32 PZI 20 Globin (p.m.)	Poor
15	35	M	10	24 i.u. Sol/48 PZI	Fair
16	31	M	15	20 i.u. Sol/40 PZI	Fair
17	33	F	29	24 Sol/40 PZI (a.m.) 12 i.u. Sol (p.m.)	Fair
18	51	F	15	375 mg. chlorpropamide	Good
19	30	M	26	16 i.u. Sol/60 PZI	Poor
20	28	M	14	24 i.u. Sol/20 PZI	Fair

Sol = Soluble insulin PZI = Protamine zinc insulin

(2) **PARTIAL ABLATION:** These patients were steroid and thyroxine dependent, but the above tests showed some residual pituitary function although this was significantly less than that determined preoperatively.

(3) **UNABLATED:** These patients retained virtually normal pituitary function, never having developed diabetes insipidus nor needing replacement hormonal therapy.

The patients were discharged from hospital 4 to 5 weeks after operation, taking the appropriate replacement therapy. Thereafter they were reviewed regularly at the Diabetic and Ophthalmic Clinics. One year after operation, or at a convenient time thereafter, pituitary function was re-assessed in hospital by the same tests and criteria detailed above with the exception of diabetes insipidus. Thyroxine treatment was stopped 6 weeks before admission and patients taking cortisone had the drug withdrawn under tetracosactrin cover (Synacthen, Ciba).

Table II *Preoperative renal function studies in twenty patients*

<i>Case No.</i>	<i>Blood urea (mg. per cent.)</i>	<i>Creatinine clearance (ml./min.)</i>	<i>Urinary protein (g./24 hrs)</i>	<i>Renal biopsy</i>
1	90	45	3.85	Advanced diffuse diabetic glomerulosclerosis Marked arteriosclerosis Patchy fibrosis – chronic pyelonephritis
2	94	54	6.00	Diffuse diabetic glomerulosclerosis Low grade chronic pyelonephritis
3	35	120	<0.03	Not performed
4	26	125	1.00	Early diffuse glomerulosclerosis
5	55	100	<0.03	Diffuse glomerulosclerosis and arteriolosclerosis Some suggestion chronic pyelonephritis
6	40	94	1.20	Advanced diffuse and nodular glomerulosclerosis
7	30	109	<0.03	Early diffuse glomerulosclerosis
8	45	120	3.40	Diffuse glomerulosclerosis and arteriolosclerosis
9	26	120	<0.03	Unsuccessful
10	65	60	1.80	Unsuccessful
11	60	60	1.30	Advanced glomerulosclerosis (diffuse and nodular)
12	46	80	0.20	Moderate diffuse glomerulosclerosis
13	32	74	0.32	Diffuse and nodular glomerulosclerosis
14	27	120	<0.03	Early diffuse glomerulosclerosis
15	34	105	0.50	Early diffuse glomerulosclerosis
16	44	80	1.20	Diffuse glomerulosclerosis
17	26	106	0.90	Early diffuse glomerulosclerosis
18	44	76	<0.03	Moderately diffuse glomerulosclerosis and arteriolosclerosis
19	32	130	0.40	Diffuse glomerulosclerosis and arteriolosclerosis
20	37	125	2.00	Diffuse and early nodular glomerulosclerosis and moderate afferent arteriolosclerosis

After reassessment the patients continued on replacement therapy, modified if necessary, and have been seen frequently as out-patients. Pituitary function was further re-evaluated at approximately yearly intervals.

An ophthalmologist (P.F.G.), who had never seen the patients before and was unaware of the degree of pituitary ablation achieved, independently assessed the ocular result by comparison of the sequential fundus photographs of each patient and, in those still living, by his own ophthalmological findings. The response to treatment was assessed on the basis of observed changes in the five following retinal components:

- (1) Primary neovascularization
- (2) Venous changes
- (3) Vitreous haemorrhage
- (4) Background retinopathy
- (5) Secondary neovascularization or retinitis proliferans

The general ocular effect was considered to be:

- (a) "Improved", if there was regression of existing and no new areas of neovascularization; no fresh vitreous haemorrhages; improvement of venous changes and background retinopathy.
- (b) "Arrested", if neovascularization was inactivated and fibrosed and vitreous bleeding considerably reduced in frequency.
- (c) "Unaffected", if initial neovascularization had increased unchecked and vitreous bleeding had not changed in frequency or had increased.

Results

Table I (see p. 218) shows the individual data of the twenty patients.

Table II (see p. 219) records the preoperative renal function in the treated patients.

Table III (opposite) gives the category of pituitary ablation at 4 weeks postoperatively, at 1 year after operation, and at the most recent review, along with the summarized ocular results.

Table IV (overleaf, p. 224) sets out the endocrine criteria used to categorize the degree of ablation achieved.

Table V (overleaf, pp. 222-223) details the results with regard to the five retinal components studied when possible in each patient.

Seven patients have died, two from postoperative meningitis, one from severe hypoglycaemia, and four from renal or cardiovascular disease (Table III).

Twelve patients were considered to be completely ablated postoperatively. Eight (Nos 1, 3, 4, 13, 15, 17, 19, and 20) have subsequently shown no sign of returning pituitary function and have benefited from the operation, the retinopathy either being arrested or showing improvement. Of the remaining four patients, three (Nos 5, 10, and 11) have shown signs of returning pituitary function and in two (Nos 10 and 11) this was associated with some reactivation and increase in the retinopathy. The fourth patient (No. 14) died before adequate follow-up was obtained, but his retinopathy appeared to have been arrested.

Seven patients were found to be only partially ablated at the initial postoperative assessment; of these one patient (No. 2) died of meningitis, and one (No. 8) showed a steady return of pituitary function to normal. His retinopathy, which postoperatively appeared to be quiescent, became active before he died. He is the only patient in whom pituitary function continued to return after a one-year assessment. The remaining five have

Table III *Results of treatment in twenty patients*

Case no.	Category of ablation			Ocular result when last seen	Date of operation	Remarks
	Postoperative	At 1 year	When last seen			
1	Complete	Complete	Complete	Arrested	Dec., 1963	Died 29 months after operation (Renal failure)
2	Partial	—	—	—	Jan., 1964	Died 4 weeks after operation (Meningitis)
3	Complete	Complete	Complete	Improved	Dec., 1963	
4	Complete	Complete	Complete	Arrested	Feb., 1964	
5	Complete	Partial	Partial	Improved	Mar., 1964	Adrenal function returned at 1 year
6	Partial	Partial	Partial	Arrested	Mar., 1964	Always residual pituitary function
7	Partial	Partial	Partial	Unaffected	Apr., 1964	
8	Partial	Partial	Unablated	Arrested	Oct., 1964	See text. Died 50 months after operation (Myocardial infarct)
9	Partial	Partial	Partial	Unaffected	Nov., 1964	Died 46 months after operation (Cerebral thrombosis)
10	Complete	Partial	Partial	Arrested	Nov., 1964	Died 45 months after operation (Renal failure)
11	Complete	Partial	Partial	Unaffected	Mar., 1965	Pituitary function returning at 1 year
12	Partial	Partial	Partial	Arrested	June, 1965	See text
13	Complete	Complete	Complete	Improved	Jan., 1966	
14	Complete	—	—	—	Jan., 1966	Died 7 months after operation (Recurrent meningitis)
15	Complete	Complete	Complete	Improved	Feb., 1966	Died 25 months after operation (Hypoglycaemia)
16	Partial	Partial	Partial	Arrested	May, 1966	Residual but static pituitary function
17	Complete	Complete	Complete	Arrested	June, 1966	
18	Unablated	Unablated	Unablated	Unaffected	July, 1966	See text
19	Complete	Complete	Complete	Arrested	Nov., 1966	
20	Complete	Complete	Complete	Arrested	Apr., 1967	

apparently had a static impairment of pituitary function. In three (Nos 6, 12, and 16) the retinopathy has remained quiescent and arrested, but in the other two (Nos 7 and 9) the retinopathy became much worse. No patient in this group showed improvement in the retinopathy.

One patient (No. 18) who was insulin independent showed no decrease in pituitary function after operation. She had a rapidly progressing retinopathy with further severe haemorrhage shortly after the procedure and was not considered suitable for further surgical treatment.

Cerebrospinal fluid rhinorrhoea is still a major postoperative complication and occurred in three cases of this series. Two patients were observed to have transient palsies of the extraocular muscles for 4 to 6 weeks following insertion of $^{90}\text{Yttrium}$.

Discussion

There is still no agreement on the most effective method of performing a pituitary ablation and on whether complete destruction of the gland is necessary to achieve the maximum therapeutic benefit in patients with diabetic retinopathy. It has been reported that pituitary irradiation causing suppression and not ablation of the gland will produce acceptable ocular results (Linfoot, 1967). In most series, however, the impression has

Table V Results for the five retinal components studied

Time of examination	Retinal component	Neovascularization		Vitreous haemorrhage	
	Eye	Right	Left	Right	Left
Postoperative result	None	7	1	7 14 15 19 20	1 2 6 7 13 18
	Early		2 19		
	Moderate	6 8 13 15	6 12 13 15	6 8 13 17	17 19 20
	Marked	1 2 3 4 5 9 10 11 12 14 16 17 18 19 20	3 4 5 7 8 9 10 11 14 16 17 18 20	1 2 3 4 5 9 10 11 12 16 18	3 4 5 8 9 10 11 12 14 15 16
Latest post-operative result	Regressed	5 13 15	5 13		
	Arrested	1 3 4 6 10 16 17 19 20	3 4 6 8 12 15 16 17 19 20	1 3 4 5 6 7 8 10 13 15 16 17 19 20	1 3 4 5 8 9 12 13 14 15 16 17 20
	Unchanged	8		11	11
	Progressed	7 9 11 12 18	1 7 9 10 11 18	9 18	7 9 18

Figures refer to case numbers

Missing numbers indicate no follow-up or component not visualized

been that the best results occur only if the pituitary gland is totally destroyed (Luft, Olivecrona, and Sjögren, 1955; Joplin, Fraser, Hill, Oakley, Scott, and Doyle, 1965; Bradley, Rees, and Fager, 1965; Rucker, Gastineau, and Svien, 1967; Field, 1967). One controlled study, which evaluated the effect of three different doses of $^{90}\text{yttrium}$ radioactivity, demonstrated that "maximal" and "intermediate" ablation appeared equivalent in effect but clearly superior to "slight" ablation. Venous irregularities improved discernibly only after maximal ablation (Joplin, Oakley, Hill, Kohner, and Fraser, 1967), and this is of particular importance as these lesions are not amenable to photocoagulation. The present results support the view that complete ablation is required to achieve maximal ocular benefit. All those having complete ablation showed either improvement or arrest of retinopathy, whereas only half of those having partial ablation showed a similar response. They also confirm the importance of careful medical pre-operative assessment, in that the three patients who did not fulfil the previously defined criteria for selection have died. The poor prognosis for vision and survival in this type of patient has recently been emphasized (Deckert, Simonsen, and Poulsen, 1967; Teuscher, Escher, König, and Zahnd, 1970).

Neovascularization, which is the most serious manifestation of diabetic retinopathy, was improved or arrested in 22 eyes of thirteen patients. Neovascularization arising from the optic disc, which was present to a varying degree in all patients of our series, appears to be effectively treated only by means of a pituitary ablation. More peripheral and localized areas of new vessel formation can, however, be effectively eradicated by photo- or laser-coagulation. In two of the patients reported (Nos 3 and 19), photocoagulation therapy was carried out 5 and 2 years respectively after pituitary operation, because of incomplete regression of peripheral neovascularization which was still considered to be a potential source of vitreous haemorrhage.

Background retinopathy		Venous change		Retinitis proliferans	
Right	Left	Right	Left	Right	Left
				7 8 14 15 17 19	1 2 5 6 14 16 17 19
				5 6 20	11 13 18 20
13 19	3 6 7 12 13 19	4 7 8 10 13 19	1 4 6 7 12 13 19	3 10 13 18	3 12
3 4 5 6 9 10 14 15 16 17 20	1 2 4 5 9 11 14 15 16 17 18 20	1 2 3 5 6 9 11 14 15 16 17 18 20	2 3 5 9 11 14 15 16 17 18 20	1 2 4 9 11 12 16	4 7 8 9 10 15
17	15	1 3 5 15 17 20	1 3 15		
4 5 6 8 10 13 16 19 20	3 4 5 6 12 13 16 17 18 20	4 8 13 16 19	4 5 12 13 16 17 18 20	3 13 15	3 13 16
	1 9 11 19	6 9 10 11	6 9 11 19		
8	7	7 18	7	1 4 5 6 7 8 9 10 11 12 16 17 18 19 20	1 4 5 6 7 8 9 10 11 12 15 17 18 19 20

Cryohypophysectomy as an alternative method of destroying the pituitary gland has been advocated (Rand and Roth, 1967). We have used this method in only three diabetic patients during our early experience of this technique and, in these, adequate destruction of the gland was not achieved. We have not, therefore, used this method again in other diabetic patients.

In conclusion, we believe that pituitary ablation, though a serious and potentially dangerous undertaking, can in properly selected patients effectively arrest various forms of advancing diabetic retinopathy which cannot be treated by photo-coagulation and would otherwise eventually lead to blindness.

Summary

The results of pituitary gland ablation in twenty diabetic patients with proliferative retinopathy are given with reference to endocrinological and ophthalmological data. The average follow-up period was 5 years. When the category of pituitary ablation achieved is related to the ocular results, it is concluded that a complete destruction of the gland should be the goal of treatment.

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Table IV *Category of ablation with criteria employed in twenty patients*

Case No.	Category of ablation postoperatively	Criteria*	Category of ablation at 1 year	Criteria*	Category of ablation when last seen
1	Complete	abcde	Complete	abcd	Complete
2	Partial	ab	—	—	—
3	Complete	abcde	Complete	abcd	Complete
4	Complete	abcde	Complete	abcd	Complete
5	Complete	abcde	Partial	ab d	Partial
6	Partial	ab	Partial	ab	Partial
7	Partial	ab d	Partial	ab d	Partial
8	Partial	a c	Partial	—	Unablated
9	Partial	bc	Partial	bc	Partial
10	Complete	abcde	Partial	b d	Partial
11	Complete	abcde	Partial	bcd	Partial
12	Partial	bcd	Partial	bcd	Partial
13	Complete	abcde	Complete	abcd	Complete
14	Complete	abcde	—	—	—
15	Complete	abcde	Complete	abcd	Complete
16	Partial	abc	Partial	abc	Partial
17	Complete	abcde	Complete	abcd	Complete
18	Unablated	—	Unablated	—	Unablated
19	Complete	abcde	Complete	abcd	Complete
20	Complete	abcde	Complete	abcd	Complete

N.B. *Letters under "Criteria" refer to the tests, detailed in the text, which showed complete ablation. (Thus complete ablation = abcde.)

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