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Pituitary Ablation for Diabetic Retinopathy

J. S. SPEAKMAN, B.A., M.D., F.R.C.S.[C],*

C. B. MORTIMER, M.A., M.D., B.Chir., F.R.C.S.[C],†

T. D. R. BRIANT, M.D., F.R.C.S.[C],‡

C. EZRIN, M.D., F.R.C.P.[C],§

W. M. LOUGHEED, M.D., F.R.C.S.[C]|| and

W. T. W. CLARKE, M.D., F.R.C.P.[C],¶ *Toronto*

ABSTRACT

Pituitary ablation was performed on 26 patients with advanced diabetic retinopathy by pituitary stalk section (nine patients) or transphenoidal hypophysectomy (17 patients). After a latent period varying from six to 12 months, retinal hemorrhages disappeared, vitreous hemorrhages stopped and new vessels regressed. Eight of 10 patients followed up for more than a year had a complete remission, although in one of two patients whose ablation was incomplete the retinopathy remained active. Preoperative visual acuity levels were preserved in 47 of 50 eyes of patients followed up for a mean period of 12 months. Three patients have died, two from causes related to their operation. Twenty of the survivors have continued in their usual occupation. Pituitary ablation is effective in preventing the progressive visual deterioration usually associated with advanced diabetic retinopathy.

SOMMAIRE

On a procédé à l'ablation de l'hypophyse chez 26 malades souffrant de rétinopathie avancée d'origine diabétique, chez neuf malades par section de la tige hypophysaire et chez 17 autres par hypophysectomie transphénoïdale. Après une période de latence variant de six à 12 mois, l'hémorragie rétinienne disparut, les hémorragies de l'humeur vitrée furent enrayerées et les nouveaux vaisseaux entèrent en régression. Sur 10 des malades qui furent suivis pendant plus d'un an, huit bénéficièrent d'une rémission complète, mais chez l'un des deux malades n'ayant subi qu'une ablation incomplète, la pathologie rétinienne demeura active. L'acuité visuelle pré-opératoire a pu être conservée dans 47 des 50 yeux qui ont été observés pendant une période moyenne de 12 mois. Trois malades sont morts, deux par suite de causes liées à leur opération. Vingt des survivants ont pu poursuivre leurs occupations normales. L'ablation hypophysaire est une opération qui permet de prévenir l'aggravation graduelle de la vision qu'on observe d'ordinaire dans la rétinopathie avancée d'origine diabétique.

DIABETIC retinopathy, one of the commonest complications of diabetes, is now one of the leading causes of blindness, and is therefore of vital interest both to the ophthalmologist and the general physician. Approximately 10 to 15% of

recently registered legally blind* persons have diabetic retinopathy. This in itself is serious enough,¹ yet these statistics do not reflect the fact that a high proportion of these individuals are young wage-earners, many of whom eventually become totally blind.

Many medical routines have been recommended for the management of this condition but none has

From the Departments of Ophthalmology, Otolaryngology, Medicine and Neurosurgery, University of Toronto, Toronto, Ontario.

*Associate in Ophthalmology, University of Toronto.

†Clinical Fellow in Ophthalmology, University of Toronto.

‡Clinical Fellow, Department of Otolaryngology, University of Toronto.

§Associate, Department of Medicine, University of Toronto.

||Assistant Professor of Surgery, University of Toronto.

¶Assistant Professor, Department of Medicine, University of Toronto.

Address for reprints: Dr. J. S. Speakman, 734 Medical Arts Bldg., 170 St. George St., Toronto 5, Ontario.

*Visual acuity of 20/200 or less in the better eye.

withstood the test of time. Most physicians, until recently, have been forced to admit that there is nothing of therapeutic value available, or hopefully advised better control of the diabetes, knowing that this has very little relation to the progression of the retinopathy.² Destruction of the pituitary gland was introduced several years ago as a treatment for diabetic retinopathy³ and in recent years a great variety of ablation techniques have been employed,⁴ including yttrium implantation,⁵⁻⁷ x-ray⁸ or proton beam irradiation,⁹ pituitary stalk section,¹⁰⁻¹² hypophysectomy utilizing craniotomy^{3, 13} or transphenoidal routes,^{14, 15} and stereotactic cryosurgery.¹⁶ This form of treatment is empirical and has not been generally accepted because of the operative mortality, complications, and questionable effect on retinopathy. Nevertheless we decided to evaluate this procedure and recommended pituitary stalk section or transphenoidal hypophysectomy in a series of 26 diabetic patients whose vision appeared to be seriously threatened by rapidly progressing retinopathy.

It is important to stress the unpredictable course which even serious retinopathy may take. The following case histories illustrate this aspect of the problem.

A 55-year-old man with diabetes of five years' duration was first seen at the eye clinic in February 1963, when visual acuity was recorded at 20/30—3 in the right eye and hand movements in the left eye. Many retinal hemorrhages were noted in the right eye, and in the left eye extensive gliosis and new vessels surrounded the disc and extended along the upper and lower temporal vessels. Two years later the visual acuity remained at 20/40 in the right eye and hand movements in the left eye. During this period early new vessel formation developed at the right disc and several vitreous hemorrhages occurred in the left eye.

Comment: This case illustrates the marked difference in the rate of progression which may occur in two eyes in the same individual.

A 35-year-old diabetic had a visual acuity of 20/70 in each eye in 1960. Proliferating retinopathy and vitreous bleeding began in March 1960 and by August 1961 her vision was reduced to hand movements in the right eye and counting fingers at 10 feet in the left. Hypophysectomy was considered in February 1962 but was not advised, and in December 1962 her vision was reduced to accurate light projection in the right eye and improved to 20/100 in the left eye. Occasional retinal hemorrhages were noted at this time, but there has been no further vitreous bleeding and retinal hemorrhages have disappeared. Extensive gliosis obscures the fundus in the right eye and surrounds the major vessels in the left eye.

Comment: This is an example of a spontaneous remission in a relatively advanced stage.

Another diabetic patient, aged 19 when first seen in May 1962, had a recorded visual acuity of 20/30 in each eye at that time. Widespread retinal hemorrhages were noted and the appearance of the fundus

suggested a bilateral central vein occlusion. Subsequently, bilateral neovascularization developed at the disc which was treated in one area by light coagulation in the right eye, but was not treated in the left eye because of recurrent vitreous bleeding. Pituitary stalk section was considered but was not advised. This patient was last examined in January 1965 because of blurred vision in the left eye, and his visual acuity was 20/20 in the right eye and 20/40 in the left eye. No retinal hemorrhages or neovascularization could be seen in either eye. In the left eye an extensive glial mass was present inferiorly and a subcapsular cataract had formed. Although the vitreous was hazy, suggesting a recent hemorrhage, no fresh blood was seen.

Comment: This patient, who was expected to deteriorate rapidly, has undergone a spontaneous remission with good preservation of vision.

These individuals illustrate the unpredictable course of diabetic retinopathy and the possibility of spontaneous remission at any stage. Unfortunately the general trend is one of rapid deterioration, and the data recorded for untreated patients suggest that in three years the majority of those acquiring proliferating retinopathy will have decreased visual acuity and a third may be legally blind.¹⁷ In another study² it was found that 50% of eyes with impaired vision become legally blind in five years. Fourteen patients in our series were legally blind in one eye and five more were legally blind in both eyes at the time of their pituitary operation (Table I). Spontaneous remissions are

TABLE I.—PREOPERATIVE VISION

Acuity	20/20 - 20/40	20/50 - 20/200	Less than 20/200
Monocular vision (eyes)	17	11	24
Binocular vision (people)	14	7	5

rarely observed in short-term follow-up studies, and all too frequently they occur late in the course of the disease when useful vision has been lost.

Although it would be ideal to assign alternate patients considered suitable for treatment to a control group, this would have been unacceptable both to referring physicians and patients. In many individuals, objective evidence of progression was recorded photographically before operation, and to this limited extent the patients acted as their own controls.

CLINICAL FINDINGS

In attempting to assess the response to pituitary ablation it is difficult to choose criteria which objectively reflect the clinical course of the retinopathy. For example, preoperative visual acuities were frequently recorded after fresh vitreous bleeding, and an immediate improvement in such an individual does not have the same significance as an improvement maintained for several months.

TABLE II.—CLINICAL FINDINGS

Patient	Age	Vision pre-operatively	Vision post-operatively	Operation	Follow-up in months	Preoperative findings	Postoperative findings
1. G.W., banker	55	20/20* L.P.	20/20 L.P.	S.S.	38	Right eye: recurrent vitreous hemorrhage, retinal folding. Left eye: mature cataract	Bleeding in right eye for three months followed by complete remission
2. B.C., secretary	27	L.P. 20/30	20/400 20/25	S.S.	25	Both eyes: new vessels. Right eye: recurrent vitreous hemorrhage	No further bleeding; new vessels disappeared; residual vitreous membranes in right eye
3. S.J., housewife	33	20/30 C.F.		S.S.	Died post-operatively	Both eyes: recurrent vitreous hemorrhage, new vessels and gliosis	Intracerebral hemorrhage immediately postoperatively
4. G.S., fur rancher	27	L.P. C.F.	L.P. N.L.P.	S.S.	18	Both eyes: recurrent vitreous hemorrhage, gliosis and new vessels	Bleeding left eye followed by rubeosis and secondary glaucoma
5. H.G., salesman	31	20/200 20/60	20/30 20/40	S.S.	18	Both eyes: recurrent vitreous hemorrhage	One hemorrhage left eye at eight months; complete remission
6. R.F., engineer	29	20/50 H.M.	20/25 H.M.	S.S.	20 Died at 24 mo.	Both eyes: recurrent vitreous hemorrhage and new vessels	No further hemorrhage, regression of new vessels, residual membranes left eye; death, probably due to hypoglycemia
7. A.B., journalist	34	N.L.P. 20/25	N.L.P. 20/25	T.S.	20	Both eyes: recurrent vitreous hemorrhage and new vessels. Right eye: retinal detachment	Partial regression of new vessels; fresh hemorrhages at 16 and 19 months in left eye
8. J.B., housewife	31	20/20 20/20	20/20 20/30	T.S.	18	Both eyes: new vessels at disc, and retinal hemorrhage. Left eye: persistent vitreous hemorrhage	Persistent hemorrhage left eye for nine months, followed by complete remission
9. J.W., secretary	19	20/50 20/60	20/20 20/30	T.S.	12 Died at 14 mo.	Both eyes: recurrent vitreous bleeding, new vessels, retinal hemorrhages	Complete remission at 12 months, thrombophlebitis and pulmonary embolus
10. L.S., secretary	26	20/100 L.P. 20/300 H.M.	20/200 C.F.	T.S. S.S.	12	Both eyes: recurrent vitreous bleeding, large hemorrhages just before second operation	Vitreous membranes, no further bleeding, posterior subcapsular cataracts
11. G.H., clerk	27	20/40 C.F.	20/40 20/100	T.S.	12	Both eyes: recurrent vitreous hemorrhage, extensive new vessel formation, gliosis, retinal folding	No further bleeding, regression of new vessels
12. B.K., housewife	22	C.F. 20/100	20/30 20/70	T.S.	11	Right eye: large preretinal clot. Left eye: amblyopic	Preretinal clot absorbed, new vessels smaller, old retinal hemorrhages still present
13. G.B., housewife	32	20/30 C.F.	20/30 20/70	T.S.	9	Both eyes: extensive new vessels, gliosis, narrowed arteries. Left eye: vitreous hemorrhages	New vessels reduced in size, one small hemorrhage left eye at eight months
14. L.A., clerk	26	20/40 20/200	20/30 20/40	T.S.	9	Both eyes: new vessels, vitreous hemorrhage, gliosis, retinal folding	No further bleeding, new vessels smaller
15. E.G., housewife	35	20/40 20/25	C.F. 20/20	S.S.	9	Right eye: massive preretinal clot. Left eye: minimal retinopathy	Early hemorrhage into vitreous in right eye. Small preretinal clots and new vessels left eye
16. N.G., shopkeeper	55	20/400 C.F.	C.F. C.F.	S.S.	9	Both eyes: new vessels, vitreous hemorrhage, gliosis, narrowed arteries	Fresh hemorrhage left eye at six months and right eye at nine months
17. F.M., housewife	45	20/70 20/40	20/50 20/50	T.S.	6	Both eyes: new vessels, vitreous hemorrhage, gliosis. Left eye: retinal folding	Vitreous clearing after early bleeding, new vessels growing smaller
18. D.H., unemployed	17	C.F. 20/100	20/70 C.F.	T.S. O.S. cyclo-diathermy. O.S. filtering operation, 6 mo.	6	Both eyes: vitreous haze. Left eye: rubeosis and secondary glaucoma	Both eyes: vitreous clearing revealing extensive new vessel formation and gliosis. Regression of new vessels on iris, fresh vitreous hemorrhages left eye
19. J.H., housewife	39	20/400 20/200	20/60 20/40	T.S.	7	Both eyes: new vessel formation, retinal hemorrhages. Right eye: vitreous bleeding	No fresh hemorrhages, new vessels unchanged
20. M.W., housewife	46	20/40 C.F.	20/25 20/30	T.S.	7	Both eyes: vitreous hemorrhage, new vessel formation, gliosis, especially left eye	Both eyes: no further vitreous hemorrhages
21. R.D., salesman	25	20/80 20/200	20/40 20/100	T.S.	3	Both eyes: widespread intraretinal hemorrhages, especially left eye	No fresh hemorrhages
22. D.G., teacher	33	L.P. 20/25	L.P. 20/25	T.S.	3	Right eye: vitreous membranes. Left eye: extensive new vessel formation and gliosis	No change
23. B.I., housewife	21	20/50, H.M. 20/40, 20/40	H.M. 20/25	T.S.	3	Right eye: retinal detachment. Left eye: extensive new vessel formation and gliosis	No change right eye; fresh vitreous bleeding left eye at three months
24. M.M., housewife	43	20/30 20/30	20/30 20/30	T.S.	3	Both eyes: vitreous hemorrhage. Right eye: new vessels and gliosis	No fresh hemorrhage
25. D.F., housewife	23	20/50 H.M.	20/50 H.M.	T.S. 2	2	Both eyes: extensive new vessel formation and preretinal gliosis	No change
26. C.C., salesman	44	20/300 20/300	20/200 20/400	T.S.	3	Both eyes: vitreous haze. Right eye: gliosis and new vessels	Partial clearing of vitreous haze

L.P. = Light perception.
C.F. = Counting fingers.

N.L.P. = No light perception.
H.M. = Hand movements.
S.S. = Pituitary stalk section.

T.S. = Trans-sphenoidal hypophysectomy.
O.S. = Left eye (*oculus sinister*).

*Right eye first in each case.

It is also difficult to assess the occurrence of minor degrees of fresh vitreous bleeding because these

episodes may be asymptomatic and produce little ophthalmoscopic change. Only the complete dis-

TABLE III.—SUMMARY OF OCULAR FINDINGS

Ocular lesion	Frequency (eyes)	Response to surgery
Macular hemorrhage..	2	Gradual disappearance; improved vision
Vitreous hemorrhage..	37	Marked reduction after nine months
New vessel formation..	42	Gradual disappearance after nine months
Gliosis.....	32	No change
Arterial narrowing....	4	No change
Retinal folding.....	5	No change
Retinal detachment...	2	No change
Grey reflex.....	6	No change
Rubeosis iridis.....	2	One eye blind, one eye partially improved
Cataract.....	2	No change

appearance of reddish-brown discolourations in the vitreous, or their conversion to white opacities or membranes, has been interpreted as indicating a cessation of vitreous bleeding. Minor changes in new vessel formations occur spontaneously and are of little importance. However, the persistent regression of large leashes of vessels emerging from the disc which can be easily recognized and photographed is of considerable significance. In view of these difficulties, several clinical findings have been recorded in order to provide a composite picture of the ocular response to pituitary surgery. These data are summarized in Tables II and III, and in Table IV the findings have been analyzed separately for patients who have been followed up for more than six months.

TABLE IV.—OCULAR FINDINGS RELATED TO DURATION OF FOLLOW-UP*

Follow-up	Six - 12 months			More than 12 mo. (average 19)		
	Maintained	Worse	Total	Maintained	Worse	Total
Monocular vision	35	3	38	19	1	20
Binoocular vision..	18	1	19	9	1	10
Recurrence of vitreous hemorrhage...	Yes 7	No 24	Total 31	Yes 1	No 16	Total 17
Disappearance of retinal hemorrhage and new vessels.....	Partial 13	Complete 1	Total 21†	Partial 3	Complete 8	Total 11

*These figures except for binocular vision refer to "eyes".
†In seven patients the response was equivocal or there was no definite change.

(a) Retinal Hemorrhage

Characteristic retinal hemorrhages were seen in the majority of patients, and in two patients (Cases 9 and 21) their concentration at the macula appeared to be a significant factor in reducing visual acuity (Fig. 1). Both of these patients showed marked improvement in vision following their operation and it would appear that fresh retinal hemorrhages at the macula do not preclude a good visual result. Although new retinal hemorrhages have been recorded photographically in several patients shortly after hypophysectomy, a significant reduction in such hemorrhages was usually observed after six months, and in the patients followed up for more than 12 months few if any retinal hemorrhages were present.

(b) Vitreous Hemorrhage (Table III)

Vitreous bleeding was a prominent finding in 37 eyes of 24 patients, and such bleeding may involve the eye in a variety of ways. Typically the patient notices a sudden loss of vision followed in a few days by improvement as the vitreous clears, although permanent visual impairment may follow the first symptomatic episode of bleeding. In two patients serious vitreous bleeding followed the progressive accumulation of a large preretinal clot. In one of these (Case 12), symptoms occurred early because of macular involvement (Fig. 2) and the visual function was preserved, but in the second (Case 15) a very large clot accumulated which remained asymptomatic because the macula was spared. Postoperatively the clot broke into the vitreous and failed to clear. Bleeding may also be asymptomatic if it occurs into the peripheral vitreous in the equatorial region (Case 8). These clots frequently form a radial pattern resembling the spokes in a wheel. They tend to persist, and the vitreous may become extensively organized without the patient's realizing the seriousness of the ocular involvement. It has been our experience that the onset of vitreous bleeding, especially when associated with the formation of preretinal clots or new vessels, frequently constitutes an emergency situation. Case 10 illustrates the rapid deterioration which may occur from recurrent hemorrhage. The visual acuity was 20/100 and 20/300 on admission, and following an attempted transphenoidal hypophysectomy (abandoned because of an anomalous cavernous sinus) she experienced further hemorrhages, which reduced her vision to light perception and hand movements. A stalk section was then performed but her visual improvement has been limited because of vitreous membranes. Small vitreous hemorrhages, in the absence of other evidence of advancing retinopathy, and persistent peripheral clots are serious signs, but it is usually safe to observe the patient at frequent intervals for evidence of further deterioration.

The early response of vitreous hemorrhage to pituitary destruction is unpredictable. In the majority of patients in the first six months there is evidence of further bleeding. The prompt vitreous clearing seen in some patients is not uniformly observed, and in seven eyes in our series fresh bleeding occurred between six and 12 months. However, after 12 months there is a marked reduction in the incidence of bleeding. If one considers only those patients with a previous history of vitreous hemorrhage who have been followed up for more than 12 months, there have been only two episodes of bleeding, both in the left eye (Case 7), in a period of 74 patient-months. The following case histories illustrate in more detail the response of patients with vitreous hemorrhage to hypophysectomy.

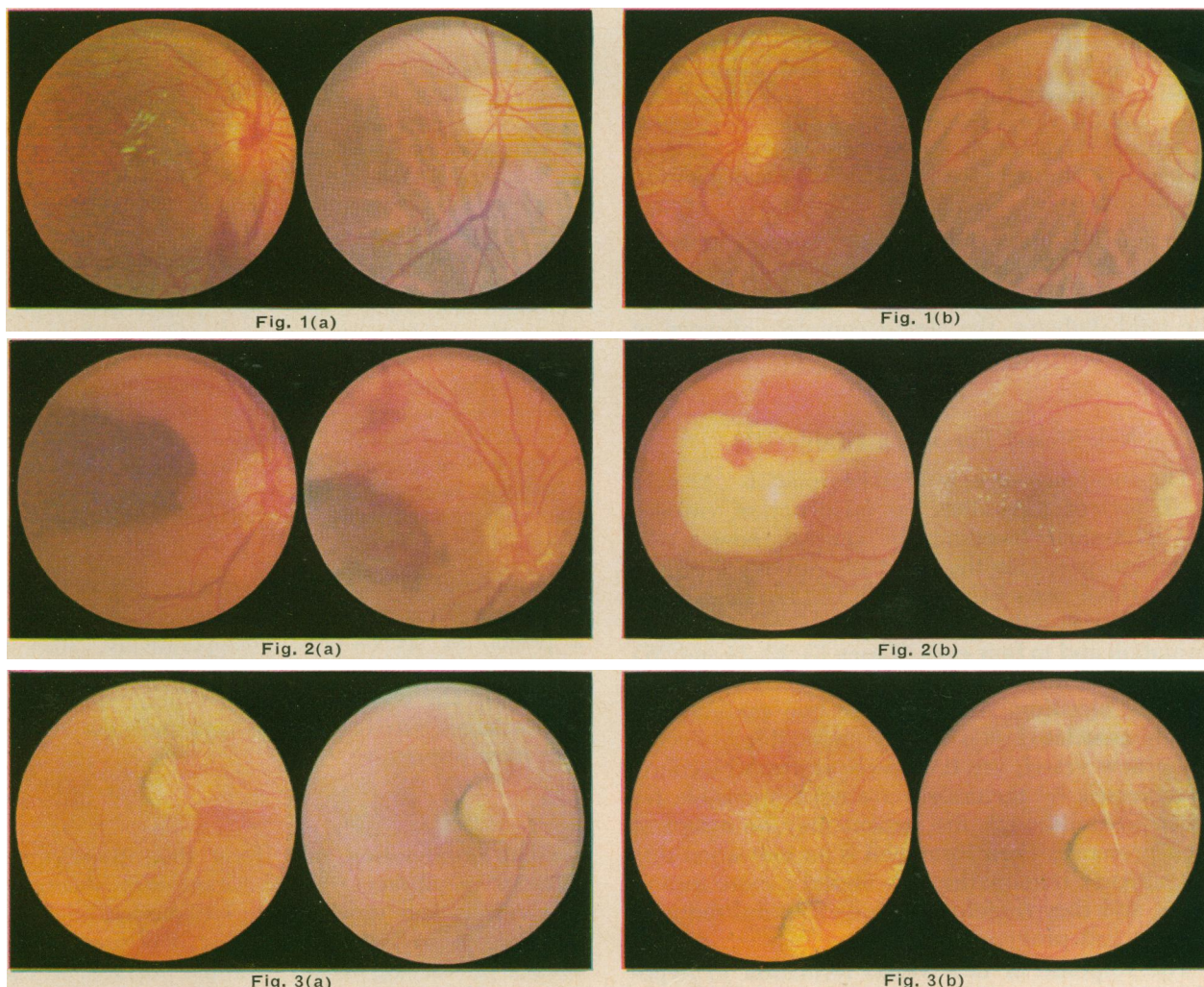


Fig. 1.—Case 9. Right eye (a) and left eye (b) before and 12 months after pituitary ablation, showing disappearance of retinal and vitreous hemorrhages and new vessel formations at the disc.

Fig. 2.—Case 12. Right eye (a) before, three weeks after, and (b) five months and 11 months after pituitary ablation, showing the transformation of a preretinal clot into a white membrane which eventually disappeared, exposing the macula again. Fresh postoperative hemorrhage developed just above the original clot (a) but did not recur.

Fig. 3.—Case 11. Right eye (a) and (b) before and six months after pituitary ablation, showing disappearance of preretinal hemorrhages and new vessels.

CASE 12.—A 20-year-old housewife, diabetic since the age of 4, had a visual acuity of 20/20 in the right eye and 20/80 in the left eye recorded in September 1962. The left eye was amblyopic owing to a small left esotropia. Between September and November 1964 she noted recurrent episodes of blurred vision in the right eye, and her oculist observed the progressive formation of a dense preretinal clot which eventually obscured the macula and reduced vision in her good eye to counting fingers (Fig. 2a). Transphenoidal hypophysectomy was performed in December 1964, and shortly afterwards the blood clot broke into the vitreous. One month later fresh bleeding occurred near the macula and subsequently a dense preretinal membrane appeared just below the macular region as the blood clot disappeared (Fig. 2b). By March the vitreous had largely cleared, and no fresh hemorrhages were noted although new vessels were still present along the upper temporal vessels in the right eye and at the left disc. By April 1965 she reported that she could thread a needle, and her most recently recorded visual acuity in November 1965 was 20/30 in the right eye and

20/70 in the left eye. The preretinal membrane (probably fibrin) had disappeared, new vessels were smaller and many old retinal hemorrhages were still present.

Comment: Pituitary surgery in this patient appeared to stop further bleeding after a latent period of a month and was associated with a dramatic improvement in vision. At 11 months the remission is not yet complete.

CASE 1.—A 55-year-old man with mild diabetes noted episodes of blurred vision in his left eye in 1956 and was told that he had had hemorrhages in his eye. Subsequently a mature cataract formed in this eye. In November 1961 he developed spots before his right eye, and on initial examination his visual acuity was 20/20 in the right eye and accurate light perception in the left eye. A linear preretinal clot was found along the lower temporal vessels in the right eye and a small tuft of gliosis at the disc. Oblique retinal folds extended across the macula. Several episodes of preretinal and vitreous bleeding occurred in subsequent months, and

two attempts were made to control this with light coagulation. Finally, pituitary stalk section was performed in May 1962, and in June and August fresh bleeding occurred. No further episodes took place thereafter, and his visual acuity in August 1965 was 20/20 in the right eye. At that time there was no evidence of bleeding and only the retinal folding and gliosis at the disc remained.

Comment: Following pituitary surgery this patient's hemorrhagic tendency stopped after a latent period of three months. Interesting features were the mild diabetes, the almost complete absence of retinal hemorrhages, exudates and neovascularization.

(c) *New Vessel Formation* (Table III)

The incidence of new vessel formation (42 eyes in 22 patients) parallels the incidence of vitreous and preretinal bleeding. In general, new vessel formation precedes the onset of vitreous bleeding but in three cases (Cases 1, 5 and 15) hemorrhage occurred with only minimal evidence of new vessel formation and in four eyes (Cases 13, 22, 23 and 25) extensive new vessel formation occurred without vitreous bleeding. Although the two findings are closely associated, it is usually impossible to decide if the new vessels are the source of fresh bleeding. New vessels by themselves are not responsible for vision loss, although the patient may be aware of their presence. Their formation is an indication that the patient's retinopathy has entered a more serious phase and they therefore provide a useful index of activity and progression.

The response of new vessel formation to hypophysectomy is variable, and several patients have shown further proliferation of new vessels in the early postoperative period. Between six and 12 months after operation, however, finer vessels usually show evidence of attenuation. Of the 11 eyes with new vessels followed up for more than 12 months, eight have shown a complete regression of new vessels and three have shown a partial regression. Of the two patients showing partial remission after 12 months, one (Case 7) who has been followed up for 18 months has an incomplete hypophysectomy which may account for the persistent new vessel formation, and the remaining patient is expected to proceed to a complete remission. A change in the colour of newly formed glial membranes from grey pink to chalk white is another prominent feature in the late follow-up period which reflects the reduced vascularity (Fig. 3). The following case history illustrates the response of new vessel formation.

CASE 9.—A 19-year-old secretary, diabetic since the age of 8, was found in March 1963 to have a visual acuity of 20/20 in each eye and a moderately active retinopathy. By May 1964 visual acuity had decreased to 20/50 in the right eye and 20/60 in the left eye, and in both eyes many retinal hemorrhages and extensive new vessel formation at the discs were noted

(Fig. 1). In addition, vitreous bleeding occurred and transphenoidal hypophysectomy was performed. No further vitreous bleeding took place and retinal hemorrhages gradually disappeared. By February 1965 the extensive new vessel formations at each disc had disappeared and visual acuity was found to be 20/20 in the right eye and 20/30 in the left eye. Her visual improvement was maintained through the summer of 1965, but at that time she developed thrombophlebitis and died suddenly in September from a massive pulmonary embolus. Both eyes were removed at post-mortem examination and no new vessels were visible when the fundi were examined under a dissecting microscope. Small patches of fibrous tissue were present at each disc and a few fresh peripheral retinal hemorrhages were noted. Serial sections of a representative area of gliosis adjacent to the disc failed to reveal evidence of new vessel formation and the newly formed tissue was relatively acellular. A digest preparation of the retina showed many microaneurysms filled with red blood cells.

Comment: This patient developed a very active diabetic retinopathy which progressed rapidly over a period of six months; postoperatively, after a latent period of nine months, a complete remission occurred. The disappearance of widespread retinal hemorrhages, vitreous hemorrhage and new vessels was most impressive.

(d) *Gliosis*

Glial proliferation may form thin, transparent vitreous membranes in association with sheets of new vessels, may grow into the vitreous in ill-defined tufts along the retinal vessels, or may form membranes of varying density on the surface of the retina. Alternatively, dense gliosis may replace large vitreous blood clots or form circumscribed plaques of scar tissue at the site of preretinal hemorrhages. The newly formed tissue may obstruct the visual pathway or, by contracting, induce folding or detachment of the retina. Although glial membranes may become thinner, there has not been a significant improvement in vision loss due to gliosis following pituitary surgery, as illustrated by the following case history.

CASE 2.—A 27-year-old typist developed several vitreous hemorrhages in her right eye which became organized into a dense white vitreous mass in front of the macula, reducing her vision to accurate light perception. New vessel formation developed at the left disc and, although her visual acuity was not impaired, a stalk section was performed in May 1963. No further bleeding was observed and a considerable reduction in vitreous haze occurred in the right eye, but visual acuity did not improve beyond 20/400 because of a residual opaque preretinal glial mass. In the left eye the new vessels at the disc and the retinal hemorrhages disappeared over a nine-month period and a satisfactory remission has been maintained for over two years.

Comment: The glial response to vitreous bleeding did not disappear in this case even though a remission was obtained following pituitary surgery.

(e) *Retinal Detachment*

Two patients (Cases 7 and 23) had retinal detachments at the time of operation. In one the detachment involved the posterior pole and the peripheral retina remained attached, leaving a fairly full peripheral field. The detachments have not changed objectively following operation although the patient with residual visual function thought that the field of vision improved. Retinal folding, which may be the first stage in the development of a detachment, was observed in five eyes and has not changed after pituitary surgery. Late detachments have not occurred so far in our series although this catastrophe has been observed in another patient 2½ years after a pituitary stalk section was performed elsewhere.

CASE 23.—A 34-year-old diabetic was referred for assessment in May 1965, when initial visual acuity levels were 20/40 in both eyes. Extensive gliosis and new vessel formation were found along the major vessels in each eye. Hypophysectomy was advised, and while the patient was trying to make a decision she experienced sudden loss of vision in her left eye. Re-examination showed a posterior detachment of the retina with no evidence of a retinal hole and preservation of a peripheral field. Hypophysectomy was performed in June 1965 and there has been no objective change in visual status, although the patient thought her visual field improved in her poor eye. Four months after operation she continued to have symptoms of retinal irritation in her good eye, and evidence of fresh vitreous hemorrhage.

Comment: Although retinal detachment is generally regarded as a late complication of diabetic retinopathy, in this patient it had an earlier onset in an eye with good visual function.

(f) *Retinal Ischemia*

Vision loss in two patients (Cases 13 and 16) seemed to be worse than the degree of retinopathy would lead one to suspect. In these individuals a marked attenuation of the retinal arteries has been observed and many of the fine perimacular branches appear to be completely obliterated. Vision was threatened by recurrent vitreous hemorrhages in both patients and for this reason hypophysectomy was performed. It is still too early to determine whether vision can be preserved in this type of patient.

(g) *Rubeosis Iridis*

The presence of rubeosis may be overlooked when more dramatic pathology is developing in the fundus, yet the secondary glaucoma which invariably follows may quickly wipe out remaining vision. For this reason the iris should be studied regularly with a slit lamp in patients under observation for progressive retinopathy.

CASE 4.—The first patient in this series to develop rubeosis had very advanced retinopathy when stalk

section was performed in May 1963. He was not seen regularly but stated that his vision improved initially but that this was followed later by further loss, apparently due to vitreous bleeding. In November 1963 he was readmitted to hospital with acute congestive glaucoma secondary to rubeosis, and subsequently the eye lost light perception.

CASE 18.—A second patient developed acute secondary glaucoma in the left eye due to rubeosis while being assessed for pituitary surgery. The glaucoma was partially controlled by penetrating diathermy and acetazolamide (Diamox) and although this serious complication was present in one eye and vision in the remaining eye was reduced to counting fingers, hypophysectomy was performed in April 1965. Initially, his visual acuity improved in each eye and the new vessels on the surface of the iris in the left eye gradually disappeared. Although the vitreous in each eye partially cleared, the retinopathy remained active, and visual acuity decreased again in the left eye, owing to further vitreous bleeding. In addition his glaucoma became harder to control and gonioscopy showed that the residual open angle, which measured approximately 15° in April, had become reduced to two small clefts at 6 o'clock. In October, five months after hypophysectomy, a filtering operation was performed employing scleral cautery and a total iridectomy. Postoperatively, filtration was at first excessive and a choroidal detachment occurred which disappeared in two weeks as the intraocular pressures again became elevated.

Comment: These cases show that rubeosis may develop after hypophysectomy if the retinopathy remains active and is favourably influenced if the retinopathy is suppressed.

(h) *Postoperative Visual Acuity*

Visual acuity has been preserved or has improved in 47 of 50 eyes* and there has been no late reduction in visual acuity in cases followed up for more than 12 months. In one of the three eyes which deteriorated a massive vitreous hemorrhage occurred immediately after a stalk section (Case 15); a second eye developed rubeosis (Case 4); and in a third, persistent retinopathy resulted in deterioration in an eye with preoperative rubeosis (Case 18). There has been deterioration of binocular vision in only one patient. The vision in a fourth patient (Case 16), who has been followed up for nine months, has fluctuated as a result of further vitreous hemorrhages, and permanent reduction in acuity may develop. These results (Table IV) appear to indicate a significant modification of the natural course of diabetic retinopathy when consideration is given to the advanced state of the disease in the majority of patients undergoing surgery.

POSTOPERATIVE COMPLICATIONS

(a) *Surgical* (Table V)

One of the three deaths in this series was due to a parietal lobe hemorrhage shortly after a stalk

*Case 9 has been excluded.

TABLE V.—POSTOPERATIVE COMPLICATIONS

Complication	Pituitary stalk section	Transphenoidal hypophysectomy
Death.....	2 (1 cerebral hemorrhage) (1 probably hypoglycemia)	1 pulmonary embolus (late)
Cerebrospinal fluid leak.....	0	1
Meningitis.....	0	2 (1 early) (1 late)
Hypoglycemic* reactions.....	3 (2 early) (1 late)	3 (2 early) (1 late)
Diabetes insipidus	4	3
Total operations..	9	18

*Reactions requiring intravenous glucose.

section (Case 3); a second was probably due to hypoglycemia (Case 7); and a third was the result of a pulmonary embolus secondary to thrombophlebitis (Case 9). Two of the three fatalities were related to the surgical procedure. The patient who presumably died from hypoglycemia lived alone in a rooming house and had had a previous admission for hypoglycemia and convulsions. His postmortem examination revealed no other cause of death. The remaining surgical complications, including cerebrospinal fluid leak (Case 5) and meningitis (Cases 9 and 21), responded promptly to treatment. When the two surgical procedures are compared, both are equally effective and there is no appreciable difference in serious complications. The transphenoidal procedure has the advantage of exposing the pituitary gland to direct observation under the operating microscope, facilitating an immediate and complete removal. This approach may not always be feasible for anatomical reasons and it is useful to have both procedures available.

(b) Endocrine

The surgically induced pituitary insufficiency requires replacement therapy with thyroid, adrenal steroid and sex hormones, and the patient becomes sterile. Although diabetes insipidus has occurred in seven patients, only one of these has proved difficult to control. The most serious endocrine complication has been the increased sensitivity to insulin, indicated by the marked reduction in insulin requirement and the incidence of hypoglycemic reactions. Minor reactions occur commonly in the early postoperative period, and six patients required treatment with intravenous glucose for such reactions. For this reason blood sugar levels are permitted to rise to higher concentrations than usual and the patients are advised not to live by themselves. Two patients who reduced their adrenal steroid intake developed an Addisonian crisis. As 16 patients have been referred for treatment from smaller centres, a close liaison with the family doctor is essential.

(c) Morbidity

The hormonal replacement regimen appears formidable and many believe that these patients become "endocrine cripples". While it is true that a reasonable level of intelligence is necessary to manage the postoperative problems, it is surprising

how few individuals complain of the cost or nuisance. All surviving patients have returned to their former occupation, excepting three individuals whose visual acuity is inadequate. Another index of postoperative morbidity is the readmission rate to hospital (Table VI). Of the 10 readmissions, six have been necessary for the treatment of complications resulting from pituitary surgery and there does not appear to be an increasing incidence of late complications.

TABLE VI.—LATE POSTOPERATIVE MORBIDITY

Readmission diagnosis	Frequency
Meningitis.....	1
Hypoglycemia.....	2
Adrenal insufficiency.....	2
Assessment of partial ablation.....	1
Uncontrolled glaucoma.....	2
Peripheral vascular disease.....	2
Return to former occupation.....	22

ASSESSMENT OF PITUITARY ABLATION

Following surgery, patients should have a profound fall in radioactive iodine uptake by the thyroid and a reduction in insulin requirement from one-third to one-fifth of the preoperative dose. In several patients sex hormones have been withheld and amenorrhea and altered libido have been observed. In one patient (Case 8) menstrual function returned after three months and thyroid medication was stopped without complication, although withdrawal of adrenal steroid resulted in symptoms of adrenal insufficiency. This patient's retinopathy remained active for nine months, after which there was a complete remission. A second patient (Case 7) did not show the expected drop in insulin requirements although the initial radioactive iodine uptake was depressed postoperatively. Subsequently his wife became pregnant and after a period of partial remission lasting 12 months, two further episodes of bleeding have occurred and new vessel formations have persisted. Withdrawal of thyroxine did not alter the protein-bound iodine level and a recent radioactive iodine uptake was normal. Both of these individuals have had an incomplete hypophysectomy, yet one obtained a complete remission. Although no attempt has been made to assess routinely the late return of pituitary function, any patient showing persistent retinopathy after 12 months should be re-examined for evidence of an incomplete ablation.

SELECTION OF PATIENTS AND TIMING OF SURGERY

Our experience indicates that pituitary ablation should be considered in any patient showing signs of visual deterioration due to retinal hemorrhages, preretinal or vitreous bleeding, new vessel formation and gliosis. In each individual case, the need for good vision, the risk of further deterioration and the general medical status must be evaluated

and these factors must be balanced against the potential benefits and complications of surgery. Very few patients have been rejected for medical reasons and six were over 40 years of age at the time of operation. In general the younger diabetic has more to gain and the tendency is to advise operation earlier because with a longer life expectancy the chances of eventual deterioration are greater.

The timing of surgical intervention is a difficult problem requiring considerable judgment in view of the unpredictable course of any retinopathy. The chief consideration has been the demonstration of progression in the retinopathy. Although no precise indications have been devised, it is helpful to divide patients into the following categories:

(a) *Early and Late Binocular Progressive Deterioration*

Patients who show progressive binocular deterioration should have surgery performed when there has been a protracted reduction in visual acuity in both eyes. Twelve patients in our series fell within this category. When vision is seriously impaired in both eyes and fundus examination is limited, assessment becomes difficult. If a grey reflex due to vitreous fibrosis is observed, together with a history of long-standing poor vision, no improvement can be expected. If, however, visual deterioration has been of recent onset and a red reflex is present, especially in the visual axis, there may be a good response to pituitary surgery. In four patients in our series (Cases 4, 10, 18 and 26) pituitary ablation was performed when vision was seriously impaired in both eyes owing to recurrent vitreous bleeding, and visualization of the fundi was impossible. Two of the four have improved, one has deteriorated and one has not been followed up long enough for assessment. The threat to vision of further bleeding in this type of patient in the immediate postoperative period is much greater.

(b) *Monocular Deterioration With and Without Progression in the Remaining Eye*

In eight patients the degree of involvement was more marked in one eye. Where possible, these patients were observed regularly and surgery was advised when the retinopathy in the second eye had progressed, preferably before visual impairment had occurred. In two patients the involvement was almost entirely monocular. In one (Case 15) it was considered justifiable to try to save the first eye from a large preretinal clot, and in the second patient (Case 8) new vessel formation had begun in the good eye but progression had not been demonstrated. It is interesting that in Case 15 the good eye developed fresh new vessels and small preretinal clots postoperatively. This individual had large preretinal clots in the poor eye preoperatively, confirming our impression that this form of retinopathy progresses rapidly. Patients with only new

vessel formation and gliosis may be observed more safely over longer periods, but it is important to realize that while these individuals lose their vision more slowly, the loss is usually irreversible and the risk of sudden deterioration from a detachment steadily increases.

The most suitable patient is one with bilateral retinopathy which has shown evidence of progression but whose visual acuity in at least one eye has not become seriously impaired. If only one eye is involved, the operation is not indicated except under special circumstances, such as the presence of amblyopia or persistent preretinal clot formation in the poor eye. The patient with advanced binocular involvement should only be considered for operation if deterioration has been recent and a good red reflex is present.

SUMMARY

Pituitary ablation has been performed in 26 patients with advanced diabetic retinopathy, by pituitary stalk section (nine cases) or by means of a transphenoidal hypophysectomy (17 cases). Both operations appear to be equally effective. Preoperative visual acuity levels have been maintained or improved in 47 of the 50 eyes followed up for up to 12 months, and no late deterioration in vision has occurred in 10 patients followed up for between 12 and 36 months. After a variable latent period of persistent activity of the retinopathy, there has been a gradual reduction in the number of retinal and vitreous hemorrhages and new vessel formations have disappeared. Eight of the 10 patients followed up for more than a year have obtained a complete remission. One patient with persistent retinopathy after a year has an incomplete pituitary ablation. Three patients have died, two from causes related to their operation. All but three of the surviving patients have returned to their previous occupation. The progressive visual deterioration usually observed in severe diabetic retinopathy can be arrested by pituitary ablation in a high proportion of suitably selected patients. On the basis of our experience so far, the visual results appear to justify the risks and complications of such surgery.

ADDENDUM

Since preparing this paper the following changes have been noted: Vision has deteriorated in both eyes (Case 18) and the left eye (Case 23) as a result of vitreous bleeding; and a vitreous hemorrhage has occurred in the left eye (Case 12) at 15 months.

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