Interstitial gamma irradiation by $^{198}$Au of the pituitary in diabetic retinopathy

Selective growth hormone blockade and ocular results

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Pituitary interstitial irradiation by stereotaxic implantation of a gamma point-emitter was performed in 110 patients with progressing diabetic retinopathy. Reduction of growth hormone secretion peaks was delayed, but was consistent and selective in all cases controlled by somatotropin stimulation tests, while other pituitary secretions remained unchanged in all but five cases. In 31 patients who had no associated photocoagulation, long-term postoperative assessment showed significant improvement of hemorrhages and intraretinal new vessels with preservation of visual acuity. Preretinal vascular proliferation (except when treatable by photocoagulation), extensive retinitis proliferans, and macular deterioration are contraindications. This technique represents a new approach in the functional pituitary neurosurgical treatment of diabetic retinopathy and differs from all other procedures that result in a more or less complete hypophysectomy.

KEY WORDS □ stereotaxic techniques □ diabetic retinopathy □ growth hormone □ gamma irradiation □ pituitary

INTEREST in pituitary surgery for diabetic retinopathy continues since long-term efficacy of various medical therapeutic agents is still unproved, treatment by photocoagulation remains symptomatic, and growth hormone has been demonstrated to play a permissive or supportive role in the development of diabetic retinopathy.

Poulsen's well known reports6,19 led neurosurgeons to perform complete gland resection or pituitary stalk sections in diabetic retinopathy.6-8,22,32,33 Later, different methods were introduced: hypophysectomy by radioactive yttrium-90 implantation in the pituitary,8,11,44 radiofrequency or cryogenic destruction of the gland,1,10,17 transsphenoidal microsurgical pituitary excision,12-14 and transcutaneous irradiation with heavy particles.8 The ocular results showed the relationship between hypopituitarism and the improvement of progressing diabetic retinopathy.
Some data strongly suggest a direct correlation between the ocular postoperative response and the blockade of growth hormone (HGH) secretion.\textsuperscript{1,18,20,26,30,32,44} Since these conclusions result from complete hypophysectomies suppressing all pituitary secretions, a unique role of HGH cannot be accurately established. Nevertheless, it has been reported that two patients who were given small amounts of HGH while undergoing metabolic studies after complete hypophysectomy promptly developed fresh retinal hemorrhages.\textsuperscript{33}

Merimée's studies\textsuperscript{24,26} on ateliotic dwarfs are of interest. In a group of dwarfs with isolated HGH deficiency and no pituitary secretion abnormalities other than those associated with genetic diabetes, the thickness of the capillary basement membrane was measured and compared with measurements obtained in diabetic and normal subjects. Measurements were similar in controls and dwarfs, and significantly less than in diabetics. Correlated with the absence of retinopathy in dwarfs and the high incidence in the diabetic group (41%) these data are consistent with a supportive, if not causative, role of HGH in the pathogenesis of retinal lesions.\textsuperscript{25} Beaumont, \textit{et al.},\textsuperscript{5} considered that the modification of the basement membrane in diabetics was due to intracellular osmotic effects of HGH secretion bursts. These data suggest that selective HGH blockade, with all other pituitary secretions left normal, could be as efficient as complete hypophysectomy.

Development of Method

The method and dosimetry of stereotaxic pituitary interstitial gamma-irradiation (Stereo-GIHF) were developed by stages. In 20 years we have performed nearly 500 hypophysectomies for metastatic breast cancer by stereotaxic implantation of \textsuperscript{198}Au by the Talairach procedure.\textsuperscript{36,37,41} Our experience with stereotaxic surgery by means of radioactive isotopes in pituitary-secreting adenomas showed the advantage of interstitial gamma-therapy with gold-198 (\textsuperscript{198}Au) as compared to other emitters.\textsuperscript{38,46} This method can selectively block somatotropic hypersecretion in acromegaly without interfering with the regulation of other pituitary hormones.\textsuperscript{49}

The 1966 series by Talairach, \textit{et al.},\textsuperscript{39} provided new data for the neurosurgical treatment of diabetic retinopathy by the comparative study of \textsuperscript{90}Y hypophysectomy and interstitial gamma-irradiation with \textsuperscript{198}Au. At that time ophthalmological indications were not clearly defined, but data showed that stereotaxic pituitary implantations of a small piece of radioactive gold wire at a moderate dose (\(\pm 15\) mCi \textsuperscript{198}Au) in diabetic patients caused no target gland deficiency, and that long-term ocular responses were comparable with complete hypophysectomy.\textsuperscript{35} The difference between \textsuperscript{90}Y hypophysectomy and intrasellar implantation of a \textsuperscript{198}Au seed is explained by: 1) different physical characteristics of the radiation emitted by these two radionuclides; 2) different placement of the seeds in the sella; and 3) the dose-range (number of microcuries) implanted.

In the case of \textsuperscript{90}Y hypophysectomy, the biological effect is produced by a pure \(\beta\) emission of \(E_{\text{max}}\) 2.24 MeV. Although the maximum range of penetration of these \(\beta\) particles in water or soft tissue is about 11 mm, 99\% of the emission is absorbed in the first 3 mm. This extremely steep fall-off of radiation results in a clear-cut perifocal necrosis to about 2 to 4 mm from the surface of a 1-mCi seed, corresponding to the 140,000 to 200,000 rads necessary for acute pituitary necrosis.

Hypophysectomy can thus be achieved by placing 20 to 30 (1.5 \times 1.3 mm) \textsuperscript{90}Y seeds of a total activity of about 2 to 3 mCi forming an approximately spherical cluster in the center of the pituitary (Fig. 1 left).

Since 1968, the Department of Functional Neurosurgery, the Center for Metabolic Diseases, and two research groups (National Institute of Health and Medical Research) have undertaken a long-term regular collaborative study. Their technical, ophthalmological, and biological results with interstitial gamma irradiation by \textsuperscript{198}Au of the pituitary in cases of diabetic retinopathy are reported in this paper.

Materials and Methods

Clinical Material

From 1968 to 1974, 110 diabetic patients with progressing retinopathy underwent neurosurgery using the Stereo-GIHF method in the Department of Functional Neuro-
Gamma irradiation of pituitary for diabetic retinopathy

**FIG. 1.** Comparison of $^{90}$Y hypophysectomy (left) and $^{198}$Au (right) implantation. In the first case, 20 to 30 $1.5 \times 1.3$ mm $^{90}$Y seeds are placed in the pituitary. High-energy beta radiation leads to tissue necrosis in a distance of about 3 mm around the centrally placed composite source. In the second, the $1 \times 0.5$-mm gold seed is introduced in a low-median position. While low-energy beta radiation is absorbed in the first millimeter, the gland will receive rapidly decreasing, but still high, gamma doses.

Surgery. Eighty patients had ophthalmological and metabolic follow-up studies in the same center for metabolic diseases during the pre- and postoperative period. Thirty patients were not available for follow-up examinations.

**Surgical Method and Radiation Dosimetry**

**Surgical Technique.** Talairach's stereotaxic apparatus for pituitary surgery was used in all cases. The anteroinferior part of the sella floor was reached by the transnasal route, under stepwise bidirectional x-ray controls. Special care was taken to choose the optimal point for penetration of the pituitary fossa. A 1.5 mm caliber probe with a lateral opening was introduced in the pituitary without pushing back the loosely fixed periosteum. A small piece of radioactive gold wire (1 mm $\times$ 0.5 mm) was thus deposited on the midline of the gland, 1 to 2 mm above the sella floor (Fig. 1 right). Small fragments of fascia lata and muscle were introduced into the opening, and a stainless steel screw was fixed in the floor. The procedure lasted 45 to 60 minutes because of the time necessary for the x-ray controls, an indispensable factor for safety and precision.

**Gold Implantation.** A $1 \times 0.5$-mm seed of $^{198}$Au has an activity of 14 to 15 mCi. The $\beta$ radiation emitted by this isotope ($E_{\beta \text{max}}$: 0.962 MeV) is less energetic than in $^{90}$Y hypophysectomy, and is absorbed in the immediate vicinity of the seed; necrosis is limited to the first millimeter around the radionuclide. Contrarily, the surrounding tissues will receive a less rapidly decreasing gamma irradiation (0.410 MeV), the doses ($D$) of which can be calculated from the normal formula:

$$D = 2.4 \cdot \frac{Q}{P} \cdot 1.44t,$$

when $Q$ = number (mCi), $l$ = distance (cm), $t$ = half life (hours), giving the following values for total disintegration of 15 mCi of $^{198}$Au: 0.5 cm: 13,271 rads, 0.75 cm: 5900 rads, 1 cm: 3317 rads, 1.5 cm: 1474 rads, 2 cm: 829 rads, and 3 cm: 552 rads.

Thus, beyond the immediate vicinity of the seed where the combined action of beta and gamma radiation induces a limited necrotic halo, the pituitary receives a rapidly decreasing but still considerable gamma irradiation with a dose range of 14,000 to 6000 rads at the periphery of the gland depending on its actual size (Fig. 2).
This article analyzes the effect of this second type of irradiation on the different pituitary secretions.

**Evaluation of Biological Results**

The procedure of HGH stimulation in diabetic patients and the interpretation of results have already been reported. Growth hormone, thyroid stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), luteinizing hormone (LH), and prolactin were determined by radioimmunoassay as previously described. It should be recalled that HGH provocative tests are performed in a laboratory equipped for continuous automated blood glucose (BG) analysis. The procedure enables adaptation of insulin and glucose concentrations for each diabetic patient so that metabolic stimuli are reproducible in intensity (BG nadir: 50 mg/100 ml) and duration (30-minute hypoglycemia before glucose infusion so as to reach a level of 200 mg/100 ml/60 min). Postoperative results are supported by repeated annual assessments performed under identical conditions.

**Evaluation of Ocular Results**

To assess changes in retinopathy after Stereo-GIHs, the Hammersmith Grading System was used. This method described by Oakley, et al., allows a quantitative study, statistical treatment of results, and comparison with other published series. In this system each component of the retinopathy is graded into one of five grades of severity by comparing color retinophotographs with the set of standard photographs of increasing severity published by the Hammersmith group. Results are expressed in number of eyes; each eye is autocontrolled throughout the postoperative period.

**Expression of Results**

In view of the high number of pre- and postoperative tests and radioimmunoassay measurements (nearly 4000 HGH assays) the biological data were calculated using a model already described. Only three mean values will be mentioned to a controlled, reproducible hypoglycemic stimulation: $S_1$ = the last baseline value of HGH, $S_2$ = the peak of
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### TABLE 1

<table>
<thead>
<tr>
<th>Assessments*</th>
<th>Growth Hormone (HGH) Secretion (ng/ml)†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S1</td>
</tr>
<tr>
<td>preoperative assessments</td>
<td></td>
</tr>
<tr>
<td>HGH responders (59)</td>
<td>1.5 ± 0.2</td>
</tr>
<tr>
<td>nonresponders (19)</td>
<td>0.4 ± 0.1</td>
</tr>
<tr>
<td>postoperative assessments</td>
<td></td>
</tr>
<tr>
<td>0 to 12 months</td>
<td></td>
</tr>
<tr>
<td>HGH responders (19)</td>
<td>1.6 ± 0.6</td>
</tr>
<tr>
<td>nonresponders (7)</td>
<td>1 ± 0.2</td>
</tr>
<tr>
<td>13 to 24 months</td>
<td></td>
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<tr>
<td>nonresponders (38)</td>
<td>0.9 ± 0.1</td>
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<tr>
<td>25 to 36 months</td>
<td></td>
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<tr>
<td>nonresponders (28)</td>
<td>0.9 ± 0.3</td>
</tr>
<tr>
<td>37 to &gt; 60 months</td>
<td></td>
</tr>
<tr>
<td>nonresponders (27)</td>
<td>0.6 ± 0.2</td>
</tr>
</tbody>
</table>

*Figures in parenthesis indicate numbers of patients tested.
†S1 = last baseline value of HGH; S2 = peak of HGH; ΔHGH = the gradient (S2–S1) of the HGH response. Values are mean ± standard error.

HGH, Δ HGH = the gradient (S2–S1) of the HGH response.

The means variance and standard error of the mean (SEM) of each parameter in each group of biological and ophthalmological data were calculated. The Student t-test was used for comparing groups with a significance threshold of p < 0.05.

### Results

#### Complications

In this series of 110 patients, there were no cases of rhinorrhea, meningitis, traumatic injury, or radiolesion of the chiasm or the optic and oculomotor nerves, and no diabetes insipidus. Three aged patients suffered complications: one had pulmonary embolism after perfusion in a thrombosed vein, one had anuria with Kimmelstiel-Wilson syndrome, and one had an infarct at the beginning of anesthesia, causing suspension of the surgical procedure.

#### Endocrine Results

**HGH Secretion.** In the preoperative period the pattern of somatotropin secretion was not simple. Previously published data strongly suggest an inconsistent temporal regulation. Identical hypoglycemic stimulations controlled by continuous automated BG analysis showed inconsistent HGH responses as a function of time in repeated tests: in about 50% of cases, normal responders become nonresponders and vice versa (Table 1). For the postoperative results only the biological data of patients studied with several long-term tests after Stereo-GIHF (Table 1) will be considered.

The postoperative course shows two periods. In the first 12 months, two different response patterns were still present, with nonresponders in nearly 35% of cases and responders in the remainder. In this period it is difficult to discriminate between the effect of the radiobiological action of Stereo-GIHF and that of the inconsistent HGH secretion pattern. Growth hormone was consistently unreactive in the group of postoperative tests performed 13 to 24 months following Stereo-GIHF (Δ HGH: 3.3 ng/ml ± 0.6). After a follow-up period of 25 to 36 months, all patients were nonresponders (Δ HGH: 2 ng/ml ± 0.7). These results were seen clearly at 37 to 46 months (Δ HGH: 1.9 ng/ml ± 0.4) and at 49 to more than 60 months (Δ HGH: 1.5 ng/ml ± 0.3).

These data show that the radiobiological action of interstitial gamma irradiation is progressive, appearing after a variable period of at least 12 months on an average, and continuing consistently after this first period. The Δ HGH values evidence the long-term sup-
C. Sehaub,

**TABLE 2**

<table>
<thead>
<tr>
<th>Postoperative Assessments</th>
<th>Growth Hormone (HGH) Secretion (ng/ml)†</th>
<th>‡AHGH</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.5 to 15 mCi (56)</td>
<td>0.55 ± 0.2</td>
<td>2.8 ± 0.7</td>
</tr>
<tr>
<td>15 to 16 mCi (13)</td>
<td>0.7 ± 0.1</td>
<td>2.5 ± 0.7</td>
</tr>
<tr>
<td>16 to 17 mCi (14)</td>
<td>0.6 ± 0.2</td>
<td>2.3 ± 0.6</td>
</tr>
<tr>
<td>17 to 18 mCi (10)</td>
<td>0.6 ± 0.2</td>
<td>2.3 ± 0.6</td>
</tr>
</tbody>
</table>

*Assessments in the period beginning at 13 months postoperatively.
†Figures in parentheses indicate number of patients tested.
‡S1 = last baseline value of HGH; S2 = peak of HGH; AHGH = the gradient (S2−S1) of the HGH response. Values are mean ± standard error.

pression of HGH peaks during provocative tests. Mean baseline HGH values are lower than 1 ng/ml in all groups from the 13 to 24 months period and onward.

The comparative study of Δ HGH levels from 13 to more than 60 months according to the activity of the gamma source is summarized in Table 2. There is no significant HGH difference in the dose range used (13.5 to 18 mCi). In the postoperative group no patient underwent a second operation.

Other Pituitary Secretions and Target Glands. These results are reported in detail elsewhere. Endocrine substitution therapy was unnecessary except in five aged diabetic patients with postoperative pituitary insufficiency. In the remaining patients, controlled hypoglycemic tests after 12 months with simultaneous study of corticotropic and somatotropic reactivity showed normal ACTH and/or cortisol secretion in contrast with absence of HGH response. All postoperative studies of TSH and prolactin responses after thyroid-releasing hormone (TRH) were normal. The results of radioactive iodine uptake and metyrapone tests of mean secretion levels in target glands in 46 patients were as follows: In 46 tests the mean preoperative adrenocortical response to metyrapone (17 OH-CS mg/24 hr) was 4.7 ± 0.2 on the first day, 12.8 ± 1.1 on the second, and 20 ± 1.8 on the third. More than 12 months postoperatively and in controls, in 91 tests it was 4.4 ± 0.2 on the first day, 9.2 ± 0.6 on the second, and 17.2 ± 0.9 on the third. Mean values for 17-ketosteroids were 8.1 ± 0.4 mg/24 hr in 46 tests preoperatively, and 9.1 ± 0.5 mg/24 hr more than 24 months postoperatively and in controls in 91 tests. The mean preoperative thyroid-iodine uptake (% I\(^{131}\)) in 46 tests was 4.8 ± 0.7 at 1 hour, 16 ± 1.2 at 4 hours, and 34 ± 1.6 at 24 hours. More than 12 months postoperatively and in controls, in 91 tests it was 5 ± 0.35 at 1 hour and 13.5 ± 0.65 at 4 hours.

Three pregnancies reached term 2 to 3 years after surgery, without any retinal postoperative deterioration. There was no significant modification in menstrual cycles of young women with long-term postoperative follow-up studies.

Postoperative Control of Diabetes. It is well known that the control of diabetes and the insulin requirements can fluctuate widely in the same patient and vary from one diabetic patient to another. To study the effect of Stereo-GIHF on insulin requirements, we selected a homogeneous group of diabetic patients whose preoperative glycemia levels were similar and consistent (150 mg/100 ml to 200 mg/100 ml), who maintained the same body weight, who needed the same type of insulin during pre- and postoperative follow-up studies, and who had a postoperative growth-hormone blockade controlled by at least two hypoglycemia tests.

The data in this group of 17 patients (nine men, eight women) who had had multiple and long-term glycemia controls (2 to 5 years) were compared with the results in three
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TABLE 3

Pre- and postoperative insulin requirements in diabetic patients with selective HGH blockade compared with three cases of postoperative hypopituitarism

<table>
<thead>
<tr>
<th>Postoperative Selective HGH Blockade*</th>
<th>Postoperative Pituitary Insufficiency†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regular Insulin</strong> (unit/day)</td>
<td><strong>Regular Insulin</strong> (unit/day)</td>
</tr>
<tr>
<td>18.4 ± 2.4</td>
<td>24.0 ± 4.1</td>
</tr>
<tr>
<td>27.0 ± 2.6</td>
<td>35.2 ± 2.9</td>
</tr>
<tr>
<td>64.8 ± 2.1</td>
<td>68.7 ± 3.4</td>
</tr>
<tr>
<td><strong>Long-Acting Insulin</strong> (unit/day)</td>
<td><strong>Long-Acting Insulin</strong> (unit/day)</td>
</tr>
<tr>
<td>22</td>
<td>9</td>
</tr>
<tr>
<td>22</td>
<td>9</td>
</tr>
<tr>
<td>22</td>
<td>9</td>
</tr>
<tr>
<td><strong>Body Weight</strong> (kg)</td>
<td><strong>Body Weight</strong> (kg)</td>
</tr>
<tr>
<td>64.8 ± 2.1</td>
<td>68.7 ± 3.4</td>
</tr>
<tr>
<td>2 to 5 yrs after Stereo-GIHF</td>
<td></td>
</tr>
<tr>
<td><strong>No. of controls</strong></td>
<td><strong>Mean values ± standard error in 17 patients.</strong></td>
</tr>
<tr>
<td>22</td>
<td><strong>NS</strong></td>
</tr>
<tr>
<td>22</td>
<td><strong>NS</strong></td>
</tr>
<tr>
<td>22</td>
<td><strong>NS</strong></td>
</tr>
<tr>
<td><strong>Student t-test</strong></td>
<td><strong>p &lt; 0.001</strong></td>
</tr>
<tr>
<td>NS</td>
<td><strong>p &lt; 0.001</strong></td>
</tr>
<tr>
<td><strong>Student t-test</strong></td>
<td><strong>NS</strong></td>
</tr>
</tbody>
</table>

*Mean values ± standard error in 17 patients.
†Mean values ± standard error in three patients.

Table 3 shows that in the group with selective HGH blockade there is no significant difference between the insulin requirements before and after Stereo-GIHF. These data suggest that in insulin-dependent patients the isolated suppression of the somatotropic-secretion peaks does not modify the previous control of diabetes. On the contrary, in three cases of postoperative hypopituitarism the insulin requirements are dramatically reduced (Table 3).

Ocular Results. Ocular response to Stereo-GIHF was evaluated in 31 operated diabetic patients with regular assessments for at least 3 years by the same ophthalmologist in the same diabetes center without associated laser photocoagulation. In accordance with the Hammersmith Grading System, ocular data are expressed in number of eyes. Three patients had unilateral blindness before Stereo-GIHF so only 59 eyes were included. The preoperative assessment shows three different groups, according to the severity of retinopathy components. The postoperative changes in the three groups are shown in Figs. 3 to 5.

In Group 1 (Fig. 3) microaneurysms and hemorrhages significantly improved from a mean grading value of 3.5 to 1.9 at the 3-year assessment following Stereo-GIHF, and from Grades 4 to 2 in the 5-year group. In this group, there were no new vessels, retinitis proliferans, or vitreous hemorrhages, and

Fig. 3. Group 1. Ocular response before (hatched bar), and after (white bar) Stereo-GIHF in 20 eyes in patients with vascular proliferative diabetic retinopathy. Mean age of patients = 48.5 ± 2.6 yrs. *** = p < 0.001. Left: Hemorrhages and microaneurysms. Right: Visual acuity.
visual acuity was maintained (mean value 6/10 ± 0.6) without any severe deterioration after long-term follow-up studies.

Group 2 (Fig. 4) is of particular interest. These eyes had background retinopathy and new vessels arising from the optic disc but generally remaining intraretinal (flat) and not accompanied by connective tissue. The postoperative response of microaneurysms and hemorrhages was similar to that of Group 1. There was a marked and significant regression of new vessels with mean grading values from 2.4 to 1 at the 3-year assessment and from 2.6 to 0.3 at the 5-year study. Minor fibrotic preoperative lesions did not increase and visual acuity remained stable as seen in Group 1.

Group 3 (Fig. 5) is characterized by preretinal or intravitreous new vessels (mean value: Grade 3.5) with more extensive retinitis proliferans (mean value: Grade 2) than in Group 2. In all cases macular vision was already poor (mean value less than 2/10). The diagram shows irreversible progression of retinitis proliferans. Visual acuity deterioration is caused by either fibrotic lesions over the posterior pole and vitreous hemorrhages (nine eyes), or extensive macular degeneration (11 eyes).

**Discussion**

Operative Complications

Neurologically, the main finding in this series of 110 pituitary stereotaxic operations using the Stereo-GIHF is the absence of immediate and/or late neurological, ocular, and metabolic complications. In this respect our results differ from all other published data concerning pituitary neurosurgery in diabetes. The study of Ray, et al. compares pituitary resection through transfrontal craniotomy in 56 patients and hypophys-
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Fig. 5. Group 3. Ocular response before (hatched bar), and after (white bar) Stereo-GIHF in 20 eyes in patients with fibroproliferative diabetic retinopathy and/or previous vitreous hemorrhages and severe macular deterioration (microcystic degeneration of the macula). The latter lesion is generally evident in elderly diabetic patients. Mean age of patients = 57 ± 2 years. * = p = 0.05 to 0.01, ** = p = 0.01 to 0.001, *** = p < 0.001. Upper Left: Hemorrhages and microaneurysms. Upper Right: New vessels. Lower Left: Fibrous retinitis proliferans. Lower Right: Visual acuity.

Operative complications in the large series of yttrium hypophysectomy performed by the Hammersmith Hospital group for diabetic retinopathy were discussed in 1971. In that series of 107 patients undergoing surgery, there were 24 cases of fistula, 10 of meningitis, 18 of diabetes insipidus, and three deaths caused by hypoglycemia. The risk of operative complications seems much smaller in cryophysectomy and transsphenoidal microsurgical pituitary resection introduced by Hardy and Ciric.

The pathophysiological goal of Stereo-GIHF in diabetic retinopathy is to induce a selective blockade of HGH secretion. Although complete hypopituitarism is the aim of all other procedures, we consider even partial pituitary insufficiency a complication of Stereo-GIHF. In our series of 110 cases we observed five cases of pituitary insufficiency in aged diabetic patients.

The literature on pituitary pathology in diabetes was reviewed in 1967 by Kerkhoven and Hedinger. As in previous postmortem findings, this study shows that, in diabetes, pituitary partial destruction due to recent necrotic lesions or several fibrotic foci may not be recognized by clinical observation, and endocrine functions may remain unaltered. In other words, in diabetic patients, even with a very low-risk procedure such as Stereo-GIHF, the neurosurgeon operates on pituitary glands that possibly suffer from long-term metabolic angiopathy.
FIG. 6. Microanatomical stereotaxic sections of the human pituitary fossa. **Left:** Sagittal sections with locator holes. 3 mm left from the midline: anterior and posterior lobes (a); midline anterior and posterior lobe, and pituitary stalk section (b); and 3 mm right from the midline: anterior lobe only due to asymmetric lateral development (c). **Right:** Horizontal sections with locator holes. Section zero: pituitary stalk section in midline (d); section 5.5 mm below section zero: anterior and posterior lobes (e); and section 7.5 mm below section zero: asymmetric lateral development of anterior lobe (f).

**Radiobiological Mechanisms**

After the Stereo-GIHF procedure (except for the five previously discussed cases) our data show a selective and consistent radiobiological action at the level of the somatotropic axis. We reported the selectivity of interstitial gamma irradiation on somatotropic hyperpituitarism in acromegaly.\(^{35,36}\) In a normally secreting pituitary, the endocrine consequences following Stereo-GIHF strongly suggest that the radiosensitivity of somatotropic cells is distinctly greater than that of other pituitary cells.\(^{36}\) The selective blockade of HGH correlated with ocular response brings new evidence for the supportive role of growth hormone and/or other still unidentified radiosensitive subcellular factors in diabetic retinopathy.

The consistency and reproducibility of radiobiological HGH blockade following Stereo-GIHF has to be compared with results of \(^{90}\)Y hypophysectomy and parallel suppression of growth-hormone secretion by this procedure. Fraser, et al., reported on the endocrinological results of \(^{90}\)Y hypophysectomy in 45 patients with diabetes;\(^{11}\) pituitary ablation was complete in 20 cases, and in the remaining 25 with intermediate or slight ablations, the HGH suppression was inconsistent and diabetic retinopathy generally not improved. Adams and co-workers\(^{1}\) reached conclusions consistent with these data in a recent report on the relationship between pituitary ablation degrees and ocular responses following cryohypophysectomy. In 28 patients, 17 cryoablations were considered complete (with HGH suppression); six were partial, and five minimal with favorable ocular response only after complete cryohypophysectomy.

Our stereotaxic method insures the orthogonal alignment of basisphenoid bone sections in the three planes using a stereotaxic frame for anatomic localization studies with double horizontal and vertical grids. The diaphragma sellae is marked with a radiopaque substance; the pituitary stalk defines the midline. Three parallel locator needles are introduced under x-ray control according to the chosen plane. The specimen is decalcified, enclosed in celloidin, and aligned on the microtome according to the stereotaxic orthogonal planes.

Inconsistent pituitary ablations may be explained by the presence of a frequent asymmetric lateral and anteroposterior development of the gland. Sagittal, horizontal, and verticofrontal sections give examples of lateroposterior asymmetric rotation of the pars distalis (Figs. 6 and 7). X-ray skull films do not provide precise information on these anatomic variations, therefore comparable yttrium implantation or cryoablations may be followed by different degrees of pituitary destruction. The Stereo-GIHF procedure provides a solution to this problem. With gamma interstitial pituitary irradiation, the whole gland will be irradiated together with the supradiaphragmatic pars tuberalis, so that anatomical variations do not play a significant role (Fig. 2).
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Our data indicate a selective and reproducible radiobiological action of Stereo-GIHF on the somatotropic axis, after variable delays. These results contrast with inconsistent effects of yttrium hypophysectomy or cryoablation and postoperative panhypopituitarism after microsurgical resection.

Ocular Results

Three points will be discussed: the consequences of delayed radiobiological results, the response to Stereo-GIHF in progressing but not proliferative retinopathy, and the problem of neovascularization in proliferative retinopathy.

For the discussion of ocular response, patients treated only by Stereo-GIHF without laser photocoagulation were selected. The preoperative and 6-month postoperative assessments show no distinct improvement regardless of the retinopathy component or group considered. This seems consistent with the delayed Stereo-GIHF effect. Except for fibroproliferation, improvement became significant in Groups 1 and 2 only after a mean period of 12 months. These results suggest that this procedure should be performed earlier in the course of the disease as compared to hypophysectomy.

Marked improvements in Group 1 (rapidly progressing background retinopathy without proliferative components and/or macular degradation) support the long-term benefit of early intervention. In this series Stereo-GIHF appears as a suitable prophylactic treatment, preventing the probable evolution to proliferative neovascularization, vitreous hemorrhages, retinitis proliferans, and loss of visual acuity. Similar results are obtained by complete or partial hypophysectomy but with polyendocrine and metabolic consequences.

The main interest of Group 2 is the highly significant postStereo-GIHF regression of proliferative retinopathy without associated photocoagulation. New vessels arising from the optic disc (in most cases still remaining "flat") showed a marked improvement (preoperative grading mean value, 2.5; 5-year mean value 0.3). These data are in agreement with ocular responses following complete hypophysectomy in other reports. Wright, et al., Fraser, et al., and Kohner, et al., showed in a total of 28 eyes that hemorrhages improved from 1.8 to 0.8 and new vessels from 1.7 to 1 (according to Oakley's Hammersmith Grading System) at the 1-year assessment after complete pituitary ablation. In our patients with more severe ocular lesions new-vessel regression following Stereo-GIHF was comparable with a longer postoperative follow-up period. Other reports by the Hammersmith Hospital team describe the responses of new vessels arising from the optic disc after various degrees of pituitary ablation. In a group of 28 eyes assessed 3 years postoperatively, new vessels showed a significant improvement after complete ablation, with only slight progression of retinitis proliferans and maintained visual acuity. After "intermediate" ablation new vessels evolved to fibroproliferation and/or vitreous hemorrhages in 55% of cases and in all cases following "slight" hypophysectomy. As already stated, only complete ablation
confers maximum benefit by this procedure. Also Krieger, et al.,17 reported that complete cryohypophysectomy was necessary for ocular improvement. Adams, et al.,1 concluded that such improvements required complete cryoablation. Others4,20,45,46 have reached the same conclusion.

In brief, the new vessel response to Stereo-GIHF is at least equivalent to results after complete hypophysectomy and appears distinctly superior to incomplete, partial, or slight pituitary destruction. In the Hammersmith Hospital series, as in this series, these results exclude preoperative progressing fibroproliferation, macular degradation, and bilateral poor visual acuity (less than 2/10).

The disappointing results in Group 3 are also in agreement with the literature. New-vessel lesions with distinct retinal forward progression, accompanied by vitreous hemorrhages and widespread retinitis proliferans or macular modifications, are not influenced even by complete hypophysectomy.11,22,23,28,33 These findings are reported by most surgeons whether the neurosurgical procedure was open craniotomy,22,23 transsphenoidal microsurgical excision,1,14 cryoablation,1,17 or 90Y implantation.8,11,20 The results in Group 3 suggest that Stereo-GIHF is contraindicated in these cases.

For the past 3 years a separate group of 26 patients has received a combined Argon laser treatment before and/or after Stereo-GIHF. This method offers the opportunity to control a dramatic evolution of progressing new vessels by symptomatic therapy during the first postoperative year, until HGH blockade becomes effective. At present, long-term assessments are not sufficient for adequate statistical study of this combined treatment group, but for the future it should be the solution in rapidly progressing proliferative retinopathy in young diabetic patients.

Conclusions

A progressive, selective, and consistent blockade of HGH secretion results from Stereo-GIHF in most cases with an average delay of 12 months, without loss of other pituitary secretions. In this respect Stereo-GIHF differs from other pituitary ablation methods in diabetic retinopathy. Medical contraindications such as renal and coronary disease and cerebral vascular insufficiency, are the same for Stereo-GIHF as for hypophysectomy. Selective HGH blockade requires no substitution therapy and does not modify the control of diabetes. Ophthalmological contraindications include preretinal or intravitreous new vessels, progressing fibroproliferation, and macular modifications (microcystic macular degeneration) with poor visual acuity.

Stereo-GIHF is indicated in rapidly progressing diabetic retinopathy threatening visual acuity by increasing retinal hemorrhages and/or evolving intraretinal new vessels.

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References

Gamma irradiation of pituitary for diabetic retinopathy


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