Surgical Ablation of the Pituitary in the Treatment of Diabetic Retinopathy*

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Pituitary ablation has been found to arrest and reverse the course of progressive diabetic retinopathy in some patients. That improvement of vision can be maintained for several years has now been demonstrated by Pearson et al.,17 by Poulsen's original case of postpartum hypopituitarism in a diabetic woman,18 and by other reports.7,12 It is still not clear how best to produce hypopituitarism in the severe diabetic with advancing retinopathy, or which patients to select for pituitary ablation.

Diabetic retinitis involves mainly small vessels and is unlike the disease commonly found in medium-sized arteries of the diabetic. At times, diabetic retinopathy of the proliferative type is self-limited and spontaneously enters a "healed" phase, during which the acute changes subside and scarring occurs.2 This may take place without complete loss of vision or, in fact, with some preservation of useful vision in at least one eye. Thus, the decision to recommend pituitary ablation for any particular patient must rest largely upon the combined experience of the internist and ophthalmologist. Observations of large numbers of diabetic patients have at least improved the accuracy of predicting which patients may progress to inevitable blindness and should be considered for a pituitary procedure early enough in their course to preserve useful vision.

Earlier reports on total hypophysectomy by Luft et al.,15 Ray,19 Kinsell20 and Javid et al.13 substantiated the initial improvement in some instances. They also emphasized the critical problems such as hypoglycemia, associated with surgical hypopituitarism at that time.

Pituitary Stalk Section

Field and his associates5,9-11 have indicated in several reports that section of the hypophysial stalk alone has been adequate to arrest the advance of retinal disease in half of their patients and to retard it in many others. Their surgical technique involves placing a dome of gold foil over the sella presumably to prevent re-establishment of the hypothalamo-hypophysial portal system. Their hope was that a favorable therapeutic result could be achieved by stalk section that would avoid some of the dreaded complications of total hypophysectomy. The rapid onset of improvement in the eyes in some patients following pituitary stalk section has raised the question whether some factors of hypothalamic origin might have been eliminated or altered in addition to the obvious ischemic effect upon the anterior lobe. It is a tempting theory, since section of the hypophysial stalk is a relatively simple procedure.

However, many conflicting and inconsistent reports have appeared in the literature concerning the effect of pituitary stalk section. Connolly and Connell4 reported on 3 glands studied following very low sections. One showed 75 per cent necrosis of the anterior lobe, the second 20 per cent, and in the third, no visible necrosis could be seen. McConnell,15 in studying the arterial supply of the pituitary, described the "loral" arteries which brought a collateral flow of arterial blood into the anterior lobe. Russell20 attempted to reconcile the divergent results, suggesting that very low section of the stalk, which included all of the superior hypophysial system, should produce extensive necrosis of the gland.

Xuereb et al.21,22 in their classical study of
the arterial and venous circulation of the pituitary, showed that there is, in fact, no direct arterial supply to the anterior lobe. The "loral" arteries (arteries to the trabecula) pass through the anterior lobe in their course toward the lower infundibular stem where, through a capillary network, blood then drains into the long and short hypophysial portal systems, and then distally into the sinusoids of the anterior lobe (Fig. 1). Daniel et al. and Adams, working with the same group, subsequently gave further evidence of the massive necrosis that can occur in the anterior lobe following low stalk section which transects the long portal system. Though there have been many arguments regarding the direction of blood flow in the portal systems, it seems quite conceivable that after obliteration of one end of these systems at the stalk, blood may at times assume an afferent or "backward" flow into part or all of the anterior lobe from surrounding venous sinuses.

**Degree of hypopituitarism necessary.** It is not yet known what degree of hypopituitarism is necessary to reverse the process in diabetic retinopathy permanently, nor does it seem possible at present to measure accurately the degree of hypometabolism which may follow a particular surgical or radiation procedure. A sudden, severe hypometabolic state will alter the insulin requirement of the diabetic patient clinically just as in Houssay's hypophysectomized, pancreatectomized animals. More important, it can rapidly effect cessation of retinal and preretinal hemorrhages, prevent further neovascularization, and at times even bring about vitreous clearing. The effectiveness of treatment may be enhanced by the hypometabolic state produced, and it is toward this end that surgical endeavors have thus far been directed. Our experience has been that simple division of the hypophysial stalk may at times compromise most of the blood supply to the anterior lobe and can be quite effective, but does not produce hypopituitarism consistently and cannot always be
Pituitary Ablation for Diabetic Retinopathy

Fig. 3. Postmortem specimen 3 weeks after pituitary stalk section. Section through anterior lobe shows marked central necrosis on one side, at least half of the lobe remaining viable.

relied upon to provide lasting improvement in diabetic retinopathy.

The pituitary gland shown in Fig. 2 tends to confirm this view. This is a postmortem specimen obtained 3 weeks after what appeared to be complete section of the pituitary stalk. The section illustrated is a horizontal one through the anterior lobe and it is evident that ischemic necrosis involves only half of this anterior lobe; the zone of infarction is surrounded by a peripheral rim of viable cells. The remaining half of the lobe appears almost normal and must certainly have been functional.

The diabetogenic action of the anterior lobe has been confirmed by numerous investigators and has been clinically demonstrable in patients with acromegaly. Anterior pituitary lobe extract counteracts the action of insulin and can produce diabetes in normal mammals. This so-called diabetogenic factor (primarily growth hormone) appears to be an important element in the perpetuation of progressive retinopathy.9

While the effect upon circulation within the anterior lobe after section of the stalk at or below the diaphragma cannot always be predicted, there is reasonable certainty that higher sections of the stalk will have no effect at all. Indeed, section of the pituitary stalk at a high level has usually produced diabetes insipidus without producing hypopituitarism or any apparent change in the course of retinopathy.

**Total Hypophysectomy**

In a number of our early operations in which only the stalk was sectioned (low section), there was an occasional patient who continued to menstruate or showed little if any evidence of hypopituitarism. In an attempt to produce some consistent degree of infarction, a portion of the gland was then excised with the hypophysial end of the stalk following very low section in the hope of producing moderate pituitary insufficiency. Since the severe diabetic is sometimes a poor operative risk, a short operation was considered desirable and an attempt at total hypophysectomy was not always deliberately made. At times, however, the gland was more accessible and in some cases practically total ablation was accomplished. It must be appreciated, however, that unless the entire gland is removed in one piece by the surgeon, skilled though he may be in hypophyssal surgery, he cannot be certain that he has produced permanent hypopituitarism, and so prevented recurrent retinal hemorrhages. It is our impression at present that the more complete surgical procedures may prove in time to be more effective than simple stalk
section. During the last few years, experience with anesthesia, postoperative management and improvements in surgical technique have made it possible to carry out hypophysectomy or subtotal hypophysectomy with very little, if any, greater risk to the patient than simple pituitary stalk section.

Since early 1961, more than 60 patients have undergone some form of surgical ablation, most of these from the Joslin Clinic and 6 patients from the diabetes service of the Lahey Clinic. However, only 52 patients have had follow-up study for more than 6 months after operation. Those of the group who have not been observed for at least 6 months after operation are not included.

**Surgical Management by Hypophysectomy**

The standard frontal approach to the pituitary gland has been made, utilizing spinal drainage, hyperventilation, and positioning of the head to provide easy retraction of the frontal lobe through a small craniotomy. Dehydrating agents are not used. In cases in which the optic nerves are short and the chiasm is in a forward position, the pituitary stalk entering the hypophysis from behind and beneath the chiasm does not always come into view when the chiasmatic cistern is opened; it can be drawn forward with a small insulated nerve hook pressed tightly against the diaphragma. When the space anterior to the chiasm is extremely small, then the tuberculum is removed after incising the dura, the sphenoid sinus is opened, displacing the mucosa anteriorly and downward, and the posterior wall and anterior part of the roof of the sinus are excised to expose the gland. The stalk is sectioned very low, not only to destroy the arterial blood supply in the "lateral" arteries and the portal systems, but also to preserve the mid and upper portions of the stalk, damage to which by traction or contusion may result in prolonged diabetes insipidus. Even with this in mind, some of the patients have a transitory polyuria from the 2nd to the 4th or 5th postoperative day.

The frontal craniotomy has generally been performed on the side corresponding to the blind eye or the one more severely impaired, although there has been no instance of significant nerve or chiasmal damage during operation. At the present time, as much of the gland is removed as possible after freeing it by blunt dissection from the anterior and posterior confines of the sella. Care is taken to avoid the "circular" or coronal venous sinus, bleeding from which makes evacuation of the sella difficult. No destructive or radioactive material has been used. In those few cases where it has been necessary to open the sphenoid sinus, large pledges of muscle have been packed into the sinus to prevent rhinorrhea. Careful dissection within the sella, exposure provided by a lighted retractor, and the use of an insulated cautery-suction have been important factors in preventing damage to the cavernous sinus and the optic nerves.

**Selection of Patients**

Scattered through the entire group of patients who have undergone either stalk resection or hypophysectomy are those who showed no arrest of retinopathy or improvement of vision but did show slowly progressive deterioration of what little vision they had before operation. As with any procedure of this type, the psychological and emotional demands have, at times, been great when blindness seemed imminent or inevitable. It is now abundantly clear that patients who have far-advanced retinopathy, marked by extensive proliferative change without macular vision in either eye cannot possibly benefit from pituitary ablation. It also seems possible that there are some cases of retinal vascular disease upon which the pituitary may exert no control, and even total abolition of the so-called diabetogenic factor or growth hormone may not arrest the process.

In some of those whose vision remained unchanged after surgery, the retinopathy appeared clinically improved but the damage had already been done. Experience has indicated the need to place great emphasis upon the ophthalmologist's evaluation of whether a macula may be salvaged. Serial retinal photographs and study of the patients before and after operation are now leading to a better selection of cases. Small areas of a recent hemorrhage or new vessel growth may regress, but extensive collagen deposit and macular scarring is hopeless. Operating on very early cases will yield a high percentage of excellent results but may subject a number of diabetics to hypopituitarism unnecessarily. For this reason it is still our practice
to reserve the procedure for those patients with clearly progressive retinopathy which continues to advance despite the best possible medical control of diabetes.

Results of Stalk Section

Early results suggested that even pituitary stalk operations held more hope of preserving vision than optimum medical management for a comparable group of patients who were not subjected to any pituitary ablation. One of us, S.R., compared the results in 39 such medically treated patients with those in 33 patients who had excision of the stalk or partial hypophysectomy. In the medical group, vision improved in only 3 and retinopathy was arrested in 8; among the surgical cases, vision improved in 17 and retinopathy was arrested in 6. However, these patients had been observed from 6 months to 2½ years, with an average follow-up of only 14 months. Initial enthusiasm for such limited surgical procedures has waned, since a number of those who had improved have subsequently regressed and their acuity had not been maintained at 20/70, the standard we have set for useful vision.

Almost without exception, in those patients who experienced early improvement manifested by resorption of hemorrhage and then regression as shown by recurring hemorrhages and vision failing again, there was clear evidence of restored pituitary function. This was associated in some with return of menses, and in others with changes in blood protein-bound iodide and radioactive iodine uptake determinations. The most consistent finding was an increased insulin requirement, the dosage of insulin gradually approaching that required before operation.

There is no evidence to suggest that this has occurred because of regeneration of the pituitary stalk. In fact, it appears quite unlikely that regrowth of the stalk itself is possible in the human. Although adequate data are not yet available to support this impression, it may well be confirmed by future studies. Dissection of the gland of 1 patient who died 2 years after stalk section disclosed that, in this length of time at least, there was no gross or microscopic evidence of regeneration and no revascularization of the arterial or portal circulation of the hypophysis. It seems more likely that the

Fig. 3. Difference between stalk excision (A) and hypophysectomy (B) is shown. Shaded area represents anterior lobe. Small adherent fragments may remain even with presumed total removal.

initial zone of infarction after stalk resection may shrink in some pituitary glands as viability of residual anterior lobe tissue improves.

Even among some of the patients operated on more recently, when it was felt that a large amount of gland was removed, there were those who sometimes showed dramatic early improvement, then later regression coincident with evidence of some pituitary function. This testifies to the surprising ability of a small fragment of gland to assume at least some function.

Hypophysectomy vs. Stalk Section

It is still too soon to make a satisfactory comparison of results of pituitary stalk resection and hypophysectomy, among all the patients who have come under our observation (Fig. 3). At present, however, data lend support to the clinical impression that the latter procedure may be more consistently effective. In Table 1 the results of pituitary stalk operations in 29 patients, in some of whom a small amount of gland was removed, are compared with the results in 23 patients who had undergone total or subtotal hypophysectomy. While the percentage of improved cases is clearly greater in the latter group, the follow-up periods are not comparable. Yet the 10 patients who have maintained improvement, a few for as long as 4 years after stalk surgery, have retained the initial hypopituitarism which followed surgery. Their insulin dosage varies from one-fourth to one-half of the preoperative levels and they require substitution therapy, in some cases including testosterone and thyroid as well as cortisone. Several of the 12 patients in this group whose vision
deteriorated had initial improvement followed by regression, and these all showed evidence of restored pituitary function. It is for this reason that the comparison may well be valid. During the last 6 months, 10 additional patients (not included) have undergone hypophysectomy, with dramatic early changes in at least 7. Although several years will yet be required for an adequate evaluation, the clinical impression is that an abrupt and severe hypopituitarism is more likely to result in rapid disappearance of hemorrhages and new vessel formation, and at times very early vitreous clearing.

Mortality

Table 2 indicates the mortality in the entire group of surgical cases to date. One operative death occurred 21 days postoperatively from frontal lobe infarction and edema. Two patients have succumbed to systemic disease, one as a result of myocardial infarction 3 months after operation, and the other from renal disease 2 years later. Neither of these obtained any improvement in their retinal disease. Death in 2 cases (7 months and 12 months after operation) was considered the result of adrenal failure. This conclusion was reached after survey of clinical data from the hospitals in which the patients died, and pathologic study of the adrenal glands of one patient. The other patient died 3 days after the onset of severe untreated upper respiratory infection. Both of these patients had shown improvement in their vision and their untimely deaths have emphasized the importance of close medical supervision, particularly during a period of infection or other illness.

Medical Management

Experience in evaluating these patients particularly from the medical standpoint and following their progress after operation has demonstrated the need for a well-organized team effort under the close supervision of a metabolic service or diabetic unit which will watch over every detail of the patient’s insulin, fluid, electrolyte, and steroid requirements. Very careful observation of these patients before and after surgery has been the major factor in their recovery, especially for those cases in which a more extensive pituitary operation was performed. Cortisone replacement dosage is kept as low as possible. It is reduced soon after surgery to lessen its hyperglycemic effect and the degree of temporary diabetes insipidus and also to take the fullest possible advantage of the hypopituitary state. A single 50 mg. dose is given on the night preceding surgery, 150 mg. during the day of operation, then gradual reduction to 25 mg. or 12.5 mg. by the end of the 1st week.

Pitressin is practically never used since the polyuria is invariably temporary. Intravenous fluids have been given when necessary to maintain balance, but a slight degree of dehydration seems favorable in the first 3 or 4 days after operation. Cerebral edema must be avoided and has to be kept in mind throughout the operative period.

When the hypometabolic state begins to develop fully in about 7 to 10 days, insulin dosage drops to about one-fourth or one-half its previous level and particularly careful observations of blood sugar and clinical state must be made to avoid hypoglycemia. In some patients at this time, there is also a tendency toward hyponatremia with in-
increased urinary excretion of salt, requiring salt substitution and occasionally 9-alpha-fluoro-hydrocortisone.

As a result of the medical and surgical experience, certain criteria have evolved for the selection of diabetics suitable for operation. The retinopathy should be so severe that it is progressing despite good control of the diabetes. There must be a potentially useful macula in at least one eye. There should be no clinical evidence of coronary insufficiency or severe sustained hypertension. The patient should have normal blood urea nitrogen, no anemia from renal disease, and creatinine clearance preferably in excess of 40 ml. per minute. The patient and some responsible relative should be sufficiently stable emotionally to understand and accept the risk of surgery, the uncertainty of its effect upon vision, and the problems connected with hypopituitarism. Neuropathy has not been a contraindication except when associated with severe visceral or autonomic disturbances, such as postural hypotension.

All patients have had follow-up fundus photography in order to document the progressive changes before surgery and those subsequent to operation. In all instances, one or more competent ophthalmologists helped in the selection and observation of patients. Useful information has been gained regarding the type of retinal disease which may be reversible. We now have convincing evidence that the early changes of venous dilatation and engorgement, arteriovenous shunts and new vessel formation are all potentially reversible to some degree. The early vitreous clearing seen in some cases is probably indicative of diminished transudation and improved fluid balance because of better absorption of the fluid into the circulation.

In a previous report, other methods of pituitary ablation have been described and the literature reviewed. A more detailed presentation covering patient selection correlated with the results of surgery, retinal findings, renal biopsies and metabolic observations will be forthcoming.

Summary

Early clinical evidence suggests that hypopituitarism can reverse or arrest diabetic retinopathy. Pituitary stalk section alone is not so consistently effective in producing the hypometabolic state as subtotal or total hypophysectomy. The joint efforts of internist, anesthesiologist, and neurosurgeon working in close association have minimized the risk of surgical pituitary ablation. Proper evaluation of candidates for surgery must include competent ophthalmologic opinion. Provision must be made for the total metabolic care of the patient and the accumulation of objective data upon which to base the evaluation of results.

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