

Pituitary Ablation for Diabetic Retinopathy*

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Ablation of the pituitary gland appears to alter the course of diabetic retinopathy in some patients. This is purely an empirical form of therapy. It developed mostly from the observation in a patient with advanced diabetic retinopathy who, following pregnancy, hemorrhage, and the onset of Sheehan's syndrome (or hypopituitarism), showed marked regression of the retinopathy. This observation was made by Poulsen (1953). Shortly thereafter, Luft, Olivecrona, and Sjögren, (1955), in Stockholm, performed surgical hypophysectomy in a group of patients with rather advanced diabetic vascular disease and diabetic retinopathy. The results were not very good on a long-term basis, but did demonstrate that in some of these patients the course of the diabetic retinopathy apparently was altered favorably. It has now been confirmed by several workers that removal of the pituitary gland can alter the course of the changes just described by Dr. Chan.

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SURGICAL RISK OF HYPOPHYSECTOMY IN DIABETICS

The idea for this therapeutic measure goes back to Houssey's observation that removal of the pituitary gland has an ameliorating effect on diabetes mellitus. There were a few early attempts to do hypophysectomies before these more recent observations, but they were probably premature because the replacement hormones necessary to maintain the hypophysectomized patient were not available and these patients all succumbed quickly. It also became very apparent that in carrying out surgical hypophysectomy in diabetic patients, there was a major threat to life. Of the first 20 patients operated on by Dr. Olivecrona (1955), about a third died in the immediate post-operative period. In other clinics, Dr. Bronson Ray began to do hypophysectomies about 1955. In his first 14 patients, there were two operative deaths. Dr. William Collins and I started our experience with the procedure about 1960 in Cleveland, and in a group of eight patients, we had one operative death. So it became apparent that although surgical hypophysectomy can be performed in other types of patients with very

little mortality and morbidity, the problem was quite different in the diabetic patient. Those patients of Dr. Luft (1962) who survived had convulsions and periods of stupor in the post-operative period. It became apparent therefore that the brain behaved quite differently in the diabetic patient. It was obvious that there must be a more subtle way of changing the hormonal environment of these patients.

BENEFICIAL EFFECT OF HYPOPHYSECTOMY; RELATION TO GROWTH HORMONE

Many studies have been carried out to try to determine by what mechanism hypophysectomy could alter the course of this disease. I think we can say emphatically that we still have no inkling. It is apparent that hypophysectomy does ameliorate the metabolic defect in the diabetic patient, in that there is a marked reduction in insulin requirement. In the juvenile diabetic, the dose of insulin drops to about a third of its previous level. Adult diabetics frequently do not require insulin after hypophysectomy. The amelioration of the diabetic defect may be due to withdrawal of growth hormone, since administration of human growth hormone to diabetics produces a marked exacerbation of the diabetic state.

More recently the ability to measure growth hormone in the serum of patients has permitted an evaluation of whether the hormone levels are normal or abnormal in the diabetic patient. Preliminary studies seem to indicate that blood growth hormone levels are perfectly normal in diabetics, including those who have diabetic retinopathy. With insulin-induced hypoglycemia, growth hormone levels rise very much as they do in normal subjects. So, a superficial look at growth hormone in these patients would seem to indicate that there is no basic abnormality such as is seen in acromegaly and in the diabetes that may be associated

with acromegaly. However, I think further data are needed because although diabetic patients may have normal growth hormone levels, these levels may be too high in relation to the elevated blood sugar. There may be fluctuations of growth hormone levels during the period of the day which may be quite abnormal in the diabetic patient as compared with the non-diabetic. But this information has not helped us really. The incidence of diabetic retinopathy in acromegalic patients does not seem to be any higher than, and certainly not as high as, in patients with ordinary diabetes mellitus, although definite microangiopathy has been seen in acromegalic patients and particularly in those who have a diabetic tendency.

EXPERIENCE WITH HYPOPHYSECTOMY BY YTTRIUM⁹⁰ IMPLANTS

To study further the clinical response of patients to hypophysectomy, it seemed worthwhile to try another approach to ablation of the pituitary gland. Dr. Forrest and co-workers (1959) in Scotland has been working on the implantation of radioactive materials into the pituitary via a trans-nasal, trans-sphenoidal approach. The early results were not very satisfactory but about five or six years ago, he adopted a technique in which he introduced two yttrium rods attached to a stainless steel screw into each side of the pituitary gland. The stainless steel screw was designed to do two things; first, it would fix the yttrium rod which would deliver a necrotizing dose of radiation to the pituitary, so that the accuracy of placement of the rod could be enhanced, and, it would plug the hole that was used to put the yttrium⁹⁰ into the pituitary, thus preventing such complications as rhinorrhea and meningitis.

Dr. Collins and I embarked on this program about three years ago and we have now had experience

with this type of implantation in 125 patients. Specifically we have had experience with 32 patients with diabetic retinopathy. We have not been able to confirm Forrest's observations (1959) that this technique is without complications. We have had rhinorrhea in three patients, and meningitis in two; all of these subsided, however, without residual damage. From a surgical point of view, the procedure is indeed a benign one and is useable in patients who are completely unsuitable for surgical hypophysectomy. We have had no mortality in the original procedure in these 32 patients, but we did have one surgical mortality in a patient who was re-operated on a year later. We have seen no significant nerve palsies.

EFFECT ON VISION AND RETINOPATHY

In this group we have studied patients with quite advanced diabetic retinopathy. In two thirds of the patients, we have seen significant improvement in terms of better vision. The most striking change that the ophthalmologist reports is a decrease in edema of the retina, a decrease in hemorrhages, in the neovascularization, and in microaneurysms. The retinitis proliferans shows no change. The fibrous changes remain, but the vascularity of this proliferative disease can regress. I specifically state that there is a decrease in these changes and not a complete disappearance of all of these vascular difficulties. But the clinical response in these patients has indeed been quite remarkable.

Of the group whom we considered to be failures, there were only three who have shown progressive changes in terms of hemorrhage going on to destroy vision. In two of these three, we felt that the hypophysectomy had been incomplete and that one of these had shown transient improvement, followed by a recurrence of hemor-

rhages which went on to destroy vision. Whether complete hypophysectomy is essential for the best results is of course not certain. But some of the data that we have suggests that the more complete the hypophysectomy, the better the results.

Also in the group that we considered to be failures were patients who had bilateral retinitis proliferans with large areas of fibrous tissue covering the disc and extending toward the macular area. A number of these patients had only peripheral vision. Visual acuity was less than 20/200 and yet we reasoned that if we could retain this degree of peripheral vision, the hypophysectomy would have been worthwhile. In five such patients we have seen no significant change except for some decrease in the vascularity of the diabetic retinopathy. But there has been no improvement in vision and these patients cannot be considered successes. It is striking, however, that a number of patients with retinitis proliferans with sparing of the macula and useful vision, seem to have shown no progression of the scarring. We have patients who have gone as long as nine years now without evidence of progression of the retinopathy.

SUMMARY

Our clinical experience and the experience of others seems to indicate that pituitary ablation can induce a significant beneficial effect on the course of diabetic retinitis, even in advanced stages. We have no strict criteria for the selection of patients. When surgical hypophysectomy is being done, the major restriction is whether the patient has a fair chance of getting through the procedure without great risk of death or serious complication. With yttrium-implant hypophysectomy, the risk of death from the procedure itself has been practically eliminated. The morbidity would be much less if the rhinorrhea and

the threat of meningitis could be eliminated completely. From our experience, the procedure appears to be futile in patients with severe retinitis proliferans with very little vision left. Where there is useful vision left, even 20/100 or less in one eye, where there appears to be a chance of reversibility, we have seen striking improvement lasting for several years.

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