CORTICOSTEROIDS IN THE TREATMENT OF OPTIC NERVE INVOLVEMENT ASSOCIATED WITH THYROID DYSFUNCTION*

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THIS STUDY REPORTS the successful use of systemic prednisone in the treatment of optic nerve involvement associated with Graves' disease. The corticosteroids have been employed in therapy for the severe eye changes of thyroid disease since they first became available,[1–3] but the early results were not encouraging. In retrospect, this undoubtedly was a result of the relatively small doses which were employed. In 1955 Igersheimer[4] reported visual improvement in exophthalmos after the use of corticosteroids, but this one case was not of proven thyroid origin. Brown *et al.*[5] in 1963 were the first to show the often dramatic effect of large doses of prednisone in patients with the eye changes of thyroid dysfunction and documented optic nerve disease. More recently Werner[6] has again emphasized the value of large doses of these drugs in the most severe instances.

The beneficial effects of the corticosteroids in ten patients with optic nerve involvement associated with thyroid dysfunction are summarized in Table 1. Each patient had the characteristic severe orbital changes seen in Graves' disease, with laboratory evidence of thyroid dysfunction, but the degree of thyroid activity bore no relation to the severity of the ocular signs. The degree of proptosis, as measured with the exophthalmometer, also was unrelated. The optic nerve changes were either unilateral or bilateral, with various types of field defects, but all the patients had at least some degree of extraocular muscle involvement. Ages varied from 36 to 66 years, with an average of 52. The maximum daily dose of prednisone required for improvement in vision ranged from 20 to 140 mg., and the number of days of treatment which elapsed before evidence of improvement varied from 2 to 37. The duration of total treatment required also varied greatly. In general,

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TABLE 1

Patient	Age	Sex	Vision before treatment	Visual fields	Disks	E.O.M. involvement	Hertel exophthalmometer readings	Thyroid status at start	Duration of visual defect before treatment	Days of treatment before onset of visual improvement	Days of treatment before maximum visual improvement	Maximum daily dose of prednisone (mg.)	Duration of treatment (mo.)	Final vision
B.F.	57	F	O.D. 20/100 O.S. 20/100	O.D. Generalized depression O.S. Nerve fiber bundle defect	Normal	+++	$\frac{21\text{–}23\frac{1}{2}}{101}$	Euthyroid	5 mo.	20	100	20	54	O.D. 20/30 O.S. 20/25
F.S.	38	F	O.D. 20/20 O.S. 20/60	O.S. Generalized depression	Normal	+++	$\frac{22\frac{1}{2}\text{–}24}{98}$	Euthyroid	2 mo.	20	20	40	3	O.D. 20/20 O.S. 20/20
M.R.	59	F	O.D. 20/200 O.S. 20/200	O.U. Central scotomas	Normal	+++	$\frac{23\text{–}23\frac{1}{2}}{101}$	Hyperthyroid	5 mo.	30	60	20	16	O.D. 20/20 O.S. 20/20
S.H.	39	F	O.D. 20/20 O.S. 20/200	O.S. Contraction; generalized depression	Normal	+	$\frac{22\text{–}24}{105}$	Euthyroid	2 mo.	2	4	40	5	O.D. 20/20 O.S. 20/20
A.M.	50	F	O.D. 20/30 O.S. CF	O.S. Central scotoma	O.S. Disc blurred	++	$\frac{17\text{–}18}{97}$	Euthyroid	2 wk.	3	17	40	1	O.D. 20/20 O.S. 20/20
R.A.	61	M	O.D. 20/40 O.S. CF	O.D. Nerve fiber bundle defect O.S. Centrocecal scotoma	Normal	+	$\frac{21\text{–}21}{100}$	Euthyroid	5 mo.	21	34	40	5	O.D. 20/20 O.S. 20/30
M.J.	66	F	O.D. 20/400 O.S. 20/60	O.D. Centrocecal scotoma	O.U. Slight temporal pallor	+++	$\frac{25\text{–}25}{100}$	Euthyroid	2 mo.	37	50	140	12	O.D. 20/30 O.S. 20/30
G.B.	48	F	O.D. 20/300 O.S. 20/70	O.U. Centrocecal scotomas	Normal	+++	$\frac{25\text{–}25}{97}$	Hyperthyroid	5 mo.	14	90	30	6	O.D. 20/20 O.S. 20/20
M.K.	66	F	O.D. 20/40 O.S. 20/20	O.D. Centrocecal scotoma	O.D. Temporal pallor	+++	$\frac{25\text{–}27}{100}$	Euthyroid	5 mo.	7	30	80	3	O.D. 20/20 O.S. 20/20
A.S.	36	F	C.D. 20/200 O.S. 20/30	O.D. Central scotoma	Normal	+++	$\frac{23\text{–}20}{100}$	Euthyroid	2 mo.	27	90	40	20	O.D. 20/25 O.S. 20/20

the longer the disease had existed prior to treatment the longer the time necessary for recovery, but in all ten patients essentially normal vision was eventually restored.

Once the diagnosis of optic nerve involvement was made the patients, under careful medical supervision, were placed on from 20 to 40 mg. of prednisone daily. The dose was then decreased or increased depending on the visual response. Concurrently the other orbital inflammatory signs decreased and the patients became more comfortable.

An example of the dramatic effect of the systemic corticosteroids is shown in Figure 1. The vision in this patient's right eye promptly

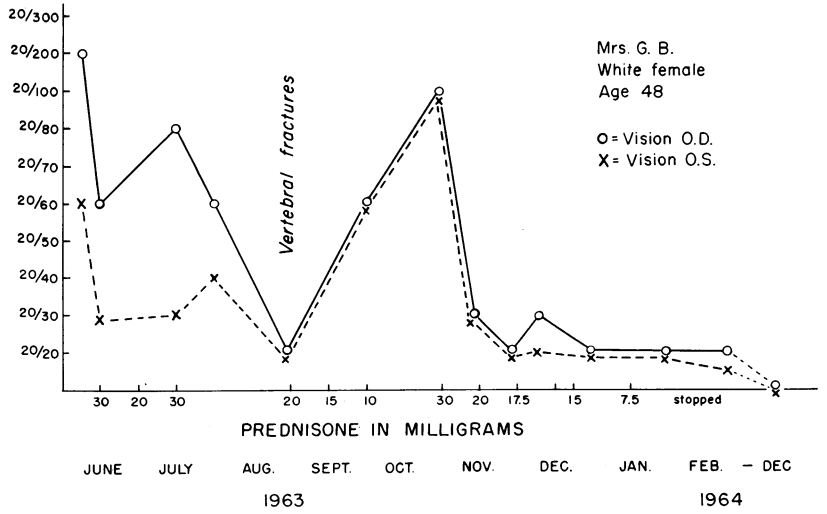

FIGURE 1

improved from 20/300 to 20/70 on 30 mg. of prednisone daily, but when the dose was reduced to 25 mg. vision slipped to 20/100. On reinstituting 30 mg. daily, vision improved to 20/30. At this time the patient suffered a compression fracture of one vertebra, being the only patient in this series to suffer this complication. The dose was decreased to 10 mg. per day and vision declined to 20/200. However, when a 30-mg. dosage was started once again vision improved to 20/30, and the dose could then be gradually decreased over the following three months. This patient illustrates the necessity of administering enough drug, whatever the dose may be. In the initial phase, 30 mg. was sufficient to result in visual improvement while 25 mg. was not.

Of 10 similar patients reported by the authors[7] in 1962, 3 were given prednisone and showed no improvement. However, the drug was administered in relatively small doses to these cases, emphasizing again that enough drug must be given. Indeed, at times massive doses may be required, as recommended by Werner[6] and as illustrated by our patient, M.J. This 66-year-old white woman who had had visual loss for two months was started on 30 mg. of prednisone daily. This was increased to 45 mg. after one week and ten days later to 80 mg. and then in three more days to 140 mg. daily before visual improvement occurred. The dosage was gradually decreased, vision progressively improved, and within six weeks her vision was normal. However, to maintain this improvement, relatively small doses had to be continued for several months.

As the corticosteroids must be administered until the disease process has run its course, which may be over many months, patients receiving them are likely to suffer serious complications. In this series the only patient to develop a severe complication was the one mentioned previously with the vertebral compression fracture. However, the other dangerous side effects of the adrenocortical drugs, such as peptic ulcer, gastrointestinal bleeding, diabetes, and psychic disturbances, must be watched for continuously. On the other hand, if the drug is stopped too soon the visual impairment will recur.

In an attempt to eliminate the side effects of these drugs Garber[8] has recommended the use of subconjunctival methylprednisolone acetate. The efficacy of this mode of treatment was not evaluated in this present study, but the relatively large doses required when the optic nerve is involved would suggest that the local deposition of the drug would not be of benefit.

The mode of action of the corticosteroids is not clear. It has been postulated that the optic nerve involvement is brought on by the enlarged extraocular muscles and generalized increased tissue pressure within the muscle cone, particularly at the orbital apex, which interfere with the blood flow to the nerve.[7] Anatomic variations in the blood supply to the nerve might well make certain patients more susceptible than others. The corticosteroids may work by decreasing inflammatory reaction,[9] deposition of mucopolysaccharide,[10] or edema.[11] The definite lessening of chemosis with prednisone therapy may well be a manifestation of a process which is also occurring in the posterior orbit.

The characteristic feature of the severe ocular changes of Graves' disease is variability. Thus, evaluation of the efficacy of any form of treatment is difficult. Many patients have return of vision without any

specific form of therapy, and it has been shown that the younger the patient the better the prognosis. Thus, in a series of 26 patients previously summarized,[7] 9 had complete visual recovery, while 11 had partial recovery and 6 had no recovery. This is in contrast to the excellent visual recovery in all 10 patients reported here who were treated as soon as the diagnosis of optic nerve involvement was made and with sufficient dosage to decrease the orbital pressure. In effect, they were treated by early medical decompression. This early therapy may also account for the higher percentage of good results than those recently reported for surgical orbital decompression where Kroll and Casten[12] found visual improvement in 10 out of 16 eyes and Long and Ellis[13] in 14 out of 18 eyes. Operation, as a rule, is not undertaken as early as the administration of corticosteroids. In addition, from a theoretical point of view, removal of a portion of the bony orbital wall would not be expected to result in as great a decrease in the pressure within the muscle cone as that resulting from the systemic drug. The series of 10 patients reported here is small, and with a larger series such uniformly good results might well not be obtained. However, the results would suggest that systemic corticosteroids are the treatment of choice. The danger of the complications which may arise from long-continued therapy must constantly be borne in mind, and the drugs should be administered as a calculated risk. This risk would appear to be justified when vision is threatened.

SUMMARY AND CONCLUSIONS

The marked beneficial effect of systemic corticosteroids on 10 patients with optic nerve involvement associated with thyroid dysfunction is reported.

Corticosteroids appear to be the treatment of choice in this condition.

The corticosteroids must be administered in sufficient dosage and often for long periods of time. Therefore, they must be given as a calculated risk, which would appear to be justified when vision is threatened.

REFERENCES

1. Scheie, H. G., G. S. Tyner, J. A. Buessler, and J. E. Alfano, Adrenocorticotropic hormone (ACTH) and cortisone in ophthalmology, A.M.A. Arch. Ophth., 45:301–316, 1951.
2. Woods, A. C., The present status of ACTH and cortisone in clinical ophthalmology, Am. J. Ophth., 34:945–60, 1951.
3. Fitzgerald, J. R., J. G. Bellows, J. M. Donegan, R. C. Gamble, A. C. Krause, W. A. Mann, M. D. Pearlman, and T. N. Zekman, Early clinical results of

ACTH and cortisone treatment of ocular disease, Arch. Ophth., 45:320–33, 1951.
4. Igersheimer, J., Visual changes in progressive exophthalmos, A.M.A. Arch. Ophth., 53:94–104, 1955.
5. Brown, J., J. W. Coburn, R. A. Wigod, J. M. Hiss, and J. T. Dowling, Adrenal steroid therapy of severe infiltrative ophthalmopathy of Graves' disease, Am. J. Med., 34:786–95, 1963.
6. Werner, S. C., Prednisone in emergency treatment of malignant exophthalmos, Lancet, 1:1004–7, May 7, 1966.
7. Day, R. M., and F. D. Carroll, Optic nerve involvement associated with thyroid dysfunction, A.M.A. Arch. Ophth., 67:289–97, 1962.
8. Garber, M. I., Methylprednisolone in the treatment of exophthalmos, Lancet, 1:958, April 30, 1966.
9. Bjorneboe, M., E. E. Fischel, and H. C. Stoerk, Effect of cortisone and adrenocorticotrophic hormone on concentration of circulating antibody, J. Exper. Med., 93:37–48, 1951.
10. Werner, S. C., H. Hamilton, and V. K. Frantz, Proc. 2nd Clinical ACTH Conference, p. 521. Philadelphia, 1951.
11. French, L. A., The use of steroids in the treatment of cerebral edema, Bull. New York Acad. Med., 42:301–11, 1966.
12. Kroll, A. J., and V. G. Casten, Dysthyroid exophthalmos, A.M.A. Arch. Ophth., 76:205–10, 1966.
13. Long, J. C., and G. D. Ellis, Temporal decompression of the orbit for thyroid exophthalmos, Am. J. Ophth., 62:1089, 1966.

DISCUSSION

Dr. John Warren Henderson. In 1961 in a discussion of the paper "Optic Nerve Involvement Associated with Thyroid Dysfunction," also given by these authors before this Society, I expressed the hope that they would bring us further observations of this disorder sometime in the future. Their paper today fulfils this wish and brings us their experiences with a method of treatment that is currently popular. Their report of 10 patients is exceedingly favorable with regard to the effectiveness of systemic steroids as a treatment for this optic nerve complication.

In an attempt to gain further information on this subject, I found among our files nine cases in which patients who exhibited the visual field defects of this optic neuropathy had received systemic steroids. The average age of this group corresponded closely to the authors' series. There were five women and four men. Four of these patients showed definite improvement while receiving systemic steroids; three did not improve. Another patient with bilateral involvement was showing definite improvement of vision after two months of steroid therapy when he became psychotic. The steroids were discontinued and his vision became worse over the next two months. However, one year after the time the steroids were discontinued the patient's vision was normal. The final patient of this group was of particular interest in that the optic nerve complication had developed during the third month of treatment with steroids administered as therapy for the ophthalmopathy.

The authors suggest that therapy early in the course of the disorder may have contributed to the high percentage of good results in their series. As I recall, other observers who have championed either roentgen therapy or orbital decompression have also advocated early treatment. We must be wary in accepting this as a valid argument, for in such situations we inevitably treat some patients who would get well without treatment. The problem we all have in judging the efficacy of any treatment proposed for this disorder is the lack of a good control series.

In an attempt to be objective about the problem, I asked myself what I would do if I had the disease. I decided that if I were euthyroid I would do nothing, because I estimate there is about a 70 per cent chance that my vision would return to normal three months to two years after the onset of the visual loss. However, if I were a worried ophthalmologist (as most of us are), treating an apprehensive patient (as all of them are), I would give systemic steroids a trial, although in smaller doses than those advocated by the authors.

The authors have had an opportunity to manage more cases of this complication than does the average ophthalmologist and I urge them to continue their discerning observations.

DR. ROBERT E. KENNEDY. The management of optic nerve suppression associated with thyroid dysfunction is a most perplexing clinical problem. The authors are to be commended for their attempt to formulate better guidelines in our treatment of these patients.

During the past decade I have encountered three patients with this problem. One, I feel, is worth describing briefly. While previously discussed at a Wilmer meeting, the history has never been published. The interesting feature is the duration of suppression of vision with the subsequent return to a normal level.

A 53-year-old female patient showed the typical congestive symptoms of thyrogenic orbital disease. The essentials of the clinical history can be summarized on this slide. [Slide] Diagrammatically the level of vision can be plotted in relation to time in months and years. I had seen the patient initially with 20/20 vision. Four months later thyroid surgery was performed and she was subsequently placed on vitamins and thyroid extract. Three months later vision began to decrease and in a few weeks' time reached the level of 20/300 in the right eye and 3/200 in the left eye. The fundi and disks remained normal throughout the clinical observation of the patient. Fields showed large dense cecocentral scotomas which eventually completely resolved. Small pericentral scotomas in the right eye persisted for about a year before clearing with normal fields.

When the vision became suppressed, the patient was seen by several other colleagues, including Drs. Frank Walsh, John Gipner, and Albert Snell of this Society. It was suggested that a course of corticosteroids be given. This was started a few weeks after vision had begun to suppress and was

carried out at full dosage for three months and then tapered off. The complete treatment lasted six months. Lateral orbital decompression or transfrontal decompression was considered but was rejected by the patient. The patient was maintained in a euthyroid state and was examined monthly. After the vision had been suppressed at the level of 20/300 in the right eye for 17 months and 3/200 in the left for 21 months, it began to show a sudden but gradual improvement returning to 20/20 in each eye. This, however, represented a total interference of vision for 21 months in the right eye and 25 months in the left eye. It is of interest that this improvement did not take place until more than a year after corticosteroid therapy.

In the last few years several authors writing on this subject have reported approximately 60 cases. The duration of optic nerve dysfunction with recovery usually ranged from a few weeks to a few months, and rarely extended to approximately a year's time. None has had the duration of suppression with recovery shown by the patient just described (approximately two years).

It is felt that the etiology of this condition is most likely a vascular insufficiency of the optic nerve resulting from the orbital pressure. However, it seems most unusual to think of the optic nerve tissue remaining suppressed for this duration, whatever the cause, and then recovering so completely.

With the relatively few reported cases, the marked variability of the disease, and its self-limiting aspect, the evaluation of any type of treatment is very difficult. After this patient had corticosteroids systemically for six months there was a lapse of a full year before visual improvement occurred. It is doubtful if much credit can be given to the corticosteroids after this interval. Had the vision improved during or shortly after the corticosteroid treatment it is likely the improvement would have been attributed to this therapy. I'm sure in some cases this can also be said of orbital decompression.

The true problem in clinical management of optic nerve suppression with thyroid dysfunction is to determine which of the patients are going to recover despite treatment and which may need all the help they can have. Even with medical treatment including corticosteroids and/or decompression of the orbit some of these patients are not going to respond. The authors have contributed toward helping to solve this dilemma.

DR. JACK S. GUYTON. I regret I feel called upon to report less promising results with the use of corticosteroids in a small series of patients whom we have treated in this manner. One of the members of our Division of Endocrinology, having been sufficiently impressed by reports on this means of therapy, has been largely responsible for our utilizing rather large doses of corticosteroids in patients who have developed some optic nerve involvement.

During the past year I have seen four such patients who, while on doses of prednisone (from 40 to 80 mg. per day), went progressively downhill from a visual standpoint over a period of one to two months. I cannot offer

this as anything more than an incidental finding to illustrate that corticosteroid therapy is not a cure-all for optic nerve involvement.

DR. HARVEY E. THORPE. The contribution of Dr. Day and Dr. Carroll is of considerable significance. My experience has been similar to theirs in several instances of acute malignant exophthalmos in dysthyroid patients except that we used ACTH (corticotropin) parenterally. The patients were of two types—acute malignant and chronic dysthyroid exophthalmos with edema. The acute cases with optic nerve involvement were more prone to respond favorably to therapy than the chronic cases of dysthyroid disease with nerve involvement.

[Slide] As you know the effect of corticosteroids is chiefly on a tissue level, whereas ACTH is known to stimulate the production of specific steroids in the adrenal cortex. This slide illustrates this effect graphically.

[Slide] Next are some photographs of a patient with an extremely severe malignant dysthyroid exophthalmos whom I treated some seventeen years ago. He improved dramatically with parenteral administration of ACTH. This case was not published. This man, aged 57, was brought to our Neurosurgical Service in March 1950 for a Naffziger decompression of his left orbit. He was sent in by a colleague who had two months previously eviscerated the right eye because of panophthalmitis following a perforated lagophthalmic corneal ulcer. The patient's left eye showed an extreme degree of exophthalmos with chemotic prolapsed conjunctiva, exposure keratitis, and markedly impaired vision (counting fingers at one meter). It was threatened with similar loss of globe integrity. The orbital edema and the lids were board-like on palpation. The lids could not be approximated to protect the cornea. The B.M.R. was plus 59. Our neurosurgeon was out of town and management of the case devolved on the ophthalmology service. (This was in the early days of ACTH and steroid use.)

We had some ACTH for investigational purposes. Twenty (20) units of crystalline ACTH were administered parenterally every six hours. Within 48 hours it was possible to approximate the lids, create intermarginal adhesions, and perform a lateral canthoplasty. The drug was continued parenterally for one month and dosage was gradually decreased. Potassium depletion was guarded against by administration of potassium chloride.

[Slide] This photograph taken two months later shows the patient's improvement with the conjunctival edema subsided and the presence of intermarginal adhesions. His metabolism dropped from 59 to 34. His vision had improved from counting fingers to 10/200. The corneal infiltration and edema had cleared so that it was possible to see the left fundus. There was pallor of the optic disk. When ACTH was discontinued his metabolic rate again became elevated. An additional course of parenteral ACTH was administered for four weeks.

[Slide] This slide shows his profile some three months after the beginning of treatment. The B.M.R. was now +32. Vision had improved to 10/70.

[Slide] This slide shows his improved appearance one year later with the exophthalmos much improved. Visual acuity has come up to 20/30. He still had pallor of the left optic disk. The B.M.R. was −5. He was followed for 15 years at intervals. He maintained this visual acuity and was euthyroid.

DR. ROBISON D. HARLEY. I would like to ask the authors if their patients received any other form of therapy for the thyroid dysfunction.

I recall examining a 41-year-old white waitress who had this typical exophthalmic goiter condition with bilateral central scotomas and vision reduced to hand movements in one eye and counting fingers in the fellow eye. On 60 mg. of prednisolone daily her vision improved rapidly to 20/200 and 20/100 in the respective eyes and the improvement was accomplished within a week.

She was continued on the steroid therapy and exhibited a little improvement in the next three months. Following this period the internist decided she should have radioactive iodine, and with this therapy her general condition improved greatly but the eye condition showed relatively little change. However, during the ensuing year and a half her vision did improve, and when I examined her at the end of this time her visual acuity had improved to 20/30 in the right eye and 20/25 in the left eye.

DR. LUDWIG VON SALLMANN. I have two brief questions.

Dr. Day has briefly mentioned local steroid treatment for endocrine exophthalmos. The results on 15 patients, reported by M. I. Garber in *Lancet* (1966), seem to provide evidence for the usefulness of repeated subconjunctival or retrobulbar injection of Depo-Medrol in these cases. I would like to know whether in the present study such relatively harmless therapy has received a fair trial.

Recently we saw a patient who had been systemically treated for long periods of time with steroids in high dosage without improvement. The complications included exposure keratitis and marked side effects of the therapy. Depo-Medrol was injected retrobulbarly in one eye but not enough time has elapsed to evaluate the result. Do the authors feel that under these circumstances local therapy should be employed?

DR. FRANK D. CARROLL. I want to thank all the discussers.

Dr. Henderson was one of the first people in this country to discuss this subject, and he wrote a report on it in 1958. Other members of this Society—Dr. Hedges and Dr. Scheie—have also contributed to our knowledge of it, so the members of this Society have really helped us a great deal. I think we are pretty much in agreement with what Dr. Henderson has said. Probably 70 per cent of these people improve spontaneously; however, we are very interested in the 30 per cent who do not improve spontaneously.

Dr. Kennedy reported a very interesting case which improved 24 months after therapy had been stopped, so this is one more instance where spontaneous recovery did take place.

The dosage is very important. We try to titrate the dosage. If the patient is improving on a dosage of, say, 40 mg. prednisone a day, we try to decrease it. If the patient gets worse, we increase it; if he gets better, we decrease it again.

Dr. Guyton has had poor results with steroids. Of course we know that in most large series of orbital decompressions there are at least one or two very bad results, with loss of all vision.

Dr. Thorpe's case reminded me very much of one that was reported at the Academy last fall, by Dr. Werner, in which a similar result was obtained with large doses of prednisone—dosages as high as 140 mg. Dr. Thorpe apparently found this out many years ago in one case using ACTH.

Dr. Harley asked whether any other treatment was used in these cases. I think in nine out of ten no other treatment was used because they were euthyroid. At the time we saw them nearly all of the ten patients were euthyroid, so corticosteroids were the only treatment used.

Dr. von Sallmann asked whether we have used retrobulbar injections. The answer is no, we have not. We have been rather satisfied with the method we are using. Dr. Day has tried subconjunctival injections of Depo-Medrol, I believe, but not with optic nerve involvement, and he has not been impressed by the results.

[Slide] This is the final result in a patient we reported here in 1961. This man had 20/20 vision when he first came to me. It was very sad to see him go downhill. This is his final result. He has optic atrophy with dense central scotomas and a visual acuity of 5/200 O.U.

These 30 per cent are very distressing patients. We have two others we have seen (although we did not manage them) who lost all vision in both eyes. So, this can be a very serious condition.

[Slide] This is one of Dr. Reese's patients, with marked unilateral papilledema, 20/20 vision, and a very enlarged blind spot. On this patient he did an orbital decompression. At the time of our last paper we had followed him for only three months and there had been no improvement. [Slide] This is the same patient one year later; the disk now appears normal. Since it took a whole year for this result to occur, we doubt that the orbital decompression had anything to do with it.