TREATMENT OF NON-MALIGNANT CORNEAL CONDITIONS WITH RADIOACTIVE ISOTOPES*

A 5-YEAR SURVEY

BY

H. FRASER AND W. J. NAUNTON

Manchester

VASCULARIZATION of the cornea and its association with recurrent keratitis is a common problem in ophthalmic practice. In 1953 a clinic was started to study treatment with beta rays, and this paper deals with the results of this treatment in the 5 years 1953 to 1958.

Applicators.—Two types were used: the Lederman Applicator Type 1, and the Swanberg Radium D Applicator.

The first covers the whole of the surface of the cornea and is used only when the lesion affects a large area. It has as its radioactive element Strontium 90 with an output of 110 reps (roentgen equivalent physical) per minute at its surface. These applicators used to have a plastic covering but as this tended to crack it was replaced by a silver covering and no trouble has been experienced with the latter.

The second has a circular treatment surface of 6.8 mm. and contains 10 mc. of Radium D, with a thin filter of magnesium to absorb the alpha rays. The output of this applicator is 180 reps per minute at its surface and it is used for more localized lesions.

The applicators are sterilized with pure ethyl alcohol, any excess being wiped off with cotton wool before use. Heat in any form will damage the delicate covering. Certain antiseptics may be incompatible with the magnesium of the Radium D applicator and may damage it.

Wilson (1952), in a review of various types of applicators for beta-irradiation of the eyes, showed that the main advantage of applicators containing Radium D or Strontium 90 was that they were almost pure beta-emitters so that handling and storage were relatively simple and nonhazardous.

Dosage.—Before use, the Radium D and Strontium 90 applicators were calibrated at the Radiochemical Centre, Amersham, and the following dosage rates were evolved as the treatment to be given during the series.

At first very small divided doses were used but these were gradually increased to the extent to be described.

* Received for publication July 28, 1960.

In cases in which superficial vascularization of the cornea was the prime reason for giving beta-rays, an initial dose of 700–1,000 reps was given, depending on the degree of vascularization, and only after an interval of 6 to 8 weeks was a further dose given, as it was found that devascularization can continue for this length of time. The usual total dosage required was 1,500–1,700 reps.

With deep vessels such as those associated with disciform keratitis up to 2,000 reps was given in divided dosage.

For corneal ulceration, whether due to pyogenic or to virus infection, with or without much vascularization, smaller doses of 300–400 reps were used, and were repeated if necessary in 3 to 4 days, but only the minimum dose possible that would promote healing was employed.

Results

During the period under review 153 cases were treated (Table, overleaf). The results may be tabulated under three headings:

- (a) Those which were avascular without recurrences after the completion of treatment and were symptom-free.
- (b) Those in which some fine vascularization still persisted but which had no recrudescence of the original lesion and no symptoms.
- (c) Those which were frank failures or had recurrences of the original lesion.

Acne Rosacea Keratitis.—The Table shows that over one-third of the patients, 54 in all, were suffering from acne rosacea keratitis. In this disease the dosage was that for superficial vascularization. It was the practice to start the beta-ray treatment when the acute phase of the attack had subsided and there was little or no ulceration of the cornea. This, of course, was not always possible and a small number of patients were treated who still had corneal ulceration. Of the 54 cases, 49 were avascular and asymptomatic after treatment, four had fine vessels but no recurrences during the follow-up period, and one had a recurrence only 3 months after therapy. The original dosage in this last case was only 700 reps. and with a further dose of 700 reps there has been no recurrence over a special follow-up period of one year.

In assessing any form of therapy for acne rosacea keratitis, it must be borne in mind that this disease has remissions without treatment but that with each recurrence more permanent damage results. It follows, therefore, that only those cases which have had a reasonably long follow-up can be used in an assessment of the efficacy of beta-ray therapy. Of the 54 cases, eighteen were followed up for 3 to 5 years, thirteen for over 2 years, fourteen for over one year, and nine for only 6 months. Of the eighteen cases followed-up for 3 to 5 years, ten had previously had cortisone therapy and three testosterone therapy but recurrences had appeared every few months under those modes of treatment. Five of the eighteen had both eyes treated

TABLE
RESULTS IN 153 CASES

Disease	Avascular Asymptomatic	Fine Vessels Asymptomatic	Failure	Total
Acne Rosacea Keratitis	49	4	1	54
Virus Keratitis	18	6	1	25
Deep Keratitis	6	2	—	8
Recurrent Keratitis	8	3	7	18
Vascularization with Trichiasis and Exposure Keratitis	6	2	1	9
Caustic Burns	3	—	2	5
Post-Corneal Grafting	6	—	—	6
Pyogenic Corneal Ulcer	10	—	—	10
Sclerosing Keratitis	—	—	4	4
Pterygium	—	—	2	2
Spring Catarrh	—	—	2	2
Mustard Gas Keratitis	—	—	1	1
Corneal Dystrophy	—	—	1	1
Angiomatosis Conjunctivae	—	—	1	1
Epithelialization of Anterior Chamber	—	—	2	2
Long-standing Ophthalmia Neonatorum	—	—	1	1
Phlyctenular Keratitis	1	—	1	2
Interstitial Keratitis	1	—	1	2
Total	108	17	28	153

with beta-rays and had no recurrence in either eye. The other thirteen had only one eye treated; five of them suffered attacks of inflammation in the untreated eye during the follow-up period, but the treated eye showed no recrudescence.

Virus Keratitis.—25 patients with known or presumed virus keratitis were treated for secondary superficial corneal vascularization. In nineteen this was due to dendritic ulcer, in two to superficial punctate keratitis, in two to herpes zoster ophthalmicus, and in two to long-standing trachoma. At the time of treatment both cases of superficial punctate keratitis had corneal staining with fluorescein, as did five of those suffering from dendritic ulcer. The remaining cases due to dendritic ulcer had had recurrent attacks of

ulceration and beta-rays were given during a quiescent period to remove the vascularization of the cornea in the hope of preventing further recurrences. The only failure in the whole group of virus keratitis cases was one patient with vascularization following recurrent dendritic ulcer. Despite adequate dosage of beta-ray there were two relapses of ulceration one year after treatment. The seven cases who stained with fluorescein at the time of treatment all healed within 7 to 10 days.

Deep Keratitis.—Although this group has been classified separately because deep vascularization was the main problem, the lesions were probably all of virus origin. Eight cases in all were treated and total devascularization was achieved in six of them; the remaining two had a few residual vessels but all remained symptom free.

The most striking example in this group was a male patient aged 50 years who before being referred to the beta-ray clinic had been under treatment for 7 months with mydriasis, cortisone, and vitamin C. At the time of treatment he had a large deep central corneal opacity with considerable deep vascularization, visual acuity reduced to counting fingers, and a very irritable eye. He was given a single dose of 1,000 reps and the treatment was continued with atropine only. By the end of 9 weeks the cornea was totally avascular, the opacification of the cornea had lessened, and the visual acuity had improved to 6/18. When he was seen 14 months after the treatment he had had no recurrence and the visual acuity was the same.

Recurrent Keratitis.—Into this group were placed all those cases in which the aetiology was uncertain and which had been subject to recurrent attacks of ulceration with gross vascularization for a considerable time.

The results were much worse than in those cases in which the aetiology was clear cut. The cause of this may be that the corneae of the majority were very grossly affected, two of them having a descemetocoele. Even so, over half the patients remained asymptomatic.

Vascularization with Trichiasis and Exposure Keratitis.—Eight cases of superficial vascularization of the cornea associated with trichiasis and one case of superficial vascularization associated with exposure keratitis due to facial palsy were treated with beta ray. Of the eight cases with trichiasis, five became avascular, two had fine vessels still remaining, and in one beta ray had no effect at all on the corneal vascularization. In all eight patients the trichiasis resisted treatment and there may well be recurrences later.

Caustic Burns.—Five cases of vascularization of the cornea following caustic burns were treated with beta ray. Three cases which did well were all relatively mild cases, and the two cases which failed to respond to therapy had had considerable destruction of corneal tissue with symblepharon, so that the beta-ray therapy made no impression on the vascularization.

Post-Corneal Grafting.—Six cases of vascularization following penetrating keratoplasty were treated with beta rays 2 to 3 weeks after the operation when the vessels in the graft were comparatively newly formed. One dose of 1,000 reps was given in each case, none of which had had pre-operative beta ray. In all six cases the vascularization in the graft disappeared with consequent clearing of the graft itself.

Pyogenic Ulceration.—Although each of the ten cases in this group had a small amount of vascularization, the prime purpose of giving beta ray was to stimulate the healing of a chronic pyogenic ulcer which had resisted treatment with mydriasis, antibiotics, and carbolization. The applicator was applied direct to the ulcer and a dose of 300–400 reps was given; daily observations were made and if the ulcer was receding no further treatment was given, but if at the end of 4 days the ulcer was seen to be static a further dose of 400 reps was given. This extra dose was required in only two cases. In all ten cases healing was complete in 2 weeks, and as the ulcer healed the vessels gradually receded.

Interstitial Keratitis.—Two cases were treated.

A girl aged 23 years had been treated for 4 months with local atropine and hydrocortisone with no improvement in the eye condition. She was given a total of 1,500 reps and within 2 months the cornea was avascular and visual acuity had improved to 6/18 and N.5. This vision was maintained when she was last seen 2 years after the beta-ray treatment.

A man aged 52 years had old-standing interstitial keratitis in both eyes. It was hoped that corneal grafting would be carried out after the corneal vascularization had been reduced. He was given a dose of 500 reps to the right eye and 3 days later developed iritis with hypopyon. He had been subject to recurrent attacks of kerato-iritis but there was no previous record of hypopyon. It is impossible, therefore, to exonerate the beta ray from being at least partly responsible for the iritis. The attack of iritis settled down in time and the patient eventually had a corneal graft.

Other Conditions.—Beta ray was found to be of no value in the few cases treated of sclerosing keratitis, pterygium, spring catarrh, mustard gas keratitis, corneal dystrophy, angiomas of the conjunctiva, epithelialization of the anterior chamber after cataract extraction, and long-standing ophthalmia neonatorum with gross vascularization. It was of doubtful value in phlyctenular keratitis.

Complications.—In most cases there was a mild reaction to beta-ray therapy, indicated by circumcorneal congestion occurring 7 to 10 days after treatment but subsiding within a few days. The only other complication noted in this series was in the case of old interstitial keratitis which developed iritis with hypopyon. Merriam (1955), in a survey of the late effects of beta radiation, found the following complications:

Telangiectasis after 3,000–5,000 reps.

Keratinization of the conjunctival epithelium after 5,000–10,000 reps.

Scleral atrophy after 20,000–30,000 reps.

Superficial punctate keratitis after 5,000 reps.
Iritis after 22,000–27,000 reps.
Iris atrophy after 20,000–22,000 reps.
Radiation cataract after 2,300–22,000 reps.
Vascularization of the cornea after 20,000–30,000 reps.
Scarring of the cornea after 25,000 reps.

Apart from one case of radiation cataract which occurred with a dosage of 2,300 reps, the other complications noted by Merriam resulted from doses far in excess of that used in this series in which the total dosage was limited to 2,000 reps (except in one case of spring catarrh in which a total of 3,000 reps was given to the lids). Lederman (1957) stated that in his series he had no record of a radiation cataract produced by beta rays.

In view of the possible danger of radiation cataract, particular note was made of the condition of the patients' lenses before treatment. Three patients had peripheral lens opacities reducing vision to 6/12 or 6/9.

All these patients have now been followed up for 5 years after beta-ray treatment and the visual acuity in each case has remained unchanged.

Hughes (1953) suspected glaucoma in seven cases in which the total dose over the entire limbal region averaged 53 g./sec. He stated that the radon applicator he was using had an output of roughly 2,000 reps per g.—which would also place the dosage far in excess of any used in this series.

Discussion

The results of the treatment of rosacea keratitis in this series are most encouraging, only one case having been classified as a failure and this being probably due to inadequate dosage. We can therefore agree with Lederman (1957) that there are very few remedies that can compare with radiotherapy in the treatment of this condition. The individual doses of beta ray that were used are similar to those used by Lederman (1952, 1957), but he tended to give the doses at shorter intervals, usually weekly, and his total dosage may therefore have been greater. Since our findings suggest that equally good results can be obtained by leaving an interval of 6 to 8 weeks between doses and keeping the total dosage below 2,000 reps, there seems to be every advantage in this regime since the risk of complications is largely eliminated.

The results of treatment of long-standing virus keratitis with either superficial or deep vascularization were also good and active ulceration did not appear to be a bar to treatment; indeed, the ulcers themselves healed quickly. It appears that beta-ray treatment should be considered as an alternative to corneal grafting in such cases, particularly since devascularization would be advantageous even if a corneal graft had subsequently to be undertaken.

In recurrent keratitis of indefinite aetiology, in caustic burns, and in sclerosing keratitis, the treatment appeared to be much less effective, particularly in cases in which the vessels were large, surrounded by much

fibrosis, and of long standing; nevertheless, at least in the recurrent keratitis group, treatment appears to be justified, since half the cases were asymptomatic after treatment. The total dosage should nevertheless be kept within reasonable proportions, probably not much above 2,000 reps.

The results of treating vascularization after a corneal graft were good in the few cases attempted using only 1,000 reps. Lederman (1957) recommended 500 to 1,000r weekly for 4 weeks, depending on the state of the eye when first seen and the extent, age, and depth of the vessels treated. His series is of course much greater, but again the present results suggest that the intervals between doses might well be prolonged.

The results of treating active pyogenic ulceration of long standing were surprisingly good, and this form of therapy might well be considered more frequently in any case of indolent ulcer.

It is emphasized that in this series excellent results have been obtained in suitable cases using relatively low doses of beta ray which would not be expected to give rise to complications. It is felt that doses should normally be given only at sufficiently long intervals to enable their effect to be fully assessed; this usually means 6 to 8 weeks between doses rather than the weekly doses used by Lederman.

Summary

153 cases of various ocular diseases involving corneal vascularization treated with beta ray in the period 1953–1958 were assessed at the end of that time. The results were most encouraging in acne rosacea keratitis, in virus keratitis, both superficial and deep, in vascularization following corneal graft, and in active pyogenic ulceration of long standing. Treatment of recurrent keratitis of unknown aetiology and in other forms of vascularizing keratitis was less successful. The total dosage used was normally less than 2,000 reps, which is unlikely to give rise to complications; there was normally an interval of 6 to 8 weeks between doses so that the effect of each dose could be adequately assessed.

We are grateful to Mr. O. M. Duthie, Dr. A. Stanworth, and other surgeons at the Manchester Royal Eye Hospital for allowing us to treat and to report upon their cases.

We are also grateful to Dr. J. Ralston Patterson and the staff of the Christie Hospital, Manchester, and to Dr. Myerscough of the Radiochemical Centre, Amersham, for their help with the technical problems concerning the applicators and the dosage rates.

REFERENCES

- HUGHES, W. F., JR. (1953). Proceedings of the 413th Meeting of the New England Ophthalmological Society, April 14, 1953.
 LEDERMAN, M. (1952). *J. Fac. Radiol.*, **4**, 97.
 — (1957). *Brit. J. Ophthalm.*, **41**, 1.
 MERRIAM, G. R. (1955). *A.M.A. Arch. Ophthalm.*, **53**, 708.
 WILSON, F. M. (1952). *Amer. J. Ophthalm.*, **35**, 645.