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# EFFECT ON THE EYE OF RADIUM USED FOR TREATMENT OF MALIGNANT DISEASE IN THE NEIGHBOURHOOD*

BY

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At University College Hospital in 1931 it became clear that profound changes could be caused in the eye by radium used for the treatment of malignant tumours in its neighbourhood. I therefore began an inquiry into the effects of radium on the eye among cases treated by the surgical staff of the hospital, to whom I am indebted for constant encouragement and support.

The tumours treated included basal-cell carcinoma, lupus carcinoma and epithelioma of the skin, meningioma and carcinoma and sarcoma occurring in the upper jaw. Several of the cases had refused or were beyond the scope of operation.

For the first two years treatment was by interstitial or surface irradiation with needles of low linear intensity, but since 1933 a 1-gramme radium unit has been available. Needles with a 0.5 millimetre platinum screen were used at the beginning, but the experience gained in the first six months led to the substitution of these so far as possible by needles with a screen of 0.8 millimetre platinum for all cases in which it was necessary to introduce radium into the orbit.

I have included the late results of a few cases treated ten years ago with radium needles of high linear intensity and light screenage.

### Conjunctival Reaction: Early Effects

When malignant disease in the neighbourhood of the eye is treated by interstitial irradiation with radium a series of morbid changes may be observed in the eye. The main effect falls on the conjunctiva and skin of the lids, the eye itself, with the possible exception of the lens, being somewhat radio-resistant.

The first sign of any damage to the eye is a change in the appearance of the conjunctiva. The reaction of the conjunctiva to radium is characterized by oedema, hyperaemia, and a serous discharge. On account of the laxity of the subconjunctival areolar tissue the oedema of the bulbar conjunctiva may be intense. With an average therapeutic exposure the reaction begins a few hours after insertion of the radium and reaches its maximum between the fifth and eighth days, fading slowly to normal about three weeks later.

When the conjunctival sac is irradiated uniformly the whole conjunctiva will become oedematous, but the swelling will be greater in the lower fornix on account of the influence of gravity. When the radium is eccentrically placed intense chemosis on the exposed side of the eye may give place to a normal membrane on the other side of the same conjunctival sac. Swelling of the conjunctiva may be so great after heavy irradiation that the lids are pushed apart and the glistening red swelling overlaps the lower lid and spreads across the limbus on to the cornea. The upper lid may be so raised that the cornea is in danger of ulceration from exposure.

Hyperaemia increases with the swelling, and its greatest intensity marks the height of the reaction. Whether the conjunctiva or the skin of the lids shows the greatest reaction in a given case appears to depend chiefly upon which of the two is nearer to the source of irradiation. It has been observed that radium implanted into the orbit behind the eye can produce a severe conjunctival reaction without ascertainable change in the skin of the lids. It is possible that oedema of the orbital cellular tissue may contribute to the swelling of the bulbar conjunctiva under these conditions, for proptosis has been observed to follow interstitial irradiation of the back of the orbit by needles introduced through an opening in its outer wall. In this case the eye came forwards as the conjunctival reaction developed and receded again as it faded. A similar transient proptosis has been reported as the result of the introduction of radon seeds behind the eyeball.

Whilst the conjunctival reaction is still increasing a serous discharge from the conjunctival sac appears usually between the third and fifth days after irradiation is commenced. This discharge is not in proportion to the degree of reaction, and may be slight even in those cases which show severe chemosis with a skin reaction. Sometimes the discharge may be sanious, especially where the neoplasm has involved the conjunctiva. Often the discharge becomes muco-purulent and the normal conjunctival reaction is masked by a true inflammatory conjunctivitis of minor degree. This complication is seen usually where a pathological micro-organism is found in the conjunctival sac before irradiation, and especially where the eye has been closed either by a severe radium reaction or as part of the treatment.

Pain is not a feature even of a severe conjunctival reaction. Pain during the stage of active and subsiding conjunctival reaction suggests the onset of irradiation iritis. The patient complains of stiffness and pricking in a normal conjunctival reaction. Conjunctivitis increases the feeling of irritation without causing actual pain.

A severe localized reaction results when radon seeds are used in close proximity to the conjunctiva. The reaction reaches its maximum during the first days after the seeds have been implanted.

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When the eye is irradiated by a 1-gramme radium unit the conjunctival reaction is slight. This observation has been made on cases of carcinoma occurring in the upper jaw, in which the eye was displaced upwards by the growth before irradiation was commenced. Treatment by the "bomb" varied from twenty to forty-eight hours, but in each case the eye was directly exposed to irradiation, and on account of the involvement of the orbital plate of the maxilla in the growth an additional screen applied to the eye direct would have rendered the treatment less efficient. The conjunctival reaction reaches its maximum after about sixteen or eighteen days at the same time as the maximum skin reaction is seen. Some chemosis occurs with little hyperaemia, but the degree of swelling is not sufficient to prevent normal blinking. Even where the skin reaction has been so intense that moist desquamation has resulted the conjunctival reaction is of a minor degree.

Fading of the conjunctival reaction after interstitial irradiation is gradual. Usually the hyperaemia disappears, leaving a straw-coloured area of oedema of the conjunctiva. This returns to normal in about three weeks after removal of the needles. Even the chemosis of the conjunctiva caused by a tumour near the orbit will disappear after irradiation, provided that the tumour has been adequately treated. Conversely, if chemosis of this type, together with some or all of the additional chemosis associated with the radium reaction, persists after irradiation there is a strong presumption that treatment has been inadequate. Sometimes, and especially in those cases where radium needles are used very near the conjunctiva, large superficial conjunctival vessels may persist permanently or may appear some weeks after the conjunctival reaction has faded. This telangiectactic effect is not usually accompanied by a discharge.

### Conjunctival Reaction: Late Effects

A severe conjunctival reaction may be followed by scarring of the conjunctiva. Three to four months after interstitial irradiation the conjunctiva begins to thicken and shrink, and often adheres to the sclera. The normal transparency is lost and the thickened conjunctiva may in the course of years become densely white. Where a localized reaction has occurred this effect may be confined to the corresponding area. In some cases a thickened band of white conjunctiva passes from the inner side of the lid to the globe, so that movement of the latter away from the scar is limited. Contraction of the scar is so gradual that diplopia is not noticed by the patient, though it may be elicited on examination.

If the whole of the conjunctival sac has been irradiated equally with a relatively large amount of radium, and the needles have been inserted into the orbit in close proximity to the conjunctiva, the whole of the conjunctival sac will be involved in the process. The fornices become obliterated and the thickened conjunctiva passes directly from the lids on to the sclera, to which it becomes so firmly adherent as to restrict movement of the globe in all directions. If an excision of the eye becomes necessary this adhesion makes it difficult to separate the conjunctiva from the sclera. Healing of the incision in the damaged conjunctiva may take months. After the eye has been removed the conjunctiva shrinks so completely that during the second year after irradiation only a narrow pink crack can be seen when an attempt is made to separate the lids.

After the use of radon seeds localized conjunctival scars, accompanied by injection of the conjunctival vessels, are very common. These scars may be confined to the bulbar conjunctiva. Thickened folds of conjunctiva radiate from a depressed centre, which is adherent to the underlying sclera.

After irradiation with the 1-gramme unit the degree of scarring of the conjunctiva is negligible. The change in the conjunctiva is more in the nature of a slight loss of elasticity and ageing rather than a pathological process. No case in which the blood vessels have been permanently enlarged has been observed, but occasionally the eye has remained slightly red for some months.

Scarring of the lid margins is common after interstitial irradiation, but damage to the tarsal plate has not been observed. The whole or a part of the lashes may be permanently lost, and when this occurs the edge of the lid becomes rounded, so that the skin passes without appreciable change into the scarred conjunctiva.

In one case movement of the eye was so much diminished that fusion between the rounded margin of the lid and the scarred conjunctiva occurred. This conjunctiva was exposed in consequence of retraction of the lids, and gradually took on the appearance of skin.

Irradiation may lead to such scarring of the skin of the lower lid as to produce cicatricial ectropion. When of lesser degree the ectropion may be limited to eversion of the lower punctum. The tears then run down the cheek. In cases where the edge of the lid has become rounded the punctum is frequently obliterated and all trace of it disappears. When localized irradiation, for instance, of a basal-cell carcinoma near the inner canthus has obliterated one or both puncta the patient will have epiphora. Where irradiation has been so intense as to abolish the secretory activity of the lachrymal gland epiphora may be absent in spite of obliteration of the puncta. A small localized scar may result from the use of radon seeds in the lower lid. The contraction of this scar may be so severe that a nick in the contour of the lid margin is formed which allows the tears to run over. Scarring of the conjunctiva and lids is especially prone to follow the use of unscreened or lightly screened radium, but with increasing knowledge of its dangers these severe scars will be seen less often.

After irradiation with the 1-gramme unit an analogous scarring of the conjunctiva and of the lid margin can occur, but the change is of a minor character. Rounding of the lid margin with permanent epilation has only once been seen, and in this case there was epiphora from eversion of the punctum.

### Involvement of the Iris

The cornea and iris are affected only by relatively intense irradiation, and should, in the light of present knowledge, show no change as a result of radiotherapy. No reaction has been observed in either as a result of treatment with the 1-gramme unit. During the stage of radium reaction in the skin and conjunctiva discomfort only is felt in the eye. Pain is a sign that the iris has been affected. It is experienced during the first few weeks after the radium has been removed, when the conjunctival reaction has reached or has just passed its height.

The changes which have been observed in the iris vary from a slight swelling—iris reaction—only measurable by failure of the pupil to respond to homatropine as fully as before irradiation, to a definite iritis characterized by posterior synechiae. I have never yet seen K.P. The synechiae are formed in that part of the iris which is most exposed to irradiation. They break down readily under the action of a mydriatic, and may do so of their own accord without treatment. Irradiation iritis is distinguished from all ordinary forms of iritis by its tendency to resolve spontaneously without relapse.

### Radium Necrosis of the Cornea

The chief morbid change in the cornea is ulceration, which may be a direct result of irradiation—radium necrosis—or may arise indirectly for one or more of the following reasons.

The cornea may become relatively dry, because the secretory activity of the lachrymal gland has been reduced by irradiation.

Closure of the eye may be prevented by massive oedema of the conjunctiva which has not been controlled by

preliminary apposition of the lids. The exposed cornea will then become superficially ulcerated, but will heal without a scar if it can be covered by the lids. Pain is more severe than in radium necrosis of the cornea.

At a later date, if ectropion has followed irradiation, the lower part of the cornea may ulcerate from exposure, even without damage to the lachrymal gland.

Radium necrosis of the cornea is the most serious result of irradiation, and is usually associated with radium necrosis of skin or bone. It appears as a delayed reaction about three months after a single intensive irradiation, but the time of onset varies and is dependent on the intensity of the irradiation. A severe necrosis may appear shortly after a repeated irradiation, even where the initial treatment has been by the 1-gramme radium unit or by deep *x*-ray therapy.

Diminution of sensation is the earliest sign of damage to the cornea. On touching the cornea lightly with cotton-wool, blinking is slower than in the normal eye. This effect may appear within a few weeks, persist for months, and disappear leaving the sensation of the cornea normal. I have seen diminution of sensation of the cornea on one occasion follow intensive irradiation with the 1-gramme unit. Normal sensation was eventually restored. But diminution of the corneal reflex to light touch may prove to be the forerunner of a radium necrosis of the cornea.

Radium necrosis begins with a loss of polish of the cornea, usually at the centre, but where the irradiation has been directed from the side the effect may be confined to the corresponding sector, the cornea at a distance being normal. Within a few hours loss of polish is followed by the appearance of one or more small superficial ulcers, which have a smooth base and undermined edges. The process may be arrested at this stage, but as a rule the ulcers spread slowly and coalesce to form one large ulcer, which may involve the whole cornea, except for a narrow rim at the periphery. Alternatively, a single ulcer may extend by stripping up the epithelium, so as to form one or more ridges radiating from its margin. The summits of these ridges split and the edges of the splits become undermined.

Up to this point radium necrosis of the cornea bears a strong clinical resemblance to neuro-paralytic keratitis, but differs from it in having a slower onset and a remarkable resistance to infection. It is only after some weeks that the onset of a mild infection is indicated by punctate infiltration around the ulcer. There is little reddening of the eye and no ciliary injection in the absence of iritis. If the eye is kept covered and a mydriatic is used the ulcer may remain stationary and the patient comfortable for months. The spread of infection in these eyes is so slow that it may be months before the ulcer begins to extend and to develop points of yellow exudate in its base. With this there is increase of the punctate infiltration and deep striation appears in the cornea. A mild iritis, which yields readily to treatment, may be set up by an extension of the corneal infection.

Pain is not an outstanding feature of radium necrosis. Even when a large ulcer is present little complaint is made.

Radium necrosis of the cornea tends to progress to perforation, and when this occurs the anterior chamber is open to invasion by micro-organisms from outside. The natural resistance of the interior of the eye to infection must be considerable, for it is usually some weeks before a mild enophthalmitis begins. Radium necrosis of the cornea is an aseptic destruction by a physical agent. When it perforates the edges of the opening do not necessarily contain pathogenic micro-organisms, though they are slow to heal because they have been irradiated. These two factors probably account for the delay in infection of the whole eye.

Occasionally a severe necrosis may take place quite rapidly. The whole cornea separates painlessly. I have seen this catastrophe in some of the earlier cases after repeated irradiation complicated by sepsis in the neighbourhood. It was not associated with conjunctivitis. In one case the cornea separated, followed by the iris and lens. The whole eye disintegrated so completely that there was no recognizable trace of the sclera three days later when the orbit was exenterated. In another case sloughing of the cornea was followed by loss of the iris and lens with subsequent panophthalmitis.

### Repair of Damaged Cornea

Provided that the reparative powers of the cornea have not been destroyed healing will take place slowly. When the ulceration is shallow and before the whole cornea is involved repair without opacity in about four months is possible. For this it is essential that the condition be recognized early and that the ulcer be covered by tarsorrhaphy. If a cornea which has been protected by tarsorrhaphy is irradiated it may still develop ulceration, but heals without opacity. A deep ulcer may take up to eight months to heal. A dense leucoma may form with superficial vascularization of the cornea, the density being proportionate to the depth of cornea lost. A perforation of the cornea from radium necrosis has been seen to heal, even without tarsorrhaphy. Ultimately vision depends on the position of the corneal opacity, on the degree of residual astigmatism, and on the possible development of an irradiation cataract.

### Irradiation Cataract

Radium cataract is usually a late reaction to irradiation, and appears two years or more after exposure. No record has been found in the literature of an early radium cataract which became mature, although one case has been reported in which small vacuoles were seen in the lens ten days after the insertion of two radon seeds. One seed was near the lens and both were of high intensity. The vacuoles disappeared within fourteen weeks.

I have been fortunate enough to see one case of early mature radium cataract. It followed an extensive interstitial irradiation, the orbital part of which consisted of six 2-milligramme needles arranged symmetrically round the eye. The lens was therefore irradiated heavily from all sides. Three days after removal of the needles a few subcortical opacities of the radiating senile type were seen in the anterior and posterior parts of the lens. Four weeks later 1.5 dioptres of myopia had developed, and vision was slightly reduced by a fine uniform haze throughout the lens. The senile striae had also increased. Seven weeks after removal of the radium the cataract was mature. The changes in the lens preceded, and therefore were not secondary to, the attack of irradiation iritis which followed.

The typical irradiation cataract is a posterior cortical one. It may follow exposure to various forms of irradiation, and its occurrence has been recorded in the literature for the last thirty years. The earlier examples followed exposure to *x* rays. After exposure to radium it usually develops during the second and third years, though its appearance may be delayed until the sixth year or later.

Radium cataract begins in the posterior part of the lens with vacuoles which are not quite circular. Fine spots and feathery lines appear among the vacuoles, and all the changes extend outwards and forwards in the lens until there is a posterior opacity, with its margin denser than its centre. The cataract may be arrested at this stage or may go on to maturity. When it goes on to maturity striae of the ordinary senile kind are formed, sometimes with vacuoles beneath the anterior capsule. Fine punctate opacities appear scattered throughout the lens. They are seen first in the part of the lens most exposed to irradiation. The cataract becomes mature by the gradual evolution of these changes. The mature radium cataract possesses no special features, but if occasion arises is amenable to operative treatment.

Among the early cases of this series there were two examples of late radium cataract, both of which were mature when first seen. Both were treated with needles of high linear intensity, lightly screened with 0.3 millimetre of platinum. In both

patients the cataract developed on the side irradiated and the other eye remained clear. After 1931 the platinum screen was increased to 0.8 millimetre for interstitial irradiation near the eye, and in 1933 a 1-gramme unit became available. Since then radium cataract has not been seen.

It is probable that delayed radium cataract arises from interference with the nutrition of the lens, caused by endarteritis and telangiectatic changes in the ciliary body. As these changes are much less in degree after mass irradiation than after interstitial irradiation it is possible that late radium cataract may not follow its use, but it is only four years since "bomb" treatment was started at University College Hospital, and it is therefore too soon to be certain.

It must always happen that many patients who suffer from malignant disease, needing treatment by radium, die of their disease before there has been time for late radium cataract to develop.

In this series of cases no changes have been seen in the fundus as a result of treatment of neighbouring tumours by interstitial or mass irradiation. This is in striking contrast with the effect of radon used in the treatment of intra-ocular growths, but, of course, these methods of irradiation are not strictly comparable.

In no case has the other eye been damaged by or involved in any type of radium reaction.

### Management of a Case in which Damage to an Eye May Occur

When interstitial irradiation of the tissues round the eye is proposed the cornea is first protected by stitching the lids together as before division of the sensory root of the fifth nerve. The degree to which the conjunctiva can swell is then limited by the pressure of the lids.

As the closure of an eye always carries a tendency to conjunctivitis the eye is washed twice a day with normal saline without disturbance of the stitch holding the lids. Muco-purulent discharge necessitates more frequent irrigation. The neighbouring skin, where exposed to irradiation, is protected from wetting by sterile vaseline. Sterile vaseline is also smeared on the lid margins to prevent the lashes sticking together. The metallic preparations such as silver or zinc should not be used, as they may give rise to secondary radiations.

The stitch holding the lids together is kept in place until the skin reaction is definitely fading. The tendency is to remove it too soon. The swollen conjunctiva immediately fills the palpebral aperture and flows over the lower lid. It then dries, and so increases the discomfort of the patient. If the stitch has been removed too soon an attempt must be made to close the eye by strapping the lids together. Occasionally the lids will not meet and must be strapped across the prolapsed conjunctiva. If it is not possible to cover the cornea with the lids a Buller's shield will keep it moist and protected from dust.

When tumours in the neighbourhood of the eye are treated by the 1-gramme unit the conjunctival reaction is often so slight that stitching, or even strapping, the lids together is unnecessary. In any case the onset of the reaction is so gradual that ample time is allowed for closure of the eye should this be required.

If the eye is displaced by a tumour it will gradually resume its normal position after irradiation. During this process any tendency to diplopia will be lessened if both eyes can be kept open.

So long as the lids are stitched together the eye cannot be examined, and the only clue to the state of the iris lies in the subjective sensations of the patient. He may feel irritation, stiffness, or pricking as a result of the conjunctival reaction, but pain suggests iritis. The pain is worse at night, when the pupil is contracted in sleep, and may be very severe. If the pain is relieved by homatropine the diagnosis of iritis is confirmed, and treatment by atropine can be instituted. The synechiae of irradiation iritis are lightly attached to the anterior lens capsule and give way easily, so that full dilatation of the pupil is soon obtained. As irradiation iritis tends to resolve spontaneously without relapse the atropine can be reduced as soon as the pain is under control. The mydriatic can be discontinued sooner than in the treatment of a true inflammatory iritis.

All cases where the eye has been exposed to intense irradiation should be seen once a week during the first six months. Radium necrosis of the cornea may begin about eight weeks after irradiation, particularly where the reaction has been so severe that an iris reaction or an irradiation iritis has occurred. The cornea is examined for diminution of sensation, as this probably precedes desquamation of the superficial layers. The greatest loss of sensation will be in the sector exposed to the maximum irradiation. Whenever it is thought possible that radium necrosis may occur the cornea is stained with fluorescein at each examination. This is particularly important after repeated irradiation. Shallow areas of necrosis give rise to so little pain and so little reddening of the eye that their existence may not be suspected unless the cornea is stained. At this early stage the cornea may heal with palliative treatment alone.

Healing without opacity is made much more certain by tarsorrhaphy, but even then may take from four to eight months. The lids should be split to secure firm union, and the stitches should be left in place for four weeks. In the presence of infection or of progressive necrosis tarsorrhaphy offers the chief hope of preventing perforation.

If the cornea perforates it is probably useless to try to save the eye. Healing of the perforation is unlikely. The usual result is an enophthalmitis of low grade, which only gives clinical evidence of its existence some weeks after the perforation. Perforation of the cornea is an indication for removal of the eye. Owing to the shrinking of the conjunctiva and of the palpebral aperture which follows irradiation an artificial eye cannot be worn.

### Conclusions

The observation of eyes which have been exposed to radium irradiation of destructive intensity has demonstrated a series of morbid changes leading progressively to radium necrosis of the cornea and loss of the eye.

When treatment of neighbouring malignant tumours is by interstitial irradiation these changes can be reduced by adequate screenage of the radium needles.

After mass irradiation by a large quantity of radium at a distance the damage to the eye is negligible.

As greater quantities of radium become available, and facilities for the use of mass irradiation become more widely distributed, it is to be hoped that damage to the eye by interstitial irradiation will cease to be of more than historic interest.

The lecture was illustrated by lantern slides. The cases upon which it is founded are reported in:

Martin, P. (1933). *Tr. Ophth. Soc. U. Kingdom*, **53**, 246.
—— (1936). Ibid., **56**, 87.

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It has been decided to wind up the Zunz Fund and each of the thirty-four London hospitals which have received grants from this fund for the past thirty-eight years has been offered by the trustees its share of the capital, which totals approximately £425,000. Wards maintained by the grants were named "Annie Zunz." The present distribution of the capital was provided for in the will of Siegfried Rudolf Zunz, a wealthy merchant who died in 1899. The winding up of the estate was to take place on the death of a specifically named annuitant, which has now occurred.