# THE RADIUM TREATMENT

of

# PRIMARY MALIGNANT DISEASE

of the

# SCLERO-CORNEAL JUNCTION

being a Thesis submitted by

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# I N T R O D U C T I O N

The Radium Treatment of Malignant Disease of the Eye has not received, in this country, great attention from Ophthalmologists or from Radium Therapists.

In America, much more has been written on the subject. The experimental work on animals has been undertaken almost entirely in Germany. As no Ophthalmologist who has been trained in Radium Therapy of the skin and mucous membranes has yet investigated the application of superficial radium treatment to the eye, the writings on the subject are, from the Radium Therapist's standpoint, incomplete.

At the Radium Institute, London, a large stock of Radium is available in a great variety of containers. Patients from London, the South of England, and the Midlands, seen by Ophthalmologists of repute, are referred to the Institute for the Radium Treatment of Malignant Disease of the Eye. The cases are viewed at regular intervals by the Ophthalmologist and the Radium Therapist, in order to ensure confirmation of diagnosis and co-operation in treatment. A very complete

knowledge of the technique of Radium Treatment has thus been accumulated during twenty-five years' experience.

Malignant Disease of the Eye is an extensive field of study. In this thesis, attention is confined to the surface of the eyeball, and, in particular, to the Corneo-scleral Junction. The choice of such a restricted area has been determined by the possession of complete records of a comparatively large series of malignant Limbal Tumours. The satisfactory results in these cases justify expression of the claim of Radium Therapy to be the method of choice in the treatment of Malignant Disease of the Limbus.

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## PHYSICS AND APPARATUS

The effects of Radium were known before Radium itself was discovered. Becquerel, in 1896, while investigating Phosphorescent Phenomena found radio-activity, as now named, in uranium, an element derived from Pitch-blende (Uranium-Oxide). Not until 1898, and owing to the work of Monsieur and Madame Curie, was Radium itself identified and isolated. When Uranium has been extracted, Pitch-blende, by repeated processes of fractional crystallisation, yields a minute quantity of Radium. The present known sources of supply of Pitch-blende are few in number, and by no means unlimited in quantity. On these counts, Radium is a very expensive substance.

A peculiar property of Radium is the constant emission of particles from the atom. This change is accompanied by electro-magnetic disturbances which are sufficiently great to discharge an electroscope. The alterations in the atom of Radium are minute but are steadily progressive, so that in roughly 1,690 years half of the element has degenerated. The substances into which Radium changes are also engaged in altering their atomic structures, causing similar particles of matter and similar etheric waves to be produced. These sub-

stances are elements whose atomic weight is slightly lower than that of the Element Radium. The final change of Radium degeneration is to lead, which is not a radio-active element.

Radon is a gas produced in a few days by the degeneration of Radium. In 3.85 days Radon has become inert to the extent of one-half the original activity. Radon is as effective as Radium and is convenient as rendering available for use imponderable quantities of Radium.

The particles produced by Radium and Radon are of two kinds - Alpha particles and Beta particles. The Alpha particle is a positively-charged atom of Helium travelling at a speed of nearly 12,000 miles per second. The range of the Alpha particle is small, and the progress of the particle can be arrested by the interposition of a sheet of paper. The Beta particle is an electron. Beta particles penetrate much further than Alpha particles; Beta particles from a source applied to the skin in man can be found even as far as one centimetre depth in the soft tissues.

The electro-magnetic disturbances produced by radio-active substances are called Gamma rays. These rays are of the nature and have the velocity of X-rays and light rays, but are of much shorter wave-length. The penetration of the Gamma rays is extreme. The Rays from Radium can be detected after their passage through 8 centimetres of lead.

Since, when Radium is held in a metal container, Gamma rays

reach the surface of the container, and secondary Gamma rays are excited from the atoms of the metal, Alpha and Beta particles are thrown off. Metal containers used for surface application in the treatment of disease are covered by paper, lint, or gutta-percha, in order to prevent the secondary Alpha and Beta particles from reaching the skin or mucous membrane.

A filter, shield, or screen is the term applied to a protective substance covering the radium or radon container. The Alpha particles, some or all of the Beta particles, and the longer Gamma rays are absorbed. A filter naturally prolongs the time of application, but is required when the penetrant effect of the Gamma rays is used for the treatment of structures more than 3 millimetres or so below the skin. A filter of platinum or gold, 0.6 millimetres thick, will absorb all the Alpha particles and practically all the Beta particles.

A measure of the activity of the exposure to radium may be obtained from the number of milligram-element-hours given, i.e. the number of milligrams of radium element in the applicator multiplied by the number of hours of application. This measurement can be expressed as an equivalent number of "millicuries destroyed", if the number of milligram-element-hours be divided by 133.3. One millicurie is the amount of energy in equilibrium with one milligram of radium. The activity of radon is expressed in millicuries and the dose in millicuries destroyed.

One of the biological units of radio-activity is the Skin Erythema Dose. This amount of exposure of the skin to radiation produces, ten to twelve days after treatment, a redness lasting one to two weeks. The physical units are not interchangeable with the biological in any simple proportion. In order to assess, biologically, any dose of radiation, the following facts must be known in the case under consideration:-

(1) The weight of radium or the strength of radon in the applicator.

(2) The active area of the applicator.

(3) The filter material and the thickness of the filter wall (a platinum or gold filter is equivalent to a lead or silver filter of twice the thickness).

(4) The distance between the radiation source and the part treated.

(5) The duration of each exposure, the interval of time between consecutive exposures, the total number of exposures.

The apparatus in which radium is held may be in the form of needles, tubes, or flat applicators. Spherical applicators and gauze impregnated with radium have been used by the earlier workers, but have now been generally discarded. The radium is used as radium sulphate in most of the apparatus now made, because this salt is insoluble in water. The bromide and the chloride of radium are soluble, hence the entrance of water would dissolve the radium salt from the container.

The radon is collected in capillary glass tubing, the tubing is divided into lengths of about ½ centimetre and the ends are sealed in a flame. The concentration of radon is adjusted so that a known quantity is contained in the determined length of capillary tubing. Each small piece of tubing is called a seed (radon seed). Formerly, the seeds were used bare and implanted permanently, but now the seed is encased in a platinum or gold wall 0.3 to 0.5 mm. thick, and the seed may be threaded to allow of withdrawal.

The applicators used for ophthalmic treatment are flat plates in which the strength of radium element is about 5 milligrams per square centimetre of active area. Circular applicators are used in nearly every case, but square applicators are employed for larger areas of growth. The sizes of the circular applicators range from 0.75 centimetres diameter and increase by 0.25 centimetres gradations to 1.5 centimetres. The square applicators are of 0.8 centimetres, 1.25 centimetres, and 1.5 centimetres edge respectively.

In the Radium Institute, London, the applicators are prepared by Mr. W.L.S. Alton, F.I.C., Director of the Chemical and Physical Laboratory, in the following manner:-

A shallow tray of Monel metal (65% nickel, 30% copper, 5% other metals) of the required dimensions is accurately levelled on a surface plate, and the edges given a preliminary

coating of silver solder. Layers of mica are laid in the tray until it is full to the edge, in order to give support to the thin metal screen which is later applied on top. The weighed amount of radium sulphate, mixed into a paste with magnesia and water, is spread over the surface of the uppermost mica sheet. This paste is carefully dried and eventually heated to 200 degrees centigrade in order to dry off all traces of water, when the film is seen as an enamel-like layer, the radium sulphate being particularly evenly distributed. Meanwhile a piece of Monel metal 0.05 millimetres thick has been cut, rather larger than the applicator, and a thin coating of solder applied to the edges of the metal. This screen is laid on a piece of hard wood, and the applicator, with the addition of another piece of mica (0.001 millimetres in thickness), is laid face downwards on the prepared screen. A screw clamp is used to keep the applicator firmly pressed against the screen. By means of a silver-soldering-iron, the smallest possible amount of solder is run round the applicator. When this has been done, applicator and screen are heated by a Bunsen Burner until the solder melts. The screw clamp is quickly tightened so as to make intimate contact between the edges of the applicator and the metal screen. A small vent-hole has been drilled in the back of the tray in order that the molten solder should not be drawn in as the applicator cools. The vent-hole is sealed with a spot of solder, and

afterwards smoothed with a file. The edges of the screen are trimmed with scissors and a protecting band of solder is run round the applicator.

A table showing the full-strength applicators used in ophthalmic treatment at the Radium Institute, London, is here shown:-

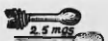
| Diameter or side in Centi-metres. | Super-ficies in sq. cm. | Weight of Radium in milli-grams. | Shape. |
|---|---|---|---|
| 0.75 | 0.44 | 2.25 | Circular. |
| 0.80 | 0.64 | 3.50 | Square. |
| 1.00 | 0.71 | 5.00 | Circular. |
| 1.25 | 1.23 | 6.20 | Circular. |
| 1.25 | 1.56 | 7.80 | Square. |
| 1.50 | 1.77 | 8.80 | Circular. |
| 1.50 | 2.25 | 10.00 | Square. |

The usual strength of the Radon Seed is 1.8 mc., but seeds containing 3 to 10 mc., have been used.

PLATE I

# FLAT APPLICATORS.

## FULL STRENGTH.

| SIZE C.MS. | | | | |
|---|---|---|---|---|
| 0.75 |  2.25 mgs. | A. $A_1$ | | |
| 1.00 |  5. mgs. | B. $B_1 B_2 B_3 B_4$ | | |
| 1.25 |  6.2 mgs. | C. |  7.8 mgs. | C. |
| 1.50 |  8.8 mgs. | D. |  10 mgs. | D. $D_1 D_2 D_3$ |
| 2.00 |  15. mgs. | E. $E_1$ |  20 mgs. | E. $E_1$ |
| 2x1 | | RECTANGLES |  10 mgs. | F. $F_1$ $F_2$ |
| MATCH HEAD EYE SPATULÆ |  2.5 mgs. 3.5 mgs. | A.B.C.D. | | |

## HALF STRENGTH.

| | | | | |
|---|---|---|---|---|
| 1.50 | | |  5 mgs. 7.5 mgs. | 1. $1_A$ |
| 2.00 |  8.25 mgs. | 2 |  10 mgs. | 2. $2_A$ $2_B$ |
| 3.00 |  17.5 mgs. | 3. $3_A$ |  22.5 mgs. | 3. $3_A$ |
| 4.00 | | |  40 mgs. | 4. $4_A$ $4_B$ $4_C$ $4_D$ |
| 3x2 | | RECTANGLES |  15 mgs. | 5. $5_A$ $5_B$ $5_C$ $5_D$ $5_E$ $5_F$ $5_G$ $5_H$ $5_I$ $5_J$ $5_K$ |

Flat Applicators. The Radium Institute, London.

## THE BIOLOGICAL EFFECT OF RADIUM

A summary of the present theories of the general effects of radiation is given by Ward and Smith (1933). A living cell exposed to the action of radium undergoes destructive changes in which the nucleus is affected first. A-typical mitosis appears, the chromatin of the cell becomes granular and tends to break up into fragments. Cells in active division, such as the spermatogenic cells of the testis, are very readily affected by the gamma rays of radium. The interstitial tissue of the testis, however, may be unaltered by the same exposure to radiation, because these cells divide slowly and at long intervals. When the skin is irradiated the greatest effect is found in the deepest layers of the epidermis. The slowly growing cells of the underlying dermis and of the more superficial epithelial layers may be unaffected by a dose of radiation which destroys the generative layers. The reaction to irradiation is not apparent in this case until the overlying epithelial layers are thrown off in the natural course. In ten to twelve days the skin becomes red and the surface appears raw. After a period of one or two weeks, the epithelial covering is restored by an ingrowth of the unaffected cells at the periphery of the irradiated area.

These examples of the selective direct action of radium show the possible value in therapy, where cells more radio-

sensitive may be destroyed without harm to their neighbours. A caustic or destructive action is produced by the gamma rays of longer wave-length and by the alpha and beta particles of radium. The caustic effect destroys both the rapidly and slowly-dividing cells. The caustic rays are soft i.e. do not penetrate deeply below the surface.

The effect of radium on a living tissue or collection of cells is modified by the simultaneous radiation of the supporting stroma of blood, lymph, nervous and connective tissues. The stroma undergoes changes which may cause the death of the special cells, this result being an indirect action of radium on these cells. The stroma also suffers permanent modification. These changes allow a quicker and more severe action to follow a subsequent exposure to radium. Fibrotic changes in the stroma result from each irradiation, producing an avascular, hard, inelastic thickening of the tissues. The late changes after irradiation (atrophy, abnormal pigmentation, loss of pigmentation, telangiectasis, ulceration) are due to this modification of the stroma.

Several factors influence radio-sensitivity. The highly malignant tumours, at the primary tumour site, are usually very sensitive to the action of radium, but metastases occur very readily. Tumours which have become infected lose their sensitivity to radium; the therapeutic application of radium

in such cases may cause exacerbation of the inflammation without appreciable effect on the tumour cells. Glandular carcinoma in most cases is more radio-resistant than new-growths from other types of tissue. Tumours possessing a good blood supply are as a rule susceptible to radiation, and, by contrast, fibrotic tissues are not radio-sensitive.

The action of X-rays and radium on the eye has been studied experimentally, in animals, and during treatment in man. Desjardins (1931) reviewed the experimental work on animals and concludes that the effect of X-rays and the gamma rays of radium are similar and resemble in character those seen in man. Peter (1930) and Aulamo (1931) repeated the experiments on rabbits, and declare that the lens and the conjuctiva are equally sensitive to irradiation, but that the lens-changes are noticeable only after many weeks have elapsed. A dose slightly less than the skin-erythema-dose affects the conjuctiva and lens. This observation upsets the view previously held, that the lens is insensitive to irradiation. Earlier experimenters had not kept the rabbits alive for a period sufficiently long to allow the development of a post-radiational cataract. The effect of radiation depends on the age of the animal. The rapid development of the eye enables it to tolerate increasing doses of radiation with impunity, so that three months after birth the eye of the cat and the rabbit is no

longer affected by doses below the tolerance limit of the skin. The conjuctiva, the lens, the cornea, the iris and ciliary body and the retina, are, in the order named, increasingly resistant to irradiation.

Hoffmann (1932) reviewed the subject of the injurious effects of X-radiation on the human eye. It is found that these injuries appear as early or late sequelae. Early sequelae occur in the eyelids, the conjuctiva, the cornea, the iris and the retina. Late sequelae occur in the lens and in the anterior chamber of the eye.

The eyelids show erythema, epilation, or oedema, according to the degree of irradiation, usually ten to fourteen days after a single over-exposure.

The epilation may be permanent. After repeated exposures, telangiectasis, pigmentation and atrophy of the skin may occur.

The conjuctiva shows hyperaemia, hypersecretion, and cell-desquamation, ten to fourteen days after exposure to 110% of the erythema-dose for the skin. In some cases these symptoms continue only a week or so, but after heavier doses of radiation there may be permanent sequelae, such as chronic thickening of the conjunctiva with contraction of the conjunctival sac. After more severe over-dosage there may result hyperkeratosis, sclerosis and permanent vascular changes. The vascular changes, consisting of fusiform dilatation of the vessels between

annular constrictions, are found in the conjunctiva, iris, choroid and retina.

Changes in the cornea are seen when the conjunctivitis is well marked. The normal shining appearance of the cornea is lost. Later, patchy desquamation forms erosions which tend to become confluent, to heal locally, and then to appear in other places. These conditions may persist for weeks or months before the cornea is restored to the normal condition. A frequent sequela to the superficial keratitis is a parenchymatous keratitis, which may undergo resolution. If persistent, however, a parenchymatous keratitis will interfere with the power of vision. Another form of corneal injury is the production of ulcers, which may become confluent and penetrate deeply. There follows a perforation of the cornea, which eventually requires treatment by enucleation of the eye. An early symptom of corneal injury, caused by doses from 80% to 120% of the skin - erythema - dose, is a diminution of sensibility to touch.

The iris, after severe irradiation, shows telangiectasis and changes in the pigment epithelium of the uvea.

The retina does not appear to be affected by X-rays without manifestations of damage to the conjunctiva or cornea. The radiation has usually been unscreened when damage has occurred to the retina. Injury to the retina and other parts of the eye has occurred in patients previously treated by ionisation

with metallic salts. In these cases, the production of secondary radiations from the metallic deposit is probably the cause of injury.

Cataract may appear as a late sequela without any history of severe early reaction. The opacity occurs usually two to three years after exposure. Lens changes in most cases follow radiations that were well screened, but may follow any full erythema-dose of X-rays irrespective of the quality of the radiation applied to the eye. The cataract usually appears in the cortical layer at the posterior pole of the lens and is densest at the centre, becoming thinner peripherally. Lebensohn (1932) states that over 50 cases of cataract following X-radiation have been described in the literature.

Glaucoma is preceded by obvious inflammatory lesions in the eye and is associated with changes in the blood-vessels. The prognosis is extremely bad. A single erythema-dose has been known to produce glaucoma.

The injuries to the eye produced by exposure to the action of radium, are identical with those which follow exposure to X-rays. Few cases of injury have been due to treatment of the eye by radium. Several cases of injury to the eye have occurred during radium treatment of conditions near the eye. Regaud and others (1926), Kumer and Sallmann (1929) and Stock (1928) state that 100% of the skin-erythema-dose is the maximum

application of radium to the eye which, with safety, may be borne as a single exposure; a total exposure to 300% of the skin-erythema-dose should be divided over a period of one year. The eyelids become erythematous after the application of 60% to 70% of the skin-erythema-dose.

Radium used in the treatment of malignant tumours of the upper jaw has caused injury to the eye and orbit. Knapp (1923) reported several cases of inflammation in the orbit and Martin (1933) described three cases of cataract which followed the insertion of heavily-filtered radium into the upper jaw near the orbit.

The therapeutic application of radium to the skin of the eyelid has caused damage to the anterior parts of the eye. Injury occurred in 34 cases of carcinoma of the lid reported by Blegvad (1931), three cases of rodent ulcer of the lid reported by Milner (1934), one carcinoma and one sarcoma of the eye-lid reported by Robinson (1926), a chronic ulcer of the skin at the outer canthus reported by Knapp (1932), a basal-cell carcinoma of the eyelid reported by Morax (1926). In the treatment of affections of the tarsal conjunctiva similar injuries have been noted in five cases of vernal catarrh reported by Quick (1930), three cases of vernal catarrh reported by Schoenberg (1920), one case of vernal catarrh reported by Schweinitz (1931), and a lesion of the eyelid

reported by Meesmann (1928).

Moore (1930 and 1931) described changes in the lens following the insertion of Radon seeds, filtered by 0.5 mm of platinum, into the globe of the eye for the treatment of one case of glioma retinae and one case of melanotic sarcoma of the choroid. Schoenberg (1920) found lenticular opacities and a ring of chorio-retinitis round a gliomatous mass on the retina of a child treated by "a few radium applications".

In the treatment of diseases of the bulbar conjunctiva only five cases of injury have been reported. Kress (1923) described the occurrence of bilateral uveitis in a man of 45, a few days after treatment for bilateral post-operative recurrent pterygia. "A single exposure to radium" had been given to each eye. Johnson (1924) reported two cases of carcinoma of the conjunctiva successfully treated by "Silver-filtered" tubes of radium held at one millimetre distance from the conjunctiva. Cataract occurred in one case. The other patient developed lens opacities and partial optic atrophy followed by glaucoma. Schweinitz (1931) reported two cases of malignant epibulbar neoplasm treated by "radium with a screen of 0.5 mm. aluminium". One patient developed a disc-shaped opacity at the posterior pole of the lens together with fine opacities beneath the anterior capsule. The second patient showed telangiectasis of the conjunctiva together

with anterior sub-capsular opacities in the lens. Considering the many cases of conjunctival disease treated by radium application, the number of reported accidents form a very small percentage.

## SURGICAL ANATOMY

Sir Arthur Keith (1921) gives a succinct account of the embryology of the anterior chamber of the eye. The lens is developed from a saccular invagination of the ectoderm, which by the severance of its connection with the ectoderm becomes a closed sac. The wall of the sac is composed of a single layer of epithelial cells. The cavity of this lenticular vesicle is gradually obliterated by the elongation of the cells of the posterior wall, which grow until they reach the anterior wall. Each elongated cell is transformed into a lens fibre. The capsule of the lens is a cuticular membrane formed by the lenticular cells. New lens fibres are added by the cells at the margin (equator). The fibres of every additional layer produced are longer than those of the previous layer, hence the arrangement of the fibres is concentric. Growth continues until puberty, and even then has not ceased. Priestley Smith found that there is an appreciable addition to the weight of the lens with each decade of life.

Like the epidermis the lens shows a tendency in the aged to be transformed into keratin. The oldest cells (the central or nuclear fibres), alter first. This may determine the central position of the cataract which occurs in old people.

The epithelial covering of the cornea is continuous with the surrounding ectoderm. Mesoderm grows in between the lens vesicle and the ectoderm to form the connective tissue basis of the cornea.

The anatomy of the eye is well described in Gray's Anatomy (1920). The bulb of the eye, enveloped by a thin membranous sac, the fascia bulbi (capsule of Tenon), is embedded in the fat of the orbit. The periscleral lymph-space is bounded externally by the capsule of Tenon: the lymph-space is continuous with the sub-dural and subarachnoid cavities. The eyeball has the shape of segments of two hollow spheres of different sizes. The anterior segment, the cornea, is one of a small sphere; it is transparent and forms about 1/6th of the bulb. The diameter of the eyeball at birth is about 17.5 mm., at puberty from 20-21 mm., and in adult life about 24 mm. The bulb of the eye is composed of three tunics enclosing the refractive media. From without inwards, the tunics are:

1. The fibrous coat, consisting of the sclera behind, and the cornea in front.
2. The vascular pigmented coat comprising, from behind forwards, the choroid, ciliary body, and iris.
3. The nervous coat, the retina.

In front, the sclera is directly continuous with the cornea, the line of union being termed the limbus, or corneo-

scleral junction. In the substance of the sclera close to this junction is a circular canal, the Sinus Venosus Sclerae (canal of Schlemm), lined by endothelium, communicating internally with the anterior chamber of the eye, and externally with the anterior ciliary veins.

The cornea is almost circular; it is dense and of uniform thickness. The cornea consists from before backwards of four layers:-

1. The corneal epithelium, continuous with that of the conjunctiva, composed of several rows of cells similar to those of the epithelium of the skin. The deepest cells are columnar, then follow two or three layers of polyhedral cells, the majority of which are prickle-cells. Then lastly, there are three or four layers of squamous cells with flattened nuclei.

2. The Substantia Propria, fibrous, tough, unyielding, and perfectly transparent, composed of about 60 flattened, superimposed lamellae, continuous with fibres of the sclera. Between the lamellae is a small amount of ground-substance in which are spaces (the corneal spaces), each containing a cell, the corneal corpuscle. The layer immediately beneath the corneal epithelium contains no corneal corpuscles and may be regarded as a distinct membrane, named the anterior elastic lamina (Bowmann's Membrane).

3. The posterior elastic lamina (Descemet's membrane), covering the posterior surface of the substantia propria. At the margin of the cornea the posterior elastic lamina breaks up into fibres which form the inner wall of the Canal of Schlemm. The trabecular nature of this wall produces the

spaces of the angle of the iris (spaces of Fontana) which allow of filtration of the aqueous humour in the anterior chamber through to the Canal of Schlemm.

4. The endothelium of the anterior chamber, covering the posterior surface of Descemet's membrane.

The cornea is a non-vascular structure, the capillary vessels of the conjunctiva and sclera ending in loops at its circumference. Lymphatic vessels have not yet been demonstrated in it, but are represented by the channels in which the bundles of nerves run; these channels are lined by an endothelium. The sclera has very few blood-vessels and nerves. As the blood-vessels (the anterior ciliary arteries and veins from the muscular branches of the ophthalmic artery and veins) approach the corneal margin, the arrangement is peculiar. Some branches pass through the sclera to the ciliary body (perforating branches); others become superficial and lie in the episcleral tissue (episcleral vessels), and form arches by anastomosing with each other some little distance behind the corneal margin. From these arches numerous straight vessels are given off, which run forwards to the cornea, forming its marginal plexus.

The lens has no blood-vessels, nerves, or connective tissue in its structure. The fibres of the outer layer of the lens are nucleated, and together form a nucleated layer most distinct towards the marginal circumference (the equator).

The anterior surface of the lens is covered by a layer of transparent, nucleated columnar epithelium. The conjunctiva is the mucous membrane of the eye. Upon the sclera the conjunctiva is loosely connected to the bulb of the eye; it is thin, transparent, destitute of papillae, and only slightly vascular. Upon the cornea the conjunctiva consists only of epithelium, constituting the anterior layer of the cornea, already described. The epithelium of the palpebral conjunctiva is columnar, that of the ocular conjunctiva and the cornea is stratified squamous. Fuchs emphasised the presence of small papillae, normally present at the limbus and not on other parts of the conjunctiva, between which a proliferation of epithelium grows in conical processes in the depth of the tissue. Lymphatics arise in a delicate zone around the cornea, and run to the ocular conjunctiva.

# PATHOLOGY

A convenient classification of epibulbar tumours has been formulated by Morax (1926).

A. (According to site):-

1. Conjunctival. (a) superficial, (b) deep.
2. Limbal. (a) superficial, (b) deep.
3. Corneal. (a) superficial, (b) deep.
4. Episcleral.

B. (According to origin):-

1. Primary.
2. Secondary to new-growth of the eyelids or the lachrymal apparatus, by extension or contact.

Epibulbar malignant new-growths are not common. Borthen (1893) saw 8 cases of sarcoma of the conjunctiva among 45,000 ophthalmic patients. Bistis (1925) saw one sarcoma of the conjunctiva in 25,000 ophthalmic cases at Athens. Licsko (1922) in Hungary saw 8 cases of sarcoma among 23,206 patients. Morax (1926) saw in the ophthalmic department of the Lariboisière Hospital, Paris, only 4 cases of malignant neoplasm of the conjunctiva out of 145,000 patients. Schweinitz and Shumway (1913) state that in 1908 Rschanitzin found in the literature 502 cases of conjunctival tumour, 252 of which were

malignant; of the malignant forms, 149 were carcinomatous and 103 were sarcomatous.

Bilateral epithelioma of the conjunctiva is rare, but three cases of epithelioma at the limbus of both eyes have been reported recently ay Andrade (1935), Lowther (1935), and Mazzi (1934).

The bulbar conjunctiva is the commonest site for malignant new-growths and the limbus is usually affected first. Koeppel (1900) found in the literature, 34 cases of sarcoma of the bulbar conjunctiva, eight of the plica semilunaris, and 13 of the other parts of the conjunctiva. Morax (1926) states that the cornea is never affected primarily by epithelioma and he could find only ten proven cases of epithelioma on the tarsal conjunctiva, to which he added a case of his own. Licsko (1922) found carcinoma of the conjunctiva more frequent on the nasal than the temporal portion.

The sexes are equally affected according to Johnson (1924) and Morax (1926), but Benedict (1929) and Freiman (1932) declare malignant tumours of the conjunctiva to be commoner in men. The age of onset is seldom before the fifth decade, but a case occurred in a child of five, following a lime-burn, and a child of 6, suffering from Xerodermia Pigmentosa, developed epithelioma of the conjunctiva. In one series of seven cases the youngest was a girl of 13 years; the oldest a woman of

84 years. In another series of seven cases, the ages ranged from 20 months to 37 years. Johnson (1924), Morax (1926), Schweinitz and Shumway (1913).

The aetiology of new-growths of the limbus is unknown. A dermoid and a naevus became epitheliomatous and a fragment of steel, easily removed from an eye 2½ years previously, was the apparent cause of an epithelioma of the conjunctiva in a man 47 years. (Johnson(1924)).

Benedict (1929) regards trauma as the cause of several cases of limbal epithelioma. An inflammatory affection of the conjunctiva has been declared the origin of an epithelioma, but Morax (1926) finds that epithelioma rarely develops after Trachoma. A Pterygium has been known to show epitheliomatous change.

The predilection of epithelioma for the very vascular limbus as a site of origin was explained by Saemisch (1904) on the grounds that epithelial transformation occurs at this site and that invaginated processes of epithelium are common irregularities of development at the limbus. The origin of pigmented sarcoma and epithelioma is probably a naevus of the conjunctiva which has undergone malignant degeneration to carcinoma. This conception is based on the appearance of the tumour cells and not on the demonstration of a naevus present before the onset of malignancy (Morax (1926) and Costroviejo

(1931)). The influence of congenital and benign melanosis of the eye on the production of a malignant new-growth is held to be slight by François (1934), who reviewed the subject. He states that Fuchs saw only three cases of melanosis in 281 cases of melanosarcoma.

Epithelioma of the bulbar conjunctiva and cornea may be a secondary extension from the skin of the eyelids. The new-growth usually invades the tarsal conjunctiva by continuity, then spreads across the fornix to the bulbar conjunctiva. Eymann (1915) reports the case of an epithelioma, invading the conjunctiva at the free edge of the lower eyelid, which spread by contact to the cornea.

Epibulbar epithelioma is found to be microscopically a basal-celled carcinoma in most of the cases investigated by Johnson (1924) and Morax (1926). Prickle-celled and squamous-celled carcinoma are exceptional findings. To Benedict (1929) however, squamous epithelioma is the commonest microscopic appearance.

The extension of an epibulbar epithelioma is believed by Morax (1926) to be slow and to continue usually one or two years before medical advice is sought. Collins (1915), on the contrary, holds the opinion that the exposed situation of the growth leads to an early discovery by the patient or his friends. He described and illustrated by photo-micrographs the route of advance of an epithelioma at the limbus.

A limbal epithelioma, if it spreads to the cornea, meets Bowman's membrane and often extends anterior to this membrane without invading the substantia propria of the cornea. When the substantia propria is reached, columns of the cancer cells, extending along the lymphatic spaces between the layers of the substantia propria, soon reach the lymphatic vessels connected with the canal of Schlemm and extend along these lymphatic vessels to the canal. From the canal of Schlemm the neoplasm permeates the spaces of Fontana and reaches the interior of the eyeball.

The epithelioma, starting at the limbus, may extend outwards and reach the large lymph-space of Tenon's capsule, spread readily, and grow round the external surface of the sclerotic. From the mass in Tenon's capsule, columns of cells extend along the lymphatic channels surrounding the blood vessels in the superficial layers of the sclerotic.

Casolino (1914) commented on the fact that the sclerotic resists epitheliomatous invasion to a greater degree than does the cornea. The presence of more numerous lymphatic spaces in the cornea serves as a readier channel to carcinomatous permeation. Schweinitz and Shumway (1913) and Schweinitz (1921) emphasise that growths situated at the limbus are much more apt to perforate the globe than those placed at a distance from the cornea. In 53 eyes, excised for epibulbar carcinoma,

perforation had occurred in 20 (i.e. 37.7%).

On the external surface of Tenon's capsule, the lymphatic vessels become permeated. Carcinoma cells invade the orbit, conjunctival fornix and the eyelids. By the extension of the growth in the anterior part of Tenon's capsule the whole cornea may become encircled, (pericorneal epithelioma). In more extensive invasion of Tenon's capsule, the whole globe is almost surrounded by growth (peribulbar epithelioma).

Extension of an epibulbar carcinoma to the pre-auricular lymphatic glands and to the sub-maxillary lymphatic glands is rare. Enlargement of these glands may be due to a lymph-adenitis following infection of an ulcerated growth. More distant metastasis is very rare, but Profeta (1911) found metastatic deposits in three out of 54 cases of epibulbar epithelioma.

## DIAGNOSIS

Diagnosis is simple if an epithelioma is secondary, by extension or contact, but a small primary epithelioma of the limbus may require differential diagnosis from Pinguecula, Pterygium, Conjunctival Keratosis, Corneal Dermoid, the Dermo-epithelioma of Parinaud (cystic epithelioma, benign epithelioma), Papilloma, hyperplastic and neoplastic changes following Xerodermia Pigmentosa (Morax (1926)).

The clinical appearance of an epithelioma of the corneal limbus is at first a thickening of the conjunctiva, causing the surface to lose its lustre. A pink elevation of the conjunctiva, resembling a small strawberry, surrounded by several slightly dilated capillaries, is next seen; it is at this stage that attention is directed to the eye by the patient or his friends. Later, the tumour grows larger, becomes more reddened in colour, and resembles in shape a raspberry by the aggregation of small lobes on the surface. The portion of the cornea not covered by growth is clear, and not infiltrated as in inflammatory lesions. If a drop of 2½% cocaine solution be instilled in the eye and a portion of the lesions seized by forceps in an attempt to fold the conjunctiva, the firmness of the neoplastic infiltration will be evident, in contrast with the softness of an inflammatory lesion; at

the limbus the conjunctiva is firmly adherent, rendering this manoeuvre impossible. Multiple nodules of epithelioma are uncommon, but may occur in a ring at the limbus. On instillation of a drop of fluorescin solution, the yellow colouration may show irregular ulceration at some part of the swelling. A chronic ulcerating type of epithelioma, resembling Mooren's ulcer of the cornea, is uncommon, but when it occurs is most frequently seen at the lower nasal quadrant of the limbus the ulcer spreading towards the temporal side by way of the lower part of the cornea (Benedict 1929).

A spot of pigment or a diffuse pigmentation on the eyeball may be noticed by the patient and advice sought. If no tumour is present, even on examination with a corneal microscope, the patient may be advised to return for inspection of the area of pigmentation in a few weeks or months, particular note being made of the extent of the pigmentation. If a pigment spot becomes a malignant neoplasm, an elevation of the conjunctiva is seen which, after a variable time, reaches the size of a very small pea, the colour (yellow-brown to black) varying with the degree of pigmentation. The rounded mass may have a broad base, or a narrow pedicle. If the tumour is not pigmented the appearance will be similar but the colour will be pink or red. No symptoms accompany the new-growth until, in neglected cases, the mass projects one to two

centimetres outside the palpebral fissure, ulcerates, and bleeds.

The limbal tumour may be found extending towards the cornea and towards the conjunctiva. Extension to the cornea is evidenced by irregularity of the surface and loss of brilliance; no loss of vision is found until the lesion extends to the central area of the cornea, but the tumour may cover the cornea and obscure vision completely. The tumour may extend out to the bulbar conjunctiva and eventually reach the fornices and the tarsal conjunctiva.

Extension into the anterior chamber of the eye occurs late, but at this stage ophthalmoscopy may be difficult because of the photophobia from an extensive superficial lesion. Extension into the orbital cavity may be evidenced by interference with the movements of the eyeball. Enlargement of the pre-auricular lymphatic glands on the side of the lesion is not to be expected unless the orbit or the eyelids are invaded by extension of growth.

A lymphadenitis due to infection of an ulcerated area on the growth may cause enlargement and tenderness of the glands, in contradistinction to the painless glands of malignant infiltration. The submaxillary lymphatic glands receive the drainage from the preauricular lymphatic glands on the side of the lesion, and may enlarge after the pre-auricular invasion.

Both malignant and pyogenic invasion may occur simultaneously in these lymphatic glands; in this type of gland enlargement, the differential diagnosis becomes impossible.

Biomicroscopy by the use of the slit-lamp is described by Butler (1927) in the diagnosis and during the treatment of tumours of the limbus. Lane (1933) states that no malignant lesion of the conjunctiva or cornea should ever be treated without most careful, frequent biomicroscopic study, since distant foci of malignant cells are often present, and, if these are not treated, recurrence is almost inevitable. At the Radium Institute, London, no biomicroscopic control of treatment has been found necessary, but most of the patients, during the course of treatment, have had repeated microscopic study by their own ophthalmologists.

Biopsy has been considered unwise at the Radium Institute, London. Benedict (1929), however, states that it is always safe to take tissue for diagnosis, and that every suspected growth in the region of the limbus should be examined microscopically. Brown (1932) of Chicago, speaking from the experience of the Radium treatment of 30 melanotic epibulbar tumours, suggested that the removal of a biopsy specimen was a dangerous procedure, as liable to cause dissemination of the malignant growth. Wätzold (1924) claims from his investigation of 8 cases of pigmented growth, and one pigment spot of

the conjunctiva, that it is most undesirable to remove a piece of growth for microscopic study. McGraw and Hartmann (1935), reviewing the literature of the subject, deny that biopsy stimulates local growth or disseminates tumour cells. In prognosis from biopsy, Hellwig (1932) declares that the histologic grading of cancer has a very limited practical value. He stresses the manifest and bewildering mass of contradiction and misunderstanding in the various findings as to the relation between the histologic character and the radio-sensitivity of tumours.

# TREATMENT

The objects of treatment in malignant tumours of the limbus are:-

1. To extirpate the neoplasm.
2. To prevent dissemination of malignant cells.
3. To retain the function of the eye as fully as is consistent with the treatment of malignant disease.

The indication for treatment is the presence at the limbus of a lesion diagnosed by a competent observer to be a malignant neoplasm. The discovery of pigmented spots or patches on the sclera is not of itself an indication for treatment. There must be, in addition, overgrowth of neoplastic cells that can be demonstrated. Wätzold (1924) advises, in subjects over 30 years of age, the removal of all naevi of the conjunctiva together with as much as possible of the surrounding healthy tissue.

Contra-indications to treatment exist:-

1. Where there is local extension of the growth into the cranial cavity.
2. Where there is distant metastasis.
3. When the general condition of the patient is unsuited to the treatment.

The enlargement of pre-auricular and submaxillary lymphatic glands on the side of the affected eye is not a contra-

indication to treatment in epithelioma of the limbus, because these glands are accessible to surgical removal or radiation therapy.

Morax (1926) discusses the prognosis and his opinions are interesting. Epithelioma of the limbus has a relatively favourable prognosis, he points out, because cerebral and other metastases are not found early although the tumour sometimes recurs locally after excision. There are, however, serious cases where extension has occurred into the globe or the orbital cavity. Old age is of favourable prognostic import. Delay in seeking medical advice, allowing extension of the lesion over a large portion of the conjunctiva or cornea, necessitates enucleation of the eye. The prognosis in sarcoma and in naevo-carcinoma of the limbus is, on the contrary, serious, especially if treatment is delayed, since local recurrence, extension to the orbit, lymphatic gland invasion and distant metastases are common.

The methods available for the treatment of malignant limbal tumours may be discussed under the following headings:-

1. Removal of the eye and the tumour.
2. Local removal of the growth:-
   - (a) Surgical excision.
   - (b) Diathermic coagulation.
   - (c) Fulguration.
   - (d) Cautery application.
   - (e) Thermophore application.

(f) X-radiation.
(g) Radium application or insertion.

Removal of the eye with complete extirpation of the conjunctival sac is necessary in cases where an epithelioma occupies so much of the conjunctiva that local removal is impossible. The ciliary margin of the eyelids should also be removed if the tarsal conjunctiva is invaded. In aged patients, or those who do not wish to wear an artificial eye, the lids may be sewn together (a permanent blepharorrhaphy). A dermo-epidermal (Thiersch) graft can be used to line the cavity in cases where it is desired later to wear a prosthesis. A plug of stent, hard paraffin, or lead is inserted to provide a pressure dressing to the graft and is allowed to remain in position for 3 or 4 weeks.

Surgical excision of the epithelioma together with a margin of healthy tissue can be performed when the epibulbar conjunctiva is invaded by growth but is freely movable on the sclera. The conjunctiva can be mobilised from its adhesions to the globe and brought across any raw area, and conjunctival wound being united by a few silk sutures. If the edges of the gap in the conjunctiva will not meet, it is possible to transplant a portion of the epithelium of the lip into the gap and fix the graft to the conjunctiva by 3 or 4 fine silk sutures (Morax (1926)). The electric cutting current can

be used for the excision of the conjunctiva (Terrien and Cousin (1931)).

In the treatment of sarcoma and of pigmented malignant tumours of the limbus, Morax (1926) emphasises the danger of local removal of the growth. Two points should be considered:-

1. The visual acuity of the other eye.
2. The age of the patient.

In a case where the other eye is blind, the tumour may justifiably be treated by local measures, recurrences being treated later as they appear. In the aged, the expectation of life may be considered against the probable course of the neoplasm; the surgeon may be satisfied by a local treatment in such cases. However, when the second eye is normal and the patient young or in adult life, the surgeon should advise radical removal of the tumour and sacrifice of the eye. Morax (1926) believes that only surgical treatment is of value, and states that Regaud does not find radio-therapy to be curative in melanotic tumours; the Drs. Costroviejo (1931) agree, but are willing to treat by local destruction and cauterization in the first place, and then proceed to enucleation if the invasion of the cornea continues.

Diathermic coagulation (Terrien and Cousin (1931)), provides a simple method of destroying the tumour, but leaves a raw area which is susceptible to infection.

Fulguration is the method of desiccating the tumour cells by a discharge of high-frequency electrical sparks. The slough separates naturally some days later, but there is a risk of infection of the devitalised tissues surrounding the necrotic mass. Benedict (1929), of the Mayo Clinic, recommends the method.

The application of the cautery (galvano-cautery) as recommended by Villard, Dejean and Temple (1932) is open to the same criticism as diathermic coagulation.

The Thermophore was designed in 1926 for the application of controlled temperatures to the eye; a temperature of 140° Fahrenheit for one minute is applied in the treatment of epilbulbar tumours, this temperature being lethal to epithelioma, but not to the conjunctiva, sclera, and cornea (Shahan (1921)). The use of the instrument in epilbulbar epithelioma is advocated by Miller (1930), Post (1931), and Weymann (1930).

These methods of local removal of the growth have given unsatisfactory results. Lagrange (1901) and Saemisch (1904) give a poor prognosis after surgical excision of carcinoma of the conjunctiva. Morax (1926) states that local recurrence and propagation by contact are common. Licsko (1922) states that recurrences after surgical excision of carcinoma of the conjunctiva appear usually within one to ten months; the earliest noted was 12 days, and the latest 7 years after

operation. The mortality of operation in his 74 cases was 27%. Lane (1933) could find only one sarcoma of the cornea, treated surgically, which had been without recurrence or metastasis for 7 years after operation.

The treatment of epibulbar tumours by X-rays has not been widely practised. Albers-Schoenberg (1920), Fejer (1929), Grandclement (1913), Heckel (1922), Janeway (1920), Peter G. (1935), and Regaud (1926), describe the use of X-ray therapy in carcinoma of the conjunctiva. The total number of cases recorded by these writers is only eight. In two of these cases, recurrences appeared one to two months after X-ray treatment; Radium application was successful in destroying the recurrent growths. The difficulties of the X-ray treatment of a very small area occur in the provision of protective screening for the surrounding healthy tissues. Lead plaques, perforated at the area to be exposed to the X-rays, may be moulded to fit the contour of the eyeball and laid over the globe. The eyelids may be held retracted. The face may be covered by lead plates which are wrapped in rubber. The occurrence of a post-radiational cataract is a not uncommon sequel to the X-ray treatment of conditions near the orbit. In the X-ray treatment of the eye itself there is, therefore, a very real risk of damage to the lens.

## RADIUM TREATMENT

Darier of France, in the year 1903, was the first to employ radium in the treatment of diseases of the eye. Stallard (1933), describing a personal case and 11 cases of the Radium Institute, London, stated that in the literature there are reported 39 cases of the Radium Treatment of epibulbar malignant neoplasms. In addition, 16 cases are described by Amat (1932), Lane (1933), and Peter G. (1935), and four cases of post-operative prophylactic treatment by radium are reported by Soria (1932). Of the cases treated at the Radium Institute, London, Collins (1915) reported the first, and Stallard (1933) reported 11, including three described previously by Butler (1932); all cases of limbal malignant neoplasm, treated at the Radium Institute, London, will be discussed in the next section of this work.

The methods of treatment by radium used in other centres may be grouped:-

(a) According to associated methods of treatment:-

1. Post-operative prophylactic treatment.
2. Post-operative treatment to residual growth.
3. Post-operative treatment to recurrent growth.
4. Primary treatment.
5. Pre-operative treatment.

(b) According to the position of the radium applicator:-

1. Distant Radiation.
2. Interstitial Radiation.
3. Contact (Surface) Radiation.

(c) According to the filtration of the Radium:-

1. Filtered, to employ only gamma rays.
2. Unfiltered or lightly filtered, to employ beta particles and gamma rays.

(d) According to the dosage of Radiation:-

1. Repeated small doses.
2. A few large doses.

Radium may be applied after the complete removal of an epibulbar tumour, in the hope that the tendency of recurrence may be diminished. The grave disadvantage of this method is shown in the treatment of cases which later relapse. A repetition of Radium treatment is less effective than a primary application, because fibrotic changes in the tissues have followed the reaction to the first irradiation. Benedict (1929) reported 8 cases treated by prophylactic post-operative radiation, and Calhoun (1921) and Duncan (1921) each reported one case. Kumer and Sallmann (1929) reported 12 cases, and Soria (1932) reported 4 cases. One prophylactic treatment was performed at the University College Hospital, London, in 1931.

The combination of incomplete surgical removal with

subsequent radium therapy offers the advantage that a smaller mass of new-growth is presented for the supplementary treatment by Radium. The disadvantages of operations which remove only a portion of a malignant growth are recognised universally. Local spread and general dissemination follow partial excision, because the lymphatic and vascular channels are laid open to malignant cells. Diathermic excision seals these channels, but healing is adversely affected by the destruction of tissues at the edges of the wound. Few cases have been treated by the method. Finnoff (1924) advises that the epithelioma be shaved off before using Radium, in order to allow a smaller dosage of radiation to be effective. Grolman (1934) recommends diathermic coagulation, followed by Radium application, but emphasises that cicatrisation is much slower than is currently admitted, and that the scars are retractile.

Surgical removal of an epibulbar malignant neoplasm is considered by some writers to be the treatment of choice, and Radium therapy is regarded as of value in the treatment of recurrent nodules. Fibrosis, produced by the operative measures employed on the eye, causes an avascularity of the tissues, with the result that radio-sensitivity is decreased. Hence, Radium therapy is placed at a disadvantage by previous surgical interference. Fejer (1929) quotes Plocher's opinion that early epibulbar tumours should be removed with the knife and their bases touched with the galvano-cautery. After

complete removal of the tumour the eye should not receive further treatment until recurrent growth is noticed. Radio-therapy should then be applied.

The primary application of radium, in the treatment of malignant new-growths of the conjunctiva, is a method more certain in result than surgical removal, but there is danger to the eye from careless or ignorant radio-therapy. In the literature, success and failure are reported. By an analysis of these findings, an estimate may be obtained of the value of Radium treatment. With the exceptions mentioned above, those who have employed radium therapy in epibulbar malignant neoplasms agree in recommending primary treatment by radium.

Ward and Smith (1933) regard pre-operative radiation as a method suitable for any case of malignant epibulbar tumour in which local removal of the growth could be performed. The response in the tumour, 6 weeks after irradiation, is the criterion for the continuation of radium treatment. Tumours which have begun to diminish in size should receive further treatment by radium. Tumours which are unaltered in appearance may either be treated surgically or receive another irradiation, followed, after an interval of 2 months, by a third radium application. At any stage of the treatment by radium, operative removal of the growth may be safely performed. No harm follows the delay of a few months in the surgical treat-

ment of a slowly-growing epibulbar tumour, and, moreover, the rapidly-growing tumours are radio-sensitive. Hence, the radium-treatment of epibulbar tumours is justifiable as a primary measure in all operable cases.

Distant radiation of the eye has been employed either through the closed lids or with the lids held retracted. The need for distant application, which makes available the penetrating rays, does not exist in the case of epibulbar new-growths. Penetration of the rays is unnecessary, because the neoplasm extends, at most, one millimetre or so into the cornea or sclera. Penetrating radiation is also harmful, leading to post-radiational cataract in some cases. Janeway (1920) advises the use of a lead plate 2 mm. thick, which is fenestrated at the site to be irradiated. Radon is placed over the hole, and fastened to the plate by wax. The Drs. Keith (1922) of Louisville, Kentucky, treated a case by radium placed at one cm. from the eye. Lane (1933) uses a platinum needle, containing radium, which is held in forceps and kept moving 2 mm. above the surface of the cornea. Peter G. (1935) of Mexico City, treated 13 cases of epithelioma of the conjunctiva by a radon capsule held 0.5 cm. from the eye. Plocher (1918) used irradiation at 2 cm. from the eye. Regaud (1926) at the Radium Institute, Paris, applies wax plaques,

moulded to the eye, carrying radium at distances 3 mm. to 2 cm. from the eye. Robinson (1926) used a soft rubber plaque laid on the eyeball, carrying radium at 1 mm. distance from the eye. Stallard (1933) at St. Bartholomew's Hospital, London, treated one case by platinum tubes, containing radium, arranged on lint and laid over the closed eyelids. Takahashi and Taheira (1924) employed radiation through the closed lids. Wilder (1924) used a radon tube held at 4 mm. distance from the growth; Brown, of Chicago, treated the same case two years later, by radium at a distance of 9 mm.

Interstitial radiation is a method which has not received much attention in the treatment of epibulbar tumours. Stallard (1933) regards treatment by the insertion of radium needles as impracticable on account of the trauma necessitated by their insertion, the relatively small size of the growth at a stage when radio-therapy is justifiable and the impossibility of retaining the needles accurately in position. Interstitial radiation is not discussed by other writers.

Contact or surface radiation is the logical method of treatment in superficial lesion of the eye, because a limited depth of tissue is affected by the relatively small doses given and an accurately localised area of the surface is irradiated. The deeper structures of the eye are thus spared unnecessary disturbance, and the healthy conjunctiva and cornea near the

tumour receive doses which produce no apparent injury. Calhoun (1921) of Atlanta, Ga., Duncan (1921) of Los Angeles, California, and Franklin and Cordes (1927) each reported a case treated by surface application of radium. Heyerdahl (1920) of Christiana reported two cases. Kumer and Sallmann (1929) used surface treatment in 16 cases. Mattice (1914) described the surface treatment given in one case by J.Meller at Vienna. Plocher (1918) used contact radiation, after preliminary treatment by radium at a distance of 2 cm. Quick (1924) at the Memorial Hospital, New York, treated 4 cases by surface application of radium. Soria (1932) fixed radium needles or tubes by conjunctival sutures to the area left after excision of an epibulbar tumour; four cases were treated in this manner. Spaeth (1930) reported a case treated by contact radiation. Wickham and Degrais (1909) reported two cases treated at the Radium Institute, Paris.

Filtration is employed in radium treatment as a means of selecting the shorter gamma rays, while absorbing the less penetrating gamma rays together with the alpha particles and the beta particles. The biological effect on the superficial tissues is lessened, allowing a larger dose of radiation to be given to the deeper layers of tissue. Obviously, in the treatment of superficial lesions any increase of the depth dose is innecessary. During radiation of the eye, prevention of injury to the lens depends on the avoidance of large doses

of penetrating rays. One erythema-dose of filtered gamma rays is sufficient to cause cataract, and three such doses may be required for the treatment of an epibulbar neoplasm. Heavily-filtered gamma radiation of the conjunctiva, therefore, is contra-indicated in the treatment of an epibulbar malignant neoplasm. However, several cases have been treated by filtered radium. Benedict (1929) in eight cases used radium "with lead, copper and rubber protection". Duncan, (1921), used a screen of 0.5 mm. platinum and 1 mm. of rubber tubing, in one case. Franklin and Cordes (1927) used a filter of 0.5 mm. silver and 0.5 mm. aluminium, in one case. Janeway (1920), in one case, used a filter of 0.5 mm. silver. Peter G. (1935) treated 12 cases with a capsule of 0.1 mm. Monel metal, filtered by 0.2 mm. silver; one case was treated with the heavier filtration of 0.5 mm. silver. Johnson (1924) reported three cases, treated by Quick with gamma radiation; Quick (1924) states that this method has been discarded at the Memorial Hospital, New York. Regaud (1926) uses tubes of platinum, with walls 0.5 to 1 mm. thick. Stallard (1933) used a screen of 1 mm. platinum, in one case. Wilder (1924) treated one case with a radon tube, screened by 2 mm. of gold.

Unfiltered or lightly-filtered radiation has been used in many cases of superficial malignant lesions of the skin and mucous membranes. The application to superficial epibulbar neoplasms should be a procedure equally simple and sure. The

duration of the application and the weight of the apparatus have an important bearing on the comfort of the patient. The duration of an exposure to lightly screened radiation is short, whereas, filtered radiation may require as much as twenty times this exposure; the weight of an applicator with a screen is considerably heavier than the unscreened applicator. Unscreened radiation allows the patient to visit for treatment, without the necessity of admission to hospital. Brown of Chicago used unscreened radium in the treatment of a case reported by Wilder (1924). Franklin and Cordes (1927) used unscreened radon, and also, radium screened by 0.1 mm. aluminium (a very light filter) in a case, previously treated by gamma radiation. Heyerdahl (1920) treated two cases with radium screened by 0.1 mm. of silver, covered by cotton-wool and gutta-percha. Janeway (1920) used unscreened radon, in one case. The Drs. Keith (1922) treated a case, using unscreened radium. Kumer and Sallmann (1929) suggest the use of a light filter in the radiation of the conjunctiva. Lane (1933) uses a platinum screen of 0.03 mm. thickness. Mattice (1914) uses unscreened radium, a mica cover separating the radium from the conjunctiva. Quick (1924) treated four cases by unscreened radon and states that the procedure of using filtered radium is more trying to both patient and operator, causes unnecessarily severe reaction and has a greater factor of error. Wickham and Degrais (1909) used unscreened radium in one case, and in another case, radium

screened by 0.02 mm. aluminium; rubber tissue was wrapped round each applicator.

The early radium therapists considered that the safest method of treatment was by the use of small doses of radiation, repeated every few days or weeks. However, the response of the tissues to radiation does not appear until ten to fourteen days after the exposure, and this response or reaction is not complete until four weeks later. Hence, treatment which is controlled by the appearance of the irradiated area during this period cannot be accurate. The late results of irradiation are found to be much more marked after repeated small doses, because the supporting stroma becomes fibrosed by every exposure, however small. Franklin and Cordes (1927) in one case gave seven small doses at intervals or 3 to 4 weeks. New and Benedict (1920) treated one case by ten daily applications of one-half-hour each. Plocher (1918) gave several doses at intervals of 7 to 14 days, followed by seven doses in three weeks. Wickham and Degrais (1909) treated one case by twelve exposures of ten minutes each in ten days, repeating the series at an interval of one month and again after another month; another case was treated by several series of daily applications of radon of 15 minutes each. Wilder (1924) treated a case of 86 applications of radon over a period of two years, the first 40 exposures being given in four months.

The use of large doses of radiation, repeated at intervals

of two months, is a method whereby several advantages are obtained. The full effect of a previous irradiation is visible before the subsequent treatment begins; the late sequelae of fibrosis and avascularity in the tissues are minimised, because of the small number of exposures; the patient need attend for treatment only a few times and at long intervals. The erythema-dose for the conjunctiva is slightly less than the skin-erythema-dose. Lest conjunctivitis be produced, Kumer and Sallmann (1929) recommend the application to the conjunctiva of only 50 to 80% of the skin-erythema-dose, repeated at 2-4 weeks intervals, for about six applications. Heyerdahl (1920) and Janeway (1920) each reporting two cases, emphasise the use of the largest possible doses of radium and the avoidance of prolonged treatment with small doses. Lane (1933) states that the dose should be large and, in extensive tumours of the conjunctiva, single. Mattice (1914) treated a case by three applications, the second a week after the first, and the third six weeks after beginning treatment. Quick (1924), in seven cases, used large doses, which usually were single. Robinson (1926) reports a case treated on five occasions, at intervals of one to two months. Stallard (1933) gave one large dose. Withers (1924) recommends that treatment be completed at one sitting, using a large dose.

The analysis of the results of radium treatment is unsatisfactory because the majority of the reported cases are

incompletely recorded. Details of radium treatment are not reported in every case, the immediate and the late results of treatment, as a rule, are not well described, and no large series of cases has been treated by one method.

There is difficulty in assessing the value of post-operative prophylactic radiation. Few cases have been treated by this method and no series of cases is available for study. The careful analysis of the results of operative treatment in epibulbar neoplasm would be a necessary preliminary to the estimation of the advantages of supplementary radiation. Of eight cases of carcinoma of the conjunctiva treated thus by Benedict (1929), using filtered radiation, 7 remained healed. One case of carcinoma of the conjunctiva at the lower fornix, treated by Calhoun (1921) using contact radiation, in three doses at intervals of two weeks, suffered contracture of the lid and adhesion of the lid to the globe; recurrence locally and metastatic pre-auricular lymphatic gland enlargement appeared one year later. Duncan (1921) reported one case showing no recurrence or disability two years after prophylactic post-operative treatment by contact radiation, with filtered radon, in one large dose. Kumer and Sallmann (1929) had good results in 12 cases, using contact radiation with lightly filtered radium, in a few doses. Soria (1932) found complete healing in 4 cases, treated by contact application of radium held in needles or tubes. To summarise these results, it may

be stated that, of 26 cases treated, only two were unsuccessful.

No description of the radium treatment of a post-operative residual growth is found in the literature. Quick (1932) mentions the treatment of a melanoma of the ocular conjunctiva "by radiation and surgical removal". No clinical evidence of disease was found ten months after removal.

The post-operative radium treatment of a recurrent carcinoma of the conjunctiva was reported by Janeway (1920). Distant, filtered radiation was given on five occasions, at intervals of about 3 weeks. Two years later no evidence of disease was found in any part of the eye. Johnson (1924) described 4 cases of recurrent carcinoma treated by Quick at the Memorial Hospital, New York. One received distant, filtered radiation, on four occasions in 6 months, and showed no recurrence six years later; a lens-opacity, however, had appeared. One case received a single dose of distant filtered radiation, which was successful in curing the lesion temporarily; in two years a recurrence appeared, which responded well to contact, unfiltered radiation; after 20 months the lesion had not recurred and vision was unimpaired. Two cases received surface, unfiltered radiation, in one and two large doses respectively. Both were free from disease, 2½ years and 1½ years after treatment. Thus, all five cases of recurrent carcinoma were successfully treated by radium application.

Primary radium treatment has been employed by several

methods, as shown in the following summary:-

| AUTHOR | DISEASE | No. of CASES | TREATMENT | RESULT. |
|---|---|---|---|---|
| Amat (1932) | Melano-sarcoma | 1. | 4 applications of 39.5 mg Ra.el. 108 hours each, for total of 63,696 mg. Ra.el. hours. | "Radical Cure". |
| Franklin and Cordes (1927) | Carcinoma. | 1. | Surface radiation, filtered and un-filtered; small repeated doses. | (1) Cured 8 months after treatment began. |
| Heyerdahl (1920) | Carcinoma. | 2. | Surface radiation, unfiltered; a few large doses. | (1) Cured 5½ years.<br>(1) Failure. |
| Janeway (1920) | Carcinoma. | 1. | Distant radiation, unfiltered; one large dose. | (1) Cured 9 months. |
| Johnson (1924) | Carcinoma. | 1. | Distant radiation, filtered; one large dose. | (1) Cured 2 years, but lens opa-city, optic atrophy and glaucoma occurred. |
| | | 2. | Surface radiation, unfiltered; one or two large doses. | (1) Cured 5 months.<br>(1) Failure. |
| Keith (1922) | Carcinoma. | 1. | Distant radiation, unfiltered; one dose. | (1) Cured 14 months. |
| Kumer & Sallmann (1929). | Carcinoma. | 4. | Surface radiation, lightly filtered; a few large doses. | (2) Cured.<br>(2) Failures. |

| AUTHOR | DISEASE | No. of CASES. | TREATMENT | RESULT. |
|---|---|---|---|---|
| Lane (1933) | Carcinoma. | 2. | Distant radiation, filtered; one large dose. | (2) Cured 5 years. |
| Mattice (1914) | Carcinoma. | 1. | Surface radiation, unfiltered; three large doses. | (1) Cured 3 months, but maculae in cornea. |
| New & Benedict (1920) | Carcinoma. | 1. | ? Surface radiation, ? filtered; ten daily treatments. | (1) Cured 2½ months. |
| Peter G. (1935) | Carcinoma. | 13. | Distant radiation, filtered; 2 to 7 daily treatments (one received about 80 daily treatments). | (13) Cured. |
| Plocher (1918) | Carcinoma. | 2. | Distant and Surface radiation. | (2) Failures. |
| Regaud (1926) | Carcinoma. | 3. | Distant radiation, filtered. | (1) Cured 1½ years.<br>(1) Cured 1 year.<br>(1) Recurred after 3 years. |
| Robinson (1926) | Carcinoma. | 5. | Distant radiation, ? filtered. | (1) Cured 5 years.<br>(2) Cured 4 years.<br>(1) Cured 2 years.<br>(1) Cured 8 months. |
| Stallard (1933) | Carcinoma. | 1. | Distant radiation, filtered; one large dose. | (1) Died from other causes a month later. |

| AUTHOR | DISEASE | No. of CASES. | TREATMENT | RESULT |
|---|---|---|---|---|
| Takahashi and Taheira. (1924) | Carcinoma. | | Distant radiation, filtered; one large dose. | Few free from recurrence 2 years later. |
| Wickham and Degrais (1909) | Carcinoma. | 2. | Surface radiation, unfiltered; several small doses. | (1) Recurred after 8 months treated again. Cured 16 months. (1) Failure. |
| Wilder (1924) | Melanoma | 1. | Distant radiation, filtered; many small doses. | No success until treated by Brown. |
| | | | Distant radiation, unfiltered (Brown) | (1) Cured 18 months. |

The cases treated primarily by radium are 44 in number, 42 being carcinomatous and 2 sarcomatous. The cases of sarcoma were cured, but among the cases of carcinoma, 7 failures occurred and one case died from other causes a month after treatment. In two cases of carcinoma, undesirable sequelae appeared after radium treatment, although the carcinoma was cured in each case.

One case of melano-sarcoma, treated by pre-operative radiation, was reported to Spaeth (1930). No recurrence was seen 6 months after operation. Contact radiation was given

on three occasions at intervals of two weeks, followed, 10 days later, by cauterisation of the growth. A fourth treatment by contact radiation was given on the day of operation, after removal of the tumour.

From the reports of the results of radium treatment conclusions may be drawn:-

1. There is not sufficient evidence to justify the use of post-operative prophylactic radiation.
2. Radium therapy is valuable as a primary treatment, and as a treatment for post-operative recurrent growth.
3. Both (a) the use of distant radiation and, (b) heavy filtration of the applicators may injure the lens.
4. Contact radiation with unfiltered radium, giving a few sub-erythema-doses, is a safe and satisfactory method of treatment for epibulbar tumours.

## TREATMENT AT THE RADIUM INSTITUTE, LONDON

At the Radium Institute, London, in the years 1914 to 1935 inclusive, there have been seen 30 cases of primary and operative recurrent malignant tumours of the limbus, all of which received radium treatment, and are here reported. Where surgical operation was successful in removing the growth and radium treatment was given later, the cases have not been included in this report, because the number of prophylactic treatments is small. Of the 30 cases of primary or recurrent growth, nine have been examined personally by the writer. During the residence of 12 months at the Radium Institute, as House-surgeon and as surgical registrar, he applied radium on 13 occasions for the treatment of limbal epithelioma.

The original technique adopted at the Radium Institute, London, was described by Pinch (1925 and 1926). The eye is anaesthetised by the instillation of a few drops of cocaine (2½% solution). A wire eye speculum is introduced and the lids widely separated. The eyeball is held steady with a pair of fixation forceps while an applicator of suitable size and shape, mounted on a rod, is placed over the tumour

on the eye. A relay of nurses and attendants is required, to maintain the applicator in contact with the appropriate part of the eye until the exposure is completed. Ward (1933) and Ward and Smith (1933) described the technique used in the previous five or six years. The applicator is not held by hand, but is attached to a probe or a metal bar fixed to the eye speculum. The eyeball is kept steady by allowing the patient to gaze at a particular fixed spot. For the treatment of lesions of the ocular conjunctiva situated in such a position that adequate exposure is impossible by means of the eye speculum, it is sometimes useful to insert a stitch in the lower lid, retract the lid strongly, and strap the thread to the cheek. Later, improvements in technique have been made. The applicator is fixed to the face by adhesive strapping, half-inch wide. Two strips, each about 5 inches long, are placed in the form of a cross, intersecting at the site of the tumour and holding the radium plate against the eye. The probe or metal bar has been discarded, but the eye speculum is retained in order to withdraw the lid margins from the source of radiation.

The applicators are described in detail in another section of this paper. The filtration employed has practically no greater effect than the stopping of the alpha particles; the thin sheet of mica and the sheet of Monel metal, 0.05 mm. thick, which cover the radium serve only as a protection to

the radium salt in the applicator. The strength of the applicator is roughly 5 mgr. of radium element per sq. cm., but various sizes of applicator are available. The shape of the lesion determines the choice between a round and a square applicator. The area of the eyeball affected by growth is measured by callipers, then an applicator is chosen which covers this surface and 2 to 3 mm. of surrounding healthy conjunctiva and cornea. The applicator is wrapped in rubber-tissue before use, and is smeared with vaseline in order to damage the cornea as little as possible. The duration of the exposure is one hour, in almost every case, but in the aged patient it is wise to limit the initial treatment to an exposure of 50 minutes. The sub-erythema-dose given does not, as a rule, produce a reaction in the conjunctiva. In the few days following the application, a mild injection of the conjunctiva may appear. This transient discomfort is due to the mechanical irritation of the applicator. A post-radiational reaction, if it occurs, begins 10 to 14 days after treatment and continues one to two weeks as a mild conjunctivitis, sometimes accompanied by photophobia and lachrymation. The reaction declines in severity in the 5th week after treatment, and by the 6th week has disappeared. The tumour usually shows no alteration in size until the sixth week when, in favourable cases, a diminution in height is noticed.

The second dose is given seven or eight weeks after the first. A reduction in the dose may be necessary, in cases where a severe reaction has occurred, and is obtained by shortening the exposure time (e.g. from one hour to 50 minutes). A sequence of changes, similar to those following the initial treatment, occurs after the second dose.

The third dose is given eight weeks later. The tumour, in some cases, has already disappeared. Probably no recurrence would follow the omission of the third treatment in these cases. In other cases, the tumour is smaller in height and area; the applicator, nevertheless should be of the same size as in the earlier treatments lest minute extensions of the growth be left untreated. Cases in which the growth appears unaltered by the two treatments may receive either;

(1) a third dose of the same amount as the second exposure.

(2) a third dose, of a greater amount of radiation, where no reaction followed the previous exposures (e.g. 70 minutes instead of one hour).

(3) Interstitial radiation (described below) or,

(4) Surgical excision of the tumour.

The patient is seen for examination, two months later, but no further radium treatment is given. The tumour has usually disappeared by this time. The patient visits either the Radium Institute, or the Ophthalmic centre, at

intervals of two months in the first year; three months in the second; four months in the third, and every six months thereafter. A repetition of radium treatment may be given, for the treatment of recurrent growth, in the year following the first, but the risk of producing late trophic changes becomes greater with every exposure. It is advisable that the maximum treatment be a total of six full doses. Recurrent growth which has proved resistant to surface radium treatment, may receive interstitial radiation, but will require, usually, surgical removal of the growth and, in many cases, enucleation of the eye.

In the treatment of a few cases of malignant new growth of the conjunctiva, interstitial radiation has been employed. Ward and Smith (1933) illustrate a case thus treated. One sarcoma of the limbus, reported below, received interstitial radiation following unsuccessful surface radiation. Interstitial radiation is used in special cases:

1. Where a flat applicator rests awkwardly on a bulky tumour.
2. Where surface radiation has failed to cure and the patient does not desire surgical operation.

Interstitial radiation is obtained by the insertion of a radon seed, previously sterilised by soaking in Lysol for one hour. As a means of sterilisation, immersion in boiling

water is probably more convenient, but there is a slight risk that the glass capillary may crack during the process.

The radon seed is 0.7 cm. long, is filtered by 0.3 mm. of platinum, and threaded at one end for ease of withdrawal. The choice of the light screen secures the advantage that an appreciable portion of the emission is composed of beta particles. The duration of the exposure is less than that required in treatment by heavily-filtered radiation, hence, an innocuous dose of penetrating gamma rays reaches the deep structures of the eye. The content of radon is high (from 3 to 10 mc) in order to curtail the period of retention of the seed. Exposures of 10 hours (10 mc. radon), and 48 hours (3 mc. radon) have been borne, without the production of the acute conjunctivitis which might result from (a) the presence of a foreign body and (b) the caustic action of the secondary radiation from the surface of the filter.

The volume of the seed is reduced by the use of light screening; the trauma produced by the introduction of the foreign body is thus minimised. Provided that the mass of growth projects more than 3 to 4 mm. from the cornea, the seed may be inserted without injuring the eye. By cutting a conjunctival flap, the seed may be buried securely without producing infection, because no wound is made in the epithelial covering of the growth and there is no open track of the insertion of the seed. The thread attached to the

seed emerges under the conjunctival flap and is tucked into one of the fornices. With the aid of anaesthesia applied to the conjunctiva, gentle traction on the thread in the direction of the long axis of the seed, suffices for withdrawal at the end of treatment.

The cases of malignant disease of the limbus treated at the Radium Institute, London, may be grouped for discussion under the following heading:-

1. Sex of the patient.
2. Age of the patient.
3. Occupation of the patient.
4. Symptoms reported by the patient.
5. Site of the tumour.
6. Size of the tumour.
7. Histology of the tumour.
8. Dosage in treatment.
9. Results of treatment.
10. Illustrative cases.

Of 21 cases of carcinoma, fourteen were male and seven female. Three men and three women suffered from malignant melanoma. One case of sarcoma was male, and two were female. All were white people of British nationality. Carcinoma appeared in men at ages ranging from 40 to 80 years; the average being 62 years. Women were affected earlier, at ages ranging from 18 to 79 years, the average being 53 years. Melanotic tumours in the male appeared at the ages 9, 65, and 76 years; in the female at the ages 22, 51 and 55 years.

One sarcoma appeared in a man aged 70 years, one in a girl of 12 years, and another in a girl of 16 years.

Two farmers suffered from carcinoma of the limbus; the other men affected by carcinoma had different occupations: gentleman, labourer, Indian army officer, quarry-man, carpenter, railway signalman, coach-builder, lamp-lighter, omnibus-driver, architect, hawker, tar-pavior. Of the three male patients suffering from melanotic tumour, one was a sand-miner, one a gardener, and one a school-boy. Sarcoma of the limbus appeared in an old-age pensioner, a man of 70 years.

The interval between the onset of symptoms and the obtaining of medical advice varied from three weeks to five years, the average being ten months. Of the 30 patients, 21 complained of a lump on the eye. In 5 cases, vision was impaired by the presence of growth on the cornea. Four patients reported a redness of the conjunctiva. Photophobia was present in two cases. Lachrymation was noted in one case. The eye was painful in only one case.

In 15 cases of carcinoma the left eye was the seat of growth; the right eye was affected in 6 cases. In one case a melanotic tumour occurred in the left eye, and, in 5 cases, in the right eye. Two patients suffered from sarcoma of the limbus of the left eye, and one patient was affected in the right eye. The outer and the inner quadrants

of the conjunctiva were more commonly attacked than the lower quadrant; the upper quadrant was affected in only one case. Carcinoma appeared on the four quadrants in the following proportions:-

Nasal quadrant.....50%.
Temporal quadrant.....24%.
Lower quadrant.....16%.
Upper quadrant..... 5%.
and, pericorneal infiltration 5%.

Melanoma was found in two cases, on the nasal quadrant, and, in four cases, on the temporal quadrant. Sarcoma appeared on the temporal quadrant in three cases.

Radium treatment was successful in cases of limbal carcinoma occupying a surface extent equal to one sq. cm., the diameter being 13 x 10 mm. in one case, 12 x 10 mm. in another, and 10 x 10 mm. in three cases. Two lesions, involving 7/12ths and 5/12ths respectively of the circumference of the cornea, were successfully treated. Of the tumour in which the area was less than one sq. cm. eleven were cured, and another is responding to treatment. Radium treatment failed in two cases. One presented a pericorneal infiltration and the other occupied an area 10 x 10 mm.

A successful result was obtained by radium treatment,

in one malignant melonoma of area 10 x 10 mm., and in four of smaller size. One melanoma 6 x 6 mm. in extent was unsuccessfully treated. One sarcoma, of area 10 x 8 mm., and two of smaller size, were successfully treated.

In 12 cases of carcinoma and one of melanoma, the clinical diagnosis of malignancy was confirmed by histological examination of biopsy or operation material. There were 21 cases of carcinoma,6 of melanoma, and 3 of sarcoma. Previous lesions were noted in two cases of carcinoma: a pinguecula, present for some years in a patient who had been exposed to the tropical sun for 28 years; herpes ophthalmicus, present 5 years. For 56 years a case of malignant melanoma had a bloodshot spot on the conjunctiva at the area which became neoplastic.

Sarcoma appeared nine years after a partial iridectomy. The area affected was 8 to 11 o'clock on the right eye, the situation in which the incision had been made at the operation.

In the treatment of carcinoma of the limbus, the average number of radium applications was three, but single applications proved curative in four cases. Sarcoma of the limbus responded to an average of four applications, but melanotic tumours required an average of five. The greatest number of applications to any one case was thirteen, in a period of 6 years, but half of the doses were small (20-35 minutes), and no exposure exceeded 50 minutes.

The results of radium treatment may be conveniently tabulated:-

(NOTE:- C - cured; D - died; F - failure of radium treatment; Ra - primary treatment by radium).

| Case No. | Period after Opn. mths. | Year treated. | Year reported. | Result. | Years observed. | REMARKS |
|---|---|---|---|---|---|---|
| | | | CARCINOMA | | | |
| 1 | 3 | 1914 | 1918 | C | 3 | Untraced, since aged 83. |
| 2 | Ra | 1919 | 1936 | C | 17 | |
| 3 | 3 | 1926 | 1934 | C | 8 | Died from other causes aged 73. |
| 4 | Ra | 1926 | 1934 | C | 8 | In 1932 developed senile cataract. Died 1934 from other causes. Aged 73. |
| 5 | 6 | 1926 | 1936 | C | 9 | |
| 6 | 60 | 1926 | 1936 | C | 9 | |
| 7 | Ra | 1927 | 1936 | C | 9 | |
| 8 | Ra | 1927 | 1936 | C | 9 | |
| 9 | 12 | 1927 | 1936 | C | 8 | |
| 10 | 1 | 1927 | 1929 | D | 1½ | Exenteration of orbit in 1929. Died, from extension of growth, aged 58. |
| 11 | Ra | 1928 | 1929 | C | 1½ | Died from other causes aged 63. |
| 12 | 1 | 1929 | 1936 | C | 6 | |
| 13 | Ra | 1932 | 1936 | C | 4 | In 1935, iritis caused loss of sight |
| 14 | Ra | 1933 | 1936 | F | 3 | at age 83. Exenteration of orbit, one year after radium treatment. In 1936, alive and well. |
| 15 | ? | 1934 | 1936 | C | 1½ | Nebulae on cornea following herpes ophthalmicus. |

| Case No. | Period after Opn. mths. | Year treated | Year reported | Result. | Years observed. | REMARKS |
|---|---|---|---|---|---|---|
| 16 | 12 | 1934 | 1936 | C | 2 | |
| 17 | 9 | 1934 | 1936 | C | 2 | |
| 18 | Ra | 1935 | 1936 | C | 8/12 | |
| 19 | Ra | 1935 | 1936 | C | 6/12 | |
| 20 | 16 | 1935 | 1936 | - | 6/12 | Responding to treatment. |
| 21 | 8 | 1935 | 1936 | C | 3/12 | |
| | | | MALIGNANT MELANOMA. | | | |
| 1 | 1 | 1925 | 1932 | F | 7 | Exenteration of orbit, in 1926. In 1932, alive and well, untraced since. |
| 2 | Ra | 1925 | 1936 | C | 10 | In 1935 a few telangiectases appeared on the conjunctiva at the site of treatment. Biomicroscopy reveals a few pigment granules in the cornea. |
| 3 | Ra | 1928 | 1936 | C | 8 | Biomicroscopy of the cornea shows a few pigment granules. |
| 4 | Ra | 1933 | 1935 | C | 2½ | Three pigment spots remain on the conjunctiva. One pigment spot remains on the conjunctiva. |
| 5 | Ra | 1934 | 1936 | C | 2 | One pigment spot remains on the conjunctiva. |
| 6 | Ra | 1934 | 1936 | C | 1 | Pigment cells remain in the cornea. |
| | | | SARCOMA. | | | |
| 1 | Ra | 1919 | 1930 | C | 11 | A slight, localised vascularity of the conjunctiva is present at the site of treatment. Patient untraced since 1930. |

| Case No. | Period after Opn. mths. | Year treated. | Year reported. | Result. | Years observed. | REMARKS. |
|---|---|---|---|---|---|---|
| 2 | Ra | 1932 | 1935 | C | 3 | |
| 3 | Ra | 1933 | 1935 | C | 2½ | In 1935, the untreated portion of the cornea became ulcerated, but there was no recurrence of growth. Enucleation of the eye was performed at age 77. |

Radium treatment is completed in 29 of the 30 cases of malignant limbal tumour, and one case continues under radium treatment.

Of the 29 cases, only 3 i.e. 10% were unsuccessfully treated; these three cases were later subjected to exenteration of the orbit. No mortality occurred during treatment and no post-radiational injury appeared. The successfully treated cases have remained free from signs and symptoms of disease, for periods ranging from 3 months to seventeen years.

It is instructive to review in detail, the records of the cases in which radium treatment failed to cure and, for comparison, records of successfully treated cases. Three reports of failures and four reports of successes are given below:-

CARCINOMA, Case 10. Male, aged 57 years. Railway signalman. Referred by Dr. J.N.Wheeler, Ophthalmic Department, Hospital of St. Cross, Rugby, as an epithelioma of the cornea. The lesion was present 14 years; treated by dissection on several occasions and last removed a month before the beginning of radium treatment. PATHOLOGICAL REPORT: Warty epithelioma.

25th October 1927. EXAMINATION: the left lower eyelid is thickened, distorted, denuded of lashes, indurated, but not ulcerated. The cornea of the left eye is blurred; vision is very poor. At 6 to 12 o'clock on the limbus of the left eye is a mass, 10 mm. diameter, irregularly triangularly, raised, pinkish-white, which has ulcerated the overlying conjunctiva. The mass has encircled the periphery of the limbus and there is a patch, at 2 to 4 o'clock on the limbus, 4 mm. diameter.

The first radium treatment was given to the medial half of the conjunctiva and cornea by the surface application for one hour, of a circular plate, 1 cm. diameter, containing 5 mg. Ra. el., unscreened. 27th January 1928. The patient states that he was unable to come to the Radium Institute for treatment in December 1927, because he had a bad "cold". The eye improved after treatment but, in the past month, relapsed, and is now worse than ever.

EXAMINATION: The growth has increased in size at the

inner and lower portion and now extends to the inner two-thirds of the lower eyelid, as an ulcerated mass.

The second radium treatment was given by the surface application, for 1½ hours, of a rectangular plate, 2 x 1 cm. diameter, containing 10 mg. Ra. el., unscreened.

9th March 1928. The patient feels that the eye is much worse.

EXAMINATION: The carcinomatous infiltration of the lower eyelid is more extensive.

No radium treatment was given, but operation was advised. Ten months later, exenteration of the orbit was performed. Owing to the delay in accepting operative treatment, metastatic deposits soon appeared in the head and abdomen.

4th May 1929. The patient died.

COMMENT: In this case, Radium treatment was attempted only because the patient refused enucleation of the eye.

In carcinoma of the limbus, pericorneal infiltration indicates a wide lymphatic extension and renders futile any local measures which do not include removal of the eye.

CARCINOMA, Case 14. Male, aged 57. Omnibus driver. Referred by Dr. Blair of Richmond as a squamous-celled carcinoma of the cornea. For 6 weeks the patient had a feeling of grit in the eye, and had gradual loss of vision. Biopsy was performed on 5th December 1932. For 2 years

patient had received treatment for Syphilis, but the Wassermann reaction was now negative.

9th January 1933. EXAMINATION: At 3 o'clock on the limbus of the left eye is a cloudy infiltration of the cornea, 10 mm. diameter. The vessels in the neighbouring conjunctiva are injected. The left pupil is larger than the right. The pupils do not respond to light. No glands in the head and neck are palpable.

The first radium treatment was given to the affected area by the surface of application, for 50 minutes, of a circular plate, 1 cm. diameter, containing 5 mg. Ra. el. unscreened.

20th February 1933. EXAMINATION: At 3 o'clock on the limbus is a scar. From 3 to 6 o'clock a fresh epithelioma has appeared, 10 mm. diameter, raised, pinkish, not ulcerated. At 7 o'clock a similar epitheliomatous mass is present, 5 mm. diameter.

The second radium treatment was given to the smaller lesion at 7 o'clock. A circular plate 0.75 c.m. diameter containing 2.25 mg. Ra. el., unscreened, was applied in contact for 50 minutes.

26th March 1933. EXAMINATION: The two areas which were treated have healed. The lesion at 3 to 6 o'clock, which was not treated, is unchanged.

The third radium treatment was given to the lesion at

3 to 6 o'clock on the limbus by the surface application for 50 minutes, of a circular plate, 1.25 cm. diameter, containing 6.2 mg. Ra. el. unscreened.

22nd May 1935. EXAMINATION. The areas which were treated have healed, but there is sclerosis and hyperaemia in the lower sector. There is an epithelioma in the upper and outer quadrant of the limbus.

The fourth radium treatment was given to this new area of disease by a repetition of the first application.

11th July 1933. EXAMINATION: There is a sub-conjunctival mass at the upper and outer quadrant of the limbus, 10 mm. diameter. The conjunctiva in the lower and the outer quadrant is hyperaemic.

15th August 1933. EXAMINATION: Pericorneal carcinomatous infiltration has appeared.

8th December 1933. EXAMINATION: The eyelids, at the outer canthus, are indurated.

22nd December 1933. Exenteration of the orbit was performed by Mr. Rupert Scott, at St. Bartholomew's Hospital, London. Radium treatment and Deep X-ray treatment were applied to the cavity in 1934 and 1935.

11th January 1935. A carcinomatous gland situated behind and below the angle of the jaw, was excised.

4th February 1936. EXAMINATION: The orbital cavity has healed. There is a slight dermatitis round the orbit.

No secondary deposit is present.

COMMENT. An interval of 5 weeks between the biopsy and the first radium treatment, is undesirable. The influence of treated Lues is problematical. The first radium treatment, in this case, was inadequate, both in the area treated and in the duration of the exposure; the use of an applicator 1.25 cm. diameter, and an exposure of an hour, would probably have been curative. The second radium treatment was again inadequate; the two lesions could have been covered for an hour by a large applicator. The response of the lesion to each of the first three applications indicates radio-sensitivity, and leads to the inference that cure could have been obtained by adequate irradiation.

MALIGNANT MELANOMA, Case 1. Female, aged 51. Housewife. Referred by Dr. O.B. Pratt, Oxford Eye Hospital, as an epithelioma of the limbus. The lesion was present 7 months and was treated by incomplete dissection a month before radium treatment began. PATHOLOGICAL REPORT: Early epithelioma.

18th February 1925. EXAMINATION: At 9 o'clock on the limbus of the right eye is a growth, 6 mm. diameter, irregularly circular, slightly raised, vascular. There is an irregular sub-conjunctival pigmentation on the upper and inner quadrant.

The first radium treatment was given by the surface application, for 50 minutes, of a square plate, 8 mm. diameter, containing 3.5 mg. Ra. el., unscreened.

16th July 1925. Dr. Pratt reports: I saw the case one month ago. There was a sound scar at the site of the tumour and no sign of any extension.

7th October 1925. EXAMINATION: The lesion has recurred as a bluish opacity. Pigmentation is still present on the upper and inner quadrant of the conjunctiva.

The second radium treatment was given similarly to the first, but the exposure was prolonged to one hour.

31st May 1926. The patient states that the eye was comfortable until the middle of April 1926.

EXAMINATION: At 9 o'clock on the limbus there is a faint corneal opacity. At 1 to 4 o'clock on the limbus, extending diffusely on the sclera, is a dark-brown growth, 10 mm. diameter, raised, soft. The pigmented growth extends to almost the whole length of the upper eyelid.

No radium treatment was given. Exenteration of the orbit was performed, by Dr. Pratt, in June 1926.

18th August 1932. The patient reports that she is well.

COMMENT: The applicator used in the treatment of this case, is small. In the first treatment the duration of the exposure is short. The application for an hour, of a plate 1 cm. diameter, would probably have been curative. In the

radium therapy of malignant tumours, it is wise to give a maximum initial dose, lest the tumour later become radio-resistant.

CARCINOMA, Case 16. Male, aged 72. Architect. Referred by Mr. R.S.Scott, Royal London Ophthalmic Hospital, as a limbal tumour. The lesion was present 17 months ago at the lower part of the cornea, and was treated by excision. PATHOLOGICAL REPORT: Epithelial hyperplasia. Four months later a tumour appeared at the upper, outer portion of the cornea and was treated by excision.

23rd February 1934. EXAMINATION: At 11 to 2 o'clock on the limbus of the left eye is a hypertrophic growth, 12 x 10 mm., overhanging the pupil. At 6 o'clock on the limbus of the left eye, a small area of growth is present. The temporal half of the conjunctiva is markedly injected. Glands in the neck are not palpable.

The first radium treatment was given to:

(a) The upper growth, by the insertion for 5½ hours of two radon seeds, each 0.6 cm. active length, filtered by 0.3 mm. of Platinum, each containing 10 mc. radon. The total dose was 0.81 mc. d. or 108 mg. hr.

(b) The lower growth by the surface application for one hour of a circular plate, 1.5 cm. diameter, containing 8.8 mg. Ra. el. unscreened.

10th May 1934. EXAMINATION: The two growths are smaller. The conjunctival injection is much less marked.

The second radium treatment was given to the lower growth by a repetition of the first surface application.

July 1934. EXAMINATION: The growths are smaller. The third radium treatment was given to the lower growth by the surface application for one hour, of a circular plate, 1 cm. diameter, containing 5 mg. Ra. el., unscreened.

12th October 1934. EXAMINATION: The eye is normal.

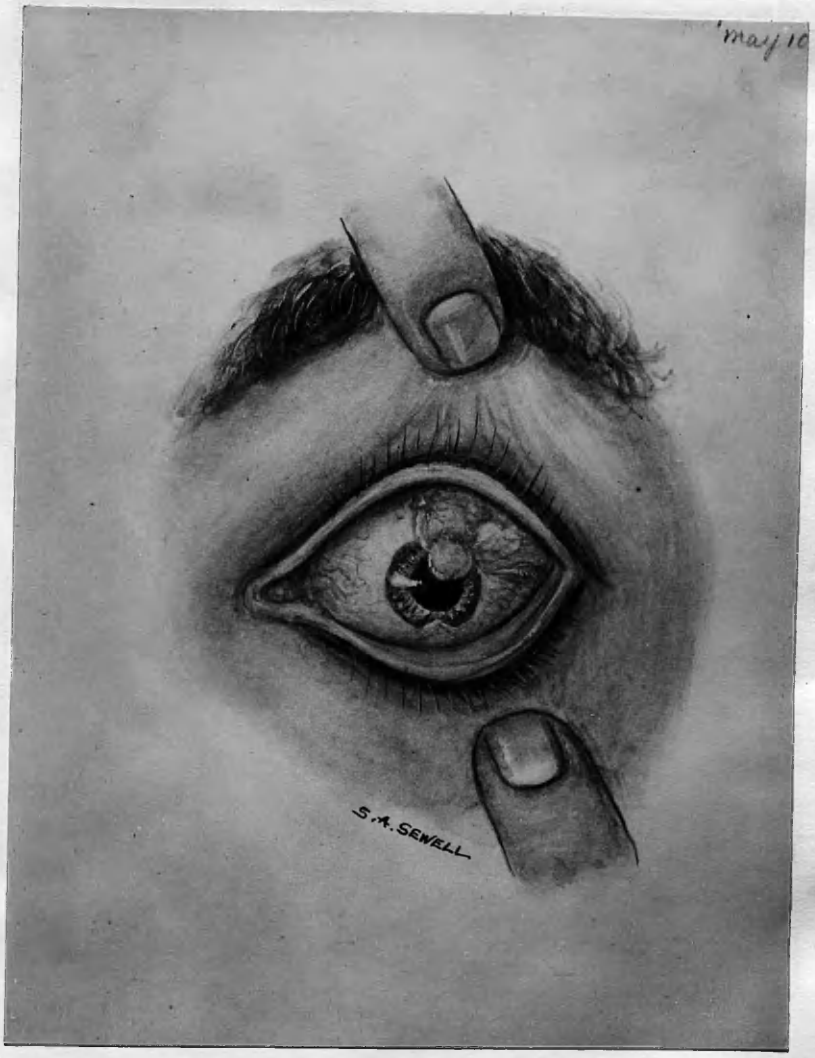
11th February 1936. The patient reports: "My eye continues to be free from trouble."

COMMENT: Despite the age of the patient, the eye tolerated a maximal dose of interstitial and surface radiation. The curative effect of one interstitial treatment was equal to that produced by three surface applications.

PLATE II

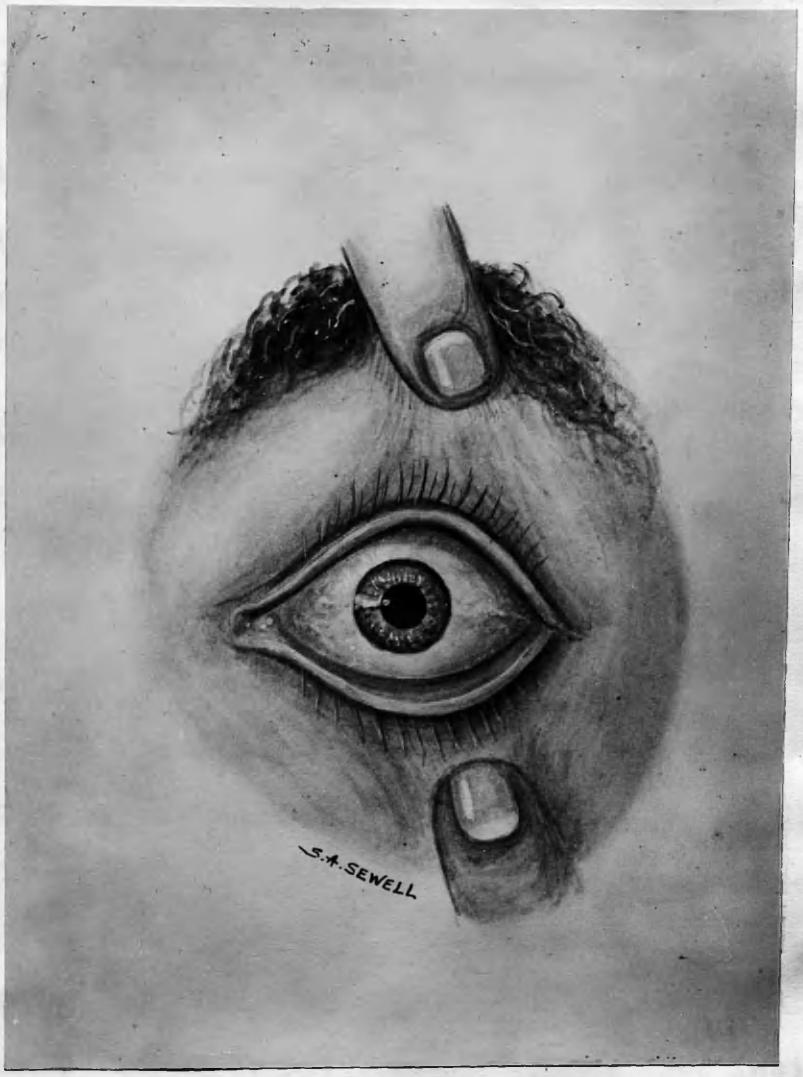

CARCINOMA of LIMBUS. Case 16.
Before treatment, 23rd Feb.1934.

PLATE III




Two months after treatment by Radon seeds to the upper mass and a surface plate to the lower mass. 10th May, 1934.

PLATE IV




One year after treatment by one interstitial insertion to the upper growth and three surface applications to the lower. February 1935.

CARCINOMA, Case 17. Female, aged 18. Domestic servant. Referred by Mr. N.F.Adeney, Bournemouth, as a limbal tumour. The lesion was noticed nine months ago, and was excised by Dr. Staples, of Bournemouth.

26th February 1934. EXAMINATION: At 2 to 4 o'clock on the limbus of the left eye is a growth, 8 mm. diameter, roughly circular, raised and overhanging, soft, red. The conjunctiva of the outer canthus is engorged.

The first radium treatment was given by the surface application, for one hour, of a circular plate, 1.25 cm. diameter, containing 6.2 mg. Ra. el., unscreened.

26th April 1934. EXAMINATION: The growth is smaller.

The second radium treatment was a repetition of the first, but the exposure was 65 minutes.

26th June 1934. EXAMINATION: A small, residual, transparent patch is present on the cornea.

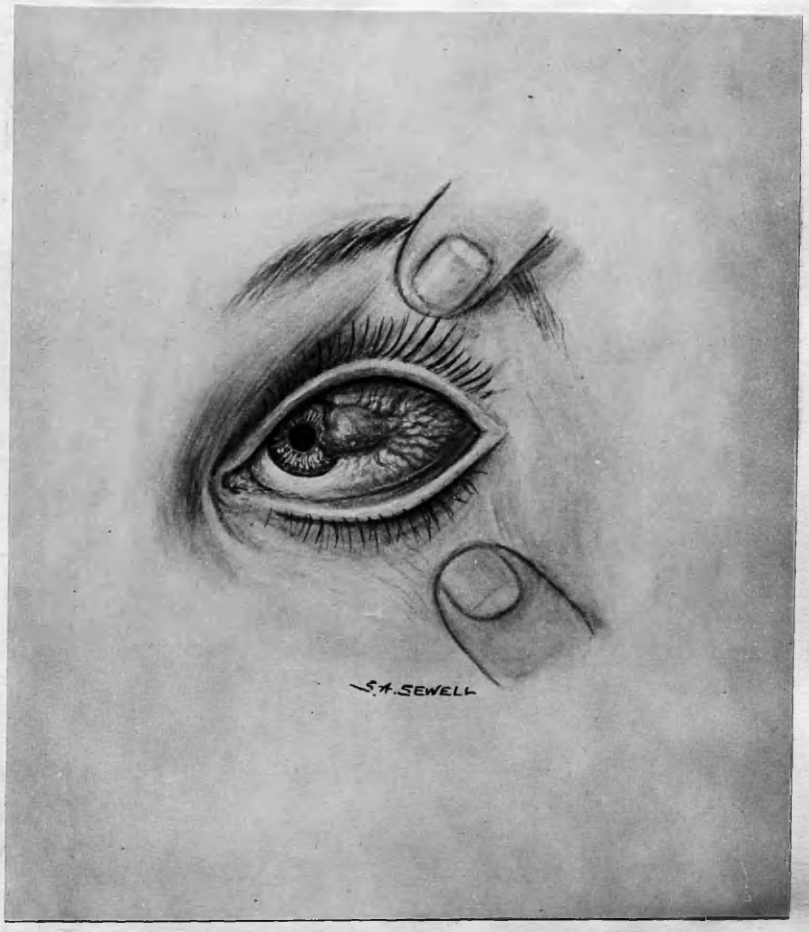
The third radium treatment was given by the surface application for 65 minutes, of a circular plate, 1 cm. diameter, containing 5 mg. Ra. el., unscreened.

15th January 1935. EXAMINATION: The lesion has disappeared.

2nd August, and January 1936. The patient states that the eye is satisfactory.

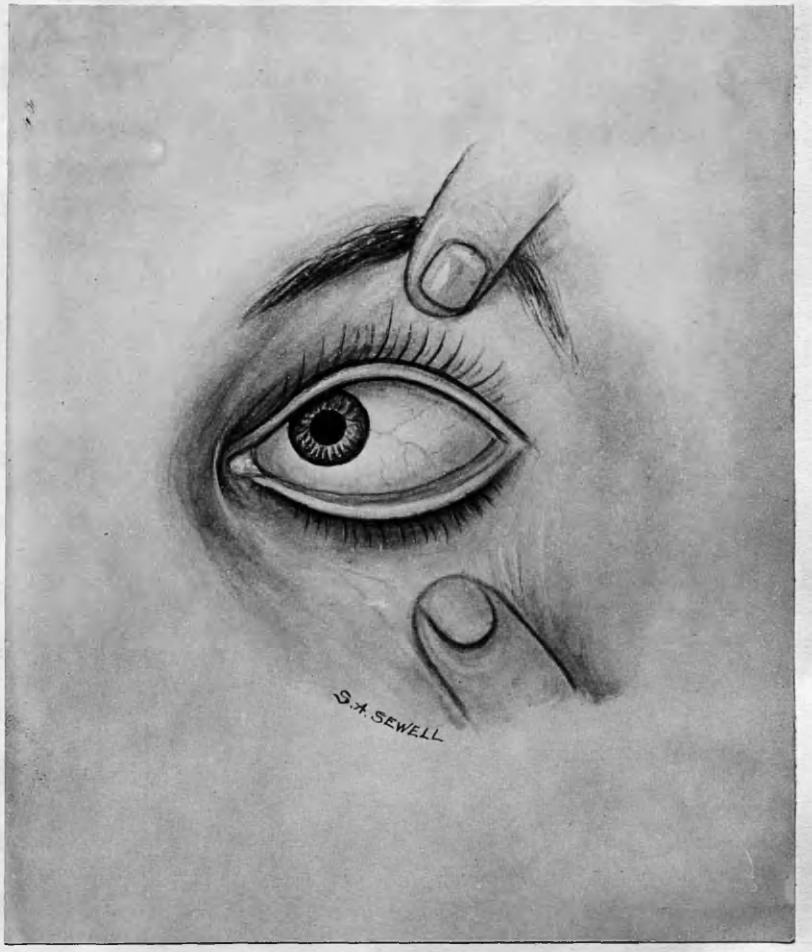
COMMENT: This case is an example of the usual course of events in successful radium treatment.

PLATE V




CARCINOMA of LIMBUS, Case 17.
Before treatment, 26th February, 1934.

PLATE VI




Eleven months after treatment by three surface applications of Radium, 15th January 1935.

CARCINOMA, Case 19. Male, aged 73. Farmer. Referred by Dr. W.E.Heath, Kent County Ophthalmic and Aural Hospital, as an epithelioma of the cornea. The lesion had been noticed four months and was gradually growing larger.

20th September 1935. EXAMINATION: At 8 to 9 o'clock on the limbus of the right eye is a mass, 5 mm. diameter, circular, raised, white. At the lateral margin of the cornea, there are several injected conjunctival vessels.

The first radium treatment was given by the surface application for one hour, of a circular plate, 1.25 cm. diameter, containing 6.2 mg. Ra. el., unscreened.

1st November 1935. EXAMINATION: The lesion has disappeared. There are a few vessels marking the site.

The second radium treatment was given by the surface application, for one hour, of a circular plate, 1 cm. diameter, containing 5 mg. Ra. el., unscreened.

3rd January 1936. EXAMINATION: There is no trace of disease or vascular engorgement.

The third radium treatment was a repetition of the second.

23rd March 1936. The patient reports: "I have not felt anything wrong with the eye."

COMMENT: Three surface applications were given, but the lesion had disappeared after the first treatment. Probably, two applications would suffice in the treatment of a radio-sensitive growth.

PLATE VII


Before treatment.
20th Sept. 1935.


After first trestment
1st November, 1935.


Four months after treatment.
CARCINOMA of LIMBUS, Case 19,
treated by three surface applications of Radium.

MALIGNANT MELANOMA, Case 5. Male, aged 65. Gardener. Referred by Mr. C.Rudd, Birmingham and Midland Eye Hospital, as a melanosarcoma of conjunctiva. The eye had been blood-shot for 7 months.

22nd January 1934. EXAMINATION: At 9 o'clock on the limbus of the right eye is a darkly pigmented mass, 8 x 4 mm., raised, fleshy. The conjunctiva on the outer side is injected. No glands in the neck are palpable.

The first radium treatment was given by the interstitial insertion for 10 hours, of a radon seed, 0.6 cm. active length, filtered by platinum 0.3 mm. containing 10 mc. The dose was 0.723 mc., or 96 mg. hr.

25th January 1934. EXAMINATION: There is a brisk conjunctivitis.

29th January 1934. EXAMINATION: The conjunctivitis has subsided in the last 48 hours. The eye was treated by irrigation twice daily.

12th March 1934. The patient states that the reaction was not severe.

EXAMINATION: The lesion is one half the original size and is flat. The leash of conjunctival vessels is much less marked.

4th April 1934. The patient states that he has no discomfort.

EXAMINATION: The lesion is possibly a little smaller.

The second radium treatment was given by the surface application, for one hour, of a circular plate, 1 cm. diameter, containing 5 mg. Ra. el., unscreened.

16th May 1934. EXAMINATION: The lesion is unchanged. The third radium treatment was a repetition of the second.

12th July 1934. EXAMINATION: The lesion is smaller. The conjunctival vascularity is still further reduced. The fourth radium treatment was a repetition of the second.

28th August 1934. The patient states that he has no symptoms.

EXAMINATION: The lesion is smaller, and is not raised.

12th March 1935. The lesion is unchanged.

15th July 1935 and 10th February 1936. Mr.C.Rudd reports: "There is a spot of pigment near the limbus, about 2 m.m. in diameter. One or two engorged conjunctival vessels are present. Glands in the neck are not palpable."

19th February, 1936. EXAMINATION: Condition found unchanged from 28th August 1934.

COMMENT: The presence of residual pigment is noted in all the cured cases of melanotic tumour. Treatment of the pigmentation by itself, is unnecessary, the indication for treatment being the demonstration of tumour formation.

# PLATE VIII


Before treatment,
22nd January 1934.


Two months after treatment by the interstitial insertion of a Radon seed.
12th March, 1934.

MALIGNANT MELANOMA, Case 5.

# SUMMARY

In this paper, a short account is given of the physical properties of radium and their application to therapy. The apparatus used in treatment is described and the biological results of radiation discussed, the effects on the eye being fully considered. A summary is given of the anatomy, pathology, diagnosis and treatment of primary malignant tumours of the limbus. The literature, on radium therapy in malignant disease of the cornea and conjunctiva, is fully analysed.

The treatment at the Radium Institute, London, of limbal malignant new-growths, is described in detail. The results of treatment are fully discussed, and illustrative cases are reported.

From this investigation, the following conclusions may be drawn:-

1. Radium should be employed in the treatment of primary malignant new-growths, in cases where the area of the tumour does not exceed 1 sq. cm. and where the limbus is infiltrated by growth to an extent not greater than one-half of the circumference.

2. The rapidity of growth and the histological character of the malignant limbal tumour do not alter the prognosis in radium treatment.

3. The age and sex of the patient do not affect the treatment, provided that the patient is able to co-operate intelligently, by lying at rest during one hour of radium application.

4. The methods advised are:

    (a) surface application.
    (b) interstitial application.

    The technique at the Radium Institute, London, is the use of plates containing 5 mg. Ra. el. per sq. cm. active area, unscreened, applied in contact for one hour. This application is repeated twice at intervals of two months. The interstitial insertion of a radon seed, 0.6 cm. active length, screened by Platinum 0.3 mm., containing 3 to 10 mc., for a period of 48 hours (3 mc.) to 6 hours (10 mc.), is employed in cases unsuitable for surface application of radium.

5. Radium will cure permanently at least 90% of the cases treated.

Radium is a therapeutic weapon which should be used in every suitable case of primary malignant disease of the sclero-corneal junction.

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