

INTRA-EPITHELIAL EPITHELIOMA* BOWEN'S DISEASE

BY

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INTRA-EPITHELIAL EPITHELIOMATA may present to the ophthalmologist on the cornea, conjunctiva or eyelids, generally of elderly men. Here they form vascularized elevated plaques, that look rather gelatinous or granulomatous, and they most often arise in sites of chronic infection, as after burns or pannus. Years later they tend to break through the basement layer of the epithelium and finally yield distant metastases. To the ophthalmologist their interest and importance lies in the need for their early recognition, since in this precancerous stage they can so readily be excised with no ultimate danger to life or eye, and this deserves especial emphasis since they are generally flat and inconspicuous, and readily mimic a pterygium or localized lid infection.

In presenting here one further case, arising as a great rarity from the tarsal conjunctiva, it seemed a good opportunity to trace the subsequent history of those other seven cases that have so far reached the pathological department of the Institute of Ophthalmology, and so to assess the prognosis after the varied therapeutic approaches that have been used.

Case Reports

Case 1, a man aged 77, was referred to me by Dr. B. Bradley at the Central Middlesex Hospital for a rather irritable ulcer on the left lower tarsal conjunctiva; this was shallow and irregular, with a white heaped-up rim, about 10 mm. by 5 mm. in size, and spreading from the lid margin half way to the lower fornix (Fig. 1). A culture yielded only diphtheroids, and scraping showed no viruses or fungi. Treatment with various antibiotics produced little more than a variable lessening of the scant discharge and irritation.



FIG. 1. — Intra-epithelial epithelioma of lower tarsal conjunctiva (Case 1) before treatment.

On January 9, 1956, 6 months after the onset of symptoms, a biopsy was performed (Figs 2—6).

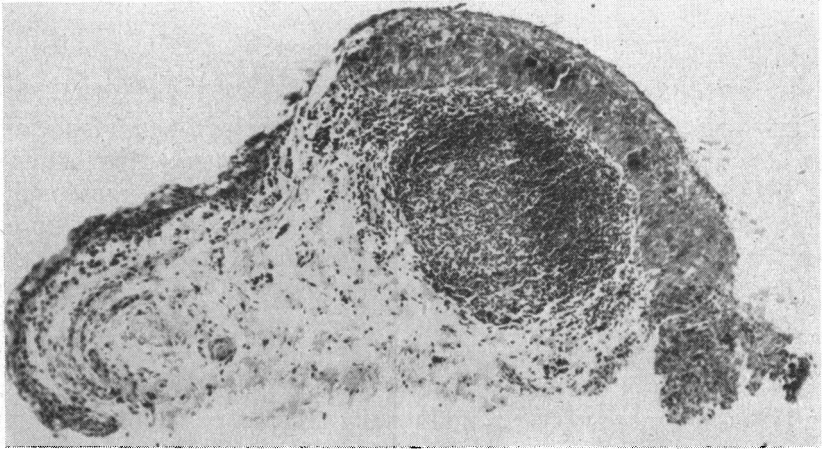


FIG. 2.—Case 1, general view of lesion, showing sharply demarcated area of epithelial hyperplasia with follicular inflammatory infiltration in subepithelial tissue. Haematoxylin and eosin $\times 67$

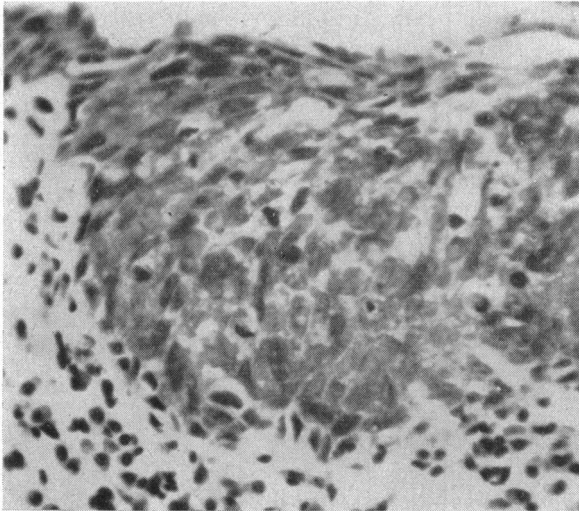


FIG. 3.—Case 1, high-power view, showing loss of differentiation in epithelial layers. The cells are pleomorphic and show large hyperchromatic nuclei with numerous mitotic figures. Haematoxylin and eosin $\times 385$

Dr. Norman Ashton reported as follows:

“Sections show a small piece of conjunctival tissue in which there is a sharply demarcated area of diffuse epithelial thickening involving two thirds of the epithelium. In consists of an undifferentiated mass of pleomorphic cells in active mitotic division and a few “monster cells” containing large hyperchromatic nuclei. There is no evidence of invasion of the subepithelial tissue which shows only diffuse and follicular infiltration with lymphocytes and plasma cells. The histological picture is typical of intra-epithelial epithelioma (Bowen’s disease) of the conjunctiva.”

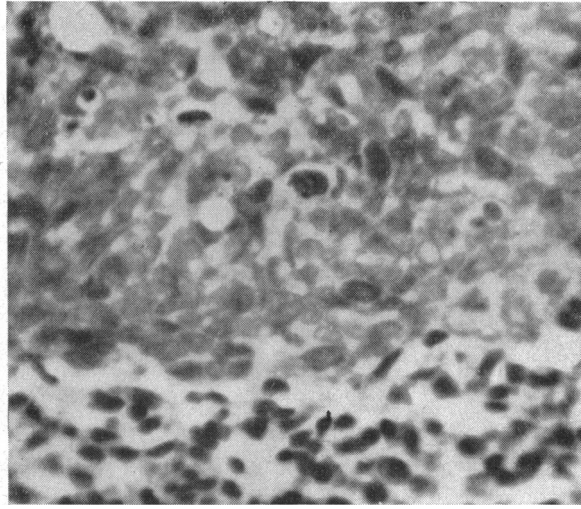
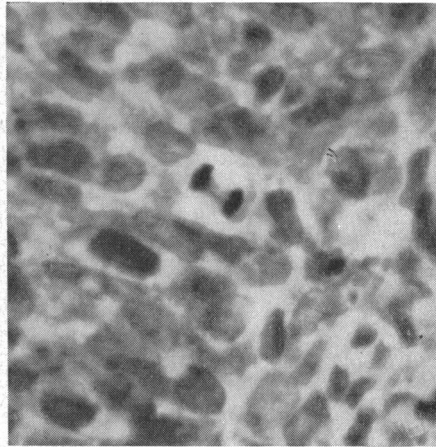
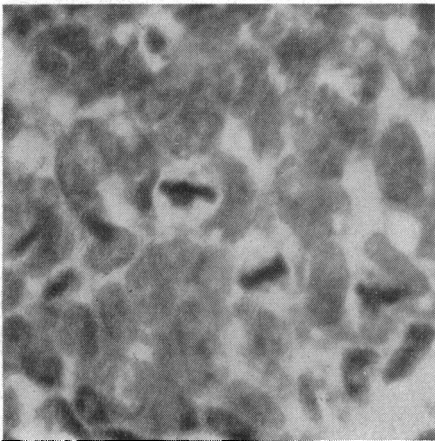


FIG. 4.—Case 1, high-power view of deeper epithelial layers showing haphazard arrangement of cells. Centrally a cell containing a single large nucleus ("monster cell") may be seen. Haematoxylin and eosin $\times 412$



FIGS 5 and 6.—Case 1, different stages of mitosis in hyperplastic epithelium. Haematoxylin and eosin $\times 675$

The affected area was then irradiated at Westminster Hospital, by closely applying to the everted lid a radio-active strontium shell (4,800 r, in six applications of 100 r/min. for 8 minutes at 2 to 3-day intervals). Within a fortnight the ulcer had completely dispersed (Fig. 7, overleaf) and has never recurred; the eye was already blind from cataract but the patient remains in other respects healthy.

Follow-up of Previous Cases from the Department of Pathology, at the Institute of Ophthalmology

Case 2, a man aged 46, had been attending the Cardiff Royal Infirmary under Mr. B. Gluck. For 8 years he had had a degenerative condition of the corneal epithelium in the form of raised white patches, some of which stained with fluorescein; and then 2 months previously had developed a greyish round patch astride the upper limbus 3 to 4 mm. in



FIG. 7.—Case 1 after treatment with β -radiation.

diameter, slightly raised, with many red spots which appeared to be blood vessels coming vertically to the surface (Fig. 8).

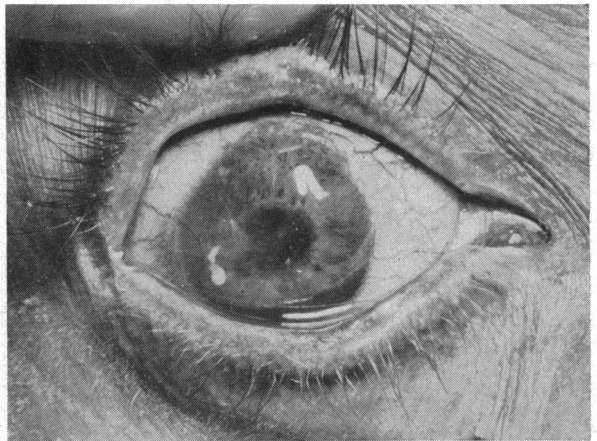


FIG. 8.—Typical intra-epithelial epithelioma of the limbus (Case 2).

A biopsy then showed the typical features of Bowen's disease, and the eye was enucleated on November 26, 1954; there has so far been no sign of any recurrence.

Case 3, a man aged 40, came from Johannesburg. His eye had been red for 6 months, with the development of a small semi-translucent lump (1 by 1.5 mm.) closely resembling a pterygium. This was excised, and, after reference through Sir Stewart Duke-Elder, was reported histologically as "Bowen's disease" (December 3, 1954). The eye has since then remained quiet, and there has been no sign of recurrence. (This was confirmed by patient and Dr. Frampton on November 15, 1956.)

Case 4, a woman aged 81, has already been reported by Greaves (1955). Her eye had been red and watery for 4 weeks, and exhibited a raised fleshy growth extending halfway across the cornea and well vascularized except over the part nearest to the corneal centre. A biopsy on December 15, 1954 showed the typical histology of "Bowen's disease". This was treated with superficial x-radiation 5000 r (400 r daily for 5 days a week). There had been no recurrence when the patient was last seen on January 1, 1956, and the vision had improved from 6/36 to 6/12, with no signs of an irradiation cataract.

Case 5, a man aged 54, was referred to Mr. C. Cook at Guy's Hospital with a localized gelatinous swelling at the limbus. This eye had been inflamed "off and on for years" and showed a "juicy swelling astride the limbus, with some corneal staining axially". After a few months' conservative treatment, a patch of xerosis developed at the limbus opposite the original growth, and then after a further few months, in which there was little change save an increasing corneal vascularization (with diminished sensation), the patient was admitted to hospital for biopsy on January 19, 1955. Both limbal swellings had the typical histology of Bowen's disease, whereupon both lumps were excised. A month later another tiny lump had arisen at the limbus midway between its two fore-runners, and this was also removed. The following month, persistence of the punctate epithelial erosions led to his reference to Dr. M. Lederman by whom the eye was irradiated (6240 r in four fortnightly applications of a strontium shell). Thereafter the cornea remained quiet but hazy and vascularized, and there had been no recurrence by January 1, 1956.

Case 6, a male Nigerian aged over 60, was seen by Dr. F. C. Rodger after 4 years of eye discomfort. A fleshy lump was found to cover the upper half of the cornea and adjacent conjunctiva, resembling a leprous sclero-keratitis; there was no associated trachoma. This was excised, and biopsy later confirmed the diagnosis of Bowen's disease. Unfortunately by that time the patient was frightened of any further measures, and had disappeared into the jungle without trace.

Case 7, a man aged 68, was under the care of Dr. R. D. Calcott of Nairobi. A limbal tumour had been removed on April 27, 1955, and the sections showed a squamous-cell carcinoma arising in a previously existing intra-epithelial epithelioma, with early invasion of the subepithelial tissues. The tumour was irradiated, and subsequently the eye remained quiet with no evidence of recurrence. However, by March 22, 1956, the dystrophic condition of the corneal epithelium had progressed with greater thickening and opacity of the cornea, although it was still clear enough at the axial area to allow 6/12 unaided vision. The patient then emigrated to Australia and has not yet been traced.

Case 8, a man aged 78, was referred to Mr. J. A. Magnus with a tumour at the limbus of the left eye that had been noted for the previous 14 weeks. This tumour was excised on December 7, 1955, apparently completely, and it was confirmed histologically to be an intra-epithelial epithelioma. No further treatment was needed and there has been no sign of recurrence.

Discussion

Bowen's disease is primarily one of a motley of precancerous conditions of the conjunctiva, well recognized since their initial description by Bowman (1849). Subsequent reports of such cases listed by Lugossy (1956) propose various names such as "tyloma", "hornification of the conjunctiva", "keratosis", "conjunctival callosity", and especially that of Lister and Hancock (1903), "epithelial plaque". These lesions have been classified clinically by Nicholls (1939) as:

- (a) epithelial plaques with xerosis,
- (b) congenital plaques,
- (c) plaques secondary to chronic initiations (some of these last show a rapid hyperplasia similar to or identical with leukoplakia elsewhere.

They have been classified histologically by Janert (1956) as epithelial hyperplasia, without dyskeratosis, with dyskeratosis, and with hyperkeratosis (corresponding to the clinical pictures of erythroplasia, Bowen's disease, and leucoplakia). Although they may arise at any site on the cornea or conjunctiva, they usually appear at the limbus.

The clinical variant on the skin, described by Bowen (1912) and established as an important ophthalmological disease by McGavie (1952), has a very characteristic histological picture and is really a frank *carcinoma-in-situ* which has simply not yet spread from the epithelium of its origin. Thus it is proper to separate it from the various epithelial plaques of which the precancerous state can only be inferred by analogy, in many cases perhaps incorrectly. Microscopically the basal cells proliferate to form elongated pegs without actual invasion of Bowman's membrane; they show marked variation in size, shape, staining characteristics, and loss of polarity, some becoming "monster cells", containing either a single large nucleus (Fig. 4) or multiple small nuclei clumped together after amitosis. Some large cells contain a vacuole encircling the nucleus, others show premature keratosis, and mitotic figures are common (Figs 5 and 6). Beneath the epithelium there are signs of a mild chronic inflammatory reaction with lymphocytes, plasma cells, and histiocytes (Fig. 2).

The eight cases from the Department of Pathology at the Institute of Ophthalmology were all reported to show the characteristic histological features detailed in Case 1; with isolated exceptions they arose at the limbus, and occurred in men aged over 40. It is doubtless a curious coincidence that three of them should have come from different parts of Africa. In one case only had the cancerous change already begun. Multiple malignancy, noted in five out of sixteen cases reported by McGavie (1942) and in four out of eighteen reported by Locke (1956), was not recorded for any of these eight patients. It is interesting, however, that in Case 5 two foci arose at opposite sides of the limbus, and a third then followed after these had been excised. Pre-existing corneal or conjunctival disease (found in six of Locke's eighteen cases) was noted in none of the eight.

These eyes had all presented a red, irritable conjunctiva in which the diagnostic nodule (or ulcer, in the one eyelid to be affected) gradually appeared some months or even years later. They sometimes persisted as an indolent superficial keratitis with crops of punctate erosions, haze, and later vascularization, which gave little clue to the cancer that lay concealed.

Case 1 is of especial interest in that the lesion arose from the conjunctiva at the lid margin. All the other seven cases from the Institute of Ophthalmology and all of Locke's eighteen cases arose from the cornea or bulbar conjunctiva.

Treatment may be by excision of the tumour (Cases 3 and 8) and this may even entail removal of the whole eye (Case 2) by irradiation (Cases 1 and 4), or by local excision followed by eradication (Cases 5 and 7). Small tumours

could doubtless be expunged with equal certainty, especially from the lid, by cauterizing chemicals or diathermy. In only one of our eight cases (Case 5) has the lesion definitely recurred although at a different section of the limbus. The corneal opacity has progressed only in Case 7. No further records were available from Case 6.

In his follow-up analysis of eighteen cases, Locke noted recurrence in three out of ten excised locally (re-operation being successful in all three) and in one of five more severe cases that had required enucleation (in this one the recurrence was by direct extension to the lacrimal sac). Three of Locke's cases had been treated by *x*-radiation, one was unsuccessful (dosage not known), and in two advanced cases where the growth was destroyed, one had a parotid metastasis, and the other lost the eye from iritis and secondary glaucoma.

The length of the follow-up period in the foregoing eight cases ranges from 1 to 2 years. This is too short for any mature conclusions to be drawn but, since the site of the tumours lends itself to such minute examination, it would be reasonable to expect by now some recrudescence to be manifest in any tumour that had been inadequately despatched.

For epibulbar tumours the choice between excision and irradiation may well be dictated by the size of the growth, the extent of the damage to sight, and the availability of *x*-radiation, but local excision is probably the simplest and surest method. The dose of *x*-radiation recommended in each case was fairly heavy, but such a dose can apparently be tolerated well by the eye.

For the rarer tumour on the palpebral conjunctiva, where distance from the eyeball renders any procedure relatively safe, daily contact-applications of the strontium shell in the out-patients' department may well be the simplest solution.

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