COMMUNICATIONS

NAEVI AND MELANOMATA OF THE CONJUNCTIVA*†

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NAEVI are the most common benign tumours of the conjunctiva, and their malignant counterparts, the malignant melanomata, although far less frequently encountered, are among the most serious of the ocular neoplasms. In typical cases the histological diagnosis of naevi and melanomata is not difficult, but many cases are not typical, and it is these atypical cases that tax the diagnostic ability of the histopathologist, particularly if the lesion shows changes suggestive of malignancy. In addition to the diagnostic problems presented by these tumours their treatment is in dispute, mainly because, with certain notable exceptions, few clinicians have treated more than a small number of these tumours during their lifetime.

The large collection of these tumours in the Department of Pathology at the Institute of Ophthalmology, London, presented an opportunity for clarifying certain aspects of melanotic lesions of the conjunctiva, and to this end all the naevi and malignant melanomata referred to the Department of Pathology between 1948 and 1961 were re-examined and their histological diagnoses either confirmed or adjusted. In addition, all those cases where a diagnosis of malignant, pre-malignant, or possibly malignant melanoma was made were followed up, by reference to the hospital notes if the patient had attended Moorfields Eye Hospital, and by writing to the referring surgeon or pathologist if the patient had attended another hospital.

The purpose of this study is threefold. First, to classify naevi and malignant melanomata of the conjunctiva both with regard to accepted nomenclature and as a result of examining 400 such neoplasms histologically. Second, to ascertain the degree of malignancy of those tumours that are frankly malignant and of those that show changes suggestive of malignancy. Third, to compare the histological appearances of naevi and malignant melanomata of the conjunctiva with those of the skin.

Review of the Literature

From the earliest days of history man has been fascinated by birthmarks and their significance, giving explanations for their occurrence that in retrospect seem naïve, bizarre, or frankly horrific. It is only in the last 150 years that a scientific approach

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to their aetiology and classification has been attempted, and only in the last few years that satisfactory solutions to some of these problems have been presented.

The word "naevus", from the Latin word meaning a mark upon the body, was originally applied to a number of different conditions appearing at or soon after birth and characterized by an alteration in the colour or texture of one part of the skin. More recently, the term "naevus" has been restricted to those benign, pigmented, and occasionally non-pigmented, tumours composed of pigment-producing cells, and it is this more narrow definition that is used here.

The malignant counterpart of the naevus, the malignant melanoma, was first described as a separate entity by Laënnec (1806) under the name "melanosis", and a few years later he (Laënnec, 1826) enlarged and clarified his description of this condition, stating that melanosis was a form of cancer. Carswell (1838) was the first author to use the word "melanoma", and Virchow (1869) classified melanotic tumours into simple melanomata, melanosarcomata, and melanocarcinomata. It is now accepted that naevi and malignant melanomata are ectodermal in origin, and although the terms "melanocarcinoma" and "naevocarcinoma" are used by some authors, the term "malignant melanoma" is widely accepted as the most suitable one to apply to malignant tumours composed of pigment-producing cells.

At the beginning of the nineteenth century it was appreciated that naevi of the conjunctiva were similar to those of the skin. Wardrop (1808), when describing fleshy excrescences of the cornea, wrote: "Of these there are two very distinct kinds. One of them appears at birth, or soon after it, and resembles the naevi materni so frequent on the skin of various parts of the body." The early literature on naevi of the conjunctiva is sparse, few authors making more than passing reference to the condition. Bader (1868) mentioned that naevi had been observed on the caruncle and in the ocular and palpebral conjunctiva, and Stellwag von Carion (1868) described melanomata of the conjunctiva as being composed of cells heavily laden with pigment. Parsons (1904) gave a good description of these tumours, stating that they resembled those of the skin. The cysts, which are a characteristic feature of over half the naevi of the conjunctiva, were described by Panas (1894) in a naevus which he believed was undergoing malignant change. Parsons (1904) appreciated that they did not have any sinister implication.

Because an understanding of the benign melanoses helps in the appreciation of the evolution and histology of naevi, their history must be considered here. Congenital melanosis of the conjunctiva was first described by Desmarres (1847) as *taches noires pigmentées de la sclérotique*, and following this a number of papers appeared which described a condition presenting as abnormal pigmentation of some or all of the following structures: skin of face, conjunctiva, sclera, iris, fundus, orbit. The confusion in the literature has resulted from lack of appreciation of the fact that pigmentation may involve different parts of the eye or its surrounding structures and yet be basically the same condition. The earlier literature on congenital melanosis of the eye has been ably reviewed by François (1934), and those cases where the skin of the face was also involved were collected by Mishima and Mevorah (1961) when discussing the naevus of Ota. Ota (1939) described the condition of melanosis bulbi associated with pigmentation of the face as "naevus fusco-caeruleus ophthalmomaxillaris"; fortunately, this name has not become popular, the condition being most commonly known as "naevus of Ota", or "oculodermal melanosis".

Melanosis bulbi is a widespread abnormality of pigmentation of the eye and is uncommon, although congenital pigment spots of the conjunctiva are not uncommon and were described by Steiner (1905). Löhlein (1929) suggested that occasionally these congenital spots may rapidly spread over the whole conjunctiva, taking on malignant characteristics. Benign acquired melanosis of the conjunctiva is far less common than the analogous condition of the skin, and Duke-Elder (1938) reviewed the literature of melanosis resulting from Addison's disease, endogenous and exogenous ochronosis, the long-continued use of adrenaline drops, keratomalacia, trachoma, and vernal conjunctivitis. In the recent literature two forms of congenital pigmentation of the conjunctiva—congenital stromal melanosis and congenital conjunctival melanosis—have been described (Reese, 1952; Greer, 1960).

Greer (1960) divided melanotic conjunctival lesions into four groups depending upon the type of junctional activity present:

- Class 1.—No junctional activity of any kind. This class includes the melanoses and deep naevi.
- Class 2.—Junctional activity of a benign type present. This class includes the junctional and compound naevi.
- Class 3.—Exhibit junctional proliferation of an anaplastic type. This class presumably includes the active junctional naevi sometimes seen in children, and the active naevi of adults, as well as precancerous melanosis.
- Class 4.—Invasive malignant melanomata.

Hogan and Zimmerman (1962) divide naevi of the conjunctiva into junctional, compound, and dermal types, and describe blue naevi as a separate type of tumour.

The first reported case of what was almost certainly a malignant melanoma of the conjunctiva was that described by Travers (1820) of a "circumscribed tumour". MacKenzie (1835) described melanosis of the conjunctiva but did not discuss it at any length. Dalrymple (1852) described three forms of malignant disease of the eye: medullary sarcoma or fungus haematodes (retinoblastoma), melanosis, and carcinoma or scirrhus. He stated that melanosis most commonly occurred around the age of 50 to 60 years and consisted of cancer cells containing dark granular pigment. Virchow (1869) considered malignant melanomata of the conjunctiva to be similar to those of the skin and described them in his lecture on melanomata. He considered that melanomata of the conjunctiva and sclera, particularly at the limbus, were frequently sarcomatous, but that prognosis was often good. Stellwag von Carion (1868) classified sarcomata of the eye according to constituent cell type; described stellate, spindle-shaped, and roundish forms; and stated that they were sometimes pigmented (melanotic sarcoma). Thus, in the middle of the nineteenth century malignant melanomata of the conjunctiva were described histologically in the same terms as were those of the skin. In the present century there has been a tendency to consider that the malignant melanotic tumours of the conjunctiva are different from those of the skin, particularly in so far as their nomenclature, management, and prognosis are concerned.

Van Munster (1872) was apparently the first author to stress the aetiological role of pigmented spots at the limbus in malignant melanomata, and Abadie (1876) considered that sarcomata of the conjunctiva may arise from congenital pigmented

spots. Kerschbaumer (1900) believed that all epibulbar sarcomata arose from pigmented naevi, while Morax (1926) described the evolution of sarcomata of the conjunctiva from acquired pigmented spots as well as from pigmented naevi. A new conception of the origin of malignant melanomata of the conjunctiva was proposed by Reese (1938) when he described precancerous melanosis, an acquired flat, diffuse, pigmentation of the conjunctiva most commonly occurring in middle age. Malignant melanomata, frequently multifocal in origin, arose from this flat pigmentation after a variable interval of time, averaging five to ten years. Reese concluded that the majority of malignant melanomata arose from precancerous melanosis rather than from the malignant transformation of a naevus, although in more recent papers (Reese, 1943; 1955; 1960; 1964) he has altered his views slightly, and now believes that one-third of malignant melanomata of the conjunctiva arise from naevi. Greer (1954) found that out of 30 malignant melanomata of the conjunctiva nine showed histological evidence of developing in precancerous melanosis, three were of naevus origin, and in eighteen there was no evidence of their exact origin. Reeh (1963) stated that while the majority of malignant melanomata of the conjunctiva arose from a pigmented naevus or from an area of diffuse pigmentation, a few may arise from what appears to be normal conjunctiva. Zimmerman (1964) found that in about half the malignant melanomata of the conjunctiva seen at the Armed Forces Institute of Pathology, Washington, their origin could not be ascribed either to precancerous melanosis or to a pre-existing naevus. Of the remaining half those arising in naevi outnumbered those arising from precancerous melanosis by about two to one.

Histological Features of Naevi of the Conjunctiva

Between 1948 and 1961, 282 benign melanotic lesions of the conjunctiva were diagnosed histologically at the Institute of Ophthalmology. Of this number, 218 were at the limbus or in the bulbar or palpebral conjunctiva, 21 were in the plica semilunaris, and 43 were in the caruncle. These benign lesions were divided into the melanoses and the naevi, and each of these groups was subdivided into lesions of epithelial origin and lesions of subepithelial origin (Jay, 1964).

Histological Features of Benign Melanoses of the Conjunctiva

Epithelial Melanosis.—There were ten cases of epithelial melanosis in this series and each was characterized by a localized area of increased pigmentation of the basal layer of the epithelium. These cases could be subdivided into three groups according to the histological appearance of the basal layer of the epithelium.

- Group 1.—Increased pigmentation of an otherwise apparently normal basal layer. In this group the number of histologically identifiable clear cells was within normal limits (Fig. 1).
- Group 2.—Increased pigmentation associated with an increased number of clear cells in the basal layer, but without nest formation (Fig. 2).
- Group 3.—Increased pigmentation associated with an increased number of clear cells, and with early nest formation. The cells comprising the junctional nests have the histological appearance of clear cells (Fig. 3).

Epithelial melanosis is also occasionally seen in the epithelium overlying a subepithelial naevus.

FIG. 1.—Epithelial melanosis of the conjunctiva. Increased pigmentation of an otherwise normal basal layer. $\times 790$.

FIG. 2.—Epithelial melanosis of the conjunctiva. Increased pigmentation associated with an increased number of melanocytes in the basal layer. $\times 790$.

FIG. 3.—Epithelial melanosis of the conjunctiva. Increased pigmentation with an increased number of clear cells showing early nest formation. $\times 390$.

FIG. 4.—Subepithelial melanosis of the conjunctiva. Fusiform melanocytes in the subepithelial tissue from a case of oculodermal melanosis. $\times 390$.

Subepithelial Melanosis.—There was one example of oculodermal melanosis in the collection at the Institute of Ophthalmology, London, this case being of particular interest as it was associated with a malignant melanoma of the orbit. The subconjunctival tissue contained heavily pigmented fusiform melanocytes, these cells not disturbing the architecture of the tissue (Fig. 4).

Histological Features of Naevi of the Conjunctiva and Plica

The age and sex distribution of these tumours is given in Table I, while the age at which the tumour first became apparent to the patient, in those cases where an adequate history is available, is given in Table II.

Naevi of the conjunctiva tend to be well-circumscribed tumours, although they are never encapsulated. Near the limbus they are usually fairly flat, extending horizontally in the epithelium and subepithelial tissue. In this situation the subepithelial tissue is scanty and the sclera appears to act as a barrier to the naevus cells. In the bulbar conjunctiva, particularly near the fornices, the tumours tend to be more polypoid in shape.

TABLE I
AGE AND SEX DISTRIBUTION OF NAEVI OF CONJUNCTIVA

Age (years)	Males		Females	
	Conjunctiva and Plica	Caruncle	Conjunctiva and Plica	Caruncle
0-9	19	0	20	1
10-19	29	2	41	7
20-29	22	3	11	6
30-39	19	2	14	2
40-49	4	2	7	5
50-59	7	1	10	3
60-69	4	3	4	1
70-79	1	1	2	1
Unknown	4	0	8	0

TABLE II
AGE WHEN NAEVI OF CONJUNCTIVA FIRST BECAME APPARENT

Age (years)	Males		Females	
	Conjunctiva and Plica	Caruncle	Conjunctiva and Plica	Caruncle
0-9	30	3	32	5
10-19	11	1	19	5
20-29	14	2	8	1
30-39	5	1	3	1
40-49	0	1	5	1
50-59	2	1	3	1
60-69	2	2	2	1
70-79	0	1	1	1

TABLE III
AGE DISTRIBUTION OF NAEVI OF CONJUNCTIVA SHOWING JUNCTIONAL ACTIVITY

Age (years)	Total No. of Naevi	Naevi Showing Junctional Activity		Naevi Showing Intra-epithelial Nests	
		No.	Per cent.	No.	Per cent.
0-9	39	39	100	18	46
10-19	70	66	94	27	41
20-29	33	26	79	8	24
30-39	33	22	67	6	18
40-49	11	4	36	0	
50-59	17	5	29	0	
60-69	8	2	25	0	
70-79	3	0		0	

Junctional Activity.—Out of 229 naevi that had an intact epithelium, 172 (75 per cent.) showed some degree of junctional activity. This activity was confined to the basal layer of the epithelium in 111 cases, the cell nests being worked downwards into the subepithelial tissue. In 61 cases, however, nests of naevus cells were entirely within the epithelium (Fig. 5). The age distribution of naevi showing junctional activity and those showing intra-epithelial nests is given in Table III.

The outstanding characteristic of benign junctional activity is the circumscribed appearance of the nests of naevus cells, the demarcation between naevus-cell nest and normal epithelium being abrupt (*see* Fig. 5). This contrasts with the diffuse nature of the junctional change in intra-epithelial melanomata and in certain malignant melanomata (*see* Fig. 17). In those instances where intra-epithelial nests are present, the upward migration of cells through the epithelium, characteristic of many cases of malignant melanomata, is not seen. Active junctional naevi, or compound naevi with an active junctional component, are found most commonly in children and young adolescents, and experience has shown that these tumours behave in a benign manner. Occasionally an active junctional naevus is found in an older adult, and in this case it must be considered to be of more ominous significance. Activity is characterized by the upward migration of cells through the epithelium, by pleomorphism of the individual cells of the nests, by loss of cohesion between the individual cells, and by the presence of mitotic figures. A distinction must be drawn, however, between the occasional mitotic figure found in normal epithelial cells and the mitotic figure found in a pigment-producing cell.

FIG. 5.—Junctional naevus of the conjunctiva. Intra-epithelial nests of naevus cells. $\times 390$.

Subepithelial Cells.—The subepithelial cells in naevi of the conjunctiva may occur in nests, in sheets, or in a combination of these two arrangements. Whatever the pattern of subepithelial cells, the characteristic feature of naevi is the uniformity of arrangement of these cells, with their gradual maturity to fibrillar forms, particularly in the naevi of adults. Epithelioid naevus cells occur most frequently in certain of the actively growing naevi of children, particularly in the superficial subepithelial tissue (Fig. 6). They are large cells with abundant eosinophilic cytoplasm containing large nuclei with prominent nucleoli. The most common cell to be found in naevi is the classical naevus cell, a small cell not unlike a lymphocyte with scanty cytoplasm and a small deeply staining nucleus (Fig. 7). Cell borders are usually indistinct, giving the appearance of a symplasm, and frequently the nuclei are grouped in a common cytoplasm forming a giant cell (Fig. 8). In those naevi where the superficial subepithelial cells are epithelioid in type, the small naevus cells are more deeply placed, suggesting that they evolve from the larger epithelioid cells. In the deepest part of the naevus, particularly in adults, the cells tend to become fibrillar in form (Fig. 9). These fibrillar naevus cells have an elongated cytoplasm and an ovoid, deeply staining nucleus.

Pigmentation.—Twenty-nine per cent. of naevi of the conjunctiva of epithelial origin were non-pigmented; the remainder were pigmented to varying degrees.

Epithelial Downgrowths.—Many naevi of the conjunctiva differ from similar tumours of the skin by the presence of epithelial downgrowths. These occurred in 66 per cent. of naevi of the conjunctiva and were either cystic or solid. Many of

FIG. 6.—Compound naevus of the conjunctiva. Epithelioid naevus cells. $\times 390$.

FIG. 7.—Subepithelial naevus of the conjunctiva. Common naevus cells. $\times 390$.

FIG. 8.—Compound naevus of the conjunctiva. Giant cell. $\times 1055$.

FIG. 9.—Subepithelial naevus of the conjunctiva. Fibrillar naevus cells. $\times 390$.

the solid downgrowths were part of a cyst, the plane of the section passing through the edge of the cyst, so missing its lumen. In a few cases, junctional activity was present in the wall of the cyst (Fig. 10).

Inflammatory Cells.—An appreciable inflammatory response was present in 24 per cent. of these naevi and usually consisted of lymphocytes or plasma cells.

Naevi of the Plica Semilunaris.—These differed in no way from naevi of other parts of the conjunctiva. Because the epithelium of the plica is rich in goblet cells, naevi of this part of the conjunctiva contain large numbers of these cells, particularly in the epithelial downgrowths (Fig. 11).

Blue Naevi of the Conjunctiva.—Two naevi in this series were considered to be common blue naevi and a further three cases were of compound naevi associated with common blue naevi. In the series of malignant melanomata there were three cases finally considered to be blue naevi: a common blue naevus, a cellular blue

FIG. 10.—Compound naevus of the conjunctiva. Junctional activity in wall of cystic epithelial downgrowth. $\times 390$.

FIG. 11.—Naevus of the plica semilunaris. Goblet cells in epithelial downgrowth. $\times 390$.

FIG. 12.—Common blue naevus of the conjunctiva. $\times 87$.

FIG. 13.—Common blue naevus of the conjunctiva. $\times 390$.

FIG. 14.—Cellular blue naevus of the conjunctiva. $\times 87$.

FIG. 15.—Cellular blue naevus of the conjunctiva. $\times 390$.

naevus, and a junctional naevus associated with a common blue naevus. The common blue naevi were composed of heavily pigmented fusiform melanocytes situated in the subepithelial tissue (Figs 12 and 13), while the cellular blue naevus consisted of large numbers of plump melanocytes, in places gathered into discrete foci (Figs 14 and 15).

Histological Features of Naevi of the Caruncle

Naevi of the caruncle tend to be larger, more polypoid, and more cellular than those of the conjunctiva. In other respects they bear a close resemblance to naevi of the conjunctiva. Junctional activity was present in 52 per cent. of these naevi of the caruncle, melanin pigment was present in 81 per cent., epithelial downgrowths in 74 per cent., and inflammatory cells in 31 per cent. There was one common blue naevus of the caruncle in this series.

Histological Features of Malignant Melanomata of the Conjunctiva

In the present series of naevi and melanomata of the conjunctiva there were 104 cases which were originally diagnosed as malignant melanomata or as intra-epithelial melanomata, these diagnoses being confirmed in the present study. There were an additional 43 cases which, although originally diagnosed as malignant melanomata or as naevi where malignancy could not be excluded, are now considered to be naevi. These two groups of cases will be discussed separately, the first group being the definitive malignant melanomata, the second being naevi with unusual histological features.

Definitive Malignant Melanomata

Malignant melanomata are divided into those of epithelial origin and those of subepithelial origin (malignant blue naevi). There were no malignant blue naevi in the present series, nor have any been reported in the conjunctiva, so the following description will apply only to malignant melanomata of epithelial origin. These may be subdivided into intra-epithelial melanomata where malignant cells are found only within the epithelium, and frank malignant melanomata where the malignant cells have invaded the subepithelial tissue. These are merely different stages of the same pathological process, one stage passing gradually into the next without any clear-cut division.

On naked-eye examination intra-epithelial melanomata are always flat lesions, while malignant melanomata of the conjunctiva vary in size from small slightly raised lesions to large polypoid masses filling the palpebral aperture. They may be pink, brown, or black in colour, depending upon the amount of melanin they contain.

Malignant melanomata may arise in normal conjunctiva (*de novo* origin), in a localized lentigo, in a widespread lentigo, or in a junctional naevus or the junctional component of a compound naevus. From the histological examination of a particular malignant melanoma it is often impossible to be certain of its mode of origin, although a combination of histological picture and clinical history frequently furnishes the answer.

FIG. 16.—Intra-epithelial melanoma of the conjunctiva. Precancerous stage. $\times 390$.

FIG. 17.—Intra-epithelial melanoma of the conjunctiva. Intra-epithelial stage. $\times 445$.

Malignant melanomata evolve from a precancerous stage (Fig. 16) to an intra-epithelial stage (Fig. 17), and then to a frankly malignant stage with invasion of the subepithelial tissue (Fig. 18). This evolution may be rapid, as in the tumour which arises in apparently normal conjunctiva, or slow, as in that which arises in a widespread intra-epithelial melanoma. The intra-epithelial stage may be localized or widespread, the latter being the condition described by Reese (1938) as precancerous melanosis.

The earliest lesion destined to become a malignant melanoma (*see* Fig. 16) may be difficult to distinguish from benign epithelial melanosis. In the precancerous condition, however, the cells of the basal layer of the epithelium are larger than those of epithelial melanosis and some degree of pleomorphism is present. As the lesion progresses, these cells invade the epithelium and pass towards its surface. There is greater variation in the size of the cell nests than is seen in a junctional naevus and the individual cells show anaplasia. There is marked variation in nuclear size and shape, these nuclei contain abnormally large or multiple nucleoli, mitotic figures may be present, the cytoplasm becomes vacuolated, and there is a tendency for the cells to become separated from one another. The adjacent subepithelial tissue frequently contains an infiltration of lymphocytes and macrophages.

Invasion of the subepithelial tissue by malignant cells occurs sooner or later in the majority of intra-epithelial melanomata. A superficial malignant melanoma results when only the subepithelial tissue adjacent to the epithelium is involved, and this is seen most frequently in malignant melanomata arising in widespread intra-epithelial melanomata. The majority of malignant melanomata, however, are deep and

FIG. 18.—Malignant melanoma of the conjunctiva. Invasion of subepithelial tissue by malignant cells. $\times 390$.

invasive. Of the 104 malignant tumours in this series, two were localized intra-epithelial melanomata, six were widespread intra-epithelial melanomata, and 12 were superficial malignant melanomata arising in widespread intra-epithelial melanomata. The remaining tumours were deep malignant melanomata.

The extent of the intra-epithelial change in the present series of malignant melanomata varied widely. In 46 cases there was a localized area of junctional activity in the epithelium over the tumour; in 22 cases there was a diffuse change throughout most or all of the epithelium over the tumour, in some cases extending for a short distance on each side of the tumour; and in 29 cases there was a diffuse involvement of the epithelium over a wide area beyond the region of subepithelial invasion. In one case the degree of epithelial involvement could not be ascertained because the specimen was received in a mutilated condition, while in a further case there was no junctional activity at all, this being a local recurrence following local excision of the original tumour.

The constituent cells of the malignant tumours in this series were one or more of the following types:

(1) *Epithelioid* (Fig. 19).—These, the most common cells found in malignant melanomata of the conjunctiva, are large polyhedral cells with abundant cytoplasm frequently containing numerous fine melanin granules. The large nuclei are round or oval with a well-marked chromatin network, and contain one or more distinct nucleoli.

(2) *Spindle* (Fig. 20).—These are large or small fusiform cells, usually with their cytoplasm extending in the long axis of the nucleus. The nuclei are oval or elongated and tend to appear rather uniform in size, although careful examination shows some variation in size with the occasional giant or multinucleated form. Nucleoli are not as prominent as in other cell types.

(3) *Naevoid* (Fig. 21).—These cells are intermediate in size between epithelioid cells and benign naevus cells. The cytoplasm, although not abundant, is usually greater in amount than is found in naevus cells. Nuclei are round, frequently hyperchromatic, with prominent nucleoli.

(4) *Bizarre* (Fig. 22).—Mononucleated and multinucleated giant cells were present in a number of the tumours.

Of the 97 malignant melanomata in this series, 44 were composed predominantly of epithelioid cells, 32 of a mixture of all types of cells (pleomorphic), thirteen of epithelioid and spindle cells, seven of spindle cells, and one of naevoid cells; 22 of the tumours contained numerous bizarre cells and twelve of the tumours contained an appreciable number of mitotic figures.

The pigment content of these tumours was found to be nil in sixteen cases, slight in 29, moderate in 53, and heavy in six. There was no relationship between degree of pigmentation and cell type.

Subepithelial inflammatory cells were present in the majority of these tumours. They were numerous in eighteen cases, moderate in number in 41, few in 28, and absent in seventeen cases.

Twelve of the malignant tumours in this series were considered to arise in a benign naevus. Seven of these tumours contained areas of benign naevus cells, two contained both benign naevus cells and epithelial downgrowths, and three contained

FIG. 19.—Malignant melanoma of the conjunctiva. Epithelioid cells. $\times 390$.

FIG. 20.—Malignant melanoma of the conjunctiva. Spindle cells. $\times 390$.

FIG. 21.—Malignant melanoma of the conjunctiva. Naevoid cells. $\times 390$.

FIG. 22.—Malignant melanoma of the conjunctiva. Bizarre cells. $\times 390$.

downgrowths alone. In none of the other malignant melanomata were epithelial downgrowths found.

In the few patients who died of melanomatosis, and where post-mortem material was available for study, the secondary deposits consisted of similar cells to those of the primary tumour, although mitotic figures and bizarre forms were more frequently seen in the secondary deposits.

Naevi with Unusual Histological Features

There were 43 tumours in this series which were originally diagnosed as malignant melanomata, naevi undergoing malignant change, or naevi where malignancy could not be excluded, but which are now considered to be benign naevi.

One group of these tumours consisted of ten naevi of the caruncle, four of the plica, and three of the bulbar conjunctiva, where the naevus was more cellular than is usually the case in these tumours. In all these cases, however, there were none of the

stigmata of malignancy. Junctional activity was either benign in appearance or absent, the subepithelial cells gradually matured as the deeper parts of the tumour were reached, and these cells did not show the pleomorphism associated with malignant melanomata.

There were two cases of common blue naevi, one of a combination of junctional naevus and common blue naevus, and one of a cellular blue naevus. In each of these cases the fusiform subepithelial melanocytes were originally thought to be spindle cells of a malignant melanoma.

In three cases occurring in children the naevi were heavily infected. The inflammatory cells, which caused concern by their mere presence, tended to disrupt the normal architecture of the naevus. In addition, the naevus cells were more pleomorphic than is usually the case even in naevi of children, and the occasional giant and bizarre form was found. In spite of these findings these naevi were considered to be benign.

Three naevi in adults had recurred, and this, in association with prominent junctional activity, was a cause for concern. The junctional activity was, however, benign in appearance, and there was no evidence of subepithelial invasion by malignant cells.

There were two cases of epithelial melanosis in this series, one being associated with a subepithelial naevus. These cases were originally considered to be examples of intra-epithelial melanomata, but the changes in the basal layer of the epithelium were entirely benign in appearance.

Of the remaining fourteen cases in this series, ten were of compound or subepithelial naevi containing one or more areas of atypical and moderately or heavily pigmented naevus cells. These cells, although differing from the remainder of the cells in the tumour, did not show pleomorphism, and the junctional activity in these tumours, when present, was entirely benign in appearance. The last four cases were entirely benign naevi of the conjunctiva and it is not known why malignant change was considered when they were originally diagnosed.

Follow-up Results of Malignant Melanomata of the Conjunctiva

The major part of this section is concerned with an analysis of the follow-up results of the 104 cases of malignant melanomata and intra-epithelial melanomata. The 43 cases which were originally diagnosed as naevi undergoing malignant change or naevi where malignancy could not be excluded will be discussed at the end of this section.

Age and Sex.—The age and sex distribution by decades is given in Table IV. The youngest patients were two males, each aged 21 years, and the oldest were two females each aged 82 years.

It became apparent during the course of this follow-up study that malignant melanomata of the conjunctiva could be divided into two groups. The first group consists of *localized* intra-epithelial melanomata and malignant melanomata arising from them, and the second group consists of *widespread* intra-epithelial melanomata and malignant melanomata arising from them. These two groups will be called *localized melanomata* and *widespread melanomata* respectively. The sex distribution

TABLE IV
MALIGNANT MELANOMATA OF CONJUNCTIVA: AGE AND SEX DISTRIBUTION

Age (years)	Males	Females	Total
20-29	5	3	8
30-39	4	6	10
40-49	10	6	16
50-59	11	16	27
60-69	12	11	23
70-79	7	8	15
80-89	0	2	2

TABLE V
MALIGNANT MELANOMATA OF CONJUNCTIVA: SEX AND AVERAGE AGES

	Sex	Average Ages (years)
All Cases	104 50 males 54 females	52·8 52·0 53·6
Localized Melanomata	73 35 males 38 females	51·7 49·8 53·4
Widespread Melanomata	31 15 males 16 females	57·4 57·0 57·8

and average ages of the two groups are given in Table V, the average ages between the two groups showing a small but significant difference.

Race.—There was one Negro in the present series, a 21-year-old man from Rhodesia. In spite of the fact that the patient lived in the “bush”, the visiting ophthalmologist was able to trace his brother and learn that the patient had been well until ten years after his eye had been enucleated, when he had returned to his village to die (cause of death unknown).

Pregnancy.—One woman aged 22 years was seven months’ pregnant when a malignant melanoma was locally excised from her limbus. A pigmented lesion had been present at the limbus since childhood and it had enlarged over the previous few months. She was well, with no signs of recurrence, four years after the tumour was removed.

History of Lesion.—The length of time that a lesion had been present at the site of the malignant melanoma is given in Table VI, while the duration of progressive changes in the lesion is given in Table VII.

Follow-up Results.—Out of the total of 104 patients in this series, 23 died as a result of their tumour. This gives an overall survival rate of 78 per cent. The five- and ten-year survival and cure rates are, however, of greater interest, and these are given in Tables VIII and IX. These results have been broken down both for sex and type of melanoma (localized or widespread).

The survival and cure rates were calculated as follows:

$$\text{Survival rate} = \frac{\text{Patients alive at end of period} \times 100}{\text{Total number of cases—(patients lost to follow-up + patients dead with no recurrence of melanoma)}}$$

$$\text{Cure rate} = \frac{\text{Patients alive without recurrence at end of period} \times 100}{\text{Total number of cases—(patients lost to follow-up with no recurrence when last seen + patients dead with no recurrence)}}$$

TABLE VI

MALIGNANT MELANOMATA OF CONJUNCTIVA: DURATION OF OBSERVABLE LESION

Duration	Total	Localized Melanomata	Widespread Melanomata
From childhood	12	10	2
Many years	20	13	7
5-10 years	8	2	6
1-5 years	24	17	7
0-1 year	27	22	5
Unknown	13	9	4

TABLE VII

MALIGNANT MELANOMATA OF CONJUNCTIVA: DURATION OF PROGRESSIVE CHANGES

Duration	Total	Localized Melanomata	Widespread Melanomata
More than 10 years	1	0	1
5-10 years	4	2	2
1-5 years	27	15	12
0-1 year	59	47	12
Unknown	13	9	4

TABLE VIII

MALIGNANT MELANOMATA OF CONJUNCTIVA: FIVE-YEAR FOLLOW-UP RESULTS

Patients	All Melanomata			Localized Melanomata			Widespread Melanomata		
	Total	Males	Females	Total	Males	Females	Total	Males	Females
Patients Treated Between 1948 and 1958	77	41	36	54	28	26	23	13	10
Alive Without Recurrence of Melanoma	43	22	21	38	20	18	5	2	3
Alive With Evidence of Melanoma	8	4	4	0	0	0	8	4	4
Died With Secondaries	12	8	4	8	5	3	4	3	1
Died With No Recurrence of Melanoma	5	3	2	1	0	1	4	3	1
Lost to Follow-up	9	4	5	7	3	4	2*	1*	1*
Five-year Survival Rates (Per cent.)	81	76	86	83	80	86	76	67	88
Five-year Cure Rates (Per cent.)	68	63	70	83	80	86	26	20	33

* Evidence of melanoma when last seen.

TABLE IX
MALIGNANT MELANOMATA OF CONJUNCTIVA: TEN-YEAR FOLLOW-UP RESULTS

Patients	All Melanomata			Localized Melanomata			Widespread Melanomata		
	Total	Males	Females	Total	Males	Females	Total	Males	Females
Patients Treated Between 1948 and 1953	25	16	9	20	13	7	5	3	2
Alive Without Recurrence of Melanoma	12	8	4	11	8	3	1	0	1
Alive With Evidence of Melanoma	1	0	1	0	0	0	1	0	1
Died With Secondaries	5	4	1	3	2	1	2	2	0
Died With No Recurrence of Melanoma	2	1	1	1	0	1	1	1	0
Lost to Follow-up	5	3	2	5	3	2	0	0	0
Ten-year Survival Rates (Per cent.)	72	67	83	78	80	75	50	0	100
Ten-year Cure Rates (Per cent.)	67	67	67	78	80	75	25	0	50

The difference between the five-year cure rate of localized melanomata and that of widespread melanomata is most unlikely to have occurred by chance ($P < 0.01$), while there is no significant difference between the five-year cure rates of males and females ($0.50 < P < 0.70$). Similarly, the difference between the ten-year cure rate of localized melanomata and that of widespread melanomata is very unlikely to have occurred by chance ($0.02 < P < 0.05$). The above and subsequent probabilities were calculated by applying the χ^2 test.

Follow-up Results of Localized Melanomata

Origin of Localized Melanomata.—From their histological appearance and clinical history localized melanomata are subdivided into the following groups according to the type of lesion from which they are assumed to have arisen:

(1) *De novo origin.* Patients with malignant melanomata arising *de novo* gave no history of a preceding lesion. They presented with a tumour which was increasing in size and which usually had a short history.

(2) *Naevus origin.* A malignant melanoma arising from a naevus contained areas of apparently benign naevus cells, or epithelial downgrowths.

(3) *Lentigo origin.* Patients with malignant melanomata arising from lentigines gave a history of a static, usually flat, lesion preceding the appearance of the tumour, frequently by many years. It is possible that some of the tumours in this group arose from naevi rather than from epithelial melanoses.

Of the 73 localized melanomata in this series, 28 were of *de novo* origin, thirteen arose in a naevus, 24 arose in a lentigo, and in eight the origin of the tumour was unknown. There was no difference in the survival and cure rates between malignant melanomata of *de novo*, naevus, and lentigo origin.

Structure of Localized Melanomata.—The relationship between predominant cell type and deaths from secondary deposits is given in Table X. There is no significant

TABLE X
LOCALIZED MELANOMATA OF CONJUNCTIVA: CELL TYPE AND PROGNOSIS

Cell Type	Total	Deaths from Secondaries
Spindle	5	0
Epithelioid	38	10
Pleomorphic	28	4

difference in the death rate between the three groups ($0.10 < P < 0.20$). Similarly, there is no significant difference in the death rates when the tumours are classified according to pigment content ($0.30 < P < 0.50$; Table XI), or according to degree of inflammatory cell infiltrate ($0.20 < P < 0.30$; Table XII).

TABLE XI
LOCALIZED MELANOMATA OF CONJUNCTIVA: PIGMENT CONTENT AND PROGNOSIS

Pigment Content	Total	Deaths from Secondaries
None	13	1
Slight	25	5
Moderate	31	8
Heavy	4	0

TABLE XII
LOCALIZED MELANOMATA OF CONJUNCTIVA:
INFLAMMATORY CELLS AND PROGNOSIS

Inflammatory Cells	Total	Deaths from Secondaries
None	13	2
Few	17	6
Moderate	26	4
Numerous	17	2

Site of Localized Melanomata.—Localized melanomata are classified according to site in Table XIII, and the five-year cure rates of tumours of these different sites are given in the same table. There is no significant difference between the five-year cure rates of tumours at different sites ($0.10 < P < 0.20$).

Treatment of Localized Melanomata.—All the localized tumours in this series were treated surgically: by local excision of the tumour, by enucleation of the eye, or by exenteration of the orbital contents. Some patients had radiotherapy as well. Cases which were treated by local excision or by enucleation are subdivided into those where histological examination showed the tumour to be completely removed, and those where it was not completely removed. The number of cases where the tumour locally recurred and the number where death occurred as a result of the tumour are

TABLE XIII
LOCALIZED MELANOMATA OF CONJUNCTIVA: SITE OF TUMOUR AND PROGNOSIS

Patients	Limbus	Bulbar Conjunctiva	Palpebral Conjunctiva	Caruncle
Total Number	52	14	6	2
Patients Treated between 1948 and 1958	38	9	5	2
Alive Without Recurrence of Melanoma	27	7	2	1
Died With Secondaries	6	0	2	1
Died With No Recurrence of Melanoma	0	0	1	0
Lost to Follow-up	5	2	0	0
Five-year Cure Rates (Per cent.)	82	100	50	50

TABLE XIV
LOCALIZED MELANOMATA OF CONJUNCTIVA:
METHOD OF TREATMENT AND PROGNOSIS

Patients	Local Excision		Enucleation		Exenteration
	CR*	NCR†	CR	NCR	
Total Number	22	23	17	1	7
Local Recurrences	3	8	0	0	0
Died With Secondaries	0	6	5	1	1
Patients Treated between 1948 and 1958	16	19	11	1	5
Alive Without Recurrence of Melanoma	12	6	7	0	4
Alive, Tumour Recurred Locally	2	5	0	0	0
Died With Secondaries	0	4	3	1	1
Died, Tumour Recurred Locally	0	1	0	0	0
Lost to Follow-up	2	2	1	0	0
Lost to Follow-up, Tumour Recurred Locally	0	1	0	0	0
Five-year Survival Rates (Per cent.)	100	73	70	0	80
Five-year Cure Rates (Per cent.)	85	35	70	0	80

* CR = completely removed. † NCR = not completely removed.

TABLE XV
LOCALIZED MELANOMATA OF CONJUNCTIVA:
COMPARISON OF SURGERY WITH SURGERY AND RADIOTHERAPY

Treatment	Total	Local Recurrences	Died with Secondaries
Local Excision, Tumour Completely Removed:			
Surgery alone	14	2	0
Surgery + Radiotherapy	8	1	0
Local Excision, Tumour Not Completely Removed:			
Surgery alone	11	7	1
Surgery + Radiotherapy	12	1	5

given in Table XIV; this table also includes the five-year survival and cure rates for the different methods of treatment. The different percentages of patients who died from secondaries are unlikely to have occurred by chance ($0.02 < P < 0.05$), and the differences in five-year cure rates are also unlikely to have done so ($0.02 < P < 0.05$). The results of surgical treatment alone compared with surgical treatment plus radiotherapy are given in Table XV; these results have not been statistically analysed because other factors, such as length of history and size of tumour, probably influence the results.

Follow-up Results of Widespread Melanomata

The cases of widespread intra-epithelial and malignant melanomata are difficult to analyse, partly because of the small number of cases available for study, and partly because of their natural history. These tumours tend to remain intra-epithelial for a number of years, before the malignant cells invade the subepithelial tissue to produce a malignant melanoma. In the present series there were six cases of widespread intra-epithelial melanomata. One patient received surgery aimed at removing the lesion completely and there had been no recurrence seven years after the operation. The remaining five cases were biopsied for diagnostic purposes; in one case a presumptive malignant melanoma developed eleven years after biopsy; in one case the lesion was found to be increased in size eight years after biopsy; and in the remaining three cases there had been no change in the appearance of the lesion four, five, and seven years respectively after biopsy.

There were 25 malignant melanomata which arose from widespread intra-epithelial melanomata, twelve being superficial in situation and thirteen deeply invading the subepithelial tissue. The follow-up results of these cases are given in Table XVI. The superficial malignant melanomata appear to have a similar prognosis to that of the deep melanomata, and there is no relationship between cell type, degree of pigmentation, presence of inflammatory cells, and prognosis.

TABLE XVI
WIDESPREAD MELANOMATA OF CONJUNCTIVA: FOLLOW-UP RESULTS

Treatment	Alive, No Recurrence	Died, No Recurrence	Local Recurrence	Distant Metastases	Death from Secondaries
Local Excision, Tumour Completely Removed	1 (3)*				
Local Excision, Tumour Completely Removed + Radiotherapy	2 (1, 2)				
Local Excision, Tumour Not Completely Removed		1 (0)	4 (2, 5, 5, 10)		
Local Excision, Tumour Not Completely Removed + Radiotherapy	1 (4)		3 (1, 2, 9)	2 (6, 7)	3 (2, 3, 7)
Enucleation		1 (0)			
Exenteration		2 (3, 5)	1 (3)	1 (2)	1 (3)
Exenteration + Radiotherapy		1 (6)			1 (3)

* Numbers in brackets refer to length of follow-up in years.

When the results of the various forms of treatment were analysed, it was found that there was no difference in the rates of distant metastases between those lesions that

were completely removed and those that were not completely removed (Table XVII). Local recurrences, however, were more common in the lesions that were incompletely removed ($0.05 < P < 0.10$), and cases that received radiotherapy developed distant metastases more frequently than those that did not ($0.10 < P < 0.20$).

TABLE XVII
WIDESPREAD MELANOMATA OF CONJUNCTIVA:
COMPARISON OF SURGERY WITH SURGERY AND RADIOTHERAPY

Treatment	No Recurrence	Local Recurrence	Distant Metastases
Lesion Completely Removed	3	1	2
Lesion Completely Removed + Radiotherapy	3	0	1
Lesion Not Completely Removed	2	4	0
Lesion Not Completely Removed + Radiotherapy	1	3	5

Follow-up Results of Naevi with Unusual Histological Features

Of the 43 tumours that were originally diagnosed as naevi undergoing malignant changes or as naevi where malignant change could not be excluded, there were no cases which developed distant metastases. Three of the tumours recurred locally after incomplete removal, and after complete local excision of the tumour there were no recurrences nine, six, and five years later respectively. These three tumours showed active junctional activity although the subepithelial cells were benign in appearance.

Discussion

Discussion of Histological Results

Naevi of the Conjunctiva.—The histological appearance of naevi of the conjunctiva supports the theory that these tumours arise from cells in the basal layer of the epithelium. Naevus cells are being produced at this junctional zone and form into nests which drop down into the subepithelial tissue to produce a compound naevus. As the naevus matures junctional activity becomes less apparent and finally ceases, when the naevus becomes subepithelial. Junctional activity is present in all naevi in the first decade of life but occurs in only 25 per cent. of naevi in the seventh decade. Intra-epithelial nests decrease with age in an even more striking manner; they are present in nearly half the naevi in the first decade of life and have disappeared from all naevi by the fifth decade.

The gradual maturation of naevus cells which occurs in compound and subepithelial naevi is evidence against Masson's (1951) dual theory of the origin of naevi. If Masson were correct, at least some of the naevi that contain fibrillar naevus cells would be expected to show a distinct demarcation between the common naevus cells of epithelial origin and the fibrillar cells of Schwannian origin. Instead, there is a gradual change in cell type. The superficial subepithelial region contains naevus cells which are either epithelioid in type (particularly in the naevi of children) or are common naevus cells, while in the deeper regions of the tumour (particularly in adults) the cells may be fibrillar in type. Fibrillar cells, however, are only found in a minority of compound and subepithelial naevi of the conjunctiva.

The appearance of junctional naevi of the conjunctiva supports the theory that these cells arise from epithelial melanocytes (Masson, 1951) rather than from epithelial cells in general (Allen, 1949). The changes that occur in the epithelial melanoses and junctional naevi suggest that these conditions are different degrees of the same pathological process. Epithelial melanoses may occur in the presence of a normal number of clear cells or an increased number of these cells, and some cases of the latter condition show evidence of early nest formation. These nests are composed of cells similar in appearance to normal clear cells (melanocytes), and this suggests that at least some junctional naevi arise from areas of epithelial melanosis, and also that these junctional naevi arise from melanocytes.

Naevi of the conjunctiva are generally considered to be congenital tumours, although they may not be apparent at birth (Duke-Elder, 1938). In the present series of naevi only 43 per cent. become apparent during the first decade of life, and although this is not evidence against the congenital nature of these tumours, for they may have been small or non-pigmented at birth, it supports the opinion of Lund and Kraus (1962) that the distinction between malformation and neoplasm is vague and impractical. Additional support for this opinion is that some naevi appear to arise from epithelial melanosis.

Subepithelial melanosis appears to be a congenital abnormality consisting of aberrant melanocytes in the subepithelial tissue, and the conjunctival changes in oculodermal melanosis appear to be basically the same condition. In the one case of oculodermal melanosis in the present series the eyelids contained discrete blue naevi as well as dermal melanosis, and this supports the statement of Dorsey and Montgomery (1954) that the histology of oculodermal melanosis varies between that of a Mongolian spot (dermal melanosis) and that of a blue naevus. A blue naevus has the histological appearance of a tumour, the constituent cells of which are derived from the same aberrant melanocytes as form a subepithelial melanosis.

Any classification of naevi of the conjunctiva should include the benign melanoses, for although the melanoses are not tumours an appreciation of their histology is necessary in order to understand the life history and differential diagnosis of the naevi. A classification should also distinguish between the melanoses and naevi of epithelial origin and those of subepithelial origin. Greer's (1960) classification, although of value in that it distinguishes between lesions with no junctional activity, those with benign junctional activity, and those with anaplastic junctional activity, places benign melanoses and subepithelial naevi in the same group, and active junctional naevi and precancerous melanosis in another group. For these reasons the following classification, similar to that of Lund and Kraus (1962) for pigmented lesions of the skin, is proposed for benign pigmented lesions of the conjunctiva:

Benign melanoses	(1) Epithelial	(i) normal number of melanocytes
		(ii) increased number of melanocytes
	(2) Subepithelial	
Naevi	(1) Of epithelial origin	(i) junctional
		(ii) compound
		(iii) subepithelial
		(iv) juvenile melanoma
	(2) Of subepithelial origin	(i) common blue naevus
		(ii) cellular blue naevus

Histological Features of Naevi of the Conjunctiva.—All the descriptions in the literature of the histological appearance of epithelial melanosis are of pigmentation of an otherwise normal basal layer of epithelium (Greer, 1960; Hogan and Zimmerman, 1962; Reese, 1963). The cases of epithelial melanosis reviewed here included examples where pigmentation of the basal layer was associated with an increased number of clear cells (Figs 2 and 3). Of greater interest is the observation that in certain cases of widespread intra-epithelial melanoma (clinical precancerous melanosis) the epithelium at the edge of the lesion showed changes indistinguishable from those of benign epithelial melanosis (Fig. 23). This suggests that acquired flat areas of pigmentation in adults, with the histological appearance of epithelial melanosis, might develop into an intra-epithelial melanoma. It also emphasizes the importance of a biopsy specimen from a case of presumptive intra-epithelial melanoma being taken from near the centre of the lesion rather than from its edge.

Some degree of junctional activity was present in 75 per cent. of naevi of epithelial origin in this series. This is a figure comparable to that reported by Reese (1963), but does not support the statement by Hogan and Zimmerman (1962) that subepithelial naevi of the conjunctiva are rarely encountered. The incidence of junctional activity decreases with the age of the patient (Table III) as it does in naevi of the skin (Lund and Stobbe, 1949), but of greater interest is the decrease in intra-epithelial nests of naevus cells with age, these nests not occurring in any of the patients over the age of 39 years. This suggests that the presence of intra-epithelial nests of cells in an adult over the age of 39 supports a diagnosis of an intra-epithelial melanoma rather than that of a naevus. As intra-epithelial melanomata rarely occur below the age of 39 this is of particular diagnostic value.

In the literature on naevi of the conjunctiva little attempt has been made to distinguish between the usual appearance of junctional activity occurring in junctional and compound naevi and that occurring in more active naevi, although Greer (1960) distinguished between junctional proliferation of a benign type and that of an anaplastic type, the latter occurring in precancerous melanosis. In many naevi occurring in young children, and occasionally in naevi occurring in adults, the nests contain naevus cells which appear to have lost their cohesion with each other and which show some degree of pleomorphism. In children this appearance of increased activity appears to have no ominous significance, but in adults it may be the precursor of malignant change. In these active naevi of adults the appearance of the subepithelial cells is all-important. If they are obviously benign in appearance the lesion is not a malignant melanoma, but if these cells show pleomorphism the lesion is undergoing, or has undergone, malignant change.

It is important to appreciate the variations in the appearance of subepithelial cells so that the distinction between subepithelial naevus cells and subepithelial malignant

FIG. 23.—Widespread intra-epithelial melanoma of the conjunctiva. Edge of lesion showing a histological appearance indistinguishable from that of benign epithelial melanosis. $\times 445$.

melanoma cells can be made. In compound and subepithelial naevi there is usually a gradual maturation in cell type as one passes from the superficial to the deep region of the tumour. This change in cell type does not occur in malignant melanomata. The superficial subepithelial cells in some naevi of children are epithelioid in type, and these epithelioid cells differentiate into the common type of naevus cells found in the majority of naevi. The deepest cells of some naevi of adults are fibrillar in type; these cells can be distinguished from dermal melanocytes by the absence of pigmentation in their cytoplasm.

Melanin pigment was present to a greater or lesser extent in 71 per cent. of naevi in this series, this being a comparable figure to that in Reese's (1963) series.

Epithelial downgrowths were present in two-thirds of the naevi in the present series, a figure identical with that quoted by Reese (1963), but more than the 43 per cent. in Ash's (1950) series. The junctional activity occasionally present in the wall of a cyst (Fig. 10) is of theoretical interest in that a malignant melanoma could arise from such an area. Although subepithelial naevi are considered to have no malignant potentialities, it would be possible for a malignant melanoma to arise from an area of junctional activity in the wall of a cystic downgrowth in a subepithelial naevus.

The presence of an inflammatory cell infiltrate in a quarter of the naevi in this series suggests that this does not indicate activity or malignant change as it does in naevi of the skin (Becker, 1954). In a small number of heavily infected naevi of the conjunctiva bizarre cells were present in the tumour (Fig. 24); these did not have any ominous significance.

FIG. 24.—Infected naevus of the conjunctiva. Pleomorphic cells. $\times 390$.

FIG. 25.—Compound naevus of the conjunctiva. Touton-like giant cell. $\times 390$.

Although a juvenile melanoma of the conjunctiva has not been reported, one of the naevi in this series contained giant cells similar in appearance to the Touton-like giant cells found in many juvenile melanomata of the skin (Fig. 25).

Naevi of the plica were similar in appearance to naevi of other parts of the conjunctiva, except for the increased number of goblet cells found in the epithelial downgrowths of these tumours (Fig. 11).

Out of a total of 430 naevi and melanomata of the conjunctiva, there were eight examples of blue naevi, three being common blue naevi, one being a cellular blue naevus, and four being combined common blue naevi and naevi of epithelial origin. The cells of the common blue naevi were so characteristic in appearance that once they were recognized no difficulty occurred in their diagnosis. The cellular blue naevus raised the greatest diagnostic problem, but the absence of junctional activity, associated with spindle-shaped cells showing little variation in size, distinguished this tumour from a malignant melanoma.

Naevi of the Conjunctiva compared with Naevi of the Skin.—The basic similarity between naevi of the conjunctiva of epithelial origin and naevi of the skin of epidermal origin is accepted by the majority of modern authors, and this similarity has been confirmed in the present study. These two groups of naevi do, however, differ in a number of respects:

(1) Two-thirds of naevi of the conjunctiva contain epithelial downgrowths which may be mistaken by the general pathologist for an epithelioid-cell malignant melanoma or for an adenocarcinoma. Epidermal cysts are uncommon in naevi of the skin, being present in about 1 per cent. of these tumours (Freeman and Knox, 1962).

(2) One-quarter of naevi of the conjunctiva contain an inflammatory cell infiltrate, frequently present just beneath the epithelium. The significance of the presence of inflammatory cells in naevi of the skin has been critically reviewed by Couperus and Rucker (1954) who concluded that an inflammatory infiltrate associated with a junctional naevus, not explained on some other basis, is indicative of malignant change until proved otherwise.

(3) Changes within the conjunctival epithelium are sometimes more difficult to evaluate than similar changes within the epidermis because of the thinness of the epithelium, it being only two or three cells thick in places.

FIG. 26.—Juvenile melanoma of the skin. Epithelioid cell type showing Touton-like giant cells. $\times 87$.

(4) Tumours similar to juvenile melanomata of the skin (Fig. 26) have not been observed in the conjunctiva, although one tumour in the present series contained giant cells similar in appearance to the Touton-like giant cells found in the epithelioid type of juvenile melanoma of the skin.

Blue naevi of the conjunctiva, whether the common type or the cellular type, were identical in appearance with similar tumours of the skin.

Malignant Melanomata of the Conjunctiva—The earliest lesions that could be classified as intra-epithelial melanomata showed changes limited to the basal layer of the epithelium (Fig. 16), these changes being difficult to distinguish from benign epithelial melanosis. This is consistent with the view that malignant melanomata arise from melanocytes (Lund and Kraus, 1962) rather than from epithelial cells in general (Allen, 1949; 1963; Allen and Spitz, 1953). When lesions were classified according to the extent of the junctional activity in the epithelium overlying and surrounding the tumour, it was found that there was a gradation of change from one area of malignant junctional activity overlying the tumour, through a diffuse junctional change involving all the epithelium over the tumour, to involvement of the epithelium over the tumour and extending for a short distance on each side of the tumour. When these degrees of junctional activity were correlated with clinical history and appearance, it became obvious that localized malignant melanomata, whether arising from a pre-existing pigmented lesion or *de novo*, could present with any of these degrees of junctional activity. There was, however, a further group of malignant melanomata which showed diffuse junctional activity extending for a considerable distance in the conjunctiva beyond the tumour. Clinically, all the tumours in this group arose in a widespread area of acquired pigmentation of the conjunctiva (cancerous melanosis arising in an area of precancerous melanosis (Reese, 1943)). As it was found that the management and prognosis of these two groups of malignant melanomata (localized and widespread) differed, their distinction was considered to be valuable.

The localized malignant melanomata arose from an area of apparently normal conjunctiva or from a pre-existing pigmented lesion. This pigmented lesion could have been an area of benign epithelial melanosis or a naevus, and it was impossible from the clinical history to distinguish between these two possibilities. On histological examination, a small number of localized melanomata contained areas of apparently benign naevus cells, and these melanomata were considered to have arisen from naevi. An additional small number of localized melanomata contained epithelial downgrowths and these tumours were also considered to be of naevus origin, because epithelial downgrowths were not seen in any of the intra-epithelial melanomata, either localized or widespread, or in malignant melanomata which had arisen in a widespread intra-epithelial melanoma.

Because of the differences in clinical appearance, management, and prognosis between localized and widespread intra-epithelial melanomata, and the malignant melanomata that arise from them, any classification of melanomata of the conjunctiva must include both these types. Histologically, intra-epithelial melanomata may be composed of cells that are benign in appearance (precancerous stage) or of cells with malignant characteristics (malignant stage). A malignant melanoma has developed when tumour cells have invaded the subepithelial tissue. Although a malignant melanoma of subepithelial origin has not yet been reported in the conjunctiva it is included in the following classification for the sake of completeness.

Melanomata of epithelial origin

- (1) Localized intra-epithelial melanoma
 - (i) precancerous stage
 - (ii) malignant stage
- (2) Widespread intra-epithelial melanoma
 - (i) precancerous stage
 - (ii) malignant stage
- (3) Malignant melanoma arising from localized intra-epithelial melanoma
 - (i) arising *de novo*
 - (ii) arising from a lentigo
 - (iii) arising from a naevus
- (4) Malignant melanoma arising from widespread intra-epithelial melanoma
- (5) Secondary malignant melanoma

Melanomata of subepithelial origin (malignant blue naevi)

The localized and widespread forms of intra-epithelial melanoma have the same histological appearance, except for the extent of the pathological process, and will therefore be discussed together. Reese (1938; 1963) described the early and late stages of precancerous melanosis (widespread intra-epithelial melanoma), and his description cannot be bettered. The term precancerous melanosis has, however, become associated with a characteristic clinical appearance, that of a widespread acquired pigmentation of the conjunctiva. As this condition has the same histological appearance as that of a localized acquired pigmentation, and as that of the epithelial changes overlying a malignant melanoma arising *de novo* or from a pre-existing naevus, it is suggested that the term "intra-epithelial melanoma" (Ashton, 1955) is more suitable for the description of the histological changes within the epithelium, the term "precancerous melanosis" being reserved for the clinical appearance to which it was originally applied. Occasionally there may be difficulty in distinguishing an intra-epithelial melanoma from an active junctional naevus, but apart from the fact that the former lesion occurs in an adult and the latter usually in a child, the intra-epithelial melanoma presents a characteristic diffuse disturbance of the basal layer of the epithelium which is rarely seen in a naevus occurring in a child.

There appears to be some confusion in the literature as to the definition of a superficial malignant melanoma. Reese (1963) stated that cancerous melanosis is established when the cells penetrate the epithelium to its free surface and invade the subepithelial tissue. In some examples of intra-epithelial melanomata the tumour cells reach the free surface of the epithelium before invasion of the subepithelial tissue is apparent, and it is difficult to determine how Reese would classify these lesions. It is suggested that Greer's (1960) definition is the more logical, for a metastasizing tumour should result only when the vascular and lymphatic-containing subepithelial tissue is invaded by tumour cells.

The histological appearances of malignant melanomata of the conjunctiva arising *de novo* or from a lentigo are identical, and it is probable that the melanoma that

apparently arises *de novo* does so from a lesion histologically indistinguishable from an area of localized intra-epithelial melanoma. It differs from the melanoma that arises from a pre-existing flat pigmented lesion only in that the tumour cells rapidly invade the subepithelial tissue so that the intra-epithelial stage is not appreciated by the patient. A malignant melanoma can be diagnosed as arising from a naevus only if areas of benign naevus cells are found within or adjacent to the tumour, or if the tumour contains epithelial downgrowths. Malignant melanomata that arise in a widespread intra-epithelial melanoma appear histologically indistinguishable from those that arise *de novo* or from a lentigo, except for the extent of the intra-epithelial change. There is no histological evidence that Reese (1943) is correct in his view that cancerous melanosis and a malignant melanoma arising from a naevus are two different tumours.

Malignant Melanomata of the Conjunctiva compared with Malignant Melanomata of the Skin.—It has only recently been appreciated that the histological appearance of intra-epithelial melanoma of the conjunctiva is similar to that of lentigo maligna (intra-epidermal melanoma) of the skin. This is rather surprising, because the first description of lentigo maligna was that by Hutchinson (1892) who described a number of cases of this condition, one of them involving the skin of the eyelids and extending on to the conjunctiva. Lund and Kraus (1962) describe and illustrate the various stages in the development of malignant melanomata of the skin arising from flat pigmented lesions, and their description of the changes within the epidermis are identical with those described above for the changes that occur in the conjunctival epithelium in intra-epithelial melanomata. The subepithelial cells that are present in malignant melanomata of the conjunctiva are similar in appearance to those described by Lund and Kraus (1962) in malignant melanomata of the skin. Epithelioid cells were the most common constituent of these conjunctival tumours, spindle-cell malignant melanomata being more uncommon in the conjunctiva than they are in the skin (they accounted for 9 per cent. of the melanomata in the present series, while making up 25 per cent. of the series of malignant melanomata of the skin reported by Petersen, Bodenham, and Lloyd (1962)).

Discussion of Follow-up Results

Out of all malignant melanomata of the eye referred to the Institute of Ophthalmology, London, only about one in 20 is situated in the conjunctiva. This accounts for the paucity of large series of these tumours reported in the literature, and the only series with which the present one can be compared is that reported by Ash (1950). In his series of 68 melanomata the average age was identical with that of the present series, and malignant melanomata of the skin also appear to have a similar age distribution and average age to those of the conjunctiva (Petersen and others, 1962). The sex ratio was approximately equal both in the series reported by Ash and in the present one, and the same is true for many of the series of malignant melanomata of the skin (Raven, 1950; Allen and Spitz, 1953).

Malignant melanomata of the conjunctiva occurring in Negroes are seldom reported; Ash reported three such cases and there is one case in the present series. These

tumours are also rare in pregnant women; the one example occurring in the present series was locally excised and the patient showed no evidence of the disease four years after its removal. Although there are many references in the literature suggesting that pregnancy worsens the prognosis of malignant melanomata of the skin, George, Fortner, and Pack (1960) presented evidence that this is not so.

From Table VI it can be seen that in only 35 per cent. of the cases did a malignant melanoma develop from a lesion present since childhood or for many years. In one series of malignant melanomata of the skin where comparable data is available (Lund and Kraus, 1962), 50 per cent. of tumours arose from a lesion present since childhood or for many years. These figures support the theory that many malignant melanomata arise *de novo* or from an acquired lesion, rather than from a naevus. From the data presented in Tables VI and VII it is apparent that widespread melanomata have a different natural history from that of localized melanomata, and that they arise from an acquired lesion which nearly always appears in adult life. It is also apparent that widespread melanomata are more slowly progressive than localized melanomata, a fact observed by Reese (1938) when he first described precancerous melanosis and the malignant melanoma that arises from it. This slow progression of widespread intra-epithelial melanomata is similar to the natural history of Hutchinson's melanotic freckle, or lentigo maligna (Mishima, 1960).

The origin of malignant melanomata of the conjunctiva was ascertained by a study of their histological appearances and clinical histories. The relative frequencies in each group are given in Table XVIII which shows that localized melanomata are nearly three times as common as widespread melanomata, while widespread melanomata are nearly twice as common as localized melanomata arising from naevi.

TABLE XVIII
MALIGNANT MELANOMATA OF THE CONJUNCTIVA: ORIGIN OF 96 TUMOURS

	No.	Per cent.
Localized melanomata	71	74
Arising <i>de novo</i>	26	27
Arising from a naevus	13	14
Arising from a lentigo	24	25
Origin unknown	8	8
Widespread melanomata	25	26

It is difficult to compare these percentages with those of other authors because each has his own criteria for diagnosing a melanoma arising from a naevus. These figures are comparable to those of Greer (1954). It would appear that Reese (1963), because of his great interest in widespread melanomata, sees a disproportionately high percentage of this condition.

Follow-up Results

The overall five-year cure rate in this series is 68 per cent. which is less than the 80 per cent. five-year cure rate in Ash's (1950) series. Although there are no other series of malignant melanomata of the conjunctiva in the literature for which

five-year follow-up results are given, there are a number of series of malignant melanomata of the skin whose five-year results can be compared with those of the present series. Petersen and others (1962) quote a number of these five-year cure rates from different authors; these vary from 21 per cent. to 52 per cent., and this suggests that malignant melanomata of the conjunctiva have a better prognosis than malignant melanomata of the skin. There are a number of possible explanations for this difference, and these include:

(1) A tumour of the conjunctiva is noticed by a patient or his relatives at an early stage in its development, and this will lead to his seeking medical advice while the tumour is small.

(2) The sclera appears to act as a barrier to the deep invasion of the melanoma cells, while the dermis does not present such a barrier.

(3) Malignant melanomata of the conjunctiva may be inherently less malignant than similar tumours of the skin.

(4) The lymphatic and venous drainage of the subepithelial tissue of the conjunctiva may be less efficient at draining this tissue than are similar vessels in the dermis.

There is no evidence that factors (3) and (4) are true, and the difference in prognosis between malignant melanomata of conjunctiva and skin can be explained by factors (1) and (2).

When the follow-up results in this series were divided into those for localized and those for widespread melanomata, it was found that the five-year cure rates for these two groups of tumours differed considerably, although the five-year survival rates did not differ appreciably between the two groups. This low five-year cure rate for widespread melanomata was largely, but not entirely, due to the cases of widespread intra-epithelial melanomata being observed rather than treated radically; these cases are included in the group "alive with evidence of melanoma". The ten-year cure rate for localized melanomata was the same as the five-year cure rate for these tumours, and this suggests that if a patient is alive without evidence of melanoma on the fifth anniversary after the removal of a localized melanoma, his chances of dying of the disease are small. The same is not true for widespread melanomata.

When localized melanomata are subdivided according to their origin, the five-year cure rates for the three groups are similar. Reese (1963) stated that malignant melanomata arising from naevi have a poor prognosis, but this could not be confirmed, the melanomata of naevus origin in the present series having a five-year cure rate of 88 per cent.

The constituent cell type of the tumour, its pigment content, and the degree of inflammatory cell infiltrate do not appear to influence the prognosis, although with a larger series it is possible that epithelioid-cell malignant melanomata might be found to be more malignant than the other types.

The five-year cure rates for localized melanomata of the palpebral conjunctiva and caruncle are lower than those for localized melanomata of the limbus and bulbar conjunctiva, although the number of cases in the present series is too small for this difference to be significant.

The overall results of surgical treatment of localized melanomata are presented in Table XIV. These results must be considered with some circumspection for the following two reasons:

(1) The distinction between complete and incomplete removal of a tumour was made by examination of histological sections, but this method, which is the only one available, is not necessarily accurate. To be certain that a tumour has been completely removed sections would have to be cut in many planes, and this is not technically possible. Even when the tumour extends to the edge of a section it does not necessarily indicate that the tumour has been incompletely removed, because the surgeon may have removed additional pieces of tissue which were not sent for histological examination or which were mislaid.

(2) The method chosen for the surgical removal of a tumour may be influenced by the extent of the lesion, and it is possible that the more extensive procedures are performed on tumours which have a worse prognosis than those which are locally excised. It is also possible that post-operative radiotherapy was more frequently given to large tumours than to small ones.

With the above criticisms in mind the following inferences can be drawn as to the efficacy of different methods of treating localized melanomata of the conjunctiva:

(1) Adequate local excision of the tumour is an effective method of treatment, while the addition of post-operative radiotherapy does not improve the results (Table XV). In addition, radiotherapy is not without risk to the eye, and in the cases where an adequate history is available the following complications, directly attributable to radiotherapy, resulted: five cases of keratitis, in four of which the removal of a blind painful eye was necessary; one case of keratitis and cataract; two cases of cataract.

(2) Inadequate local excision of the tumour increases the risk of local recurrence, and, more seriously, of the development of distant metastases. Post-operative radiotherapy appears to reduce the incidence of local recurrences, but not of distant metastases (Table XV).

(3) Enucleation of the globe has not, in this series, been a successful method of treating these tumours (Table XIV). As malignant melanomata do not usually invade more than the most superficial lamellae of the sclera, it appears quite unnecessary to enucleate an eye for this condition, and adequate local excision combined with a lamellar sclerectomy (Lister, 1951) appears to be a more logical and less mutilating method of treatment.

(4) Exenteration of the orbital contents, a method recommended by Reese (1963) for the treatment of melanomata arising from naevi, appears to be an effective method of treating these tumours, but it is a mutilating procedure and does not appear to be justified in the majority of localized melanomata of the conjunctiva. The lymphatics of the conjunctiva drain into the pre-auricular and submaxillary nodes while it is only some of the conjunctival veins which drain into veins in the orbit (Duke-Elder and Wybar, 1961). In only one case in the present series was there deposition of tumour cells on the posterior sclera and this patient died of melanoma following enucleation of the eye. This spread was almost certainly via veins and when this occurs exenteration of the orbital contents would not prevent the occurrence of distant metastases.

The management of widespread melanomata must be considered from two aspects, that of widespread intra-epithelial melanomata, and that of malignant melanomata arising from this widespread intra-epithelial condition.

There were six widespread intra-epithelial melanomata in the present series and in view of the natural history of this condition it is impossible to draw any firm conclusions from such a small number of cases followed for a relatively short period of time. In the occasional case where it is feasible to do so, it would appear logical to

excise the lesion completely (Hogan, 1964). It appears to be safe to watch the majority of cases of this condition, after the diagnosis has been confirmed by biopsy, and treat them only when they are showing unmistakable signs of progression. Their management is then the same as that of malignant melanomata arising from widespread intra-epithelial melanomata (Reese, 1964; Lederman, 1964).

The follow-up results and the results of various forms of treatment of the 25 malignant melanomata arising from widespread intra-epithelial melanomata are given in Tables XVI and XVII. In view of the natural history of this condition it would be unwise to draw firm conclusions from the results of these cases, but the following comments can be made:

(1) There appears to be no difference in prognosis between superficial and deep malignant melanomata, although with a larger series of cases a difference might become apparent. In malignant melanomata of the skin the superficial tumours have a better prognosis than the deep tumours (Petersen and others, 1962).

(2) Complete removal of the lesion, whether by local excision or by exenteration, with or without post-operative radiotherapy, appears to give a slightly better prognosis than incomplete removal of the lesion (Table XVI).

(3) There appears to be no difference in prognosis between the two standard methods of treatment, exenteration (Reese, 1964) and radiotherapy (Lederman, 1964). Both methods of treatment resulted in the development of local recurrences or distant metastases in over half the cases.

(4) Some of these widespread melanomata appear to be at least partially radiosensitive as the tumour disappeared following incomplete removal and post-operative radiotherapy.

It is suggested that in the present state of our knowledge the most satisfactory way of managing widespread melanomata is as follows: biopsy should be performed on clinical widespread intra-epithelial melanomata (precancerous melanosis) to confirm the diagnosis and then the patient should be observed at regular intervals. If at any time the lesion shows unmistakable signs of progression, and particularly if a raised tumour develops, the patient should receive treatment. Wide local excision of the tumour, followed by radiotherapy, appears to be the most logical method of treatment. Exenteration of the orbital contents should be reserved for those cases that are known to respond badly to radiotherapy, the bulky tumours that fill the fornix and invade the eyelid, and cases which have already received full doses of radiotherapy but in which the tumour has locally recurred (Lederman, 1964).

Conclusions

The following classification is proposed for pigmented lesions of the conjunctiva:

Benign Melanoses

- (1) Epithelial (i) normal number of melanocytes
 (ii) increased number of melanocytes
- (2) Subepithelial

Naevi

- (1) Of epithelial origin
 - (i) junctional
 - (ii) compound
 - (iii) subepithelial
 - (iv) juvenile melanoma
- (2) Of subepithelial origin
 - (i) common blue naevus
 - (ii) cellular blue naevus

Malignant Melanomata

- (1) Of epithelial origin
 - (i) localized intra-epithelial melanoma
 - (ii) widespread intra-epithelial melanoma
 - (iii) malignant melanoma arising from localized intra-epithelial melanoma
 - (iv) malignant melanoma arising from widespread intra-epithelial melanoma
 - (v) secondary malignant melanoma
- (2) Of subepithelial origin (malignant blue naevus)

In some cases of epithelial melanosis where the melanocytes are increased in number, early nest formation is apparent. This suggests that at least some naevi develop from areas of epithelial melanosis.

Oculodermal melanosis (naevus of Ota) is essentially a dermal and subepithelial melanosis located on the side of the face and involving the eye.

A naevus is defined as a benign tumour composed of characteristic naevus cells. It is not defined as a congenital malformation because many naevi do not become apparent until after the first decade of life, and because some naevi appear to arise from areas of epithelial melanosis.

The histological appearances of naevi of the conjunctiva of epithelial origin support the theory that these tumours develop from epithelial melanocytes.

In naevi of the conjunctiva there is a striking decrease in intra-epithelial nests of naevus cells with age. These nests are present in 46 per cent. of naevi in the first decade of life, but did not occur in any of the naevi in patients over the age of 39 years. The presence of intra-epithelial nests in patients over this age is suggestive of an intra-epithelial melanoma.

Epithelial downgrowths are present in 66 per cent. of naevi and in five per cent. of malignant melanomata of the conjunctiva. When a malignant melanoma contains these downgrowths it indicates that the tumour has arisen in a naevus.

An appreciable inflammatory response is present in 24 per cent. of naevi of the conjunctiva and does not have the sinister implications attached to its presence in naevi of the skin.

The histological features of naevi of the conjunctiva and skin are similar except for the presence of epithelial downgrowths and the occurrence of an appreciable inflammatory cell infiltrate in some naevi of the conjunctiva.

The similarity in the histological appearances of certain acquired areas of flat pigmentation (both localized and widespread) of the conjunctiva, and of the epithelial changes overlying malignant melanomata, favours the use of the term "intra-epithelial melanoma" to describe these changes.

Intra-epithelial melanomata of the conjunctiva may be either localized or widespread. The widespread condition is known clinically as "precancerous melanosis", and this term should not be used to describe its histological appearance.

Most intra-epithelial melanomata can be distinguished histologically from junctional naevi by the diffuse nature of the change in the basal layer of the epithelium, by the pleomorphism of the tumour cells, and by the invasion of the epithelium by these cells.

A superficial malignant melanoma develops from an intra-epithelial melanoma when tumour cells invade the subepithelial tissue.

Localized malignant melanomata may arise *de novo* or from a pre-existing pigmented lesion. This pre-existing lesion may be an epithelial melanosis (lentigo) or a naevus. A malignant melanoma of the conjunctiva which contains areas of benign naevus cells or epithelial downgrowths is considered to be of naevus origin.

Intra-epithelial and malignant melanomata of the conjunctiva have a similar histological appearance to intra-epidermal and malignant melanomata of the skin.

The follow-up results indicate that the localized malignant melanomata of the conjunctiva have a shorter history of progressive change and a better prognosis than widespread malignant melanomata.

The five- and ten-year survival and cure rates for localized melanomata are the same. This suggests that if a patient is alive without evidence of melanoma five years after removal of the tumour, his chances of being cured are high.

The differences between the five- and ten-year survival and cure rates for widespread melanomata indicate that local recurrences and distant metastases may develop more than five years after treatment is carried out.

Localized malignant melanomata of the conjunctiva are nearly three times as common as widespread malignant melanomata, while the latter tumours are nearly twice as common as localized melanomata arising from naevi.

Irrespective of the origin of a localized malignant melanoma (whether arising *de novo*, from a naevus, or from a lentigo) its prognosis is the same. The five-year cure rates for these tumours are about 80 per cent.

Localized malignant melanomata of the conjunctiva are most satisfactorily treated by adequate local excision of the tumour. Enucleation of the globe is an illogical and unsatisfactory form of treatment, while exenteration of the orbital contents is an unnecessarily major procedure for most of these tumours. There is no evidence that post-operative radiotherapy improves the prognosis of these tumours, while it is not without risk to the eye.

Widespread intra-epithelial melanomata of the conjunctiva are best managed by diagnostic biopsy followed by periodic observation. This biopsy specimen should be removed from near the centre of the lesion, rather than from near its edge, because the edge of a widespread intra-epithelial melanoma may be histologically indistinguishable from a benign epithelial melanosis. Signs of unmistakable progression of the lesion necessitate treatment as for widespread malignant melanomata.

Widespread malignant melanomata are probably best treated by adequate local excision of the tumour followed by post-operative radiotherapy. There is no evidence that exenteration of the orbital contents gives a better prognosis than local excision followed by radiotherapy, unless the tumour is situated in the fornix and is invading the eyelid, or unless the patient has already received full doses of radiotherapy to the eye.

Malignant melanomata of the conjunctiva have a better prognosis than similar tumours of the skin, probably because they are noticed by the patient early in their development, and because the sclera acts as a barrier to deep invasion by tumour cells.

Summary

The purposes of this study are: to classify the pigmented tumours of the conjunctiva, to ascertain the prognosis of these tumours, and to compare the histological features of naevi and malignant melanomata of the conjunctiva with those of the skin.

The histological features of ten cases of benign epithelial melanosis and 272 cases of naevus of the conjunctiva are described. Particular interest is taken in the changes that occur in the basal layer of the epithelium.

The description of the histological features of 104 malignant melanomata of the conjunctiva commences with the appearance of intra-epithelial melanomata. These lesions, which are localized or widespread, may develop into malignant melanomata. In the majority of cases intra-epithelial melanomata may be distinguished from junctional naevi, and the differences between these two types of lesion are described.

The follow-up study is particularly concerned with the 104 malignant melanomata, and the five-year cure rates have been related to origin, variations in structure, and methods of treatment of these tumours.

The discussion of histological results is concerned with the origin, classification, and histological features of malignant melanomata of the conjunctiva. The discussion of follow-up results is particularly concerned with the prognosis and correct management of these tumours.

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