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MAJOR REVIEW

Conjunctival Melanoma

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Abstract. Conjunctival melanoma is an uncommon tumor that is likely to recur and carries an overall mortality rate of approximately 30%. The seemingly unpredictable and enigmatic character of this entity has initiated much debate over the past decades regarding the etiology, histogenesis, prognosis, and preferred management. This review outlines the historical perspective; incidence and demographics; etiologic factors; histogenesis; cytogenetic findings; clinical characteristics; histopathologic and ultrastructural features; differential diagnoses; classifications; management of primary, recurrent, and systemic disease; survival after conjunctival melanoma; and diverse factors of potential prognostic significance. Finally, a brief outlook on present and future research objectives is provided. (**Surv Ophthalmol 42**:321–350, 1998. © 1998 by Elsevier Science Inc. All rights reserved.)

Key words. conjunctival melanoma • malignancy • melanoma • prognostic factors • tumor

Nearly five decades ago, conjunctival melanoma was believed to be one of the most malignant tumors encountered in ophthalmology and even a minimal growth was considered to require orbital exenteration to remove all potentially diseased tissue.[241] Although management now includes less extensive surgery, conjunctival melanoma remains one of the most dreaded and unpredictable ocular tumors and one of the most debated topics of ocular oncology.

It was once said that much of what had been written on pigmented lesions of the conjunctiva was either anecdotal, speculative, or controversial.[129] To some extent this claim is still valid and, until recently, most data were based on case reports and series of referred patients. However, such data are inherently skewed and any loss to follow-up will cause unrecognized bias. Currently, a number of additional issues have been raised, such as the possible association with cutaneous melanoma, the evaluation of various prognostic markers, and the recognition of risk factors for tumor development.[306] All of these aspects warrant a detailed review of conjunctival melanoma.

When reviewing data available on conjunctival melanoma, conclusions derived from conjunctival tumors should be clearly separated from conclusions based on melanomas appearing in other sites. Melanoma of the uvea or skin is much more common than conjunctival melanoma, and there is a marked (but unfortunate) tendency to extrapolate data from tumors in these sites to conjunctival melanocytic lesions. Also, uveal melanoma and melanoma of the conjunctiva are often regarded as a single entity and labeled *ocular melanoma*. The term *ocular* is in itself ambiguous; however, in common usage the orbit and adnexal structures would not be included. When surveying the literature, it is sometimes unclear if ocular melanoma is equivalent to uveal melanoma or if conjunctival tumors are included. Therefore, the original nomenclature has sometimes been retained in this review. However, it will be recalled that not only are uveal and conjunctival melanomas separate histopathologic entities, but their clinical behavior is also distinctly different. Consequently, the phrase *ocular melanoma* is currently discouraged.[274]

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I. Melanocytes and the Conjunctiva

A. ANATOMIC AND DEVELOPMENTAL ASPECTS

The conjunctiva forms a smooth, flexible, protective sac that covers the pericorneal surface of the anterior portion of the eye and lines the posterior surface of the eyelids. At the sixth week of embryonic development, the surface ectoderm adjacent to the site of the future cornea begins to bulge outward, forming the buds that subsequently develop into the lid folds. The conjunctiva develops within the lid folds, and differentiation of the conjunctival epithelium from that of the skin can be seen as early as the tenth week of embryonic development.[279] The conjunctiva is covered by two or more layers of stratified columnar epithelium, except at the limbus and palpebral margins where stratified squamous epithelium is present. Melanocytes migrate from the neural crest to become lodged in the basal layers of the epithelium, at or close to the epithelial basement membrane. These melanocytes appear identical to the dendritic melanocytes of the skin.[130] The conjunctival stroma is composed of fibrovascular connective tissue of varying intensity and thickness; in the palpebral region it is thin and compact, whereas it is thick and loose in the fornices and in the bulbar part. The bulbar conjunctiva is loosely connected to the sclera and episclera, and this lax attachment allows free eye movements. In contrast, the palpebral conjunctiva is strictly adherent to the tarsus by numerous septal connections. Lymphatic channels are present in all parts of the conjunctival stroma, and these vessels drain medially to the submandibular lymph nodes and laterally to the preauricular lymph nodes.[279]

B. THE NORMAL MELANOCYTE

The melanocytes of the conjunctival basal layer contain a variable number of melanin granules, responsible for their pigmented appearance. Melanin is an insoluble brown or black pigment formed by the enzymatic oxidation of tyrosine within the cytoplasm of melanocytes.[130] This synthesis takes place in organelles called melanosomes, and the end product is the stage IV melanosome, or melanin granule.[103] These granules may then be discharged by incontinent melanocytes to be engulfed by dermal melanophages or epithelial cells.[198]

In black people, the limbal pigmentation is due primarily to melanin granules transferred from the basal melanocytes to epithelial cells.[130] In the conjunctiva, similar to what is found in the skin, the density of melanocytes is probably constant, and it is the increased metabolic activity of the melanocytes that accounts for the increased pigmentation of black individuals.[128,130] Melanocytes tend to reside in the neighborhood of blood vessels and will usually occur in the corneal epithelium only in the event of corneal vascularization.[128]

C. NOMENCLATURE

Some conceptual issues on terminology will be addressed briefly. In current usage, the term *melanoma* is synonymous with malignant melanoma. This may cause some confusion in interpreting the older literature; e.g., juvenile melanoma, now recognized as the spindle and epitheloid nevus of Spitz, is in fact a benign lesion. Also, in current clinical practice, the terms *neoplasia* and *tumor* are often used interchangeably. However, there are some distinctive differences. Whereas a neoplasm literally is a new growth of cells, a tumor formation does not necessarily represent a neoplastic proliferation of cells. In surgical pathology, the presence of a tumor indicates no more than a mass or a swelling, which may represent overt neoplasia, but also may be induced by inflammation or some other nonneoplastic cause. Conversely, neoplastic cells may proliferate to form a mass or a tumor, but may also extend along a surface and appear as a flat lesion. However, for convenience we will use *tumor* as a synonym for a neoplastic mass.

II. Historical Perspective

The first detailed description of a malignant melanoma, irrespective of site, dates back to 1806 when Laënnec referred to skin melanoma as *melanosis.*[174] He later recognized that melanosis was a malignant entity and reported the autopsy findings of a few patients with metastatic cutaneous melanoma.[173] The actual word *melanoma* was introduced by Carswell in 1838, who divided melanoma into *true melanosis* (today recognized as malignant melanoma) and *spurious melanosis* (including dark hematogenous discoloration of tissues).[44] Thus, in the early years of the 19th century, the concepts of melanoma and melanosis were not distinct.

The historical aspects of conjunctival melanoma have been covered in depth by others,[72,151] who agree that the first published case of an unequivocal conjunctival melanoma was reported by Travers in 1820.[302] He encountered a dark-purple tumor protruding between the eyelids and excised the growth by simply sectioning the anterior hemisphere of the eye. However, it was MacKenzie who recognized the similarity of Travers' case to Laënnec's description of melanosis of the skin (i.e., cutaneous melanoma).[191] Duke-Elder and Leigh[72] claim that the first comprehensive case report of a patient with conjunctival melanoma was provided by Baumgarten in 1852,[27] but there is at least one earlier, detailed account (published in Swedish in 1843) of a recurrent,

multifocal conjunctival melanoma in a 58-year-old man.[32] In 1852 Dalrymple noted that conjunctival melanomas contain pigmented cells,[63] and a few years later Stellwag von Carion recognized the stellate, spindle-shaped, and rounded cells comprising these tumors.[284] The first larger case series include the 73 cases documented by Verhoeff and Loring in 1903[311] and the 80 cases collected by Parsons.[233] However, clinical data from these series are scarce.

The origin of conjunctival melanoma has been debated for more than a century. While Kerschbaumer thought that all conjunctival melanoma arose from pigmented nevi,[160] Morax believed that both pigmented nevi and acquired pigmented spots could function as precursor lesions of conjunctival melanoma.[210] Today, these acquired pigmented spots are recognized as primary acquired melanosis (PAM), a potential precursor lesion of conjunctival melanoma.

The first case report of a conjunctival melanoma undoubtedly arising from PAM dates back to 1872,[81] and was later reviewed by Dr. Algernon Reese.[240] Reese studied acquired conjunctival melanosis extensively, and in 1955 he detailed the "waxing and waning" of the pigment content and urged that "precancerous melanosis" must be differentiated from congenital melanosis.[243] The term *precancerous melanosis* had been adopted by Reese in 1938[240] from the work of Dubreuilh,[71] who himself had elaborated on Hutchinson's original characterization of lentigo maligna of the skin.[140]

Even though Reese admitted that some patients with precancerous melanosis never develop invasive melanoma, he advocated extreme measures and claimed that exenteration was the only effective therapy for a growing acquired melanosis when histopathologic examination had revealed malignant (highly atypical) cells.[242,243] Most contemporary authors of the early 1960s agreed that this procedure might be appropriate for bulky, invasive, or multifocal disease, but not all felt that exenteration should be used to irradicate all conjunctiva in acquired melanosis.[324] Zimmerman argued that the term *precancerous* "made a prophet out of its user," and to avoid this, he coined the term benign acquired melanosis."[323] However, others viewed Zimmerman's classification as "disarmingly casual," urging that the association with overt malignancy be better recognized.[143]

The terminology used for PAM over the past decades reflects conflicting opinions and uncertainty. Primary acquired melanosis was preceded by designations such as *precancerous melanosis*,[240] *pagetoid melanocarcinoma*,[8] *superficial melanocarcinoma*,[9] *melanoma* in situ,[28] *intraepithelial melanoma*,[15] *benign acquired melanosis*,[323] and *idiopathic acquired melanosis*.[108] In 1980, the World Health Organization introduced PAM as a unifying concept.[325] However, it was argued by some that the terminology should be based on the available dermatopathologic classification. The use of labels such as *atypical melanocytic hyperplasia*[123,205] or even *melanoma* in situ[2,5] was advocated. Those favoring the concept of PAM disagreed, and this issue has been debated repeatedly.[89,90,119]

III. Characteristics

A. CLINICAL FEATURES

The clinical appearance of malignant and premalignant conjunctival lesions has been detailed in a survey by Jakobiec and associates,[148] and the benign melanocytic lesions were reviewed in a companion article by Folberg and colleagues.[88] Briefly, the potentially premalignant PAM is a flat and variably brown unilateral lesion, usually presenting in middle-aged or elderly whites (Figs. 1 and 2). It must be distinguished from junctional nevi, "racial" melanosis, congenital ocular, or oculodermal melanosis, as well as from pigmentation due to systemic diseases (e.g., Addison's disease) and deposits from mascara and topically instilled drugs.[148] The precancerous variant of PAM cannot be separated from PAM without atypia on the clinical appearance alone; this requires cytologic or histopathologic examination (Figs. 3 and 4).[92] There is also some confusion regarding the appropriate terminology for small PAM-like lesions (Fig. 5).[84]

Conjunctival melanoma may arise in the context of PAM (Figs. 6 and 7) and the first clinical sign of microinvasive melanoma may be a subtle plaquelike thickening of PAM, but microinvasion may be impossible to recognize clinically, and usually the lesion will have to be biopsied and examined histo-

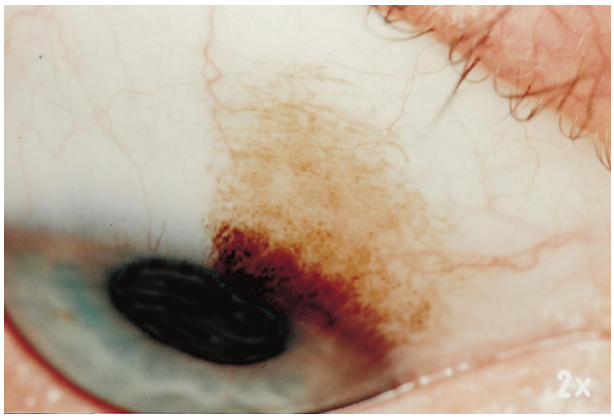

Fig. 1. Primary acquired melanosis featuring a 7-mm dark brown to golden pigmentation of the conjunctiva. Note that pigmentation appears darkest and most dense at the limbus. Histopathologic examination after excision failed to reveal atypia.

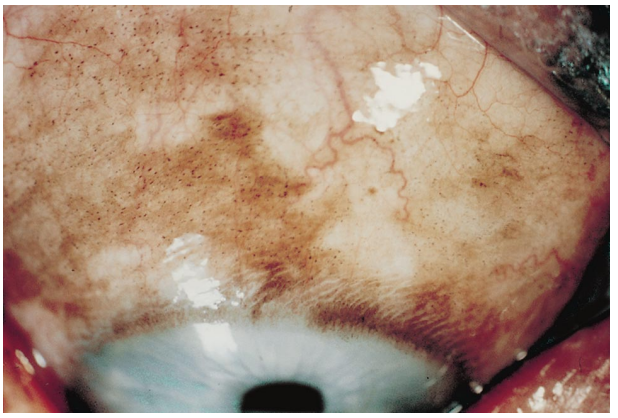

Fig. 2. Extensive, flat, primary acquired melanosis of bulbar conjunctiva of 67-year-old man who later developed conjunctival melanoma.

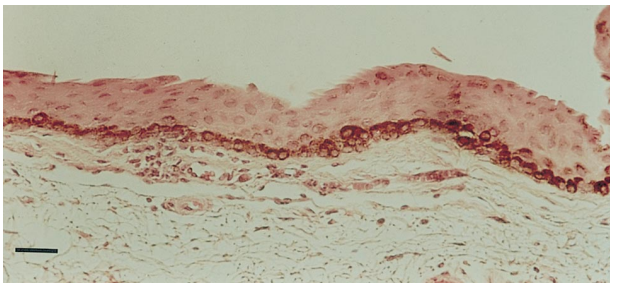

Fig. 3. Micrograph of conjunctival epithelium showing junctional melanocytic hyperpigmentation corresponding to primary acquired melanosis without atypia. A conjunctival ephelis may show similar histopathologic features. Bar = 50 μm (hematoxylin and eosin).

pathologically (Fig. 8).[148] While most conjunctival nevi never will progress to melanoma (Fig. 9), some melanomas apparently derive from pre-existent nevi. Conjunctival melanoma may also present *de novo*. Occasionally, conjunctival nevi coexist with PAM and the precursor lesion may then be difficult to identify. Usually, the features of an invasive melanoma are those of a pigmented or nonpigmented, smooth vascularized limbal nodule, but the growth may in rare cases be pedunculated (Fig. 10).[314,315] Conjunctival melanomas may present in all conjunctival areas, including the tarsus, fornices, and caruncule. In fact, melanocytic nevi of the palpebral conjunctiva are exceedingly rare,[42] and a melanocytic lesion in this site usually signifies a malignant melanoma (Fig. 11).[148]

Griffith and associates originally described a conjunctival melanoma arising from an area without clinically detectable PAM, i.e., without clinically detectable pigmentation.[118] However, histopathologic examination revealed extensive atypical intraepithelial melanocytic proliferation with minimal or nondetectable pigmentation and, hence, the term *acquired melanosis* sine pigmento was coined. This condition is clinically bothersome, as the PAM cannot be exactly delineated.[149,226]

In the late 1980s, Jakobiec and coworkers conceptualized the "in-transit" metastases of conjunctival melanoma.[147] These are small secondary nodules of conjunctival melanoma growing beneath an intact epithelium and believed to be caused by local lymphatic spread within the conjunctiva. The concept of in-transit metastases could in part explain the occurrence of multifocal conjunctival melanoma; however, multifocal disease will most often appear as new primary tumors associated with pigmented or

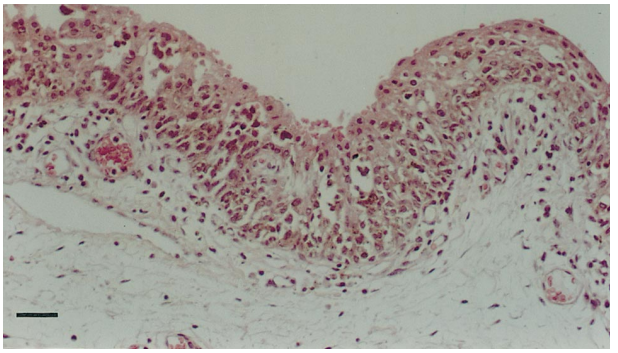

Fig. 4. Micrograph of conjunctival epithelium with full thickness proliferation of atypical melanocytes. Most ophthalmic pathologists refer to these features as primary acquired melanosis with (advanced) atypia, while some would regard this as melanoma *in situ*. Bar = 50 μm (hematoxylin and eosin).

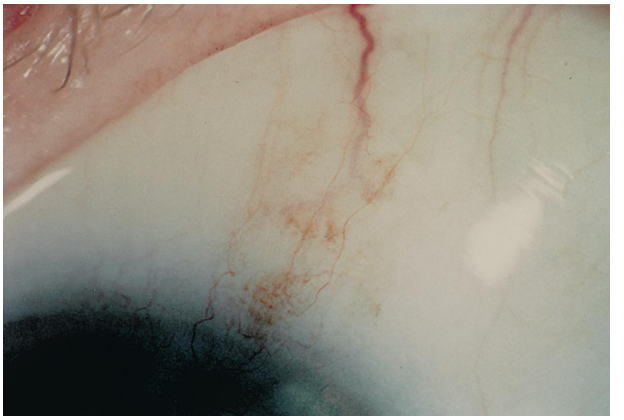

Fig. 5. Juxtalimbal area covering 5 × 3 mm of subtle conjunctival pigmentation in 77-year-old woman. This area is normally covered by the upper eyelid and not exposed to sunlight. For this reason, some would refer to this lesion as primary acquired melanosis rather than an ephelis.

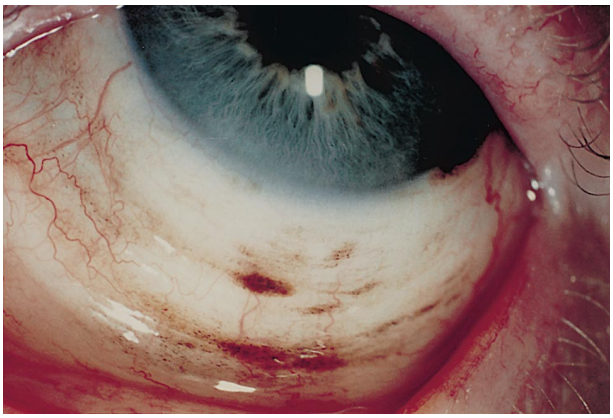

Fig. 6. Primary acquired melanosis in the lower bulbar region of a 57-year-old man. An associated conjunctival melanoma was present (same patient as in Fig. 7).

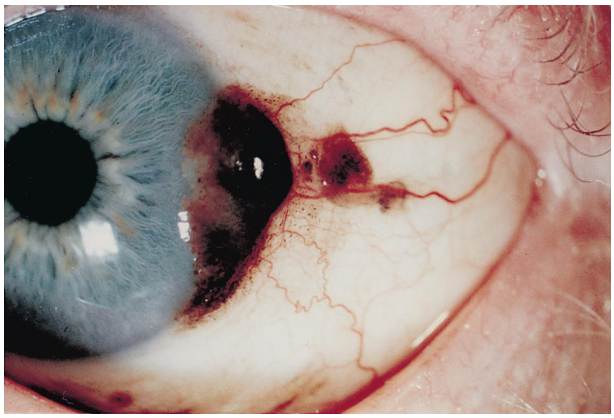

Fig. 7. Conjunctival melanoma including a small, additional lesion peripheral to the main juxtalimbal tumor. Associated primary acquired melanosis was present (same patient as in Fig. 6).

nonpigmented PAM.[45] Conjunctival in-transit metastases are probably very rare, and histopathologic examination would be required to differentiate this type of lesion from multifocal primary disease. Prior to the report by Jakobiec and associates,[147] a similar case of "local metastasis" was described in the lower fornix, attributed to dissemination at the time of initial excision.[221] Also, local metastases from the upper conjunctiva to the lower eyelid have been reported.[157]

Multifocal disease in the setting of conjunctival melanoma is not uncommon (Fig. 7); in one case series, 22 of 52 patients with invasive melanoma had multicentric disease.[149] Two thirds of these 22 patients had multifocal melanoma in the setting of clinically detectable PAM, but histopathologic examination of the remaining 7 patients showed atypical PAM *sine pigmento* or conjunctival in-transit metastases covered by an intact epithelium. While most multifocal melanomas thus appear to originate from PAM, isolated cases may arise from conjunctival nevi.[126]

The cornea may be invaded by malignant growth from the limbus, but this infiltration is usually superficial and does not penetrate Bowman's membrane. However, pigmented tumor cells have been reported to grow between corneal lamellae in the deep stroma and create a "black cornea."[229] Whereas a conjunctival melanoma may cover part or all of the corneal surface (Fig. 12), primary melanomas of the cornea are very rare, but a few have been reported.[122,229,259,299,301,318] However, the origin of corneal melanomas is often unclear and serial sections

Fig. 8. Flat melanocytic lesion, 2 mm in diameter, in 39-year-old woman. Histopathologic examination after excision revealed primary acquired melanosis with atypia and microinvasive melanoma. After multiple tumor recurrences in other conjunctival areas and in the lacrimal sac, the patient died of disseminated disease 5 years later. (Published courtesy of *Läkartidningen.*[271])

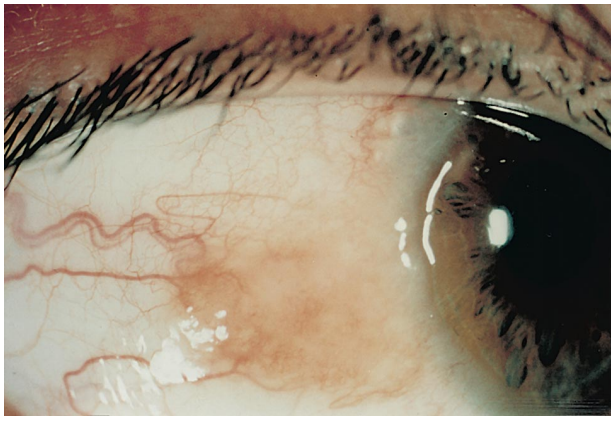

Fig. 9. Nonpigmented conjunctival nevus containing cysts in a 13-year-old boy.

Fig. 10. Juxtalimbal, nonpigmented, polypoid melanoma of a 69-year-old woman.

Fig. 11. Amelanotic melanoma of the upper palpebral conjunctiva in an 87-year-old woman. The eyelid had to be everted for the tumor to be detected. (Published courtesy of *Läkartidningen.*[271])

are mandatory to rule out corneal invasion of conjunctival melanocytes from the limbus. Intraocular extension of a conjunctival melanoma is extremely infrequent, but may occur.[40,46,111] The intraocular appearance may then be that of a flat, diffuse, choroidal tumor.[46] The conjunctiva is only partially removed by enucleation of the globe, and malignant melanoma of presumed conjunctival origin has been reported to arise from the anophthalmic orbit.[263] In some cases, conjunctival melanoma may have an indolent course. Brownstein and associates reported a melanoma that in 10 years evolved from an epibulbar nodule to a mass occupying the entire interpalpebral aperture,[41] and Schichtel documented survival for 17 years following incomplete excision of a conjunctival melanoma before the patient's demise of metastatic disease.[257] Also, initiation of growth from a melanocytic lesion, clinically assumed to be a nevus, may require 20–50 years.[125,293] In some authors' experience, as many as 5% of conjunctival melanomas arising from PAM with atypia eventually spread through the nasolacrimal duct to the nasal cavity and paranasal sinuses.[108,227] It has been suggested that this may occur by direct extension or bloodborne regional metastases[245] or by the shedding of exfoliated melanoma cells in the tear film.[227]

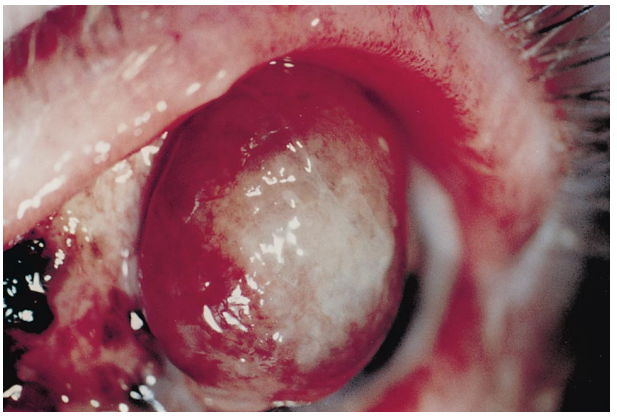

Fig. 12. Recurrent, juxtalimbal melanoma of a 61-year-old woman occluding most of the cornea. The epithelium is partly eroded and covered by fibrin. Note associated pigmented primary acquired melanosis.

Unlike melanoma of the uveal tract, which spreads hematogenously with a preference for the liver, conjunctival melanoma usually first spreads via the lymphatics to regional lymph nodes.[85,93] Occasionally, a metastasis appears in the ipsilateral parotid gland.[303] Eventually metastases from conjunctival melanoma may present in most sites of the body, including the skin, adrenals, brain, lungs, heart, peritoneum, bowels, pancreas, kidneys, bones, and spleen.[93]

B. HISTOPATHOLOGIC AND ULTRASTRUCTURAL FEATURES

The histogenesis of conjunctival melanoma has been debated at considerable length. Reese argued that melanomas originating from precancerous melanosis (or PAM) outnumbered those arising from nevi by 10–15:1,[241] but this view was challenged by Zimmerman.[324] Reese later agreed that a proportion of 2:1 was the most likely.[243] More recent data suggest that 75% of conjunctival melanomas are associated with PAM and that conjunctival nevi are present in 20% of melanomas.[92] However, some conjunctival melanomas may feature a coexisting nevus

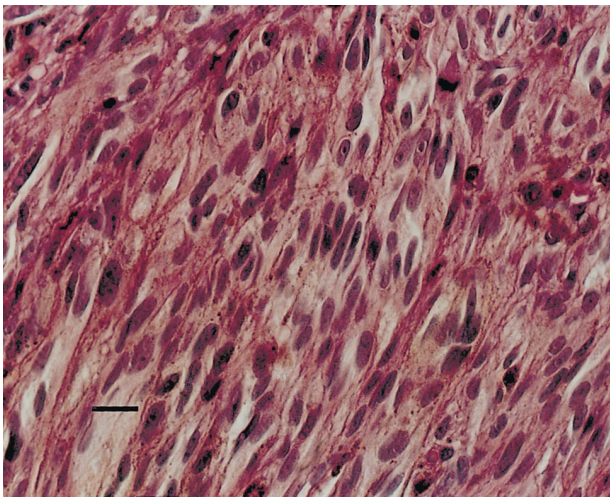

Fig. 13. Micrograph of conjunctival melanoma composed of spindle cells. Bar = 25 μm (hematoxylin and eosin).

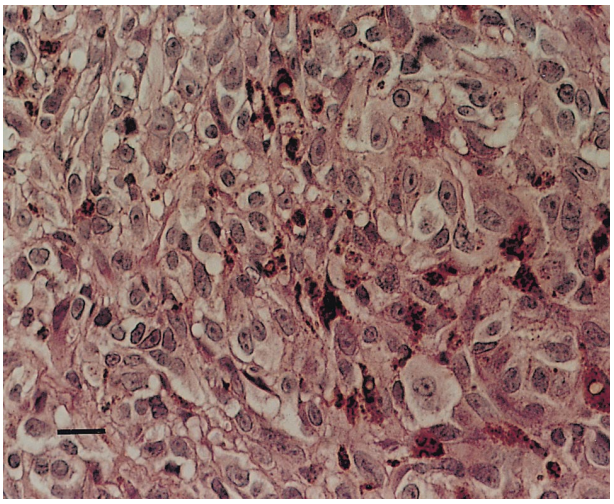

Fig. 14. Micrograph of epithelioid cell conjunctival melanoma. Atypical tumor cells with prominent nuceoli feature an eosinophilic cytoplasm. Bar = 25 μm (hematoxylin and eosin).

and PAM, and the precursor lesion may then be difficult to identify.[272] In exceptional cases, PAM may give rise to benign melanocytic tumors, such as melanocytomas.[79] Primary acquired melanosis without atypia has been noted in conjunction with conjunctival melanoma in a few cases. However, it is unclear if a melanoma may arise from a lesion only, including basilar melanocytic hyperplasia, or if the melanomatous events noted in these cases were coincidental.[204]

Jakobiec and colleagues recognized four types of atypical melanocytes that may be encountered in conjunctival melanomas: small polyhedral, spindle, balloon, and round epithelioid cells with eosinophilic cytoplasm (Figs. 13 and 14).[148] Whereas epithelioid cells tend to grow in a sheetlike, patternless fashion or be segregated in nests, some invasive modules may be composed entirely of spindle cells. A subset of these lesions may elicit a desmoplastic stroma in which bipolar or multipolar hyperchromatic cells are scattered.[148] On some occasions, these spindle cells form bundles and create a neuroidal pattern.[212] However, differentiating a conjunctival nevus from a melanoma solely based on the cytologic features may occasionally prove to be a diagnostic challenge.[196]

The ultrastructural features of conjunctival melanoma have been detailed in an extensive survey by Jakobiec.[144] Briefly, these include dispersion of the nuclear euchromatin, a large wiry nucleus, cytoplasmic polyribosomes rather than the monoribosomes seen in nevi, cytoplasmic deposits of autophagocytosed melanosomes, collection of mitochrondria, and an aberrant granular melanosomal morphology. Ultrastructural assessments are usually not required to make the diagnosis of conjunctival melanoma, but Jakobiec claims that electron microscopy may be particularly beneficial in melanomas composed of small polyhedral cells.[144] Some additional studies also highlight the diagnostic value of electron microscopy in selected cases.[171,307]

C. DIFFERENTIAL DIAGNOSES

Numerous lesions may simulate a conjunctival melanoma. Melanocytic lesions such as the common conjunctival nevus may be difficult to separate from melanoma.[148] However, conjunctival nevi usually present in children and adolescents, whereas conjunctival melanomas occur in the middle-aged and elderly. Any pigmented lesion resembling a conjunctival nevus but presenting after the age of 40 years should be viewed with suspicion. The common acquired nevus does not involve Tenon's capsule and should be freely mobile across the episcleral surface using a cotton tip applicator or similar device.[84] Virtually all conjunctival nevi arise from the bulbar conjunctiva or from the caruncle. A pigmented lesion presenting in the palpebral conjunctiva should raise concern for the presence of a malignancy.[148]

Melanomatous growth on the epibulbar surface may derive from a ciliary body melanoma or melanocytoma featuring extraocular extension.[253] This may be clinically indistinguishable from primary conjunctival melanoma, but the true nature should in most cases be easily identified by ultrasound biomicroscopy and in nearly all cases by histopathologic examination. Very rarely, a ciliary body melanoma may spread along corneal lamellae and (if concurrent extrascleral extension is present) simulate a

conjunctival tumor with intracorneal growth.[273] Though exceedingly rare, the differential diagnoses include metastasis from skin melanoma,[35,124,164,287] occasionally as the initial sign of dissemination,[171b] or from other malignancies (notably from primary tumors of the breast or lungs) to the conjunctiva.[164] Nonmelanocytic lesions that may simulate conjunctival melanomas include staphylomas, subconjunctival hematomas, foreign bodies, and hematic cysts.[46,181b] Also, lesions such as Moll gland cystadenomas and apocrine adenocarcinomas may clinically suggest a melanoma of the palpebral conjunctiva.[268] Occasionally, even a pterygium may be confused with conjunctival melanoma with associated PAM.[148] Because the squamous epithelial cells of the conjunctiva are already pigmented in dark-skinned patients, squamous cell dysplasia, squamous cell carcinoma, and squamous papillomas may be dark enough to clinically resemble melanoma.[88] One case of an epithelial inclusion cyst after cataract surgery had been clinically mistaken for malignant melanoma of the conjunctiva.[142]

Even by histopathologic examination some nevus variants may cause confusion. The presence of an epithelial inclusion cyst in the common acquired nevus may be interpreted as a sign of malignancy by a pathologist unaccustomed to ocular pathology. The presence of vacuolated balloon cells in a conjunctival pigmented lesion was once considered to rule out malignancy. However, balloon cells have been detected in conjunctival melanomas and this feature is no longer regarded as a specific sign of benign disease.[148] Even by histopathologic examination, some nonmelanocytic lesions, such as the spindle cell variant of squamous cell carcinoma, may be difficult to distinguish from an amelanotic melanoma.[270] In these cases, immunohistochemical studies for the detection of S-100 and HMB-45 may prove helpful.[270]

IV. Incidence and Demography

A. INCIDENCE OF CONJUNCTIVAL MELANOMA

Most published data on conjunctival melanoma appear as case reports or small case series. Whereas data derived from populations would be useful for epidemiologic purposes, such data are comparatively scarce. In contrast, most published case series are founded on consecutive histopathologic specimens accumulated over a considerable period of time[14,31,59,67,92,98,123,151,154,182,278] or on series of patients treated at one or more referral centers.[30,127,137,178,188,203,231,282,308,329] Such data are likely to be skewed because they are often based on referral patterns that are either unadjusted for or unrecognized. Some authors report one new case of conjunctival melanoma for every 7,500 patients with ocular disease,[20] whereas most reports suggest one new case of conjunctival melanoma for every 18,000–50,000 patients.[21,237]

[The difference is probably the result of patient selection and referral bias. In 1995, we registered 100,490 outpatient ophthalmologic consultations (greater than 95% of patients residing in Stockholm county) at all clinics of Saint Eriks Eye Hospital (unpublished data). During the same year, four patients were seen for conjunctival melanoma, but three of these patients had recurrent tumors and were referred from areas outside of Stockholm. The patient from Stockholm county generated three outpatient examinations during 1995, suggesting a frequency in the range of one visit for conjunctival melanoma per 30,000–40,000 outpatient visits. Similarly, a total of 10,166 surgical procedures were performed at Saint Eriks Eye Hospital in 1995 (greater than 95% on patients residing in Stockholm county), but only one procedure (excluding referred patients) involved excision of a conjunctival melanoma in a patient residing in Stockholm (unpublished data).] Thus, adjusting for referral bias, approximately 1 per 10,000 surgical procedures in ophthalmology may involve excision of a conjunctival melanoma.

True estimates of the incidence rate will have to be based on population-based data. To date only two or possibly three national surveys have been published,[68,219b,272] but, in addition, Lommatzsch and associates noted that the records of the National Cancer Registry of the former German Democratic Republic suggested an annual incidence of 0.080 cases per 100,000 inhabitants between 1960 and 1985.[188] These findings agree with recalculated data based on an earlier survey of a defined population from a Swedish county, suggesting an annual incidence of 0.070 cases per 100,000 over a period of 23 years. However, this report was based on a population of 250,000 inhabitants and only 4 cases of conjunctival melanoma were included.[122] The national survey from the Netherlands was based on questionnaires submitted by the Dutch ophthalmologic community and indicated that on average, 4 to 5 new cases presented every year in a population of 14.5 million over a period of 16 years.[68] This suggests that the annual incidence rate of conjunctival melanoma in the Netherlands is in the range of 0.028–0.034 cases per 100,000 inhabitants, but it may be argued that the study design using questionnaires is likely to underestimate the true incidence. Nevertheless, the Swedish national survey from 1969 through mid-1991 reported an annual incidence rate of 0.024 cases per 100,000 inhabitants.[272] This data set was based on the Swedish National Cancer Registry and encompassed a dual, compulsory registration procedure involving both pathologists and clinicians. It is conceivable that the latter type of study design

would be less exposed to bias and earlier studies indicate that 95% of cancers in Sweden are filed with the Registry.[199] Primarily based on the two surveys from Sweden and the Netherlands,[68,272] and including recent Danish data,[219b] a conservative estimate of the annual incidence rate of conjunctival melanoma in a Western population would range from 0.02 to 0.05 cases per 100,000 inhabitants.

In agreement with population-based data, several extensive case series suggest that conjunctival melanoma account for only 2–5% of ocular malignant melanomas,[47,159,262,330] or make up less than 3% of excisional biopsies of conjunctival lesions.[121] Correspondingly, conjunctival melanoma supposedly occurs in a ratio of 1:20 up to 1:40 to that of uveal melanoma.[151,181] Melanoma of the vulva, vagina, deep soft tissues, and rectum is probably more common than conjunctival melanoma (Table 1).[262]

In 1993, the Swedish National Cancer Registry filed 1,393 new cases of skin melanoma (population 8.6 million),[288] whereas on average, only 2 or 3 cases of conjunctival melanoma present each year in Sweden.[272] Moreover, the incidence of skin melanoma in Sweden is rising by 4% annually,[288] and a similar increase in skin melanoma is also seen in other Western countries.[192] The trend of incidence over time is best assessed using age standardization, whereby a standard population with a fixed age structure is introduced. The incidence for any special population is then adjusted to allow for discrepancies in age structure between the standard and special populations.[12] Clearly, any such comparison requires a minimum number of unflawed cases to provide meaningful data, but unfortunately the incidence rate of conjunctival melanoma is too low and the populations studied are too small to provide meaningful data.[267] However, surveys combining the incidence rates of intraocular and conjunctival melanoma do not suggest a change in incidence over time.[330] In conclusion, epidemiologic data indicate that melanoma of the skin is currently 450–900 times more common than conjunctival melanoma and this difference is increasing rapidly.

TABLE 1

Distribution of Noncutaneous Melanoma

Location	Number of Patients	Percent of Noncutaneous Melanomas
Skin	2598	
Uvea	250	58.1
Conjunctiva	7	1.6
Ocular site unknown	84	19.5
Vulva	31	7.2
Soft tissue	11	2.6
Rectum	10	2.3
Vagina	9	2.1
Upper respiratory tract	7	1.6
Gum and mouth	5	1.2
Gastrointestinal tract	3	0.7
Other sites	13	3.0
Total	3,028	100.0

Modified from Scotto et al.[262]

B. AGE AND SEX DISTRIBUTION

Whereas some case series have detected an overall female to male ratio of up to 3:2,[14,146,231] population-based data show that an equal number of men and women develop conjunctival melanoma.[68,272] There is also no evidence of a lateral preference. Overall, conjunctival melanoma is a disease of the middle-aged and elderly; few if any cases appear to arise in children or adolescents.[68,272] According to Dutch national data, 64% of patients were between the age of 40 and 70 years when they first noted their melanomas. In the Dutch survey, the median age was 58 years and the youngest patient was 21 years old at the time of presentation.[68] Calculations of the age-specific incidence of conjunctival melanoma in Sweden concur with these findings (Table 2).[267] The youngest patient ever to have had a conjunctival melanoma appears to have been a 10-year-old boy, who was included in the case series by Bernardino and associates.[31] Also, the histopathology files of one center were reviewed for 71 conjunctival melanocytic lesions in patients younger than 20 years of age.[201] Only three of these specimens contained conjunctival melanomas, including that of a 12-year-old boy with subsequently biopsy-proven metastasis of an ipsilateral parotid lymph node.[201] However, the youngest reported patient with disseminated disease caused by a presumed conjunctival melanoma was an 11-year-old boy who underwent orbital exenteration.[60]

TABLE 2

Age-Specific Incidence of Conjunctival Melanoma

Age (y)	Cases Observed	Incidence*
< 30	0	0
30–49	12	0.027
50–69	24	0.055
> 70	9	0.053

*Average annual age-specific incidence per 100,000 individuals.

Modified from Seregard.[267]

C. RACIAL AND ETHNIC DISTRIBUTION

Conjunctival melanoma is distinctly uncommon in black populations and probably also in other nonwhite groups. There are a few reports of corneal or conjunctival melanoma occurring in black individuals,[49,161,206,261,318] and occasionally conjunctival melanoma may present in the caruncle in blacks.[158] However, the overall white-to-black ocular melanoma risk ratio is believed to be at least 8:1.[113] Grossniklaus and colleagues included five additional cases of conjunctival melanoma of black patients, indicating a white-to-black ratio of 13.6:1.0 in their series.[121] Two reports from Egypt and Thailand suggest that conjunctival melanoma is an extreme rarity in these nonwhite populations.[75,238]

D. CONJUNCTIVAL MELANOMA IN ANIMALS

Even though Cotchin found one limbal melanoma in his summary of 1,150 canine neoplasms,[58] this was not mentioned by Morgan in his review on ocular tumors in animals.[211] However, later reports confirm that conjunctival melanoma is an occasional tumor not only of dogs,[29,179,197,235] but of cats.[57,235] Possibly, melanoma associated with PAM may present in the canine conjunctiva.[235]

V. Etiology

A. ULTRAVIOLET RADIATION

Massive data now clearly indicate that high doses of ultraviolet radiation (UVR) may cause skin melanoma.[289,290] It would be tempting to conclude that UVR also may induce malignant melanocytic transformation in other sites, and most conjunctival melanomas appear to arise from the UVR-exposed bulbar surface. Conversely, a substantial proportion of the conjunctiva lines the inner surface of the eyelids, but very few tumors present in the tarsal conjunctiva.[68,231,272] A few case reports support a potential role for UVR in the tumorigenesis of conjunctival melanoma. In particular, the findings of atypical PAM,[225] and conjunctival melanoma[10,193] in patients with xeroderma pigmentosum, indicate that neoplastic melanocytic lesions of the conjunctiva may be more common in that setting. Patients with xeroderma pigmentosum are prone to develop diverse UVR-inducible tumors, in support of the hypothesis that UVR exposure also may induce conjunctival melanoma. Similarly, a few case-control studies suggest that substantial exposure to UVR is associated with a small-to-moderate increased risk of harboring uveal melanoma (relative risk ranging from 1.7 to 2.7),[135,264] but caution would be advised in extrapolating these findings to implicate exposure to UVR in the etiology of conjunctival melanoma. In conclusion, there are (as yet) no compelling data to suggest that UVR is a causative agent in the formation of conjunctival melanomas.

B. PRIMARY ACQUIRED MELANOSIS

Many ophthalmic pathologists currently prefer the term *PAM*[91] for acquired conjunctival lesions that clinically appear as variably brown (ranging from golden- to chocolate-brown), flat patches.[148] These patches may cover large areas and all aspects of the conjunctiva, necessitating eversion of the eyelids for complete examination (Figs. 1 and 2).[148] By histopathologic examination, these lesions may be divided into two groups based on the absence or presence of atypia (Figs. 3 and 4).[91] In a pivotal study based on a set of selected specimens, no lesion without atypia underwent malignant transformation, whereas almost half of lesions with atypia ultimately progressed to invasive melanoma.[91] The criteria used to define atypia were purely cytologic, but, even so, histologic patterns appeared important. In a subset of lesions, representing PAM with atypia, 90% of those with histologic patterns other than basilar hyperplasia progressed to melanomas.[91] Moreover, population-based data indicate that 71% of conjunctival melanomas feature associated PAM with atypia,[272] confirming that this is the most common precursor lesion of conjunctival melanoma.

Findings derived from a small set of specimens featuring PAM with atypia, that later evolved to melanoma, suggest that the median interval to the formation of an invasive tumor is 2.5 years, with the malignant transformation occurring within a period of 10 years.[93] It is conceivable that PAM without atypia in a few cases progresses to PAM with atypia, even if this is a comparatively rare event.[86] Some circumstantial evidence for this concept is provided by the fact that patients who have PAM without atypia are on average 5 years younger than patients who have PAM with atypia.[91] Also, an animal model using a topically applied chemical carcinogen on normal conjunctiva generated PAM-like lesions that progressed from PAM without atypia to PAM with atypia and ultimately to melanoma.[87] However, there is no single patient reported in whom multiple biopsies performed over time showed continuous progression of atypia leading from PAM without atypia to invasive melanoma. It is conceivable that in these cases the excision modifies the natural history of a lesion that otherwise would have progressed from PAM without atypia to PAM with atypia.[93]

The prevalence of PAM in the general population is unclear, but if minute pigmented lesions are included, this condition may be quite common. Gloor and Alexandrakis recognized PAM in 36% of outpatients visiting a corneal and external disease service,[107] but these data may be biased because of

patient selection (notably a large proportion of patients had southern European ancestry and 25% of pigmented lesions were bilateral, which suggested racial melanosis rather than PAM). However, we recently detected small, unilateral, pigmented conjunctival lesions in 10% of controls randomly selected from a census file of an urban population.[269] If the prevalence of PAM is as high as 10% in the general population, and the annual incidence of conjunctival melanoma is 0.024 cases per 100,000,[272] only 1 case of conjunctival melanoma would occur once a year in 400,000 individuals with PAM, provided all conjunctival melanomas do arise from PAM. Thus, the risk for malignant transformation in the individual with a minute patch of pigmented conjunctiva appears to be minimal. Many of these small lesions are probably never noticed by the patient, but may be incidentally discovered at a routine ophthalmologic examination. Previous data suggest that as many as 28% of Hispanics, 36% of Orientals, and 92% of blacks feature grossly visible conjunctival pigmentation.[128] This condition is associated with darker skin types, being more common in heavily pigmented individuals, and is usually bilateral.[88] It is recognized as complexion-associated pigmentation or racial pigmentation by some[88] and as benign epithelial melanosis or racial melanosis by others.[56] However, the equivalent of racial melanosis exists among whites, and approximately 5% of a white population will feature grossly visible, small, pigmented patches in the interpalpebral conjunctiva (Fig. 5).[128] These pigmented patches are even more common by slit-lamp examination of the conjunctiva.[88] Whereas earlier reviews were reluctant to recognize these patches as ephelides (freckles),[88] it is currently accepted that this entity may be present in the conjunctiva.[84] These lesions may easily be confused with small areas of PAM, and there appears to be a clinical and histopathologic overlap between ephelides and PAM.[84] Thus, accepting that both of these lesions may be present in the conjunctiva, there is a potential risk of PAM being overdiagnosed in the absence of clearly defined criteria for differentiating small areas of PAM from ephelides. If the clinical and histopathologic definitions of a cutaneous ephelis were transferred completely to the conjunctiva, then ephelidis would develop only in the sun-exposed portions of the conjunctiva. Pigmentation elsewhere in the conjunctiva would not qualify as an ephelis.[86]

The risk of malignant transformation occurring in larger pigmented patches is substantially higher than in small patches, particularly when multifocal PAM is present (Figs. 6 and 7).[148] For practical purposes it has been suggested that a flat melanocytic lesion of the conjunctiva should be considered suspicious when it measures more than 7.5 × 10 mm in size.[84] This would spare almost all ephelides from unnecessary biopsies, but, unfortunately, it would also exclude some lesions that by histopathologic examination would reveal atypical features. In fact, PAM with atypia has been detected in lesions of 4 mm in diameter[84] and microinvasive melanoma in flat pigmented lesions of only 2–3 mm in diameter (Fig. 8).[271] Thus, the clinical dilemma persists in separating flat pigmented lesions unlikely to progress to melanoma from those with a high risk of malignant transformation. We currently perform excisional biopsies of lesions 2–3 mm in diameter, particularly if the patient is middle-aged or elderly and if the lesion has been detected recently. However, in our experience (unpublished data) nearly all lesions (greater than 95%) measuring 3 mm or less do not have atypical features by histopathologic examination. A few lesions have shown moderate atypia, but it is unclear if progression to melanoma would have taken place if the lesion had not been excised.

C. CONJUNCTIVAL NEVI

Conjunctival nevi usually present as well-defined lesions in the juxtalimbal area or in the plica or caruncle.[88] Whereas the color usually ranges from light tan to deep chocolate brown, approximately 30% are almost entirely nonpigmented by clinical examination (Fig. 9).[88] Undoubtedly, conjunctival nevi occasionally give rise to melanoma, but this appears to be rare.[84,102] Also, the adjacent tissue of some conjunctival melanomas may feature both a nevus and PAM and in these cases the precursor lesion may be difficult to identify.[172] Most conjunctival nevi present during childhood or early adolescence (and are designated "common acquired nevi"),[88,102] whereas conjunctival melanoma is a disease of the middle-aged and elderly.[272] Furthermore, the common acquired nevus of the conjunctiva is comparatively frequent, but conjunctival melanoma is distinctly uncommon. Nevertheless, malignant transformation occasionally takes place in a nevus that has been present for 20–60 years.[65,125,293] It is therefore advised that any conjunctival nevus with signs of enlargement in adulthood should be excised.[148] Some authors also urge that excision should be performed in adults with limbal or carbuncular nevi with large nutrient vessels, significant inflammation, or increased pigmentation.[102] However, these features are not definite signs of malignancy and, for example, feeder vessels are just as commonly seen in benign nevi as in conjunctival melanoma.[88] Nevi of the palpebral or forniceal conjunctiva are extremely rare,[42,150] and a pigmented lesion in this location usually signifies melanoma and should be excised.[88,102] Population-based data indicate that by his-

topathologic examination, 17% of conjunctival melanomas feature associated nevi.[272] However, in most of these cases PAM with atypia is also present. An aberrant form of skin nevus, the so-called dysplastic nevus, has raised considerable interest because of its association with cutaneous melanoma. Whereas the clinical skin findings and dermatopathologic features of the dysplastic nevus are well recognized,[77] there are no reliable criteria by which dysplastic nevi may be identified in the conjunctiva.[84] Jakobiec and associates reported a conjunctival nevus in a patient with numerous dysplastic skin nevi.[150] The conjunctival lesion showed atypical melanocytic hyperplasia as well as a superficial component of atypical cells within the conjunctival stroma. The second, deeper portion consisted of bland, unpigmented nevus cells, causing the appearance of a mixed pattern. Based on the histopathologic findings and the setting in a patient with numerous dysplastic skin nevi, this lesion was interpreted as a dysplastic nevus of the conjunctiva.[150] Other rare variants of conjunctival nevi include the spindle and epitheloid nevus of Spitz (once referred to as "juvenile melanoma").[280] This is an infrequent entity of childhood,[313] but the Spitz nevus of the conjunctiva may extremely rarely present in adults and then sometimes appear as a pure epitheloid cell nevus.[150] In contrast to the dysplastic nevus, the Spitz nevus is not believed to be associated with an increased risk of malignant transformation, but both these types of lesions may be misdiagnosed as melanomas because of their unusual histopathologic features.[88,150]

D. PRESENTATION *DE NOVO*

Conjunctival melanomas occurring *de novo* are probably far less common than melanomas deriving from PAM or nevi. Whereas there are no signs of associated PAM or nevi in 12% of conjunctival melanomas by histopathologic examination,[272] it is possible that in some of these cases the precursor lesion may no longer be recognized and presentation *de novo* may in fact be even rarer.

E. ASSOCIATION WITH CUTANEOUS MELANOMA

Much data derived from cutaneous melanoma are transferred and used in the study of conjunctival tumors. In particular, dermatopathologic classifications have repeatedly been used for conjunctival melanoma,[23,31,127,128] the relevance of which is continuously debated[2,5,89] There are apparent histopathologic similarities; for example, the pagetoid type of PAM closely resembles that of the superficial spreading melanoma recognized in the skin and PAM with basilar hyperplasia is reminiscent of lentigo maligna of the skin. However, the histology of the skin and conjunctiva are not comparable in all aspects; the conjunctiva is a mucous membrane lined by an epithelium containing goblet cells and the stroma lack the dermal stratification. In contrast, the skin is lined by keratinized squamous epithelium and the stroma contains adnexal structures such as hair follicles and sebaceous glands. The transitional zones between skin and conjunctiva include the caruncle; a roundish body at the medial canthus lined by conjunctival epithelium, but with a stroma featuring the adnexal structures otherwise only present in the dermis.

Some data suggest that conjunctival melanoma arising from the caruncle has a particularly ominous prognosis, possibly because the caruncle is a skin derivative.[231] Primary eyelid melanoma may secondarily invade the conjunctiva,[214] but on rare occasions, primary conjunctival melanoma may be present in conjunction with a separate eyelid melanoma.[104] The implications of this dual appearance are unclear, but data indicate that patients with conjunctival melanoma associated with ipsilateral pigmentation of the eyelid margin do worse; in one study, 12 of 17 patients with conjunctival melanoma, including associated eyelid pigmentation ranging from increased pigmentation of the melanocytes to invasive cutaneous melanoma, died of metastatic disease.[246] However, recent findings from a series of 47 patients with primary eyelid melanomas also indicate that patients with tumors extending to the eyelid margin have a worse prognosis than patients without lid margin involvement.[291] Even though these data are difficult to interpret because of the small number of patients involved, they may suggest an association between conjunctival and skin melanoma. Some authors believe that the common denominator could be the dysplastic nevus syndrome.[200]

F. THE DYSPLASTIC NEVUS SYNDROME

The recognition of a syndrome consisting of clinically atypical cutaneous nevi sometimes occurring in the setting of familial cutaneous malignant melanoma was conceptualized in 1978 as the B-K mole syndrome[53] and the familial atypical mole melanoma syndrome.[190] Whereas the dysplastic nevus syndrome (DNS) initially was defined as clinically or histopathologically abnormal cutaneous nevi occurring in patients with nonfamilial cutaneous melanoma,[76] the DNS concept now usually includes both sporadic and familial forms.[77] A slightly different definition requires the presence of multiple dysplastic nevi in two or more family members.[217]

The clinical criteria for a dysplastic skin nevus include an irregular tan or brown lesion more than 5 mm in diameter and featuring an irregular border or irregular pigment pattern, whereas the histopathologic definition emphasizes nuclear atypia, a

prominent junctional activity, and a lymphocytic or mesenchymal response.[77] In 1983 Kraemer and coworkers introduced an extensive DNS classification comprising both individuals with sporadic moles and those with familial dysplastic nevi.[169] Briefly, individuals are graded from A (individuals with DNS phenotype but no personal or family history of cutaneous melanoma or family history of DNS) through D1 and D2 (individuals with familial DNS with one [D1] or two or members [D2] having both dysplastic nevi and cutaneous melanoma). However, there has been some debate as to what constitutes a cutaneous dysplastic nevus,[3,77,251] and while the NIH Consensus Conferences[217,218] only accepted the familial setting, some controversy still exists regarding the minimal criteria required for inclusion of individuals or families within the syndrome.[22,77] Whereas the prevalence of one or more clinically defined, sporadically occurring cutaneous dysplastic nevi of the skin may be as high as 18% in Sweden,[18] only 32,000 individuals in the United States are believed to have dysplastic nevi in association with hereditary malignant melanoma of the skin.[22] Individuals with the DNS are considered to be at high risk for developing skin melanoma,[114,115] and for individuals with the D2 phenotype, the risk is estimated to be 395 times that of the unaffected population.[169]

The first case report of a cutaneous and uveal melanoma occurring in the same individual emerged in 1959,[234] but unfortunately, published data are insufficient for a retrospective recognition of DNS. Subsequently, a few reports of coincidental cutaneous and uveal melanoma occurring without the presence of a DNS phenotype have been published.[17,105,168]

In 1961, Lederman published a photograph of a woman who had innumerable moles scattered over the body and later died of metastatic conjunctival melanoma.[175] Similarly, a few years later, Duke-Elder and Leigh reported a patient with numerous large and probably dysplastic skin nevi who subsequently died of an associated metastatic conjunctival melanoma (probably same patient as reported by Lederman).[72] Although both these reports preceded the concept of the B-K mole syndrome, they are probably the first accounts of a conjunctival melanoma occurring in conjunction with the DNS. Unfortunately, no data on the presence of a familial aggregation of dysplastic nevi or skin melanomas were provided. Similarly, most information on ocular melanoma associated with dysplastic nevi or the DNS phenotype are based on individual cases,[1,6,96,155,200,249] or on very small series.[24,222,223,312] However, there is a comparatively large study reporting a ninefold increase in the DNS among 211 patients with uveal (84%) and conjunctival melanoma (16%) compared with controls.[26] This study may have been biased because examiners were not blind to case-control status and a large proportion of controls were hospital patients.[26] Another study reports the first unequivocal case of a conjunctival melanoma occurring in a woman with sporadic dysplastic nevi.[96] In their close to identical case series, Vink and associates[312] and Oosterhuis and colleagues[222] report one individual with sporadic dysplastic nevi and one patient with the D1 phenotype who both featured a malignant melanoma of the conjunctiva. A fourth case comprised sporadic dysplastic nevi and a conjunctival melanoma occurring in the same individual.[200] The same year, Bataille and associates listed three patients with PAM of the conjunctiva in conjunction with the DNS.[24] Two patients had the D1 phenotype; one of these had a conjunctival melanoma associated with PAM, and the other had PAM without atypia. The remaining individual probably had sporadic dysplastic nevi, but also proved to have a conjunctival melanoma associated with PAM. Thus, the literature currently includes two, or possibly three, individuals with conjunctival melanoma in the setting of the DNS D1 phenotype.

Some authors believe that the many case reports of individuals or families with both skin and ocular melanomas in themselves provide evidence that these malignancies are related. This is because both tumors are relatively rare, and the probability for coincidental occurrence in a single individual is claimed to be negligible.[6] In fact, the probability for the coincidental occurrence of a cutaneous and ocular melanoma in the same individual has been estimated to be 4.2 in 10.0[10] if both tumors were to occur in the same year and 1 in 400,000 if they were to occur in the same individual over a 75-year life-time.[96]

Some studies have been based on small groups of individuals, and Greene and associates concluded from a study based on 2 kindreds and 26 individuals with hereditary skin melanoma or familial DNS that the association of intraocular melanoma with cutaneous melanoma or DNS may be coincidental.[116] However, these conclusions were later challenged.[99] In contrast, the findings of three other studies indicated that iris nevi were more common in patients with cutaneous melanoma than in controls.[7,23b,219] Two of these studies used nonmatched controls that were selected from a prison and a hospital ward, and this potential bias will have to be recognized.

Similarly, some work has been based on the dermatologic examinations of individuals with intraocular and conjunctival melanoma. Taylor and coworkers studied 44 patients with uveal malignant melanoma and found a 4.5% prevalence of dysplastic nevi; a frequency similar to what would have been expected in the general population, but considerably less than the 41.0% prevalence of dysplastic nevi

found in 46 nonmatched controls with cutaneous malignant melanoma.[294] A fairly recent work reports 5 cases of coexistent primary premalignant or malignant ocular melanocytic lesions and cutaneous melanoma in a consecutive series of 207 patients.[25] One of these 5 patients had PAM, 1 had a conjunctival melanoma, and 3 patients had choroidal melanomas. No controls were used, but data were compared to the expected frequency (0.4 cases) of cutaneous melanoma in the United Kingdom in a similar number of subjects and the difference was found to be highly significant.[25] Recent information also indicates that individuals with either uveal or conjunctival melanomas more often feature clinically dysplastic skin nevi than controls.[26] Also, these individuals tend to display the DNS more often than controls.[26]

The prevalence of uveal and conjunctival nevi in individuals with sporadic dysplastic nevi of the skin has been assessed,[247,248] comparing 257 cases with 264 significantly younger, nonmatched controls.[247] The proportions of individuals with nevi of the iris, conjunctiva, and choroid were all significantly larger in the group featuring dysplastic nevi compared with those of the control group. However, this study was challenged because of its choice of controls and because the investigator was unmasked.[162] Recently, the respective prevalence of PAM and nevi of the uvea and choroid in 119 individuals with DNS D2 phenotype was compared with controls, matched for sex and age, but otherwise randomly selected from a census file.[269] In contrast to previous reports, data indicated that individuals with this high-risk variant of DNS did not have PAM or uveal or conjunctival nevi more often than controls. Also, excisional biopsies of four conjunctival lesions of the DNS D2 group revealed only PAM without atypia, suggesting that these particular lesions would have been unlikely to progress to melanoma even if surgery had not been performed.[269]

In conclusion, there is yet no definite evidence of an association between cutaneous and conjunctival melanoma, and because of the low incidence of both conjunctival and uveal melanoma, new tumors will probably rarely be detected by repeat examinations. Regardless of the uncertain and possible small clinical value, several authors advocate that periodic ocular examinations should be performed in individuals with the DNS.[86,138,217,222]

G. CYTOGENETIC FINDINGS

Tumorigenesis may be regarded as a multistep procedure in which each step is preceded by a genetic alteration.[82] One of the most studied genes involved in tumorigenesis is the p53 gene, now recognized as a tumor suppressor gene.[180] The interest in the p53 gene heightened as findings indicated that some 75% of colorectal carcinomas have allelic deletions of the short arm of chromosome 17, including the site of the p53 gene.[19] Additional data later showed that mutations of the p53 gene not only occurred in colorectal carcinoma, but in diverse human tumors.[134,216,292] Other studies suggested that p53 gene alterations may also be implicated in the tumorigenesis of uveal melanomas.[152,298] However, recent work including p53 gene sequencing now concludes that mutation of the p53 gene rarely occurs in uveal melanoma.[165] Sufficient accumulation of p53 protein to allow immunohistochemical detection suggests p53 gene alteration, but this has only been recognized in a single case report of PAM with atypia that later progressed to melanoma.[305] Moreover, the nearly complete absence of detectable p53 protein expression in PAM with atypia and minimal immunoexpression in only a small subset of conjunctival melanomas not correlating with cell growth indicates that p53 gene alterations are infrequent and late events in conjunctival melanoma.[266] The *c-myc* is a nuclear oncogene, and findings in uveal melanoma now indicate that immunohistochemical detection of the *c-myc* protein correlates with tumor cell proliferation and may be of prognostic value.[252] However, similar findings have not been reported in conjunctival melanoma.

To date, cytogenetic abnormalities in conjunctival melanoma have been documented in two cases; McCarthy and associates showed a clonal translocation between chromosomes 1 and 14 in a patient with the dysplastic nevus syndrome,[200] and Dahlenfors and colleagues demonstrated a clonal abnormality, albeit present only in 3 of 25 karyotyped cells.[62] Cytogenetic studies also suggest that chromosomal abnormalities differ between uveal and conjunctival melanoma.[16] There are currently no recognized chromosomal abnormalities implicated in the tumorigenesis of conjunctival melanoma.

H. ASSOCIATION WITH OTHER ENTITIES OR CONDITIONS

Similar to malignant melanoma in other locations, conjunctival melanoma appears to be associated with neural crest disorders like neurofibromatosis.[297,303] In contrast to the uveal tract, ocular and oculodermal melanocytosis are not associated with malignant melanocytic transformation of the conjunctiva.[88] Single case reports indicate that tumor progression of conjunctival melanoma may occur during pregnancy,[151,175,213] suggesting a possible hormonal influence. Indeed, estrogen receptors were once claimed to be present in conjunctival melanoma,[228] but more recent studies now conclude that conjunctival melanomas do not contain estrogen receptors.[94]

VI. Classifications

The past decades have seen a plethora of proposed histopathologic classifications for conjunctival melanoma emerge and decline into oblivion. Most of them are rarely used but may still cause confusion. Briefly, Greer graded conjunctival melanocytic lesions based on the degree of junctional melanocytic activity,[117] whereas Jay suggested that conjunctival melanomas be divided into two groups, depending on the presence of localized or widespread intraepithelial growth.[151] Zimmerman proposed a somewhat similar scheme with stage IIA corresponding to atypical PAM with minimal invasion and stage IIB denoting a conjunctival melanoma with a marked invasive component.[323] Bernardino and associates used dermatopathologic criteria[51] to divide 23 conjunctival lesions into "superficial spreading," "lentigo maligna melanomas," and "nodular melanomas."[31] However, several authors claim that most conjunctival melanomas cannot be categorized according to this concept and challenge the adoption of a dermatopathologic classification.[128,182,250,278] Whereas some insist that dermatopathologic criteria be used,[11] others suggest a histogenetic classification[323] or simply apply the term *invasive melanoma* for any lesion in which tumor cells invade the substantial propria from the overlying epithelium.[278] In the mid-1980s, Guillén and colleagues[123] introduced a new dermatopathologic nomenclature for conjunctival melanoma. Here the concept of a radical growth phase (including lentiginous, pagetoid, and mixed patterns) was stressed. At the same time, Folberg and associates underlined the concept of PAM and urged that conjunctival melanoma should be classified as with or without PAM[91] and that any present risk factor should be stated.[92]

For clinical purposes, most neoplastic entities may be categorized according to the (Tumor, Lymph Node, Metastasis) TNM-classifications by the International Union Against Cancer (UICC), comprising data on the extent of the primary tumor (T), the absence or presence of regional lymph node metastasis (N), and the absence or presence of distant metastasis (M). The present clinical classification of conjunctival melanoma, although not much used, is detailed in Table 3.[309] There is also a corresponding histopathologic classification in which a tumor thickness of 2 mm and tumor location are important for tumor grading.[309]

VII. Management of Conjunctival Melanoma

A. PRIMARY SURGICAL TREATMENT

The primary treatment for conjunctival melanoma is usually surgical, and all traces of invasive melanoma are removed.[84] Most lesions present on the bulbar surface at or adjacent to the limbus and may be excised in local anesthesia without difficulty.[275c] The neoplastic nature of these tumors is usually apparent and incisional biopsies are discouraged; however, it would be appropriate to confirm the clinical diagnosis of tumors that may require orbital exenteration.[275b,275c] It is currently suggested that a conjunctival melanoma be removed with a 3–5-mm free conjunctival margin, after which supplemental cryotherapy to the surgical margin is performed.[66,275b,275c] Tumor excision could possibly be followed by beta irradiation to the surgical margin.[230] Some authors use absolute alcohol to devitalize corneal epithelial cells adjacent to a melanoma of the corneal limbus before excision,[275c] and advocate that the removal of limbal tumors should include a lamellar scleroconjunctivectomy.[275d] For technical purposes, wide surgical margins may sometimes be difficult to achieve, but margins could be reduced using microscopically controlled surgery as suggested for conjunctival squamous cell carcinoma and periorbital melanomas.[43b,209] Margins may also be monitored with use of frozen sections, but many surgeons do not believe that this is required when wide margins are used.[275c] Moreover, frozen sections are more difficult than permanent sections to assess for clear margins, but if the tumor is thought to extend to the surgical margin at the time of excision, marginal biopsies for permanent sections may be performed.[275c]

Although earlier reports claim that corneoscleral grafting is required to manage invasion of the cornea,[183] any corneal spread is usually superficial and may easily be scraped or peeled off Bowman's layer.[86,275b] This layer serves as a barrier against tumor invasion and should be retained unless deep corneal invasion has supervened.[275b] Only in exceptional cases featuring deep corneal spread may lamellar corneal dissection,[258,259] or possibly even corneal grafting, be required. Although not reported in the literature, single melanocytic cells lodged in the corneal stroma could possibly be destroyed with excimer laser keratectomy; however, this treatment would also ablate the adjacent, normal corneal stroma to a certain depth. Most defects of the bulbar conjunctiva after excision may be allowed to heal by second intent; however, some suggest primary closure of these defects using fresh, uncontaminated, instruments.[275b] Defects in other conjunctival areas often need to be reconstructed.[156] The shortage of conjunctiva following wide conjunctivectomy may be overcome by the transplantation of full thickness mucosal grafts harvested from the mouth or the contralateral eye.[230] Also, a conjunctival flap from the upper eyelid may be used for reconstruction of defects in the palpebral conjunctiva

TABLE 3

TNM-Classification of Conjunctival Melanoma

T - Primary Tumor		N - Regional Lymph Nodes		M - Distant Metastasis	
TX	Tumor(s) cannot be assessed	NX	Cannot be assessed	MX	Cannot be assessed
T0	No evidence of primary tumor	N0	No lymph node metastasis	M0	No distant metastasis
T1	Tumor(s) involving one quadrant or less of bulbar conjunctiva	N1	Lymph node metastasis present	M1	Distant metastasis
T2	Tumor(s) involving more than one quadrant				
T3	Tumor(s) involving fornix, caruncule, and/or palpebral conjunctiva				
T4	Tumor(s) invading eyelid, cornea, and/or orbit				

Modified from UICC.[309]

of the lower lid.[156] If a part of the conjunctival fornices must be removed, the use of a contact lens may be advantageous in preventing the formation of symblepharon.[277] Areas of adjacent PAM should also be eradicated, using surgery, cryotherapy, laser ablation, brachytherapy, topical chemotherapy, or a combination of some of these methods.[84]

Before the specimen is submitted for histopathologic examination, care should be taken to provide optimal working conditions to the pathologist. The thin conjunctival specimen tends to curl during fixation unless mounted flat, and, potentially, a curved conjunctival specimen may cause a false diagnosis of pagetoid spread when only basilar hyperplasia is present.[80] Therefore, the biopsy specimen should be placed flat onto an absorbent mount before fixation. Metallic pins should not be used for mounting, as they tend to disrupt the small amount of tissue usually submitted and also may rust and deposit iron into the specimen.[84] To better identify each surgical margin, these may be indicated on the mount using a ballpoint pen or ink. A clinical photograph or sketch may also aid the pathologist. More details on optimal biopsy techniques[316] and on the preparation of specimens for histopathologic examination are provided elsewhere.[300]

B. EXENTERATION

The surgical techniques to manage conjunctival melanoma may be divided into local excision, enucleation of the globe with removal of some of the bulbar conjunctiva, and exenteration of the orbital content. The latter procedure usually comprises anterior en bloc excision of the eyelid margins, conjunctival sac, globe, and anterior orbital contents, including the ocular muscles, optic nerve, and orbital fat.[230] Orbital exenteration for conjunctival melanoma may often be performed as a lid-splitting procedure, thereby saving the eyelid skin and improving cosmesis.[230,275] Reese once claimed that early exenteration was the preferred treatment even when only PAM was present,[240] but he later advocated that exenteration only should be used for invasive melanoma and for histopathologically proven PAM with atypia showing clinical signs of progression.[241–243] He insisted that mortality would be much lower if patients having PAM with atypia had early exenteration[241,242] and regarded any surgery confined to enucleation as contraindicated, because this would leave potentially diseased conjunctiva.[243] However, the concept of performing an extensive, mutilating procedure for a minimal growth was forcefully challenged,[181,323,324] and many argued that exenteration should be performed only for tumors involving the fornix or eyelid, tumors that have not responded to radiotherapy,[151] or possibly, for widespread PAM with severe atypia.[194,195] Other workers advocated an extreme approach for melanomas that involved the palpebral conjunctiva or the caruncle or that invaded the eyelid skin.[34] This technique, however, now rarely used, would involve en bloc orbital resection, parotidectomy, and radical neck dissection.[304] However, the value of prophylactic lymphadenectomy remains highly controversial in the management of conjunctival melanoma,[34] and lymph node dissection is now only performed when evidence exists of metastatic disease.[230] Whereas current management includes total eradication of tumor, this usually does not require orbital exenteration, but may often be achieved through a combination of debulking surgery and adjunctive cryotherapy or brachytherapy.[139]

Exenteration of the orbit is currently reserved for advanced stages of conjunctival melanoma with orbital invasion[139] and is rarely performed when evidence exists of metastatic disease, in the very old, or when the affected orbit contains the only seeing eye.[230] Whereas removal of the orbital content, including complete conjunctivectomy, potentially may reduce the risk of local recurrence, occasional regrowth of tumors may occur in the orbital socket

many years after exenteration.[230] Prognosis after thick (greater than 1–2 mm) conjunctival melanoma is not improved if exenteration is performed shortly after diagnosis, rather than delayed in the event recurrent disease emerges after failure of local excision or brachytherapy.[230,278] Invasion of conjunctival melanoma into the orbit is a very poor prognostic sign, and orbital exenteration is often unable to prevent metastatic spread and alter the clinical course of the disease.[93] Therefore, orbital exenteration should probably be reserved as a palliative treatment for advanced stages of conjunctival melanoma that have entered an aggressive phase.[230]

C. RADIOTHERAPY

Lederman pioneered the use of radiotherapy in conjunctival melanoma,[175–177] claiming that contemporary management was prejudiced by surgical dogma and that a subset of melanomas (in particular epibulbar melanomas) were radiosensitive.[175] Conjunctival melanomas are currently not believed to be particularly radiosensitive, but several (mainly European) authors have tried radiotherapy in selected cases with some success.[175–177,184–188,207,220,239, 243,260,295,296,319]

Lederman reported on radiotherapy of conjunctival melanoma in the late 1950s and early 1960s, based on a combination of surface beta and gamma irradiation with low- and high-voltage X-ray therapy.[176] Using brachytherapy for epibulbar melanoma, he changed from radon seeds to strontium foil.[176] Additional authors continued to use strontium applicators,[295,296] but the modern use of brachytherapy for conjunctival melanoma was popularized by Lommatzsch.[184–188] Using beta irradiation ($^{90}Sr/^{90}Y$ applicators), he suggested a daily dose of 10 Gy up to a total dose of 150–200 Gy applied to the tumor surface, depending on the thickness of the tumor.[187] Regression of the tumor takes place after several weeks or months, and in some instances a small amount of pigment is left in the center of the radiogenic scar.[187] Fairly recent data suggest that brachytherapy combined with other modalities will achieve complete regression of the initial tumor in 75% of cases.[188] However, most conjunctival melanomas suitable for brachytherapy (e.g., epibulbar tumors) may also easily be surgically excised. Moreover, only a minority of cases reported as having strontium radiotherapy (12 of 81) were solely treated by brachytherapy,[188] suggesting that brachytherapy is probably best used in combination with surgery. If brachytherapy is used, either as the sole treatment or as an adjunctive to surgery, impression cytology may possibly be used to monitor results after plaque radiotherapy for conjunctival melanoma.[167]

For some time, it has been recognized that external beam irradiation using X rays for epibulbar melanomas will cause extensive ocular damage, and this technique is no longer performed.[131] However, side effects occur substantially less when proton beam radiotherapy is used, and this modality has been used for some patients who otherwise would have undergone orbital exenteration for extensive conjunctival tumors.[38,39,50] A few authors have claimed that proton beam radiotherapy may be successful for large sets of patients,[38,39,326] but patients should probably be carefully selected and the current use of proton beam radiotherapy for conjunctival tumors remains controversial. Possibly, individualized treatment including not only proton beam radiotherapy, but also surgical excision and brachytherapy, provides the overall best chance to avoid exenteration.[327] Local recurrences using this multimodality approach are, however, likely to be common. Relative contraindications for any radiation therapy include bulky tumors in the fornix, tumor involvement of the palpebral conjunctiva, and recurrent melanoma previously treated with radiation.[46]

D. CRYOTHERAPY

Cryotherapy is used in combination with surgery and never as the sole primary treatment of conjunctival melanoma.[146] It has been advocated as an adjuvant treatment after surgery, both for PAM and conjunctival melanoma.[41,145,146,149,172] Results indicate that this technique may be of value for local tumor control, but it appears to have no additive effect in preventing metastatic disease.[149] A double freeze-thaw cycle is preferred, in which the cryoprobe remains in place for 10–20 seconds until an ice ball forms.[145] The epibulbar conjunctiva may be ballooned by the subconjunctival injection of anesthetic. This creates an absorptive barrier that will minimize the risk for damage to the globe.[145] It is currently suggested that cryotherapy is applied to the margins of exposed conjunctiva after tumor excision, but not to the scleral bed because of risks for damage to the underlying retina, uveitis, cataract formation, and ciliary body shutdown with hypotony.[275d] Heavy cryotherapy to the scleral bed after tumor excision may on rare occasions cause scleral melt.[305b] While earlier reports suggest that $-15°$ to $-20°$ C is adequate for the treatment of intraepithelial growth,[145] more recent data indicate that the application of a double freeze-thaw cycle at $-70°$ to $-80°$ C will destroy the epithelium without causing serious side effects.[13] Cryotherapy enables the potential destruction of clinically invisible PAM, i.e., PAM *sine pigmento*, which may be present beyond the surgical margin.[149] This may in part explain why patients treated with tumor excision alone appear to have a higher recurrence rate than those treated initially with excision and supplemental cryotherapy.[67] Adjunctive cryotherapy is possibly of less

value when margins are monitored by microscopically controlled surgery.

E. ADDITIONAL TECHNIQUES

Other modalities may be useful in the management of conjunctival melanoma; xenon arc photocoagulation was once used for this purpose.[141] Few patients receiving xenon arc photocoagulation for conjunctival melanoma are still reported,[320] but the overall results have been discouraging.[328] The carbon dioxide laser may be useful to treat thin proliferative lesions of the conjunctival epithelium.[55] Although most clinical data using carbon dioxide laser are confined to lesions like small papillomas,[36,153] some recent reports suggest that more extensive lesions may also be managed successfully.[208] Topical application of compounds such as mercury chloride and sodium hypochlorite after surgery was originally proposed to alleviate recurrences of conjunctival melanoma[310] but is now rarely used in clinical practice. Topical chemotherapy using mitomycin C has recently been introduced in the treatment of conjunctival melanocytic lesions,[83] and limited data suggest that this drug may be beneficial in treating conjunctival melanoma[61] and corneal intraepithelial neoplasia.[97,170]

From an experimental perspective, the Calmette-Guerin bacillus has been used to treat conjunctival melanoma in the golden Syrian hamster, but these studies have not had any clinical implications.[254] Similarly, the Q-switched ruby laser was recently used experimentally to destroy melanocytes of the canine conjunctiva.[95] Plasminogen activator activity is raised in human tears of patients with conjunctival melanoma, but levels are also elevated in patients with a wide range of inflammatory and traumatic conditions of the conjunctiva and cornea, and the possible therapeutic significance remains unclear.[33]

F. SIDE EFFECTS OF TREATMENT

Each of the treatment modalities indicated above may have serious side effects with potentially devastating visual consequences. Extensive debulking surgery may lead to the formation of symblepharon and decreased ocular motility.[230] Orbital exenteration will not only cause a total loss of vision, but it is also disfiguring and may induce emotional stress[136] or even lead to suicide.[281] Cryotherapy can generate symblepharon and motility disturbances, and it may cause loss of cilia and a dry eye.[40,149] Brachytherapy may cause conjunctival teleangiectasia, corneal ulceration, and lens opacities.[188] The topical application of mitomycin C appears to be well tolerated, but possible adverse effects may be recognized later. Charged particle irradiation using helium ions and proton beam radiotherapy for uveal melanoma may cause anterior segment complications such as dry eye, eye lash loss, and neovascular glaucoma in some 20–30% of patients.[48,110,112] However, data on side effects related to proton beam treatment for conjunctival melanoma are minimal, but some of the complications associated with proton beam therapy for uveal melanoma can arise with the addition of corneal melting.[39]

G. MONITORING THE PATIENT AFTER PRIMARY TREATMENT

There are two main reasons for monitoring patients after primary treatment of conjunctival melanoma. Local recurrences are very common and occur in more than half of patients, usually within the first 5 years after primary treatment, but occasionally much later.[45,67] Following-up these patients is also justified because one third of them ultimately develop metastatic spread to the regional lymph nodes.[272] During follow-up it is important to recognize any suspected growth in the ipsilateral preauricular, submandibular, or cervical lymph nodes, as regional lymph node dissection may successfully arrest regional disease.[91,149] In contrast, there is no effective method of treatment beyond palliation once systemic spread has developed.[148]

Ophthalmologic assessments should include slit-lamp examination of all parts of the conjunctiva. A recurrent melanoma nodule may be restricted to the superior fornix, a site that requires the use of a lid retractor for assessment and may easily be overlooked by the examining clinician.[146] Local recurrences are most likely to present in any remaining PAM but may also occur in nonpigmented conjunctiva some distance from the site of the initial tumor. Rarely, obstruction of the nasolacrimal duct is caused by a local tumor recurrence. When a new tumor arises from conjunctiva that otherwise appears normal by clinical examination. PAM *sine pigmento* may be present or an in-transit metastasis may have developed. Conjunctival scarring or remaining PAM could delay the detection of a local recurrence, and serial photographs may be valuable in monitoring subtle changes. Primary acquired melanosis too extensive for complete surgical excision may be monitored using multiple small incisional biopsies to detect advanced atypia or early microinvasion.[90] Incisional biopsies provide information on the proliferative state, which may predict which lesions will develop into melanomas.[266] To avoid biopsies, PAM may be monitored for cytologic atypia using smears from the conjunctiva for exfoliative cytology[100,189,255] or impression cytology.[74,224] Furthermore, tear film may be sampled and evaluated for exfoliated melanoma cells, as shedding of atypical melanoma cells to the tear film has been demonstrated in conjuncti-

val melanoma.[317] However, cytologic samples may be misleading because melanocytes lodged in the deeper part of the epithelium will not be included and false-negative cytology reports may initiate inadequate management of PAM with atypia. Therefore, it is currently advised that surface cytology should be used judiciously and not replace biopsy for suspected neoplastic conditions.[84,120]

H. RECURRENT DISEASE

Recent data from a case series comprising 68 individuals with malignant melanoma of the conjunctiva showed that 56% of patients develop one or more recurrences and that 32% eventually experience multiple recurrences.[67] Similarly, population-based data suggest that recurrences take place in 56–62% of patients.[68,270] The mean interval between the first treatment and the first recurrence ranges from 0.4 to 14 years, with a mean time interval of 2.5 years.[67] Whereas some data suggest that recurrent disease is associated with the development of metastases,[67] other reports are conflicting.[272] Patients receiving cryotherapy after surgery seem to have fewer recurrences than those treated by surgery alone.[67] Moreover, patients with multifocal conjunctival disease are more likely to have recurrences than patients with unifocal nodules,[149] and orbital exenteration is more often performed because of recurrent disease than as a primary procedure.[230] Some data suggest that recurrent disease is more common in conjunctival melanoma associated with PAM, but also that tumors that histologically appear incompletely excised may not necessarily recur.[68] A number of adjuvant treatments have been suggested to reduce the risk of local tumor recurrence. However, no single modality has proven to substantially reduce the risk of local recurrence.[226,230] In extreme cases exenteration may even be followed by a relapse more than 20 years later.[227]

In conclusion, when local recurrence is confirmed this is usually managed in a way similar to the initial tumor. Possibly, recurrent disease may be managed by adjunctive brachytherapy after tumor excision.[101] Orbital exenteration should be considered when local excision is no longer feasible for technical reasons.[230,272]

I. MANAGEMENT OF SYSTEMIC DISEASE

Metastatic disease confined to the regional lymph nodes may in some cases by successfully managed by lymph node dissection.[148] However, in many cases subclinical distant metastases are present and overt dissemination will eventually develop. Most patients with widely disseminated conjunctival melanoma receive systemic chemotherapy possibly combined with interferon. The actual regimen will often be based on what is currently used for patients with metastatic skin melanoma at any particular center. However, prognosis is poor, with a life expectancy in the range of a few months and rarely more than a year after clinical detection of disseminated disease.[148]

VIII. Survival After Conjunctival Melanoma

A. CASE SERIES

Probably the most extreme standpoint was taken by Reese when he claimed that conjunctival melanoma was the most malignant tumor encountered in ophthalmology.[244] While survival data from some more recent case series show a considerable variation, most are in conflict with his view (Table 4). Few of these series are comparable, as crude survival and melanoma-related survival are used interchangeably, and data are based on different, potentially skewed sets of referred patients or specimens. Also, cumulative survival proportions are used only in a fraction of reports and loss to follow-up is sometimes not accounted for.

B. POPULATION-BASED DATA

Only population-based data on incident cases may provide a nonbiased approximation of patient survival. Loss to follow-up should be eliminated, or at least minimized, as no method can adjust for the bias of failure to obtain complete follow-up.[132] In Sweden, all causes of death are filed with the National Causes of Death Registry, which is linked to the National Cancer Registry. The joint efforts of these registries provide reliable survival data without loss to follow-up for all subjects with cancer.[199] Data from the national survey in Sweden estimate a 5-year cumulative, tumor-related mortality rate of 19% and a 10-year mortality rate of 30% after conjunctival melanoma.[272] Similarly obtained Danish data estimate the mortality in metastatic conjunctival melanoma to be 16% at 5 years and 29% at 10 years after diagnosis.[219b]

The first population-based study of conjunctival melanoma included data from two previous case series[69,215] and cases provided by questionnaires distributed to the Dutch ophthalmologic community.[68] Based on the population of the Netherlands during a 17-year period, this survey claimed a tumor-related mortality rate of 37% for 59 patients followed-up for 5 years or longer after diagnosis.[68]

C. CUMULATIVE SURVIVAL RATES

In survival studies, the life table method should be used, as it permits the use of all follow-up information for all patients[73] and provides estimates of the cumulative probability that an event (such as death of tumor-related disease) will occur.[276] However, life table analy-

TABLE 4

Summary of Prognostic Studies 1950 Through 1996 Comprising Patients With Conjunctival Melanoma

Author(s)	Year	Reference #	Study Design	Patients	Mortality (%)	Comments
Ash	1950	14	Case series	60	9	Survival data on 45 patients. Survival time unknown.
Jay	1965	151	Case series	104	16	Lesions include PAM. Five-year rate for 77 patients.
Bernardino et al	1976	31	Case series	23	30	Crude survival data. Survival time unknown.
Silvers et al	1978	278	Case series	28	43	Follow-up 3 to 37 years. No 5-year rate available.
Crawford	1980	59	Case series	19	28	Five-year rate = 16%.
Liesegang and Campbell	1980	182	Case series	42	14	Five-year rate = 10%. Loss to follow-up unknown.
Haye et al	1982	127	Case series	38	52	Five-year rate = 27%. Another 16 had skin melanoma.
Hugonnier et al	1982	137	Case series	26	61	Crude 5-year rate.
McGhee et al	1982	203	Case series	55	30	Five-year rate = 21%. Follow-up data on 38 patients.
Lederman et al	1984	178	Case series	63	51	No 5-year rate. Crude survival only. Primary acquired malanosis excluded.
Folberg et al	1985	92	Case series	131	24	Cumulative 10-year rate. Five-year rate = 18%. Crude survival.
Benderitter et al	1985	30	Case series	18	44	No 5-year rate available.
Guillén et al	1985	123	Case series	23		No survival data available.
Jeffrey et al	1986	154	Case series	37	27	No survival time or loss to follow-up available.
Stefani	1986	282	Case series	44	9	No survival time or loss to follow-up available.
Jakobiec et al	1988	149	Case series	52	15	No 5-year rate available.
Fuchs et al	1989	98	Case series	26	27	Five-year rate = 19%. Possibly no loss to follow-up.
de Wolff-Rouendaal	1990	68	Population based	59	37	Five-year rate. Primary acquired melanosis excluded. Possibly minimal loss to follow-up.
Zografos et al	1990	329	Case series	37	20	Five-year rate. Loss to follow-up unknown.
Lommatzsch et al	1990	188	Case series	81	24	Five-year cumulative rate. Ten-year rate = 40%. Follow-up unclear.
Seregard and Kock	1992	272	Population based	45	22	Five-year and 10-year rates = 18% and 30%. No loss to follow-up.
Paridaens et al	1994	231	Case series	256	31	Ten-year rate. Five-year rate = 17%. Follow-up unclear. Includes all patients from reference #151.
Norregaard et al	1996	219b	Case series	55	27	Ten-year rate. Five-year rate = 14%. Includes most of the Danish population. Probably minimal loss to follow-up.

PAM = primary acquired melanosis.

ses have been adapted only for a few case series[92,188,231] and for two population-based surveys.[219b,272] Whereas studies not founded on population-based[92,272] data are exposed to referral bias, survival data from available case series are remarkably consistent with results from the national surveys. Thus, the 5-year tumor-related mortality rate in case series with conjunctival melanoma is 12–19%, whereas the 10-year mortality rate is 23–30%.[92,188,231,272]

IX. Prognostic Factors

A. TUMOR DEPTH AND SIZE

The prognosis for cutaneous melanomas is intimately associated with tumor thickness[37] and grade

of dermal invasion.[52] However, the grade of stromal invasion is difficult to assess in the conjunctiva as the substantia propria is not stratified into layers analogous to the papillary stroma and reticular dermis of the skin,[31,89] but depth of invasion from the surface of the epithelium may easily be measured using a calibrated ocular micrometer.[86] Silvers and associates recognized that patients with conjunctival melanoma with a depth or thickness no greater than 1.5 mm did well regardless of therapy,[278] and other studies have confirmed the prognostic value of tumor depth.[92,98,272,329] In 1980 it was claimed that tumor thickness was the "sole sovereign prognosticator in conjunctival melanoma."[143] Most authors agree on the prognostic value of tumor depth, but there has been some controversy regarding the critical thickness. Some maintain that 1.5 mm is critical,[154] whereas others claim that prognosis is worse in tumors thicker than 0.8 mm,[92,98,283] 1.0 mm,[231] or 2.0 mm.[188,272] Moreover, some include the tumor depth of the primary lesion or any subsequent recurrence,[93] whereas others include only the primary lesion.[231,272] In conclusion, there appears to be a continuous worsening in prognosis with increasing tumor thickness, but no clear threshold to determine prognosis. Size also has prognostic implications, and patients with tumors larger than 10 mm appear to do worse.[272] Similarly, Lommatzsch and colleagues used the TNM classification and showed that large (pT3) tumors had a worse prognosis than small tumors (pT1).[188]

B. TUMOR LOCATION

Involvement of the palpebral or caruncular conjunctiva has been regarded by many as heralding a poor prognosis.[59,98,151,154,231,278,282] Caruncular melanomas seem to have a particularly ominous prognosis, irrespective of treatment modality.[230] Recently, Paridaens and associates used a large data set for multivariate analysis and concluded that tumors in presumed unfavorable locations, i.e., those involving the palpebral conjunctiva, fornices, plica, caruncle, and lid margins were associated with 2.2 times greater mortality than melanomas confined to the bulbar conjunctiva.[231] Furthermore, tumor thickness only carried prognostic significance in melanomas in "unfavorable" locations. In contrast, multifocality only had a poor prognostic value in melanomas in "favorable" sites.[231]

C. HISTOPATHOLOGIC FEATURES

Folberg and associates reported that the outcome in patients with conjunctival melanoma was similar regardless of the presence of PAM.[92] The presence of pagetoid spread predicted adverse prognosis,[92] patients with mixed cell tumors had about three times greater mortality than patients with spindle cell melanomas, and histologic evidence of lymphatic invasion carried a fourfold increase in the death rate.[92] Clinical origin of tumor (PAM, preexisting nevi, or *de novo*) were not useful prognostic indicators.[92]

D. TUMOR CELL PROLIFERATION

A high capacity for growth is reflected in the relative or total number of tumor cells that feature mitotic figures and in conjunctival melanoma; a high mitotic rate is associated with an adverse prognosis.[30,59,92,272,283] It has been suggested that the mitotic rate and tumor depth should be combined for a prognostic index.[283] However, only a small proportion of cycling cells are in mitosis, but most cells in late G1 and S phases show immunoreactivity for the proliferating cell nuclear antigen. This nuclear protein may be used to enhance the sensitivity in detecting cycling cells and the total number of tumor cells per square millimeter featuring immunoreactivity is strongly associated with a poor prognosis, even after adjusting for possible confounding factors.[265] The proliferating cell nuclear antigen may also be used for grading of conjunctival melanocytic lesions.[43,64] and will predict which lesions featuring PAM with atypia may progress to melanoma.[266]

E. NUCLEOLAR ORGANIZER REGIONS

In eukaryotic genomes, hundreds or thousands of ribosomal RNA repeats are clustered at sites on several chromosomes. A cluster of genes encoding the large pre-rRNA (a site known as nucleolar organizer region) may be recognized by a simple silver-staining method.[109,236] There is evidence that the antigen nucleolar organizer region counts increase with tumor progression in conjunctival melanocytic lesions.[256] However, antigen nucleolar organizer region counts do not correlate with prognosis.[232]

F. OTHER POTENTIAL MARKERS

The S-100 protein has been detected in some normal and neoplastic tissues, and while the specificity is rather low, it remains a valuable marker for melanocytic tumors and has been recognized in conjunctival melanoma.[163] Whereas the HMB-45 antibody appears to be less sensitive but more specific for melanomas, HMB-45 may not be used to differentiate conjunctival nevi from melanoma.[106] Neither S-100 protein nor HMB-45 appear to convey prognostic information in conjunctival melanoma.[98,106,133,202,285,286] Data also suggest that neuron-specific enolase lacks prognostic value in conjunctival melanoma[98] and that immunohistochemical detection of p53 protein is unlikely to prove useful as a prognostic indicator.[266] Whereas a single report based on a single conjuncti-

val melanoma suggests that these tumors express the adrenocorticotropic hormone and vasoactive intestinal polypeptide, the implications are unclear.[70] Some experiments on the cell-mediated immunity of conjunctival melanoma have been undertaken, but these tests have failed to separate patients with an adverse prognosis from patients that survive.[54]

X. Summary

Malignant melanoma of the conjunctiva is an extremely uncommon tumor affecting middle-aged and elderly whites. Despite recent advances, this neoplasm remains one of the most unpredictable and enigmatic entities of ophthalmology. Whereas exposure to UVR has been put forward as a potential causative agent, the etiology of conjunctival melanoma is largely unknown. Most conjunctival melanomas arise from PAM with atypia, but occasionally malignant transformation may take place in a conjunctival nevus and in some cases tumors arise *de novo*. Many tumors feature a pigmented, nodular growth at the limbus with or without associated flat melanosis, but melanoma may present anywhere in the conjunctiva. Whereas surgical excision, possibly combined with cryotherapy, constitutes the preferred management for most cases, some authors advocate brachytherapy and proton beam radiotherapy for selected cases. Local recurrences are common, but follow-up should include not only evaluation of the entire conjunctiva, but also palpation of the ipsilateral, regional lymph nodes where metastatic disease is likely to present initially. The tumor-related mortality after conjunctival melanoma is in the order of 23–30%. Poor prognosis is associated with thick tumors and tumors arising from the palpebral or caruncular conjunctiva. Melanomas with a high proliferative capacity, histopathologic evidence of lymphatic invasion, and tumors with mixed cells have an adverse prognosis. Present research includes the investigation of topical mitomycin C treatment and comparison of adjunctive cryotherapy with brachytherapy after surgical excision of conjunctival melanoma. To date, there are no cytogenetic abnormalities implicated in the tumorigenesis of conjunctival melanoma, but future research may reveal chromosomal aberrations of prognostic and potential therapeutic importance.

While many patients with conjunctival melanoma are currently being managed by designated ocular oncology units, referral to a specialized center more often takes place after recurrent disease has supervened. Even if surgical excision of an epibulbar melanoma is a comparatively straightforward procedure in technical terms, adequate management also comprises adequate tissue preparation and appropriate follow-up. Until experience with conjunctival melanoma is centralized, the true character of this entity is unlikely to unfold.

While not identical, conjunctival melanoma possibly shares some etiologic features with skin melanoma. In fact, the differences between conjunctival and skin melanoma are probably less pronounced than those between conjunctival and uveal melanoma. It would therefore seem appropriate to look for cytogenetic abnormalities similar to those that are currently being unraveled in skin melanoma. In the event that one or more such chromosomal aberrations may be implicated in the tumorigenesis of skin melanoma, it is possible that they may also induce malignant transformation in the conjunctiva. Moreover, if any chromosomal pattern could be linked with events such as local recurrence, multifocal involvement, and early metastatic spread, such tumors could be managed differently from tumors predicted to have an indolent course. Simple excision would probably suffice for the latter tumors, whereas adjunctive treatment would need to be considered at an early stage for melanomas likely to develop a more aggressive behavior.

Determining the preferred management of conjunctival melanoma will probably prove difficult. Whereas some information on the effectiveness of any given treatment may be elucidated from a case series of selected patients, this kind of data provide virtually no means to assess the difference between two treatment regimens. That requires a prospective, randomized trial, but the feasibility of such trials are clearly hampered by the low incidence rate of conjunctival melanoma requiring multicenter cooperation. Indeed, in Europe consideration is currently being given to multinational clinical trials in which the relative effectiveness of various treatments for conjunctival melanoma or PAM will be assessed.

With the previously claimed anecdotal nature of conjunctival melanoma in mind, it has to be recognized that significant progress already has been made. We no longer have to base our therapeutic decisions or prognostic assessments on single case reports or small and highly biased case series. Whereas the final part of this century has been devoted to detailed histopathologic studies and improved clinical data reporting, it is likely that the beginning of the next will conceive better methods to differentially manage conjunctival melanoma and potential precursor lesions. Such techniques may include studies to predict metastatic potential, tumor vaccines, and refined chemotherapy for widespread disease.

Methods of Literature Search

The literature review was based on comprehensive Medline and Embase searches generating references

on conjunctival melanoma published from 1967 through mid-1996. This was followed by checking the references and the references of the references. A previous survey indicated that this approach would retrieve at least 75% of relevant articles.[166]

References

1. Abramson DH, Rodriguez-Sains RS, Rubman R: Cutaneous and ocular malignant melanoma. Arch Ophthalmol 98: 1397–1399, 1980
2. Ackerman AB: Response to Dr. Folberg et al (letter). Mod Pathol 5:6–8, 1992
3. Ackerman AB: What nevus is dysplastic, a syndrome and the commonest precursor of malignant melanoma? A riddle and an answer. Histopathology 13:241–256, 1988
4. Ackerman AB: Primary acquired melanosis (letter). Hum Pathol 16:1077–1078, 1985
5. Ackerman AB, Sood R, Koenig M: Primary acquired melanosis of the conjunctiva is melanoma *in situ*. Mod Pathol 4:253–263, 1991
6. Albert DM, Chang MA, Lamping K, et al: The dysplastic nevus syndrome. A pedigree with primary malignant melanomas of the choroid and skin. Ophthalmology 92:1728–1734, 1985
7. Albert DM, Searl SS, Forget B, et al: Uveal findings in patients with cutaneous melanoma. Am J Ophthalmol 95:474–479, 1983
8. Allen AC: A reorientation on the histogenesis and clinical significance of cutaneous nevi and melanomas. Cancer 2:28–56, 1949
9. Allen AC, Spitz S: Malignant melanomas. A clinicopathological analysis of the criteria for diagnosis and prognosis. Cancer 6:1–45, 1953
10. Aoyagi M, Morishima N, Yoshino Y, et al: Conjunctival malignant melanoma with xeroderma pigmentosum. Ophthalmologica 206:162–167, 1993
11. Arif NN, Henkind P: Conjunctival melanomas. J Dermatol Surg Oncol 5:369, 1979
12. Armitage P, Berry G: Statistical methods in medical research. London, Blackwell, 1987
13. Arocker-Mettinger E, Haddad R: Zur Behandlung der primär erworbenen Melanose der Bindehaut. Klin Monatsbl Augenheilkd 187:353–355, 1985
14. Ash JE: Epibulbar tumors. Am J Ophthalmol 33:1203–1219, 1950
15. Ashton N: Malignant tumors of the eye and adnexa, in Raven RW (ed): Cancer, Vol II. London, Butterworth, 1957, pp 599–616
16. Aubert C, Rouge F, Reillaudou M, Metge P: Establishment and characterization of human ocular melanoma cell lines. Int J Cancer 54:784–792, 1993
17. Augsburger JJ, Shields JA, Mastrangelo MJ, Frank PE: Diffuse primary malignant melanoma after primary cutaneous melanoma. Arch Ophthalmol 98:1261–1264, 1980
18. Augustsson A, Stierner U, Suurküla M, Rosdahl I: Prevalence of common and dysplastic nevi in a Swedish population. Br J Dermatol 124:152–156, 1991
19. Baker SJ, Markowitz S, Fearon ER, et al: Suppression of human colorectal carcinoma cell growth by wild-type p53. Science 249:912–915, 1990
20. Balestrazzi E: Malignant melanoma of palpebral conjunctiva. Ophthalmologica 162:183–187, 1971
21. Ball JM, Lamb DH: Epibulbar melanotic sarcoma. Arch Ophthalmol 52:80–83, 1923
22. Barnhill RJ, Roush GC: Correlation of clinical with histological features in atypical melanocytic nevi. Cancer 67:3157–3164, 1991
23. Barthélémy F, Sargoussi JJ, Guimaraes MR: Que peut-on attendre des critères histologiques actuels de Clark et McGovern concernant le mélanome malin de la conjunctive. Bull Mem Soc Fr Ophthalmol 93:179–182, 1981

23b. Bataille V, Bishop JA, Sasieni P, et al: Risk of cutaneous melanoma in relation to the numbers, types and sites of nevi: a case-control study. Br J Cancer 73:1605–1611, 1996

24. Bataille V, Boyle J, Hungerford JL, Newton JA: Three cases of primary acquired melanosis of the conjunctiva as a manifestation of the atypical mole syndrome. Br J Dermatol 128:86–90, 1993
25. Bataille V, Pinney E, Hungerford JL, et al: Five cases of coexistent primary ocular and cutaneous melanoma. Arch Dermatol 129:198–201, 1993
26. Bataille V, Sasieni P, Cuzick J, et al: Risk of ocular melanoma in relation to cutaneous and iris nevi. Int J Cancer 60:622–626, 1995
27. Baumgarten: Title unknown. Arch Heilk 16:270, 1852. Cited by Duke-Elder S, Leigh AG: Diseases of the outer eye: pigmented tumors, in Duke-Elder S (ed): System of Ophthalmology, Vol 8, London, Henry Kimpton, 1965, p 1220
28. Becker SW, Fitzpatrick TB, Montgomery H: Human melanogenesis: cytology and histology of pigment cells (melanodendrocytes). Arch Derm Syphilol 65:511–523, 1952
29. Belkin PV: Malignant melanoma of the bulbar conjuctiva in a dog. Vet Med Small Anim Clin 70:957–958, 1975
30. Benderitter T, Berard M, Bonerandi JJ, Lebreuil G: Les proliferations melaniques de la conjonctive. Etude histopathologique a propos d'une serie de 40 cas. J Fr Ophthalmol 8:411–422, 1985
31. Bernardino VB, Naidoff MA, Clark WH: Malignant melanomas of the conjunctiva. Am J Ophthalmol 82:383–394, 1976
32. Bergstrand CH: Chirurgiska iakttagelser. Tumörer av ovanlig beskaffenhet förekommande på ögonklotet. Operation (thesis). Uppsala, Leffler & Sebell, 1843, pp 30–43 (Swedish)
33. Berta A, Tozser J, Holly FJ: Determination of plasminogen activator activities in normal and pathological human traumatic lesions of the cornea and the conjunctiva. Acta Ophthalmol 68:508–514, 1990
34. Birns JW, Jenkins HA: Melanoma of the conjunctiva. A rational approach to management. Head Neck Surg 2:99–106, 1979
35. Boente R: Metastatische melanoblastome. Klin Monatsbl Augenheilkd 82:732–740, 1929
36. Bosniak SL, Novick NL, Sachs ME: Treatment of recurrent squamous papillomata of the conjunctiva by carbon dioxide laser vaporization. Ophthalmology 93:1078–1082, 1986
37. Breslow A: Thickness, cross-sectional areas and depth of invasion in the prognosis of cutaneous melanoma. Ann Surg 172:902–908, 1970
38. Brovkina AF, Zarubei GD: Opyt lecheniia opukholei organa zreniia uzkim meditsinskim protonnym puchkom. Med Radiol (Mosk) 32:61–66, 1987
39. Brovkina AF, Zarubei GD, Khoroshkov VS: Results of proton beam irradiation therapy of conjunctival malignant tumors (abstract), in Frezzoti R, Balestrazzi E, Falco L, Esente S (eds): Proceedings of International Symposium on Intraocular and Epibulbar Tumors, Florence, Italy, 3–5 March, 1994. Bologna, Monduzzi Editore, 1994, pp 175–176
40. Brownstein S, Henry M, Bernardo AI: Malignant melanoma of the conjunctiva after 11 years. Can J Ophthalmol 14:142–146, 1979
41. Brownstein S, Jakobiec FA, Wilkinson RD, et al: Cryotherapy for precancerous melanosis (atypical melanocytic hyperplasia) of the conjunctiva. Arch Ophthalmol 99:1224–1232, 1981
42. Buckman G, Jakobiec FA, Folberg R, McNally LM: Melanocytic nevi of the palpebral conjunctiva. An extremely rare location usually signifying melanoma. Ophthalmology 95:1053–1057, 1988
43. Buhrmann R, Davidsson JK, Cabrera A, et al: Expressivity of proliferating cell nuclear antigen on conjunctival melanocytic lesions (abstract). Invest Ophthalmol Vis Sci 35 (Suppl):1926, 1994

43b. Buus DR, Tse DT, Folberg R: Microscopically controlled excision of conjunctival squamous cell carcinoma. Am J Ophthalmol 117:97–102, 1994

44. Carswell R: Pathological anatomy, illustrations of the ele-

mentary forms of disease. Melanoma. London, Longman, Orme, Brown, Green & Longman, 1838
45. Cassady JV: Malignant melanoma of the corneal limbus. Trans Am Ophthalmol Soc 66:379–393, 1968
46. Char DH: Clinical ocular oncology. New York, Churchill Livingstone, 1989
47. Char DH: The management of lid and conjunctival malignancies. Surv Ophthalmol 24:679–689, 1980
48. Char DH, Quivey JM, Castro JR, et al: Helium ions versus iodine 125 brachytherapy in the management of uveal melanoma: A prospective, randomized, dynamically balanced trial. Ophthalmology 100:1547–1554, 1993
49. Charles NC, Stenson S, Taterka HB: Epibulbar malignant melanoma in a black patient. Arch Ophthalmol 97:316–318, 1979
50. Chauvel P, Caujolle JP, Sauerwein W, et al: Proton therapy as a possible salvage treatment for conjunctival melanomas (abstract), in Frezzoti R, Balestrazzi E, Falco L, Esente S (eds): Proceedings of International Symposium on Intraocular and Epibulbar Tumors, Florence, Italy, 3–5 March, 1994. Bologna, Monduzzi Editore, 1994, pp 177–181
51. Clark WH Jr: A classification of malignant melanoma in man correlated with histogenesis and biologic behaviour, in Montagna W, Hu F (eds): Advances in Biology of the Skin. The Pigmentary System. London, Pergamon Press, 1967, pp 621–647
52. Clark WH Jr, From L, Bernardino EA, Mihm MC: The histogenesis and biologic behaviour of primary human malignant melanomas of the skin. Cancer Res 29:705–726, 1969
53. Clark WH Jr, Reimer RR, Greene M, et al: Origin of familial malignant melanomas from heritable melanocytic lesions. "The B-K mole syndrome." Arch Dermatol 114:732–738, 1978
54. Cochran AJ, Foulds WS, Damato BE, et al: Assessment of immunological techniques in the diagnosis and prognosis of ocular malignant melanoma. Br J Ophthalmol 69:171–176, 1985
55. Codere F, Brownstein S, Garwood JL, Dresner SC: Carbon dioxide laser treatment of the conjunctiva and the cornea. Ophthalmology 95:37–45, 1988
56. Conlon MR, Alfonso EC, Albert DM: Tumors of the cornea and conjunctiva, in Albert DM, Jakobiec FA (eds): Principles and Practice of Ophthalmology, Vol 1. Philadelphia, WB Saunders, 1994, pp 276–294
57. Cook CS, Rosenkrantz W, Pfeiffer RL, MacMillan A: Malignant melanoma of the conjunctiva in a cat. J Am Vet Med Assoc 186:505–506, 1985
58. Cotchin E: Melanotic tumors of dogs. J Comp Path 65:15–129, 1955
59. Crawford JB: Conjunctival melanomas: Prognostic factors. A review and an analysis of a series. Trans Am Ophthalmol Soc 78:467–502, 1980
60. Croxatto JO, Iribarren G, Ugrin C, et al: Malignant melanoma of the conjunctiva. Report of a case. Ophthalmology 94:1281–1285, 1987
61. Czechonska G, Finger PT: Topical mitomycin-C chemotherapy for conjunctival melanoma (abstract). Invest Ophthalmol Vis Sci 37 (Suppl):S242, 1996
62. Dahlenfors R, Törnqvist G, Wettrell K, Mark J: Cytogenetic observations in nine ocular malignant melanomas. Anticancer Res 13:1415–1420, 1993
63. Dalrymple J: Pathology of the human eye. London, Churchill, 1852
64. Davidson JK, McLean IW, George DP, et al: Proliferating cell nuclear antigen as an immunohistochemical marker for atypia in primary acquired melanosis of the conjunctiva (abstract). Invest Ophthalmol Vis Sci 34 (Suppl):966, 1993
65. Daxecker F, Philipp W, Mikuz G, Lisch K: Late manifestations of conjunctival malignant melanoma. Ophthalmologica 197:176–178, 1988
66. De Potter P, Shields CL, Shields JA: Malignant melanoma of the conjunctiva. Int Ophthalmol Clin 33:25–30, 1993
67. De Potter P, Shields CL, Shields JA, Menduke H: Clinical predictive factors for development and recurrence of metastasis in conjunctival melanoma: a review of 68 cases. Br J Ophthalmol 77:624–630, 1993
68. de Wolff-Rouendaal D: Conjunctival melanoma in the Netherlands: a clinico-pathological and follow-up study (thesis). Katwijk, All in BV, 1990
69. de Wolff-Rouendaal D, Oosterhuis JA: Conjunctival melanoma in the Netherlands: a follow-up study. Doc Ophthalmol 56:49–54, 1983
70. Di Tondo U, Balestrazzi E, Santeusanio G, et al: Steroids and neuroendocrine hormones detected by the immunoperoxidase technique from malignant melanomas and nevi of the choroid and conjunctiva. Ophthalmologica 192:34–38, 1986
71. Dubreuilh MW: De la mélanose circonscrite précancéreuse. Ann Dermatol et Syphiligr (Paris) 3:129–154, 1912
72. Duke-Elder S, Leigh AG: Diseases of the outer eye: pigmented tumors, in Duke-Elder S (ed): System of Ophthalmology, Vol 8. London, Henry Kimpton, 1965, pp 2110–1239
73. Ederer F: Refereeing clinical research papers for statistical content (editorial). Am J Ophthalmol 100:735–737, 1985
74. Egbert PR, Lauber S, Maurice DM: A simple conjunctival biopsy. Am J Ophthalmol 84:798–801, 1977
75. El-Bolkainy MN, Ebeid AM: Malignant melanoma in Egypt. Tumori 59:429–435, 1973
76. Elder DE, Goldman LI, Goldman SC, et al: Dysplastic nevus syndrome: A phenotypic association of sporadic cutaneous melanoma. Cancer 46:1787–1794, 1980
77. Elder DE, Greene MH, Guerry DI, et al: The dysplastic nevus syndrome. Our definition. Am J Dermatopathol 4:455–460, 1982
78. Elder DE, Murphy GF: Atlas of tumor pathology. Melanocytic tumors of the skin. Fascicle 2. Washington DC, Armed Forces Institute of Pathology, 1991
79. Elsas FJ, Green WR, Ryan SJ: Benign pigmented tumors, arising in acquired conjunctival melanosis. Am J Ophthalmol 78:229–232, 1974
80. Eng AM, Rosner M: Conjunctival melanomas. Int J Dermatol 34:349–353, 1995
81. Fano G: Mélanose et tumeur mélanique de la conjonctive. Gaz d hop 45:651, 1872
82. Fearon ER, Vogelstein B: A genetic model for colorectal carcinogenesis. Cell 61:759–767, 1990
83. Finger PT, Milner MS, McCormick SA: Topical chemotherapy for conjunctival melanoma. Br J Ophthalmol 77:751–753, 1993
84. Folberg R: Melanocytic lesions of the conjunctiva, in Spencer WH (ed): Ophthalmic Pathology. An Atlas and Textbook, Vol 1. Philadelphia, WB Saunders, 1996, 4 ed, pp 125–155
85. Folberg R: Tumor progression in ocular melanoma. J Invest Dermatol 100:326S–331S, 1993
86. Folberg R: The familial occurrence of cutaneous melanoma, intraocular melanoma and the dysplastic nevus syndrome (letter). Am J Ophthalmol 96:815–816, 1983
87. Folberg R, Baron J, Reeves RD, et al: Animal model of conjunctival primary acquired melanosis. Ophthalmology 96:1006–1013, 1989
88. Folberg R, Jakobiec FA, Bernardino VB, Iwamoto T: Benign conjunctival melanocytic lesions. Clinicopathologic features. Ophthalmology 96:436–461, 1989
89. Folberg R, Jakobiec FA, McLean IW, Zimmerman LE: Is primary acquired melanosis of the conjunctiva equivalent to melanoma *in situ*? Mod Pathol 5:2–5, 1992
90. Folberg R, McLean IW: Primary acquired melanosis and melanoma of the conjunctiva: terminology, classification, and biologic behavior. Hum Pathol 17:652–654, 1986
91. Folberg R, McLean IW, Zimmerman LE: Primary acquired melanosis of the conjunctiva. Hum Pathol 16:129–135, 1985
92. Folberg R, McLean IW, Zimmerman LE: Malignant melanoma of the conjunctiva. Hum Pathol 16:136–143, 1985
93. Folberg R, McLean IW, Zimmerman LE: Conjunctival melanosis and melanoma. Ophthalmology 91:673–678, 1984
94. Foss AJE, Alexander RA, Guille MJ, et al: Estrogen and

progesterone receptor analysis in ocular melanoma. Ophthalmology 102:431–436, 1995
95. Fox DM, Soll D, Fern C: Q-switched ruby laser irradiation of melanotic conjunctiva (abstract). Invest Ophthalmol Vis Sci 34 (Suppl):958, 1993
96. Friedman RJ, Rodriguez-Sains R, Jakobiec F: Ophthalmologic oncology: conjunctival malignant melanoma in association with sporadic dysplastic nevus syndrome. J Dermatol Surg Oncol 13:31–34, 1987
97. Frucht-Pery J, Rozenman Y: Mitomycin C therapy for corneal intraepithelial neoplasia. Am J Ophthalmol 117:164–168, 1994
98. Fuchs U, Kivelä T, Liesto K, Tarkkanen A: Prognosis of conjunctival melanomas in relation to histopathological features. Br J Cancer 59:261–267, 1989
99. Fusaro RM, Lynch HT, Osterhuis JA, Went LN: The familial occurrence of cutaneous melanoma, intraocular melanoma and the dysplastic nevus syndrome (letter). Am J Ophthalmol 97:802–803, 1984
100. Gelender H, Forster RK: Papanicolaou cytology in the diagnosis and management of external ocular tumors. Arch Ophthalmol 98:909–912, 1980
101. Gelvez de Martinez RM, Menapace R, Guad HD: Behandlung rezidivierender Bindehautmelanome dursch lamellierende Resektion und Kontaktbestrahlung. Klin Monatsbl Augenheilkd 187:356–358, 1985
102. Gerner G, Norregaard JC, Jensen OA, Prause JU: Conjunctival nevi in Denmark 1960–1980. Acta Ophthalmol Scand 74:334–337, 1996
103. Ghadially FN: Ultrastructural pathology of the cell and matrix, Vol II. London, Butterworths, 1988, ed 3
104. Giblin ME, Shields JA, Shields CL, Eagle RC Jr: Primary eyelid malignant melanoma associated with primary conjunctival malignant melanoma. Aust NZ J Ophthalmol 16:127–131, 1988
105. Gilbert CM, El Baba F, Schachat AT, et al: Nonsimultaneous primary choroidal and cutaneous melanoma. Report of a case. Ophthalmology 94:1169–1172, 1987
106. Glasgow BJ, McCall LC, Foos RY: HMB-45 antibody reactivity in pigmented lesion of the conjunctiva. Am J Ophthalmol 109:696–700, 1990
107. Gloor P, Alexandrakis G: Clinical characteristics of primary acquired melanosis. Invest Ophthalmol Vis Sci 36:1721–1729, 1995
108. Gonder JR, Wagoner MD, Albert DM: Idiopathic acquired melanosis. Ophthalmology 87:835–840, 1980
109. Goodpastiure C, Bloom SE: Visualization of nucleolar organizer regions in mammalian chromosomes using silver stainings. Chromosoma 53:37–50, 1975
110. Gordon KB, Char DH, Sagerman RH: Late effects of radiation of the eye and ocular adnexa. Int J Radiat Oncol Biol Phys 31:1123–1139, 1995
111. Gow JA, Spencer WH: Intraocular extension of an epibulbar malignant melanoma. Arch Ophthalmol 90:57–59, 1973
112. Gragoudas ES, Seddon JM, Egan K, et al: Long-term results of proton beam irradiated uveal melanomas. Ophthalmology 94:349–353, 1987
113. Graham BJ, Duane TH: Ocular melanoma task force report. Am J Ophthalmol 90:728–733, 1980
114. Greene MH, Clark WH Jr, Tucker MA, et al: Acquired precursors of cutaneous malignant melanoma. The familial dysplastic nevus syndrome. N Engl J Med 312:91–97, 1985
115. Greene MH, Clark WH Jr, Tucker MA, et al: High risk of malignant melanoma in melanoma-prone families with dysplastic nevi. Ann Intern Med 102:458–465, 1985
116. Greene MH, Sanders RJ, Chu FC, et al: The familial occurrence of cutaneous melanoma, intraocular melanoma and the dysplastic nevus syndrome. Am J Ophthalmol 96:238–245, 1983
117. Greer CH: Ocular pathology. Oxford, Blackwell, 1963
118. Griffith WR, Green WR, Weinstein GW: Conjunctival malignant melanoma originating in acquired melanosis *sine pigmento*. Am J Ophthalmol 72:595–599, 1971
119. Grossniklaus HE: Ocular surface and anterior segment cytology. Ophthalmol Clin North Am 8:59–66, 1995
120. Grossniklaus HE: Correspondence re: Ackerman AB, Sood R, Koenig M: Primary acquired melanosis of the conjunctiva is melanoma *in situ*. Mod Pathol 4:253, 1991 (letter). Mod Pathol 5:473, 1992
121. Grossniklaus HE, Green WR, Luckenbach M, Chan CC: Conjunctival lesions in adults. A clinical and histopathologic review. Cornea 6:78–116, 1987
122. Grönvall H, Mark J: Malignant melanoma of the eye and its acceory organs. An analysis of a Swedish hospital material. Acta Ophthalmol 41:659–670, 1963
123. Guillén FJ, Albert DM, Mihm MC Jr: Pigmented melanocytic lesions of the conjunctiva—a new approach to their classification. Pathology 17:275–280, 1985
124. Günther I: Augenmetastasen beim malignen Melanom der Haut. Klin Monatsbl Augenheilkd 162:821–823, 1973
125. Hada Y, Onishi K, Yokoyama D, Inoue M: Two cases of conjunctival malignant melanoma. Jpn J Clin Ophthalmol 49:919–922, 1995
126. Haddad R: Multiple maligne Melanome der Bindehaut. Klin Monatsbl Augenheilkd 174:635–638, 1979
127. Haye C, Saragoussi JJ, Asselain B, et al: Le pronostic des melanomes malins de la conjonctivite et des paupieres: etude statistique sur 56 patients. J Fr Ophtalmol 5:159–166, 1982
128. Henkind P: Conjunctival melanocytic lesions: natural history, in Jakobiec FA (ed): Ocular and Adnexal Tumors. Birmingham, Aesculapius, 1978, pp 572–582
129. Henkind P, Benjamin JV: Conjunctival melanocytic lesions. Natural history. Trans Ophthalmol Soc UK 97:373–377, 1977
130. Henkind P, Friedman AH: External ocular pigmentation. Int Ophthalmol Clin 11:87–111, 1971
131. Heydenreich A: Pigmentgeschwülste der Bindehaut. Nebst kritischer Bemerkungen zur Röntgenbestralung. Acta Ophthalmol 48:369–382, 1970
132. Hillis A: Improving reporting of follow-up data. Am J Ophthalmol 93:250–252, 1982
133. Holbach L, Hofmann C: S-100 Protein in nicht-pigmentierten melanozytaren und neuroektodermalen Tumoren der Konjunktiva. Klin Monatsbl Augenheilkd 190:105–108, 1987
134. Hollstein M, Sidransky D, Vogelstein B, Harris CC: p53 mutations in human cancers. Science 253:49–53, 1991
135. Holly EA, Aston DA, Char DH, et al: Uveal melanoma in relation to ultraviolet light exposure and host factors. Cancer Res 50:5773–5777, 1990
136. Hosein AM: Exenteration: the nursing approach. J Ophthalmic Nurs Technol 8:91–96, 1989
137. Hugonnier R, Maugery J, Sagalow M, Hullo A: Les melanomes malins de la conjonctive. Bull Soc Ophthalmol Fr 82:857–860, 1982
138. Hungerford JL: Surgical treatment of ocular melanoma. Melanoma Res 3:305–312, 1993
139. Hussain I, Partington K, Bonshek R, Tullo AB: Melanotic lesions of the conjunctiva (letter). Br J Ophthalmol 78:592, 1994
140. Hutchinson J: Senile freckles. Arch Surg (London) 3:319–322, 1892
141. Höpping W: Discussion of pigmented tumors of the conjunctiva, in Boniuk M (ed): Ocular and Adnexal Tumors. St Louis, CV Mosby, 1964, pp 40
142. Jahnle RL, Shields JA, Bernardino VB Jr, et al: Conjunctival inclusion cyst simulating malignant melanoma. Am J Ophthalmol 100:483–484, 1985
143. Jakobiec FA: Conjunctival melanoma. Unfinished business (editorial). Arch Ophthalmol 98:1378–1384, 1980
144. Jakobiec FA: The ultrastructure of conjunctival melanocytic tumors. Trans Am Ophthalmol Soc 82:599–752, 1984
145. Jakobiec FA, Brownstein S, Wilkinson RD, Katzin HM: Adjuvant cryotherapy for focal nodular melanoma of the conjunctiva. Arch Ophthalmol 100:115–118, 1982
146. Jakobiec FA, Brownstein S, Wilkinson RD, et al: Combined surgery and cryotherapy for diffuse malignant melanoma of the conjunctiva. Arch Ophthalmol 98:1390–1396, 1980

147. Jakobiec FA, Buckman G, Zimmerman LE, et al: Metastatic melanoma within and to the conjunctiva. Ophthalmology 96:999–1005, 1989
148. Jakobiec FA, Folberg R, Iwamoto T: Clinicopathologic characteristics of premalignant and malignant lesions of the conjunctiva. Ophthalmology 96:147–166, 1989
149. Jakobiec FA, Rini FJ, Fraunfelder FT, Brownstein S: Cryotherapy for conjunctival primary acquired melanosis and malignant melanoma. Ophthalmology 95:1058–1070, 1988
150. Jakobiec FA, Zuckerman BD, Berlin J, et al: Unusual melanocytic nevi of the conjunctiva. Am J Ophthalmol 100:100–113, 1985
151. Jay B: Nevi and melanomata of the conjunctiva. Br J Ophthalmol 49:169–204, 1965
152. Jay M, McCartney ACE: Familial malignant of the uvea and p53: a Victorian detective story. Surv Ophthalmol 37:457–462, 1993
153. Jean B, Thiel HJ, Stumper K: CO_2 Laser Vaporisation von Papillomen an Bindehaut und Lidern. Fortschr Ophthalmol 86:672–675, 1989
154. Jeffrey IJ, Lucas DR, McEwan C, Lee WR: Malignant melanoma of the conjunctiva. Histopathology 10:363–378, 1986
155. Jensen OA, Movin M, Müller J: Malignant melanoma of the choroid in an infant with the dysplastic naevus syndrome. Acta Ophthalmol 65:91–100, 1987
156. Johanson B, Linnér E, Eriksson, Eldh J: Reconstruction of a large conjunctival defect with conjunctival flap. Scand J Plast Reconstr Surg 16:221–222, 1982
157. Jordan DR, Mamalis N, White GL Jr, et al: Amelanotic malignant melanoma of the conjunctiva with local metastasis to the eyelid. Can J Ophthalmol 25:34–47, 1990
158. Kalski RS, Lomeo MD, Kirschgraber PRN, Levine MR: Caruncular malignant melanoma in a black patient. Ophthalmic Surg 26:139–141, 1995
159. Keller AZ: Histology, survivorship and related factors in the epidemiology of eye cancers. Am J Epidemiol 97:386–393, 1973
160. Kerschbaumer RP: Das Sarkom des Auges. Wiesbaden, Bergmann, 1990
161. Kielar RA: Limbal melanoma in a Negro. Arch Ophthalmol 87:392–395, 1972
162. Kincaid M: Discussion re: Rodriguez-Sains RS: Ocular findings in patients with the dysplastic nevus syndrome. Ophthalmology 93:661–665, 1986 (editorial). Ophthalmology 93:665, 1986
163. Kindblom LG, Lodding P, Rosengren L, et al: S-100 protein in melanocytic tumors. An immunohistochemical investigation of benign and malignant melanocytic tumors and metastases of malignant melanoma and a characterization of the antigen in comparison to the human brain. Acta Pathol Microbiol Immunol Scand 92:219–230, 1984
164. Kiratali H, Shields CL, Shields JA, De Potter P: Metastic tumors to the conjunctiva—report of 10 cases. Br J Ophthalmol 80:5–8, 1996
165. Kishore K, Ghazvini S, Char DH, et al: p53 gene and cell cycling in uveal melanoma. Am J Ophthalmol 121:561–567, 1996
166. Kleijnen J, Knipschild P: The comprehensiveness of Medline and Embase computer searches. Searches for controlled trials of homeopathy, ascorbic acid for common cold and gingko biloba for cerebral insufficiency and intermittant claudication. Pharm Weekbl Sci 14:316–320, 1992
167. Koch JM, Bornfeld N, Waubke TN, Wessing A: Impressionszytologie der Bindehaut nach hochdosierter Brachytherapie maligner Melanome der Uvea mit 106Ru/106Rh-Applikatoren. Fortschr Ophthalmol 85:642–645, 1988
168. Korting HC, Blick U, Hamperl WD: Coincidence of primary malignant melanoma of skin and eye. Report of a case without B-K mole syndrome but with a further malignancy. Dermatologica 167: 317–321, 1983
169. Kraemer KH, Greene MH, Tarone R, et al: Dysplastic nevi and cutaneous melanoma risk (letter). Lancet:1076–1077, 1983
170. Krallman R, Sundmacher R, Ross B, Böcking A: Mitomycin C therapy for carcinoma *in situ* of the cornea and conjunctiva (abstract). Invest Ophthalmol Vis Sci 37 (Suppl):S243, 1996
171. Kulnig W: Zur Differentialdiagnose pigmentierter Bindehautveranderungen (Licht- und elektronenmikro-skopische Befunde). Fortschr Ophthalmol 83:138–140, 1986
171b. Kwapiszeski BR, Savitt ML: Conjunctival metastasis from a cutaneous melanoma as the initial sign of dissemination. Am J Ophthalmol 123:266–268, 1997
172. Langmann G, Kleinert R, Wirnsberger GH, et al: Proliferationsmarker, Enzymmarker und Onkogenexpressionsprofile bie intraokularen Melanomen. Ophthalmologe 90:528–532, 1993
173. Laënnec RTH: De l'ausculation médiate, ou traité du diagnostic des maladies des poumons et du coeur. Paris, Brosson & Chaudé, 1826, ed 2
174. Laënnec RTH: Extrait du mémoire de M. Laënnec sur les mélanôses. Bull Fac Med Paris 2:24–26, 1806
175. Lederman M: Radiotherapy of malignant melanomata of the eye. Br J Radiol 34:21–42, 1961
176. Lederman M: Radiotherapy of epibulbar malignant melanomata. Trans Ophthalmol Soc UK 73:399–432, 1953
177. Lederman M, Jones CH: Beta irradiation of the conjunctival sac: description of a new applicator. Br J Radiol 39:867–869, 1966
178. Lederman M, Wybar K, Busby E: Malignant epibulbar melanoma: natural history and treatment by radiotherapy. Br J Ophthalmol 68:605–617, 1984
179. Levene A: Precancerous and cancerous melanosis of the canine conjunctiva. J Comp Pathol 83:253–257, 1973
180. Levine AJ, Momand J, Finlay CA: The p53 tumor suppressor gene. Nature 351:453–456, 1991
181. Lewis PM, Zimmerman LE: Delayed recurrences of malignant melanomas of the bulbar conjunctiva. Am J Ophthalmol 45:536–543, 1958
181b. Lieb WE, Shields JA, Shields CL, et al: Postsurgical hematic cyst simulating a conjunctival melanoma. Retina 10:63–67, 1997
182. Liesegang TJ, Campbell RJ: Mayo Clinic experience with conjunctival melanomas. Arch Ophthalmol 98:1385–1389, 1980
183. Lister A: Malignant pigmented tumors in the neighbourhood of the limbus treated by radical excision followed by corneoscleral graft: report of three cases. Trans Ophthalmol Soc UK 71:100–110, 1951
184. Lommatzsch PK: Beta-ray treatment of malignant epithelial tumors of the conjunctiva. Am J Ophthalmol 81:198–206, 1976
185. Lommatzsch PK: Conjunctival tumors and their radiotherapy, in Albert WE, Sagerman RH (eds): Radiotherapy of Intraocular and Orbital Tumors. Berlin, Springer Verlag, 1993, pp 227–237
186. Lommatzsch PK: Beta-ray treatment of malignant epibulbar melanoma. Graefes Arch Clin Exp Ophthalmol 209:111–124, 1978
187. Lommatzsch PK: Beta irradiation of conjunctival melanomas. Trans Ophthalmol Soc UK 97:378–380, 1977
188. Lommatzsch PK, Lommatzsch RE, Kirsch I, Furmann P: Therapeutic outcome of patients suffering from malignant melanoma of the conjunctiva. Br J Ophthalmol 74:615–619, 1990
189. Lopez Cardozo P, Oosterhuis JA, de Wolff-Rouendaal D: Exfoliative cytology in the diagnosis of conjunctival tumors. Ophthalmologica 182:157–164, 1981
190. Lynch HT, Frichot BCI, Lynch HF: Familial atypical multiple mole-melanoma syndrome. J Med Genet 15:352–356, 1978
191. MacKenzie W: A practical treatise on the diseases of the eye. London, Longman, Rees, Orme, Brown, Green & Longmans, 1835, ed 3
192. MacKie R, Hunter JA, Aitchinson TC, et al: Cutaneous malignant melanoma, Scotland 1979–89. The Scottish Melanoma Group. Lancet 339:971–975, 1992
193. MacKiewicz E, Switka-Bachnik E, Dröbecka-Brydak E: Xeroderma pigmentosum—przypadek wásny. Klin Oczna 96: 176–178, 1994

194. Manschot WA: Melanotic lesions of the conjunctiva. Mod Probl Ophthalmol 45:536–543, 1975
195. Manschot WA: Melanotic lesions of the conjunctiva. Trans Ophthalmol Soc UK 93:733–738, 1973
196. Margo CE, Roper DL, Hidayat AA: Borderline melanocytic tumor of the conjunctiva: diagnostic and therapeutic considerations. J Pediatr Ophthalmol Strabismus 91:268–270, 1991
197. Martin CL: Canine epibulbar melanomas and their management. J Am Anim Hosp Assoc 17:83–90, 1981
198. Masson P: Pigment cells in man, in Miner RW, Gordon M (eds): The Biology of Melanoma. New York, New York Academy of Sciences, 1948, p 15
199. Mattsson B, Wallgren A: Completeness of the Swedish Cancer Registry: non-notified cancer cases recorded on death certificates in 1978. Acta Radiol Oncol 23:305–313, 1984
200. McCarthy JM, Rootman J, Horsman D, White VA: Conjunctival and uveal melanoma in the dysplastic nevus syndrome. Surv Ophthalmol 37:377–386, 1993
201. McDonnell JM, Carpente JD, Jacobs P, et al: Conjunctival melanocytic lesions in children. Ophthalmology 96:986–993, 1989
202. McDonnell JM, Yu Sun Y, Wagner D: HMB-45. Immunohistochemical stainings of conjunctival melanocytic lesions. Ophthalmology 98:453–458, 1991
203. McGhee CN, Ni C, Albert DM, Chu FR: Conjunctival melanoma. Int Ophthalmol Clin 22:35–56, 1982
204. Mihm MC Jr, Barnhill RL, Sober AJ, Hernandez MH: Precursor lesions of melanoma: do they exist? Semin Surg Oncol 8:358–365, 1992
205. Mihm MC, Guillén FJ: Classification of non-nevoid pigmented lesions of the conjunctiva (letter). Hum Pathol 16:1078, 1985
206. Miller B, Abrahams C, Cole GC, Proctor NS: Ocular malignant melanoma in South African blacks. Br J Ophthalmol 65:720–722, 1981
207. Miller D, Carroll JM, Holmberg A, et al: Radioactive scleral shells in the treatment of conjunctival tumors. Am J Ophthalmol 70:783–786, 1970
208. Miller DM, Brodell RT, Levine MR: The conjunctival wart: Report of a case and review of treatment options. Ophthalmic Surg 25:545–548, 1994
209. Mohs FE: Microscopically controlled surgery for periorbital melanoma: fixed-tissue and fresh-tissue techniques. J Dermatol Surg Oncol 11:284–291, 1985
210. Morax V: Cancer de l'appareil visuel. Paris, Gaston Doin, 1926
211. Morgan G: Ocular tumors in animals. J Small Anim Pract 10:563–570, 1969
212. Morris DA, Jakobiec FA, Henkind P, et al: Recurrent conjunctival melanoma with neuroidal spindle cell features. Ophthalmology 94:56–60, 1987
213. Muhlbauer-Ries E, Amon M, Zethmayer M: Amelanotisches, nodularen Melanom der Bidehaut wahrend der Schwangerschaft. Anmerkungen zur Pathogenese, Prognose und Diferentialdiagnose. Spektrum Augenheilkd 9:221–224, 1995
214. Naidoff MA, Bernardino VB, Clark WH: Melanocytic lesions of the eyelid skin. Am J Ophthalmol 82:371–382, 1976
215. Napel JA: Conjunctival melanoma, a retrospective study. Doc Ophthalmol 42:321–328, 1977
216. Nigro JM, Baker SJ, Preisinger AC, et al: Mutations in the p53 gene occur in diverse human tumor types. Nature 342:705–708, 1989
217. NIH Consensus Conference: Precursors to malignant melanoma. JAMA 251:1864–1866, 1984
218. NIH Consensus Conference: Diagnosis and treatment of early melanoma. National Institutes of Health Consensus Statement, 1992
219. Nordlund JJ, Kirkwood J, Forget BM, et al: Demographic study of clinically atypical (dysplastic) nevi in patients with melanoma and comparison subjects. Cancer Res 45:1855–1861, 1985
219b. Norregaard JC, Gerner N, Jensen OA, Prause JU: Malignant melanoma of the conjunctiva: occurrence and survival following surgery and radiotherapy in a Danish population. Graefes Arch Clin Exp Ophthalmol 234:569–572, 1996
220. Notter G: Das maligne epibulbäre Melanom. Strahlentherapie 96:518–537, 1955
221. Oosterhuis JA, de Wolff-Rouendaal D: Local metastasis in conjunctival melanoma. Doc Ophthalmol 56:55–59, 1983
222. Oosterhuis JA, Went LN, Bergman W: Ocular melanoma associated with the familial atypical mole melanoma (FAMMM) syndrome, in Lynch HT, Fusaro RM (eds): Hereditary Malignant Melanoma. Boca Raton, CRC Press, 1991, pp 53–62
223. Oosterhuis JA, Went LN, Lynch HT: Primary choroidal and cutaneous melanomas, bilateral choroidal and familial occurrence of melanomas. Br J Ophthalmol 66:230–233, 1982
224. Paridaens AD, McCartney AC, Curling OM, et al: Impression cytology of conjunctival melanosis and melanoma. Br J Ophthalmol 76:198–201, 1992
225. Paridaens AD, McCartney AC, Hungerford JL: Premalignant melanosis of the conjunctiva and the cornea in xeroderma pigmentosum. Br J Ophthalmol 76:120–122, 1992
226. Paridaens AD, McCartney AC, Hungerford JL: Multifocal amelanotic conjunctival melanoma and acquired melanosis *sine pigmento*. Br J Ophthalmol 76:163–165, 1992
227. Paridaens AD, McCartney AC, Lavelle RJ, et al: Nasal and orbital recurrence of conjunctival melanoma 21 years after exenteration. Br J Ophthalmol 76:369–371, 1992
228. Paridaens ADA, Alexander RA, Hungerford JL, et al: Oestrogen receptors in conjunctival malignant melanoma: Immunohistochemical study using formalin fixed paraffin wax sections. J Clin Pathol 44:840–843, 1991
229. Paridaens ADA, Kirkness CM, Garner A, Hungerford JL: Recurrent malignant melanoma of the corneal stroma: a case of "black cornea." Br J Ophthalmol 76:444–446, 1992
230. Paridaens ADA, McCartney ACE, Minassian DC, Hungerford JL: Orbital exenteration in 95 cases of conjunctival malignant melanoma. Br J Ophthalmol 78:520–528, 1994
231. Paridaens ADA, Minassian DC, McCartney ACE, Hungerford JL: Prognostic factors in malignant melanoma of the conjunctiva: a clinico-pathological study of 256 cases. Br J Ophthalmol 78:252–259, 1994
232. Paridaens ADA, Seregard S, Minassian D, et al: AgNOR count in conjunctival malignant melanoma lack prognostic value. Br J Ophthalmol 76:621–623, 1992
233. Parsons JH: The pathology of the eye, Vol I. London, Hodder & Stoughton, 1904
234. Paton D, Thomas LB: Simultaneous occurrence of primary malignant melanomas of the eye and skin. Arch Ophthalmol 62:645–652, 1959
235. Pfeiffer RL: The differential diagnosis of pigmented ocular lesions in the dog and cat. Calif Vet 5:14–18, 1981
236. Ploton D, Menager M, Jeanneson P, et al: Improvement in the staining and in the visualization of the argyrophilic proteins of the nucleolar organizer regions at the optical level. Histochem J 18:5–14, 1986
237. Polychronakos DJ, Economou A: On two cases of melanoma of conjunctiva. Ann Ophthalmol 3:779–783, 1971
238. Pour P, Tantachamrum T, Althoff J, Mohr U: Melanoma in the north of Thailand in the last ten years. Report from Chiang Mai University. Z Krebsforsch 80:31–35, 1973
239. Rasmussen KE: Behandling af overfladiske öjensygdomme med strontium 90 beta-stråle applikator. Nord Med 81:333–337, 1969
240. Reese AB: Precancerous melanosis and diffuse malignant melanoma of the conjunctiva. Arch Ophthalmol 19:354–365, 1938
241. Reese AB: Precancerous and cancerous melanosis, in Boniuk M (ed): Ocular and Adnexal Tumors, St Louis, CV Mosby, 1964, pp19–23
242. Reese AB: Tumors of the eye. New York, Harper & Row, 1963, ed 3
243. Reese AB: Precancerous and cancerous melanosis of the conjunctiva. Am J Ophthalmol 39:96–100, 1955
244. Reese AB: Tumors of the eye. New York, Harper & Brothers, 1951

245. Robertson DM, Hungerford JL, McCartney ACE: Malignant melanomas of the conjunctiva, nasal cavity, and paranasal sinuses. Am J Ophthalmol 108:440–442, 1989
246. Robertson DM, Hungerford JL, McCartney ACE: Pigmentation of the eyelid margin accompanying conjunctival melanoma. Am J Ophthalmol 108:435–439, 1989
247. Rodríguez-Sains RS: Ocular findings in patients with dysplastic nevus syndrome. An update. Dermatol Clin 9:723–728, 1991
248. Rodríguez-Sains RS: Ocular findings in patients with dysplastic nevus syndrome. Ophthalmology 93:661–665, 1986
249. Rodríguez-Sains RS: Are concurrent or subsequent malignant melanomas of the skin and eye related or coincidental? J Dermatol Surg Oncol 6:915–918, 1980
250. Rodríguez-Sains RS: Do the eyes have it (letter)? J Dermatol Surg Oncol 5:666, 1979
251. Roth ME, Grant-Kels JM, Ackerman AB, et al: The histopathology of dysplastic nevi. Continued controversy. Am J Dermatol 13:38–51, 1991
252. Royds JA, Sharrard RM, Parsons MA, et al: C-myc oncogene expression in ocular melanomas. Graefes Arch Clin Exp Ophthalmol 230:366–371, 1992
253. Rummelt V, Naumann GOH, Folberg R, et al: Surgical management of melanocytoma of the ciliary body with extrascleral extension. Report of four patients. Am J Ophthalmol 117:169–176, 1994
254. Rutgard J, Peyman GA, Frenkel M, Saks S: Calmette-Guerin bacillus treatment of experimental conjunctival malignant melanoma. Arch Ophthalmol 95:2214–2217, 1977
255. Sanderson TL, Pustai W, Shelley L, et al: Cytologic evaluation of ocular lesions. Acta Cytol 24:391–400, 1980
256. Saornil MA, Marcus DM, Doepner D, et al: Nucleolar organizer regions in determining malignancy of pigmented conjunctival lesions. Am J Ophthalmol 115:800–805, 1993
257. Schichtel RF: Melanoma of epibulbar conjunctiva. Eye Ear Nose Throat Mon 48:181–184, 1969
258. Schlieter F: Konservative Therapie des malignen Melanoms der Bindehaut, entstanden auf dem Boden einer melanotischen Präblastomatose Dubreuilh. Klin Monatsbl Augenheilkd 161:416–424, 1972
259. Schlieter F, Kleifeld O: Über das maligne Melanom der Hornhaut und seine Therapie. Klin Monatsbl Augenheilkd 167:404–412, 1975
260. Schulz MD, Wipfelder R: Reactor-activated applicators for treatment of conjunctival neoplasms. Radiology 92:1553–1556, 1969
261. Schwab L, Green WR: Conjunctival melanoma in Africa. Ophthalmic Surg 18:900–903, 1987
262. Scotto J, Fraumeni JF, Lee JA: Melanomas of the eye and other noncutaneous sites: epidemiologic aspects. J Natl Cancer Inst 56:489–491, 1976
263. Scuderi G, Balastrazzi E: Conjunctival melanoma in an anophthalmic orbit. Ophthalmologica 166:172–174, 1973
264. Seddon JM, Gragoudas ES, Glynn RJ, et al: Host factors, UV radiation, and risk of uveal melanoma. A case-control study. Arch Ophthalmol 1087:1274–1280, 1990
265. Seregard S: Cell proliferation as prognostic indicator in conjunctival malignant melanoma. Am J Ophthalmol 116:93–97, 1993
266. Seregard S: Cell growth and p53 expression in primary acquired melanosis and conjunctival melanoma. J Clin Pathol 49:338–342, 1996
267. Seregard S: Malignant melanoma of the conjunctiva and potential precursor lesions (thesis). Stockholm, Karolinska Institute, 1995
268. Seregard S: Apocrine adenocarcinoma arising in Moll gland cystadenoma. Ophthalmology 100:1716–1719, 1993
269. Seregard S, af Trampe E, Månsson-Brahme E, et al: Prevalence of primate acquired melanosisi and nevi of the uvea and conjunctiva in the dysplastic nevus syndrome. A case-control study. Ophthalmology 102:1524–1529, 1995
270. Seregard S, Kock E: Squamous spindle cell carcinoma of the conjunctiva. Fatal outcome of a pterygium-like lesion. Acta Ophthalmol Scand 73:464–466, 1995
271. Seregard S, Kock E: Maligna melanom i conjunctiva. Läkartidningen 90:575–576, 1993
272. Seregard S, Kock E: Conjunctival malignant melanoma in Sweden 1969–91. Acta Ophthalmol 70:289–296,1992
273. Seregard S, Ladenvall G, Kock E: Massive intracorneal invasion of a ciliary body melanoma. Acta Ophthalmol 72:257–259, 1994
274. Shields JA: Management of uveal melanoma. A continuing dilemma (editorial). Cancer 72:2067–2068, 1993
275. Shields JA: Diagnosis and management of orbital tumors. Philadelphia, WB Saunders, 1989
275b. Shields JA, Shields CL: Tumors of the conjunctiva and cornea, in Smolin G, Thoft RA (eds): The Cornea. Scientific Foundations and Clinical Practice, Part 2, Clinical Aspects. Boston, Little, Brown, ed 3, pp 579–595
275c. Shields JA, Shields CL, De Potter P: Surgical management of conjunctival tumors. The 1994 Lynn B McMahan lecture. Arch Ophthalmol 115:808–815, 1997
275d. Shields JA, Shields CL, De Potter P: Surgical management of circumscribed conjunctival melanomas. Ophthal Plast Reconstr Surg (in press), 1997
276. Siegel D: Analysis of follow-up data (editorial). Arch Ophthalmol 103:647–648, 1985
277. Siegert J, Wiegand W, Kroll P: Radikale Konjunktivektomie bei der Therapie des malignen Melanoms der Bindehaut. Klin Monatsbl Augenheilkd 203:413–417, 1993
278. Silvers DN, Jakobiec FA, Freeman TR, et al: Melanoma of the conjunctiva: a clinicopathological study, in Jakobiec FA (ed): Ocular and Adnexal Tumors. Birmingham, Aesculapius, 1978, pp 583–599
279. Spencer WH: Conjunctiva, in Spencer WH (ed): Ophthalmic pathology. An Atlas and Textbook, Vol 1. Philadelphia, WB Saunders, 1996, ed 4, pp 38–44
280. Spitz S: Melanomas of childhood. Am J Pathol 24:591–609, 1948
281. Stallard HB: Discussion of pigmented tumors of the conjunctiva, in Boniuk M (ed): Ocular and Adnexal Tumors. St Louis, CV Mosby, 1964, p 47
282. Stefani FH: Das maligne Melanom der Bindehaut—Klinischer Verlauf und histopathologischer Befund. Fortschr Ophthalmol 83:141–145, 1986
283. Stefani FH: A prognostic index for patients with malignant melanoma of the conjunctiva. Graefes Arch Clin Exp Ophthalmol 224:580–582, 1986
284. Stellwag von Carion C: Treatise on the diseases of the eye. New York, Wood, 1868
285. Steuhl KP, Rohrbach JM, Knorr M: Die Verteilung melanomassoziierter Antigene (HMB-45 und S-100) in benignen und malignen melanozytaren Tumoren der Konjunktiva. Klin Monatsbl Augenheilkd 199:187–191, 1991
286. Steuhl KP, Rohrbach JM, Knorr M, Thiel HJ: Significance, specificity, and ultrastructural localization of HMB-45 antigen in pigmented ocular tumors. Ophthalmology 100:208–215, 1993
287. Strempel I: Bindehautmetastase eines primären Hautmelanoms. Ophthalmologica 185:52–57, 1982
288. Swedish National Board of Health and Welfare (Centre for Epidemiology): Cancer Incidence in Sweden 1991. Stockholm, Fritzes, 1994
289. Swerdlow AJ: Incidence of malignant melanoma of the skin in England and Wales and its relation to sunshine. BMJ 2:1324–1327, 1979
290. Swerdlow AJ, Cooke KR, Skegg DC, Wilkinson J: Cancer incidence in England and Wales and New Zealand and in migrants between the two countries. Br J Cancer 72:326–343, 1995
291. Tahery DP, Goldberg R, Moy RL: Malignant melanoma of the eyelid. A report of eight cases and a review of the literature. J Am Acad Dermatol 27:17–21, 1992
292. Takahashi T, Nau MM, Chiba I, et al: p53: a frequent target for genetic abnormalities in lung cancer. Science 246:491–494, 1989
293. Takehara A, Dake Y, Amemiya T: Treatment of malignant melanoma of conjunctiva. Jpn J Clin Ophthalmol 49:431–434, 1995

294. Taylor MR, Guerry DI, Bondi EE, et al: Lack of association between intraocular melanoma and cutaneous dysplastic nevi. Am J Ophthalmol 98:478–482, 1984
295. Thiel R: Die bösartigen Geschwülste der Bindehaut. Buch Augenarzt 44:154–178, 1965
296. Thiel R: Die bösartigen Geschwülste der Bindehaut. Ophthalmologica 151:68–74, 1966
297. To KW, Rabinowitz SM, Friedman AH, et al: Neurofibromatosis and neural crest neoplasms: primary acquired melanosis and malignant melanoma of the conjunctiva. Surv Ophthalmol 33:373–379, 1989
298. Tobal K, Warren W, Cooper CS, et al: Increased expression and mutation of p53 in choroidal melanoma. Br J Cancer 66:900–904, 1992
299. Tokuda K, Ishbashi T, Oshida N, Kobayashi H: A huge malignant melanoma of the cornea. Nippon-Ganka-Kiyo 21:295–301, 1970
300. Torczynski E: Preparations of ophthalmological specimens for histopathological examination. Ophthalmology 88:1367–1371, 1981
301. Tragakis M, Pollalis S, Karantinos D, et al: Mélanome primitif malin de la cornée. J Fr Ophthalmol 2:29–31, 1979
302. Travers B: A synopsis of the diseases of the eye, and their treatment. London, Longman, Hurst, Rees, Orme & Brown, 1820
303. Travis LW, Rice DH, McClatchey KD, Wallace SW: Malignant melanoma of conjunctiva metastatic to parotid gland. Reports of cases and discussion of surgical management. Laryngoscope 87:2000–2007, 1977
304. Tucker MA, Shields JA, Hartge P, et al: Sunlight exposure as risk factor for intraocular malignant melanoma. N Engl J Med 313:789–792, 1985
305. Tucker NA, Kroll S, Frigillana H, et al: Immunohistochemical detection of p53 in primary acquired melanosis and melanoma of the conjunctiva (abstract). Invest Ophthalmol Vis Sci 35 (Suppl):1722, 1994
305b. Tucker SM, Hurwitz JJ, Pavlin CJ, et al: Scleral melt after cryotherapy for conjunctival melanoma. Ophthalmology 100:574–577, 1993
306. Tullo AB, Bonshek R: Conjunctival melanoma (editorial). Br J Ophthalmol 78:514, 1994
307. Ueno H, Tamai A, Noda K, et al: Light and electron microscopic studies of malignant melanoma of conjunctiva and palpebra. Jpn J Ophthalmol 27:459–467, 1983
308. Uffer S: Melanomes malins de la conjunctive. Klin Monatsbl Augenheilkd 196:290–294, 1990
309. UICC (International Union Against Cancer): Ophthalmic tumors, in Hermanek P, Sobin LH (eds): TNM-Classification of Malignant Tumors. Berlin-Heidelberg-New York, Springer-Verlag, 1992, ed 4, pp 161–187
310. van Delft JL, de Wolff-Rouendaal D, Oosterhuis JA: Irrigation with mercury chloride and sodium hypochlorite to prevent local recurrence after excision of conjunctival melanoma. An experimental study. Doc Ophthalmol 56:61–67, 1983
311. Verhoeff FH, Loring RG: A case of primary epibulbar sarcoma with secondary growths in limbus and sclera, and invasion of the choroid, ciliary body and iris. Arch Ophthalmol 32:97–102, 1903
312. Vink JV, Crijns MB, Mooy CM, et al: Ocular melanoma in families with dysplastic nevus syndrome. J Am Acad Dermatol 23:858–862, 1990
313. Wachtel JG, Caplan CW, Makley TA Jr: Juvenile melanoma (mixed spindle cell and epitheloid cell nevus) of the conjunctiva. Surv Ophthalmol 12:12–16, 1967
314. Wakelin D, Campbell JS, Watson AG: Pedunculated malignant melanoma of conjunctiva—the sequel. Can J Ophthalmol 10:90–91, 1975
315. Watson AG, Campbell JS, Tolnai G, Hill DP: Pedunculated malignant melanoma of conjunctiva. Can J Ophthalmol 5:386–391, 1970
316. Wayte DM: A Christmas lesson: biopsy techniques for the young clinician. J Clin Pathol 45:1045–1046, 1992
317. Weiss JS, Perusse P, Reale F: Tear cytology in conjunctival melanoma. Am J Ophthalmol 111:648–692, 1991
318. Welsh NH, Jhavery Y: Malignant melanoma of the cornea in an African patient. Am J Ophthalmol 72:796–800, 1971
319. Wetzel W: Strahlentherapeutische Behandlung eines malignen Melanoms der Dorneoskleralzone. Klin Monatsbl Augenheilkd 186:371–373, 1985
320. Zeisberg B, Bleckmann H: Die Behandlung des malignen Melanoms der Bindehaut. Fortschr Ophthalmol 83:172–175, 1986
321. Zimmerman LE: Melanocytic tumors of interest to the ophthalmologist. Ophthalmology 87:497–502, 1980
322. Zimmerman LE: The histogenesis of conjunctival melanoma, in Jakobiec FA (ed): Ocular and Adnexal Tumors. Birmingham, Aesculapius, 1978, pp 600–630
323. Zimmerman LE: Criteria for management of melanosis (letter). Arch Ophthalmol 76:307–308, 1966
324. Zimmerman LE: Discussion of pigmented tumors of the conjunctiva, in Boniuk M (ed): Ocular and Adnexal Tumors. St Louis, CV Mosby, 1964, pp 24–48
325. Zimmerman LE, Sobin LH: Histologic typing of tumors of the eye and its adnexa. International Histologic Classification of Tumors, no 24. Geneva, World Health Organization, 1980, pp 23–24
326. Zografos L, Bercher L, Egger E, et al: Le traitement des tumeurs oculaires par faisceau de protons accélérés. Sept ans d'expérience. Klin Monatsbl Augenheilkd 200:431–435, 1992
327. Zografos L, Uffer S, Bercher KL, Gailloud C: Chirurgie, cryocoagulation et radiothérapie combinée pour le traitement des mélanomes de la conjonctive. Klin Monatsbl Augenheilkd 204:385–390, 1994
328. Zografos L, Uffer S, Gailloud C: Les mélanomes de la conjonctive. Bull Mem Soc Fr Ophthalmol 93:174–178, 1981
329. Zografos L, Uffer S, Gailloud C, Bercher KL: Les melanomes de la conjunctive et leur traitement. Klin Monatsbl Augenheilkd 196:285–289, 1990
330. Österlind A: Trends in incidence of ocular malignant melanoma in Denmark 1943–1982. Int J Cancer 40:161–164, 1987

Outline

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