OCULAR SURFACE

- Conjunctiva vs external eye diseases
- Lids, tears, mucus and epithelial surfaces all interact to produce a complex physico-chemical system that ensures an optimal corneal environment
- Chronic inflammation may cause imbalance of this system

IMBALANCE OCULAR SURFACE
Loss of normal conjunctival surface morphology and associated structures:
- Alteration of lid/globe interaction
- Reduction of tear flow
- Secondary infection
Progressive and powerful insult to the outer eye:
- Corneal scarring, vascularisation, perforation, endophthalmitis
- Eventually loss of the eye

PHYSICO-CHEMICAL PROTECTION MECHANISMS
Physical, cellular, humoral protection

PHYSICAL PROTECTION
- Effective lid function and closure (aperture, blink rate, reflex blinking)
- Tears (washing and dilution)
- Mucus from goblet cells ("sticky trap")
- Lipids from lid margin glands (spreading effect, conserve moisture)
- Corneal and conjunctival epithelium (barrier)

CELLULAR PROTECTION
- Neutrophils
- Macrophages
- Langerhans/dendritic cells
- Lymphocytes

HUMORAL PROTECTION
- Lactic and fatty acids (from sebaceous glands), pH
- Immunoglobulins
- Complement
- Lysozyme
- Lactoferrin
- Beta-lysin
- Other antibacterial factors
- Interferons
- Tumor necrosis factor
PATTERNS OF INFLAMMATORY RESPONSE

Identification of the *principal features* of ocular inflammation can help in the differential diagnosis of chronic ocular surface disease.

**CLINICAL FEATURES OF CHRONIC INFLAMMATION**

LYMPH NODES: Swelling
LIDS: Floppy lid, blepharitis, aberrant lashes, entropion
CONJUNCTIVA: Infiltration of the tarsal plate, papillae, follicles, keratinisation, scarring, granuloma, phlyctenules
CORNEA: Punctate epithelial keratopathy, erosions, epithelial filaments, stromal changes, stromal keratitis, peripheral keratitis, stromal neovascularisation, endothelial changes
SCLERA: Scleritis

**PAPILLARY CONJUNCTIVITIS**
ALLERGIC: Seasonal and perennial allergic conjunctivitis, VKC, AKC, GPC
CHRONIC IRRITATION: Keratoconjunctivitis sicca, contact lenses, prostheses, nylon suture ends
TOPICAL DRUGS: Atropine sensitivity and other medication, drop and ointment vehicles, preservatives

**FOLLICULAR CONJUNCTIVITIS**
VIRUSES: HSV, VZV, EBV, adenovirus, molluscum contagiosum
CHLAMYDIA: Trachoma, paratragoma, zoonoses-psittacosis, cat scratch fever
INFECTION: Actinomyces, streptococci, moraxella
TOPICAL DRUGS: Eserine, epinephrine (adrenaline), DFP, idoxuridine

**LABORATORY INVESTIGATIONS IN CHRONIC INFLAMMATION**

MICROBIOLOGY: General, chlamydia
IgE: Serum, tears
PLASMINOGEN: Deficiency in ligneous conjunctivitis
CYTOLOGY
HISTOLOGY
SCHIRMER’S TEST, BUT (Break-up-time)
**SELECTED CONDITIONS**

Important inflammatory conditions, inflammation unresponsive to steroids, pigmented lesions, stem cell concept

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**BLEPHARITIS**

<table>
<thead>
<tr>
<th>Location</th>
<th>STAPHYLO-COCCAL</th>
<th>SEBORRHEIC</th>
<th>MEIBOMIAN GLAND DYSFUNCTION</th>
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<tbody>
<tr>
<td>Loss / whitening</td>
<td>anterior eyelid</td>
<td>anterior eyelid</td>
<td>posterior eyelid</td>
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<tr>
<td>of lashes</td>
<td>frequent</td>
<td>rare (+/-)</td>
<td>(-)</td>
</tr>
<tr>
<td>Lid crusting</td>
<td>fibrinous scales</td>
<td>(+/-)</td>
<td>hard crusts</td>
</tr>
<tr>
<td>Lid ulceration</td>
<td>occasional</td>
<td>(-)</td>
<td>(-)</td>
</tr>
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<td>papillary mild</td>
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<td>papillary tarsal reaction</td>
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<td>+</td>
<td>+</td>
</tr>
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<td>Seb. Dermatitis</td>
<td>-</td>
<td>+</td>
<td>++</td>
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<tr>
<td>Rosacea</td>
<td>-</td>
<td>+</td>
<td>++</td>
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</tbody>
</table>

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**STAPHYLOCOCCUS-ASSOCIATED INFLAMMATION IN CHILDREN**

EPIDEMIOLOGY: Small fair children; history of folliculitis/chalazia.

LOCATION: Primarily anterior eyelid.

PATHOPHYSIOLOGY: Staphylococci > toxin > host’s local immune response = main problem.

LIDS: Loss/whitening of lashes, fibrinous scales, crusts (“collarette”), ulcerationen, minimal signs not uncommon in children.

CONJUNCTIVA: (mild) papillary changes, conjunctivitis

CORNEA: Inferior PEE, marginal infiltrates, phlyctenulosis, vascularisation.

OUTCOME: Often of limited duration, transformation into „adult blepharitis” possible.

COMPLICATIONS: Focal limbal insufficiency („vascular pannus”), conjunctivalisation of the cornea, stromal opacities, Salzmann nodules.

**NB:** „Blepharitis” in children is not a banality!

**NB:** Lid margin changes may be minimal > < adults

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**THERAPY**

**Acute without corneal complication:**

- Fucidic acid (Fucithalmic) SDU 2x/24h, Lidcare (parents, Q-tips !) 1x/24h, fluorometholone (FML) 1-3x / 24h.

**Acute corneal complication:**

- Dexamethasone SDU 3x/24h (in place of FML)

**Exacerbation/decompensation:**

- In addition: azithromycine p.o.

**Maintenance therapy:** Fucithalmic SDU at night (if possible only 1x/week), Lidcare in the morning (if possible only 1x/week) , FML max. 1x/24h (if possible only 1x/week or without)
ATOPIC DISORDERS OF THE OCULAR SURFACE

CLASSIFICATION
Seasonal and Perennial Allergic Conjunctivitis
Vernal Keratoconjunctivitis (VKC)
Atopic Keratoconjunctivitis (AKC)
Giant Papillary Conjunctivitis (GPC)

VERNAL KERATOCONJUNCTIVITIS
EPIDEMIOLOGY: Age of onset is below 10 years (82%), most patients are male (85%). History of other atopic diseases. There may be a seasonal profile.
SYMPTOMS: Itching, redness, watering, stringy exudation, blurred vision, photophobia, blepharospasm, plus the specific symptom "morning misery".
TARSAL CONJUNCTIVA: Giant (>1mm) papillary hypertrophy. In active disease, tissues hyperaemic, infiltrated, mucus-covered. Reticular scarring, no shrinkage.
LIMBUS: Oedema, vegetations, Trantas's dots.
CORNEA: Punctate epithelial keratopathy (PEK), macro-erosion, plaque.
OUTCOME: The disease is self-limiting, lasting 2 to 10 years. In a few patients it transforms after puberty into AKC.
LABORATORY: Serum and tear levels of IgE are high. Eosinophils are present in conjunctival scrapings.
NB: Severity of the disease equates with degree of corneal involvement. VKC may be highly asymmetrical!

THERAPY
Acute without corneal complication:
In addition to the maintenance therapy: ketotifen (Zaditen) 2x/24h, at an initial stage steroids as additional option
Acute corneal complications:
In addition dexamethasone SDU up to 8x/24h.
Maintenance therapy: Dinatriumchromoglykate 3-4x/24h (Opticrom SDU or Allergo-COMOD)
NB: No effect on symptoms or signs caused by degranulated histamine

ATOPIC KERATOCONJUNCTIVITIS
EPIDEMIOLOGY: Adult equivalent of VKC. Young atopic adults, with males predominant. Associated with facial and lid eczema, and chronic lid margin disease. May develop from VKC.
SYMPTOMS: Itching, soreness, "dry" sensation, photophobia, blurred vision.
LIDS: Chronically inflamed lid margins with rounded posterior borders. Meibomian dysfunction.
TARSAL CONJUNCTIVA: Hyperaemia, cellular infiltration, scarring with shrinkage.
CORNEA: Rapid break-up of precorneal tear film. Punctate epithelial keratitis, often more severe in lower half. Corneal vascularisation, thinning, plaque.
ASSOCIATIONS: Keratoconus, atopic cataract, corneal graft failure

GIANT PAPILLARY CONJUNCTIVITIS
Localised allergic response to a physically rough or deposited surface (Contact lens, prosthesis, suture)
SYMPTOMS: Itching (especially on removal of lenses or prosthesis), stringy exudate, lens displacement, reduced wearing time.
SIGNS: Papillary hypertrophy (>1mm) of upper tarsal conjunctiva, hyperaemia, cellular infiltration and focal scarring. Rarely, limbal inflammation as in VKC. No corneal signs.
THERAPEUTIC OPTIONS
- Avoid antigen (if known)
- Inhibition of mast cell degranulation
  NB: No effect on symptoms and signs caused by histamine that has already been released
- Topical and systemic antihistamines
- Steroids
- Desensitization

TOPICAL ANTIHISTAMINES CH
Inhibition of mast cell effects (H1-Blockers)
- Antazoline (only in combination with vasoactive substances: Antistin-Privin, Spersallerg)
- Levocabastine (Livostin)
- Emedastine (Emadine)
- Azelastine (Oculastin)

MAST CELL STABILISING AGENTS CH
Release of mediators ("mast cell stabiliser")
- Sodium cromoglykate (Opticrom, Allergo-Comod)
- Nedocromil sodium (Tilavist)
- Lodoxamide (Alomide)
Release of mediators (histamine, leukotriens) and suppression of eosinophils
- Ketotifen (Zaditen)
Release of mediators, complement system antagonists
  - (Iso-) Spaglumat (Naaxia "New Formula")

DUAL-ACTING AGENTS CH
Dual-acting agents: Release of mediators (histamine, leukotriens) and antihistamine effect
- Olopatadine (Opatanol)

CHRONIC CONJUNCTIVITIS UNRESPONSIVE TO STEROIDS

<table>
<thead>
<tr>
<th>Young patients</th>
<th>Elderly patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLK</td>
<td>Mucous membrane pemphigoid</td>
</tr>
<tr>
<td>ligneous</td>
<td>lid malposition</td>
</tr>
<tr>
<td>floppy eye lid</td>
<td>CIN *</td>
</tr>
<tr>
<td>foreign body *</td>
<td>All ages</td>
</tr>
<tr>
<td></td>
<td>artefact *</td>
</tr>
<tr>
<td></td>
<td>toxicity</td>
</tr>
<tr>
<td></td>
<td>canaliculitis *</td>
</tr>
</tbody>
</table>

* unilateral

Exclude
- infection
- lid disorders (rosacea)
- CL-associated hyperaemia
- scleritis
INTRODUCTION

- “Cicatrising conjunctivitis” = spectrum of conditions ranging from physical and chemical damage, infections, oculocutaneous disorders to drug-induced effects (Table)
- Not synonymous with mucous membrane pemphigoid (MMP)
- Different forms of cicatrising conjunctival response

CONDITIONS ASSOCIATED WITH CICATRISING CONJUNCTIVITIS

PHYSICAL
- Heat
- Ionising radiation

CHEMICAL
- Trachoma
- Membranous conjunctivitis (bacterial and viral)

OCULOCUTANEOUS DISORDERS
- Erythema multiforme
- Stevens-Johnson syndrome
- Toxic epidermal necrolysis
- Mucous membrane pemphigoid *
- Linear IgA disease *
- Bullous pemphigoid
- Epidermolysis bullosa
- Dermatitis herpetiformis
- Pemphigus group
- Chronic atopic keratoconjunctivitis

OTHER ASSOCIATED SYSTEMIC DISORDERS
- Rosacea
- Sjogren’s syndrome
- Inflammatory bowel disease
- Graft-versus-host disease
- Paraneoplastic syndromes *

DRUG INDUCED
- Systemic
- Topical (pseudopemphigoid) *

The distinction between temporally limited and chronic progressive cicatrisation is of utmost importance, since the therapeutic approach to these two forms differs greatly.

PATHOPHYSIOLOGY

- Most cases of cicatrising conjunctivitis occur as acute tissue injury with subsequent scarring ⇒ cicatrisation temporally limited after withdrawal of the noxious factors ⇒ static fibrous scar
- Chronic progressive cicatrisation: mucous membrane pemphigoid (MMP), linear IgA disease, as part of certain paraneoplastic syndromes and after long-term treatment with topical medications
- Chronic progressive forms are potentially antibasement membrane antibody-mediated

DIAGNOSIS / CLASSIFICATION

- Analysis of biopsy specimens by immunopathological methods is the only diagnostic technique for the distinction between temporally limited and chronic progressive cicatrisation. Limitation: diagnostic information only provided in 50% ⇒ does not replace clinical considerations!

Currently it is the combination of medical history, clinical signs and immunopathological findings in the conjunctiva that is used to classify cicatrising conjunctivitis.
HISTORY
- Acute tissue injury after chemical and thermal burns, membranous conjunctivitis, acute oculocutaneous disorders such as Stevens-Johnson syndrome associated with temporally limited conjunctival scar tissue formation
- History and the type of extraocular lesions (with a dermatology assessment) ⇒ differentiation of oculocutaneous disorders
- History of ocular medication ⇒ diagnosis of drug-induced scarring

CLINICAL SIGNS
The pattern of conjunctival fibrosis helps in the differentiation:
- Subepithelial fibrosis without obvious involvement of the conjunctival epithelium: MMP ⇒ Membranous conjunctivitis after infection typically followed by superficial scarring
- Diffuse subepithelial fibrosis: "shrinkage" (loss of architecture with flattening of the normal folds, plica and caruncle) ⇒ conjunctival shrinkage with involvement of canthal structures important early clinical sign of MMP
- Drug-induced cicatrization initially involves the lower fornix ⇔ early changes of MMP
- Drug-induced disease may be unilateral

IMMUNOPATHOLOGICAL FINDINGS

When progressive disease is suspected, conjunctival tissue should be taken to confirm the clinical diagnosis. Particularly important with regard to systemic immunosuppressive therapy.

- Conventional histology of such biopsies does not yield diagnostic information
- Only immunopathological analysis of the tissue allows the condition to be classified as immune-mediated cicatrising conjunctivitis
- It is believed that these conditions are initiated by the binding of circulating antibodies to the basement membrane of the conjunctiva with subsequent complement activation ⇒ biopsy finding of linear deposits of immunoglobulin and/or complement at the basement membrane zone ⇒ Diagnosis of mucous membrane pemphigoid and related disorders
- Biopsies from other mucous membranes or lesional skin in presence of extraocular manifestations
- Direct immunofluorescence classical investigation for bullous skin disorders ⇒ used in most Dermatology Units ⇒ ophthalmologists should seek collaboration with a dermatologist
- Results of direct immunofluorescence frequently negative or inconclusive. Positive results in about 50 % of patients with cicatricial pemphigoid and related disorders
- Negative biopsy does not rule out this diagnosis!

CLASSIFICATION
- Highly specialised immunological investigations to identify antigens in the basement membrane zone allows further classification
- Indirect immunofluorescence to detect circulating anti-BMZ antibodies, immunobLOTS or immunoprecipitation for the characterisation of potential target-antigens
- Findings in MMP: Rarely anti-BMZ Ab in routine testing. Indirect immunofluorescence on salt-split skin: Epidermal and dermal (both sides?) antibody binding: 180-kD BPAg2 (and 230-kD BPAg1); 168-kD epidermal Ag; 45-kD Ag; laminin 5 (dermal); 90-kD, 130-kD, 140-kD, 205-kD epidermal components

Large number of potential antigens ⇒ heterogeneity among patients with similar clinical features

- Findings to further classify and understand the group of disorders encompassed by the term "MMP"
- Two studies: sera of patients with pure ocular pemphigoid (ocular lesions only) did not react with the bullous pemphigoid antigens. IgA-antibodies reacted with a 45-kD basement membrane zone antigen ⇒ "pure ocular cicatricial pemphigoid"?
Antibodies of the \textit{IgA-class} directed against the bullous pemphigoid antigens (170- to 180-kd and 220- to 230-kd) may be related to the occurrence of mucosal lesions. Patients with anti-laminin 5 antibodies typically have lesions of their mucous membranes and skin.

Autoantibodies serve as diagnostic markers in many immune disorders. In cicatrising conjunctivitis, the investigation of autoantibodies has only started. It may be expected that the assessment of anti-laminin 5 and further autoantibodies will help in future to evaluate patients with cicatrising ocular disease.

**DISEASE ACTIVITY**

The assessment of disease activity is of practical importance, since this influences management decisions.

- Scarring can occur with or without clinical inflammation, but rapid progression of fibrosis typically occurs during or after manifest inflammation.
- Clinical signs of inflammatory activity: conjunctival hyperaemia, conjunctival oedema with tissue thickening, conjunctival ulceration, limbitis.
- Conventional histopathological study of the conjunctiva not very helpful to determine disease activity (epithelial changes only reflect the ocular surface condition, similar inflammatory infiltrate is found in several chronic conjunctival disorders).
- Immunohistopathology gives clues regarding the disease activity and helps in the investigation of disease mechanisms (inflammatory activity in mucous membrane pemphigoid goes parallel with increased numbers of neutrophils, macrophages, CD4+ cells and Langerhans’ cells in the conjunctival stroma).
- The variability of the subepithelial cellular infiltrate with disease activity and the involvement of several cell lines provides the rationale for using broad-spectrum, rather than T-cell specific immunosuppressive agents.
- Other chronic conjunctival disorders show similar characteristics in the composition of the cellular infiltrate \(\Rightarrow\) clinical characteristics are not primarily determined by cell morphology, but by differences in the secretory activity of these cells.
- Several lines of evidence indicate that TGF-beta plays a decisive role in the pathogenesis of conjunctival fibrosis.

**DISEASE PROGRESSION / KERATOPATHY**

- Traditional thinking: conjunctival inflammation in MMP leads to drying, with subsequent metaplasia, scarring, vascularisation and opacification of the cornea.
- Prospective study of 66 patients with MMP: persistent epithelial defects, microbial keratitis and limbal inflammation main factors associated with reduced corneal visual acuity (KCS only very late).

**MANAGEMENT**

**ANTIINFLAMMATORY TREATMENT**

- Untreated cicatrising conjunctivitis has a variable course, not always progressive.
- Since inflammation typically followed by rapid shrinkage of the conjunctiva, progressive fibrosis more likely in advanced stages \(\Rightarrow\) careful monitoring of the disease activity crucial.
- Requirement of therapy dependent on the inflammatory activity and the progression of fibrosis. Before the inflammatory signs are attributed to the disease process itself, other aetiologies must be considered (ocular infections, toxic or allergic reaction to medication or preservatives, trichiasis and exposure).
- Handling of secondary problems is as important as institution of a systemic antiinflammatory therapy.
- There is no known specific treatment for progressive cicatrising conjunctivitis. Studies have focused on the use of various types of immunosuppression.
- Topical therapy: steroids ineffective, cyclosporin-A: preliminary data show no clinical improvement.
Generalised immunosuppression or immunomodulation the only effective treatments to halt the process of conjunctival fibrosis

- Systemic corticosteroids effective in the treatment of the acute manifestations, however an equivalent of 40 mg prednisone per day would be necessary to control disease progression ⇒ systemic steroids mainly used in combination with cyclophosphamide for the initial treatment of acute, rapidly progressive manifestations
- Cyclophosphamide most effective, used for very active disease (very inflamed eyes)
- Mycophenolate
- Dapsone for the treatment of milder forms of progressive disease
- Sulphapyridine, sulphasalazine and sulphamethoxypyridazine are alternatives to dapsone
- No role for oral cyclosporin-A

SYMPTOMATIC TREATMENT

- Ocular surface disease  Follow general principles, least toxic drugs, unpreserved medication
- Conjunctival trauma triggers the disease process, resulting in an inflammatory flare up with rapid scarring
- Disastrous effect of ocular surgical procedures in general, and plastic surgical procedures in particular when carried out in patients with active cicatricial pemphigoid
- Surgery should only be performed when control of the disease process has been achieved, procedures which avoid direct trauma to the conjunctiva are preferred
- Lid Surgery  Trichiasis: electro- or kryoepilation. Entropion repair: Jones procedure for lower lid, anterior lamellar reposition for upper lid. Mucous membrane grafts: not in very dry eyes and advanced disease
- Biopsy of the fornix conjunctiva is contraindicated!

DO NOT HARM! - WHAT SHOULD BE AVOIDED?

- "There is no therapy available"
- Toxicity with topical medication
- Surgical procedures in inflamed eyes
- Plastic surgical interventions with direct trauma to the conjunctiva
- Biopsies of the fornix conjunctiva

REFERENCES

COMPLICATIONS OF TOPICAL MEDICATION

“Doctors pour drugs, of which they know little, for conditions about they know less, into patients about whom they know nothing” Voltaire (1694-1778)

- Severe adverse effects unfrequent
- Significant ocular morbidity
- Toxic and allergic reactions second in frequency among all external eye diseases

- Spectrum of adverse effects
  (subclinical epithelial changes <-> corneal blindness)
- Grossly two groups of reactions:
  - Toxic effects
  - Allergic reactions
- Toxic reactions far more common than allergic ones (Frequency 9:1)
  NB: > 10 days needed for sensitization!
  [Wilson II FM. Surv Ophthalmol 1979; 24: 57-88]

PREVENTION
- Accurate diagnosis !
- Lack of diagnosis leads to overtreatment syndrome
  (adverse effects are misinterpreted as failure of therapy)
- Knowledge of potential toxicities
- Abandon the idea that most drug reactions are allergies and not toxicities
  (misconception that a change in therapy will solve the problem)

- Selection of the least toxic drug
- Monotherapy when possible
- Unpreserved formula
- Contact lenses:
  - Disinfection using unpreserved peroxide systems or heat rather than chemical disinfection
  - Disposable soft lenses (daily wear)

PIGMENTED LESIONS

- Benign epithelial melanosis (racial melanosis)
- Benign melanocytic nevi (classified like those of the skin; most are compound or subepithelial)
- Primary acquired melanosis (PAM)
- Secondary melanosis
- Malignant conjunctival melanoma

BENIGN EPITHELIAL MELANOSIS (RACIAL MELANOSIS)

- Common in darkly pigmented individuals
- Perilimbal and interpalpebral pigmentation
- Bilateral, may be asymmetric
- Increased metabolic activity of resident melanocytes, increased production of melanin granules
- No risk of malignant degeneration
**Benign Melanocytic Nevi**

- Most common pigmented lesion
- Bulbar conjunctiva, plica, caruncle, lid margin
- Nevi on palpebral or fornical conjunctiva rare > CAVE: melanoma
- Freely mobile over surface of the globe
- 20-30% nonpigmented
- Cystic spaces within the lesions diagnostic

- 5% melanocytes in normal basal epithelium (dendritiform, difficult to distinguish from adjacent epithelial cells)
- Abnormal benign proliferation of melanocytes, in basal epithelium, form clusters („junctional nests“)
- Appear in the first two decades of life (< > PAM, melanoma)
- 2./3. decade: cells sprinkle down into the substantia propria (compound nevus)
- 3./4. decade: epithelial and junctional component regress > nevi cells left in the substantia propria (subepithelial nevus)

**Primary Acquired Melanosisis (PAM)**

- Proliferation of intraepithelial conjunctival melanocytes
- Unilateral, flat, patchy golden-brown
- New areas of conjunctival involvement develop while other areas disappear
- Spread of melanocytes on the cornea frequent (not feature of racial melanosis or nevi)
- Malignant potential
- Difficulty in predicting the individual risk for melanoma

- Two categories: without features of cellular atypia <> with features that are likely to undergo malignant degeneration
- Cellular atypia: spread of epitheloid cells higher than basement membrane region of the epithelium

- „No PAM in children, no junctional nevus in adults“
- Excisional biopsy for small lesions
- Multiple biopsies with mapping for extensive lesions
- Cryotherapy for PAM with atypia (triple freeze thaw)

**Malignant Conjunctival Melanoma**

- From preexisting nevi, derived from acquired melanosis, and from previously normal conjunctiva
- In case of PAM: development of nodular thickening, tendency to become fixed
- Tumor thickness the most important prognostic factor
- It remains impossible for the ophthalmologist to obtain reliable prognostic signs
- 10-year cumulative incidence of initial regional metastasis 0.11, for initial systemic metastasis 0.18 (series of 85 caucasian patients).


Therapeutic outcome of 81 patients:
- treated between 1960 and 1988
- median follow-up 5.5 years
- 62 complete remission (76.5%), 19 recurrences (23.5%), 15 died of metastases (18.5%)
- Local excision followed by beta-irradiation or cryotherapy treatment of choice