LOUIS A. WILSON

External diseases of the eye

External Diseases of the Eye

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Preface

Amongst the clinical specialty of ophthalmology perhaps the greatest demand is made of the practitioner in managing external diseases of the eye. Here he must be prepared to differentiate and deal with ocular infectious and noninfectious inflammations as well as neoplastic, degenerative, and hypersensitivity disorders. He must take into account the variables of age, sex, race, geography, and climate. He must recognize the consequences of physical and chemical trauma, as well as those of surgery on the eye. In addition, his knowledge of therapy must include a rational approach to the selection of drugs with reference to local and systemic use, particularly antimicrobials. Since disorders of the external eye constitute some of the most frequently encountered problems in ophthalmic medicine, a review of these broad requirements in a single text was the basis for this volume's conception.

Originally prepared as the section on external diseases for the Clinical Ophthalmology loose-leaf series, the material presented in this text has been both updated, when indicated, and expanded. It is intended as a collation of clinically useful information on frequently encountered external ocular disorders, with no attempt to prepare an encyclopedic assemblage of data. While it has not been possible or practical to maintain the same style in each chapter, the pattern of introduction, incidence, clinical features, disease mechanisms, therapy, and prognosis has been followed. Some emphasis has been given to the clinical application of simple laboratory techniques and the preparation of commercially unavailable fortified antimicrobial solutions, since teaching experience has indicated these to be areas of some confusion, yet of much interest among practicing ophthalmologists. Aside from indicating that surgery is one of the therapeutic options or perhaps the treatment of choice, no detailed description of surgical technique has been included. For such, the reader is referred to any of the excellent currently available texts on ocular surgery.

Finally, the Editor would like to express his deepest sense of appreciation to the contributors, each an expert in external diseases of the eye, whose lucid manuscripts, patience, and forbearance made this volume possible.

Louis A. Wilson, MD
1979

External Diseases of the Eye

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Laboratory Aids in Diagnosis

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Use of the laboratory in evaluating infections of the eye may yield valuable information which together with clinical findings allows a specific or presumptive diagnosis to be made. Infrequently, more sophisticated procedures may be indicated; in the majority of situations, however, the simple techniques for cultures of the outer eye and for microscopic examination of stained smears of conjunctival and/or corneal scrapings are sufficient.

INDICATIONS

Like other diagnostic procedures in ophthalmology, it is best to become as familiar as possible with the use of laboratory methods early during one's training. During training and in the early years of practice, laboratory studies should be used to assist in the diagnosis of all infections of the eye. As soon as the physician is experienced in correlating etiologic factors with clinical findings, laboratory studies are not routinely indicated in obvious clinical situations.

It is most important to remember that laboratory studies should be performed whenever there is any doubt concerning the diagnosis. The following are some conditions in which laboratory studies are mandatory:

1. Neonatal conjunctivitis
2. Hyperacute conjunctivitis
3. Membranous conjunctivitis
4. Central corneal ulcers (not obviously herpetic)
5. Postoperative infections (anterior chamber and/or vitreous aspirations)
6. Any severe long-standing conjunctivitis

Some conditions in which cultures and scrapings are often helpful include the following:

1. Any chronic conjunctivitis
2. Unilateral conjunctivitis
3. Infectious eczematous conjunctivitis
4. Keratoconjunctivitis sicca
5. Vernal conjunctivitis
6. Atopic conjunctivitis

MATERIALS (FIG 1-1)

CULTURE MEDIA

The use of solid media in clinical ocular microbiology has definite advantages. They are easily stored, are convenient to use in Petri dishes, and facilitate the early identification of organisms. Samples can be streaked on a medium's surface with an inoculating swab or spatula; the resulting growth is visible on the streaks. Growth off a streak is assumed to be a contaminant. The added advantage of being able to roughly quantitate isolated bacteria is frequently of value. For example, in a case of suspected bacterial blepharitis the cultivation of 10 to 15 colony forming units (cfu) of *Staphylococcus epidermidis,* normally considered resident microbiota of the outer eye, would not usually suggest lid margin therapy. However, confluent cfu growth of the same bacterium would suggest a microbial population density on the lid margin in excess of normal and capable of causing disease. In such a case, therapy would be warranted.

Table 1-1 correlates various suspected infections with the appropriate culture media.

Bacterial Media

Blood agar is a widely used, general purpose isolation medium which is readily available from hospital and private laboratories. Basically it is a trypticase-soy agar to which 5% to 10% sterile, defibrinated blood (sheep or rabbit) has been added. It affords early recognition of complete or partial hemolysis and is suitable for the primary isolation of common outer eye pathogens with the exception of the *Haemophilus* and *Neisseria* organisms. Since blood agar is relatively inexpensive when prepared or purchased in quantity, most diagnostic laboratories will gladly supply several plates once or twice weekly to any ophthalmologist in their community.

Fig 1-1. Materials needed in laboratory workup. Solid media from left to right are chocolate agar, blood agar, and Sabouraud's agar. Fluid media in test tube rack are fluid thioglycollate and trypticase-soy broth. Precleaned frosted-end slides are ready for use. An alcohol lamp and individually packaged, sterile applicators are in the foreground.

Chocolate agar is essentially a polypeptone agar base which has been enriched with hemoglobin and a chemically defined supplement. The presence of hemin and diphosphopyridine nucleotide makes this medium well suited for the cultivation of *Haemophilus* as well as other fastidious pathogens such as gonococcus and meningococcus. As a general rule, all bacteria which can be cultivated on blood agar may also be isolated on chocolate agar, but not vice versa. Therefore, in areas where *Haemophilus* conjunctivitis is endemic, such as the southeastern portion of the United States, chocolate agar is probably the primary isolation medium of choice.

Thayer-Martin medium is a selective, chemically enriched, chocolate agar which contains 3.0μg of vancomycin, 7.5μg of colistimethate, and 12.5 units of nystatin per milliliter of solid medium. This medium's value in ophthalmology is in culturing material from patients with suspected gonococcal conjunctivitis. Especially in culture material obtained from a neonate, contaminants may inhibit the growth of gonococci if nonselective media are used alone. Therefore, when a patient is suspected of having a gonococcal infection it is routine on the eye service of the Emory University affiliated hospitals to employ both chocolate and Thayer-Martin agar.

Lowenstein-Jensen medium is used for the isolation and cultivation of mycobacteria, especially *Mycobacterium tuberculosis*. This medium is prepared as a solid slant, should be kept moist, and should be stored in the refrigerator. Like all of the other media discussed in this chapter, it should be brought to room temperature prior to inoculation. In suspected ocular mycobacterial infections, the culture material is immediately inoculated onto at least two tubes of Lowenstein-Jensen medium and the tubes are tightly resealed. The tubes should be checked after 4 to 7 days of incubation for rapidly growing mycobacterium (*M fortuitum*) and then weekly for *M tuberculosis*.

Nocardia organisms can also be cultivated on Lowenstein-Jensen medium.

Ophthalmologists infrequently encounter anaerobic infections. When such an infection is suspected it is essential that the clinical specimens (corneal scrapings, canalicular concretions, aqueous or vitreous aspirations) be cultivated as quickly after collection as possible. A number of selective and nonselective media are available for the isolation of anaerobic bacteria. In ophthal-

TABLE 1-1. Culture Media in Ocular Microbiology

Suspected Infection	Blood Agar	Chocolate Agar	Thayer-Martin Medium	Lowenstein-Jensen Medium	Cystine-Glucose-Blood Agar	Sabouraud's Agar	Fluid Thioglycollate Medium
Acute bacterial conjunctivitis	+	+ (southern US)					
Blepharitis	+	+				+	
Chronic conjunctivitis	+	+				+	
Hyperacute conjunctivitis (purulent)		+					
Neonatal conjunctivitis		+	+				
Oculoglandular conjunctivitis		+		+	+	+	+
Canaliculitis	+	+				+	+
Dacryocystitis	+	+				+	+
Corneal ulcer	+	+		+*		+	+
Endophthalmitis	+	+		+*		+	+
Orbital cellulitis	+	+		+*		+	+

* If cytology suggests a mycobacterium infection.

mologic practice, however, the limited clinical material available dictates the use of a general utility medium capable of supporting strictly anaerobic, microaerophilic, and aerobic organisms; fluid thioglycollate medium is generally used for this purpose.

Special media, selective and nonselective, enriched and nonenriched, may be indicated in certain clinical situations. If the ophthalmologist suspects a bacterial infection and the clinical signs suggest a specific agent, the hospital microbiologist may be able to suggest the best isolation medium. For example, a young adult presents with ulcerative oculoglandular conjunctivitis, subsequently develops systemic signs, and has a history of having recently eviscerated a wild rabbit. The possibility of a *Francisella* (*Pasteurella*) *tularensis* infection must be seriously considered; in this instance, cystine-glucose-blood agar would be one of the cultivation media recommended.

Mannitol-salt agar is a selective medium used for the cultivation of pathogenic staphylococci. The salt content provides for selective inhibition, and a color change from red (phenol red) to yellow indicates mannitol fermentation, a sign of pathogenicity. This medium is not suggested for primary isolation of bacteria but rather for diagnostic laboratory use.

The coagulase and mannitol fermentation characteristics of pathogenic staphylococci are obvious on coagulase-mannitol agar (containing plasma). Like mannitol-salt agar, this medium has its main use in the diagnostic laboratory.

Fungal Media

The medium most commonly employed in cultivating fungi from ocular infections is Sabouraud's agar, a combination of glucose, peptone, and agar. The culture material from the ocular lesion should be immediately inoculated onto the agar plates which are then incubated at 27 C. If tubed medium is used, several tubes should be inoculated.

While plain Sabouraud's agar is satisfactory in most instances, some additives may increase the chance of successfully cultivating a small amount of inoculum. Yeast extract, as a 0.1% additive to the basic medium, represents an excellent source of B complex vitamins, an important nutritional requirement for most fungi. Bacterial contamination may be avoided if one incorporates an antibiotic into the medium. Chloramphenicol in a concentration of 0.5 gm/liter has proved most satisfactory for this purpose.

Cycloheximide, an inhibitor of saprophytic fungal growth, is a frequent component of some fungal media (ie, Mycosel [Baltimore Biological Laboratories, Cockeysville, MD]). It should not be present in the media used for mycotic keratitis since most cases are due to so-called saprophytes.

A 250-ml flask containing 50 ml of 2.0% glucose-1.0% peptone-0.1% yeast extract (GPY) and

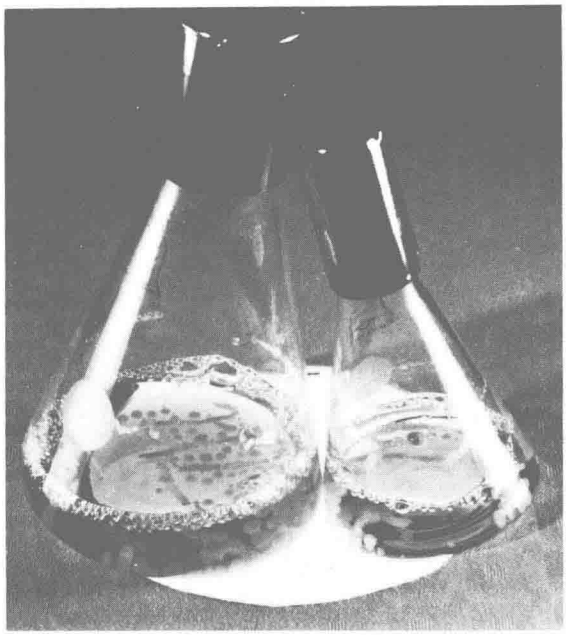


Fig 1-2. Glucose-peptone-yeast extract broth inoculated with scrapings from a fungal corneal ulcer and incubated at 27 C on a gyrotary shaker for 36 hours. The organism is *Aspergillus versicolor*. Note numerous globose hyphal pellets in both flasks.

125 mg of chloramphenicol has proved to be a valuable backup method for isolating fungi difficult to cultivate on solid media. Brain-heart infusion broth with an antibiotic added is an alternate liquid isolation medium. The inoculated medium is incubated at 27 C on a gyrotary shaker for aeration. Agitation of the culture during the growth exposes the organism to a uniform environment in all spacial directions; therefore, the colony is usually a globose structure (Fig 1-2).

Once fungal growth has been noted, it should be subcultured promptly onto fresh media for storage and to induce sporulation. Sporulation media employed in morphologic identification are potato-dextrose agar, cornmeal agar, and Czapek agar.

Viral Media

In general, viral culture media for use in clinical ophthalmology are not readily available. The maintenance of a tissue culture system, involving perhaps several different cell lines for routine diagnostic purposes, is prohibitively expensive for the community hospital. Fortunately, the clinical findings in two of the more common viral infections of the outer eye (ie, herpes simplex and adenovirus) often permit a presumptive diagnosis. Nonetheless, in unusual, chronic or epidemic situations, the identification of a viral agent may be indicated. In such cases, conjunctival or corneal material, obtained by swabs and/or scraping, is placed in a transport solution (ie, Hanks' or Earle's balanced salt solution with antibiotics) supplied by the viral laboratory. This solution is then chilled in ice until inoculation of the culture medium, which should be within 6 hours. If the medium is to be stored for more than 6 hours it should be quick-frozen and stored at −20 C; for prolonged storage it should be kept at −60 C. Serums from the acute and convalescent stages should be obtained from the patient to assist in serologic identification of the isolate. This may also be stored frozen. Unless a research facility is available to the clinician, frozen specimens are forwarded to the respective state health department laboratories.

STAINS

Scrapings and smears are studied by the use of different stains. A Giemsa stain (Table 1-2) is

TABLE 1-2. Giemsa Stain

Materials needed
- 3 or 4 Coplin slide jars
- Stock Giemsa solution*
- 95% methanol
- 95% ethanol
- Buffered distilled water (pH 7.2)

Procedure

Rapid 15-minute technique
1. Air dry slide for at least 5 minutes.
2. Fix in 95% methanol 5 to 10 minutes.
3. Air dry slide.
4. Mix two drops of stock Giemsa solution per milliliter of buffered distilled water (volume prepared depends on number of slides to be stained); pool mixture on slide for 15 minutes.
5. Wash slide in buffered distilled water.
6. Quickly rinse slide in 95% ethanol.
7. Rinse slide in fresh buffered distilled water.
8. Air dry slide.

One-hour technique—same as rapid technique, except staining solution consists of one drop of stock Giemsa to one drop of buffered distilled water in Coplin slide jar. Staining time is 60 minutes.

Special precautions
1. Use a high-grade stock Giemsa solution.
2. Mix staining solutions fresh daily.
3. Use only buffered distilled water (pH 7.2) to ensure an even staining pattern.

* Giemsa stock solutions available from HARLECO, 60th and Woodland Ave., Philadelphia, PA 19143.

used when information concerning the type of inflammatory cell, the condition of epithelial cells, and the presence or absence of cytoplasmic inclusions is desired. In general, in a case of conjunctivitis of unknown cause more information is obtained by a Giemsa stain than by a Gram stain. In a good number of patients, the conjunctivitis can be diagnosed as bacterial, viral, or allergic by studying the Giemsa-stained scrapings.

The Hansel stain (Table 1-3) is a simple and rapid (1 minute) technique which lends itself well to office use. Its major use in ocular cytology is for quick identification of an eosinophilic response. The eosinophilic granules stain red, contrasting sharply with the blue color of epithelial cells, neutrophils, and mucous strands. Bacteria also stain blue. While the general cytologic pattern may frequently be noted, the Hansel stain is not recommended for identification of cytoplasmic inclusions.

The Gram stain (Table 1-4) gives information regarding bacteria and often gives information about fungal elements which may be present on the slide. A corneal ulcer scraping almost always requires a Gram stain because the primary interest is in the organism and not the cytologic response. Preferably, one should perform both the Giemsa technique and the Gram technique in any given case. However, if only one slide can be prepared, the stain which will be most helpful in aiding the suspected diagnosis should be chosen.

Special techniques are occasionally indicated. A 10% or 20% potassium hydroxide aqueous solution (or 20% potassium hydroxide in 40% dimethyl sulfoxide) may be useful in identifying hyphal fragments in corneal scrapings obtained from patients with suspected keratomycosis. However, in at least one series, the Gram and Giemsa techniques proved more reliable for such immediate identification (1). Other stains for fungi, such as periodic acid-Schiff (PAS) and Gormori methamine silver (GMS), are reliable but must be requested specifically from the pathology laboratory.

If the clinical findings suggest that the infection is due to *M tuberculosis* or atypical mycobacteria, then one of two general methods for selective staining should be employed because the organisms may be misinterpreted as diphtheroids using the conventional Gram technique. With the widely used Ziehl-Neelsen acid-fast stain, mycobacteria are observed as red-staining organisms against a blue background. A newer fluorochrome technique for rapid selective staining utilizes the stains auramine and rhodamine. With fluorescent microscopy the mycobacteria may be seen as yellow-orange fluorescent bacilli on a dark background. The acid-fast *N asteroides* also gives this microscopic appearance, and final identification must await cultivation of the organism.

TABLE 1-3. Hansel Stain

Materials needed
- 95% methanol
- Hansel's stain*
- Distilled water

Procedure
1. Air dry smear.
2. Place 2 to 3 drops of 95% methanol on slide for 1 to 2 minutes.
3. Pour alcohol off slide and air dry.
4. Flood slide with Hansel's stain for 30 seconds
5. Add distilled water to take up stain; allow to stand for another 30 seconds.
6. Wash slide with distilled water.
7. Wash slide quickly with 95% methanol (3 to 5 seconds).
8. Wash with distilled water.
9. Air dry slide.

*Hansel's stain ready for use is available from Lide Laboratories, Inc., 515 Timberwyck, St. Louis, MO 63131.

TABLE 1-4. Gram Stain

Materials needed*
- Gentian violet
- Gram's iodine
- 95% ethanol
- Safranin

} all in stain bottles

Procedure†
1. Fix by flaming slide lightly.
2. Flood with gentian violet (approximately 15 seconds).
3. Rinse with tap water.
4. Flood with Gram's iodine (approximately 15 seconds).
5. Rinse with tap water.
6. Decolorize with 95% ethanol until thinnest areas are clear.
7. Rinse with tap water.
8. Flood with safranin (approximately 15 seconds).
9. Rinse with tap water.
10. Blot dry.

*All staining solutions may be secured in stock form ready to use from HARLECO, 60th and Woodland Ave., Philadelphia, PA 19143.

†From Paine TF, Jr.: Gram staining without the clock. N Engl J Med 268:941, 1963.

TECHNIQUES

BLEPHARITIS AND CONJUNCTIVITIS

Conjunctival and lid margin specimens are obtained without the use of a topical anesthetic since the preservative may markedly reduce the recovery of some bacterial pathogens. The conjunctival cul-

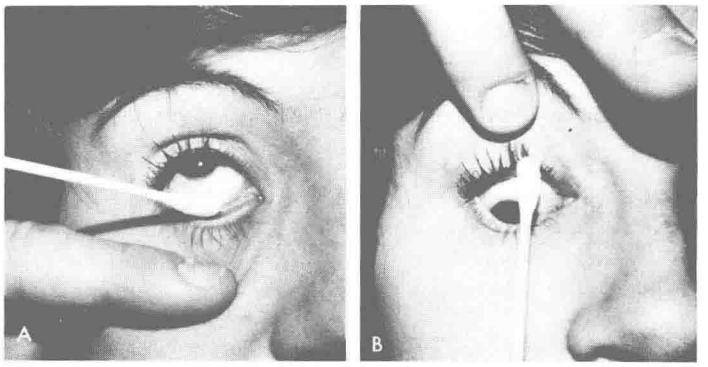


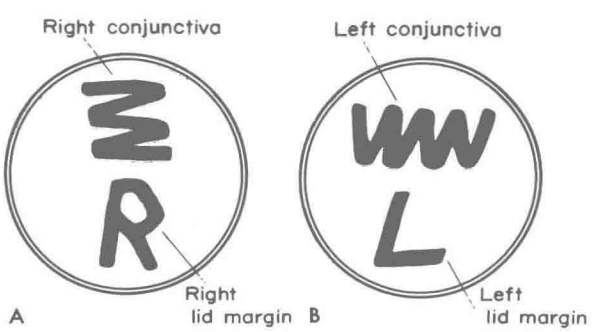
Fig 1-3. A. Obtaining a specimen from the inferior conjunctival sac with a premoistened, sterile applicator. **B.** Obtaining a specimen from a lid margin with a premoistened, sterile applicator.

ture is obtained by everting the lower lid and wiping a sterile moistened cotton-tipped applicator along the entire lower cul-de-sac (Fig 1-3, *A*) and then directly plating the swab onto a blood or chocolate agar plate. The swabs should be moistened with sterile saline or bacteriologic broth prior to use. Dacron-tipped or calcium alginate-tipped swabs are acceptable and perhaps preferable substitutes for cotton-tipped applicators. The lid margins (upper and lower) are then wiped with an applicator (Fig 1-3, *B*) and this is streaked on the same plate. Both eyes are cultured even though the patient may exhibit disease in only one eye. A different plate is used for the material from each eye since crowding these cultures onto one agar plate may create technical difficulties for laboratory personnel when they attempt to pick out and identify representative cfu. Regardless of the solid media used, a routine pattern of streaking the plates is preferred (Fig 1-4, *A* and *B*) so that one may identify the location from which the organisms are cultivated.

Since most yeastlike fungi (ie, *Candida* organisms) are readily cultivated on blood or chocolate agar, fungal media are not routinely used unless a mold infection of the lid and/or conjunctiva is suspected.

Following inoculation of the culture plates, a topical anesthetic is instilled. A platinum spatula (instrument No. E-1091, Storz Instrument Co., St. Louis, MO) is flamed, sterilized, and allowed to cool to room temperature. The lid (upper and lower) is everted, and the epithelial surface is gently scraped (Fig 1-5, *A*), care being taken to avoid any conjunctival bleeding. In instances of localized disease the scraping should be from the site of maximum involvement. The material obtained is spread in a thin layer on a precleaned glass slide. If lid margin scrapings are obtained (Fig 1-5, *B*) they may be spread thinly on the far end of the same slide. If possible, scrapings to be stained with the Giemsa technique should be immersed in 95% methanol for 5 to 10 minutes and then allowed to air dry. Staining may follow immediately or at a later time.

Fig 1-4. A. Pattern of inoculating streaks on solid media for a routine culture of the right eye. **B.** Pattern of inoculating streaks on solid media for a routine culture of the left eye.



CORNEAL ULCER

The laboratory workup of a central corneal ulcer, regardless of suspected etiology, must be performed in a deliberate and meticulous manner; failure to do so often accounts for the failure to identify the infecting organism and to initiate prompt, specific antimicrobial therapy. Therefore, in a corneal ulcer which is obviously not viral the following technique should be rigidly followed:

1. Material from the conjunctiva and lid margins of the involved eye is cultured, as previously described, on blood or chocolate agar and on a fungal medium containing antibacterials but lacking cycloheximide. Results of cultures obtained from the conjunctiva and lid margins