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The eye is an external organ, and is susceptible to injury, infection, and irritation, as well as to organic and functional disorders. The products and preparations for ophthalmic use therefore comprise a broad category and include medications, diagnostic agents, and medical device formulations.

Over-the-counter and prescription medications are used to treat chronic ailments (e.g., glaucoma, blepharitis, and dry eye), as well as temporary conditions (e.g., infections, allergic reactions, and injuries).

Ocular diagnostic agents are a specialized group of drugs and dyes utilized primarily for ocular examination and the identification of potential disease conditions. Medical device products are used for the hydration, wetting, cleaning, and disinfection of contact lenses.

1. Anesthetics

Topical anesthetics diminish sensory nerve impulse generation and conduction locally and are used to anesthetize the ocular surface during short corneal or conjunctival procedures (e.g.,
Oxybuprocaine hydrochloride [5887-82-6], 2-
diethylaminoethyl 4-aminosulfonobenzoic acid monohydrochloride, benoxinate hydrochloride, 
C₂₁H₂₅N₂O₂·HCl, M, 344.9.
Trade names: Alcon Ophtalm Bovisana (Alcon); 
Celsius (Ocraux-Blanché); Combicas (Médi); 
Myrune Benicsana Hidrocloro, Mérins Oxybuprocaine Hydrochloride (Smith & Nephew); 
Venofic (Depesta); Novamin (िदान); Novocain (Chibret, Wunder), 
Ophthol 

I.2. Regional Anesthetics

Bupivacaine hydrochloride [14001-40-7] (monohydrate [14232-80-3]), 1-butyl-N-(2,6-dimethyl-
phenyl)-2-piperidinooxo-benzoic acid monohydro-
chloride monohydrate, C₁₇H₂₃N₂O₂·HCl·H₂O, 
M, 343.9.

Epi-decane hydrochloride [88657-09-7], N-
(2,6-dimethylphenyl)-2-(ethylpropylamino)bu-
tanamide monohydrochloride, C₁₇H₂₅N₂O·
HCl, M, 312.9.

Hexylcaine hydrochloride [532-78-1], 2-cy-
clohexylamino-3-methylbenzoic acid monohy-
drochloride, C₁₇H₂₃N₂O·HCl, M, 257.8.

Lidocaine hydrochloride [71-78-0] (anhy-
drous), monohydrate [6106-90-5], 2-diethyl-
aminoethoxy-N-(2,6-dimethylphenyl)acetamide monohydrochloride monohydrate, 
C₁₀H₁₆N₂O·HCl·H₂O, M, 208.8.

Meipacaine hydrochloride [1722-62-9], N-
(2,6-dimethylphenyl)-1-methyl-2-piperidino-
BOXe hydrochloride, C₁₇H₂₃N₂O·HCl, M, 
262.8.

Pilocarpine hydrochloride [7789-81-8], N-2-me-
ethylphenyl-2-piperidinoacetophenone monohy-
androchloride, C₁₅H₂₃N₂O·HCl, M, 256.8.

Procaine hydrochloride [51-05-8], 2-diethyl-
aminoethoxy 4-aminobenzoate hydrochloride, 
C₁₇H₂₅N₂O₂·HCl, M, 272.8.

Tetracaine hydrochloride (see Section 1.1).

1.2. Regional Anesthetics

Bupivacaine hydrochloride [14001-40-7] (monohy-
drate [14232-80-3]), 1-butyl-N-(2,6-dimethyl-
phenyl)-2-piperidinooxo-benzoic acid monohy-
chloride monohydrate, C₁₇H₂₃N₂O₂·HCl·H₂O, 
M, 343.9.

Epi-decane hydrochloride [88657-09-7], N-
(2,6-dimethylphenyl)-2-(ethylpropylamino)bu-
tanamide monohydrochloride, C₁₇H₂₅N₂O·
HCl, M, 312.9.

Hexylcaine hydrochloride [532-78-1], 2-cy-
clohexylamino-3-methylbenzoic acid monohy-
drochloride, C₁₇H₂₃N₂O·HCl, M, 257.8.

Lidocaine hydrochloride [71-78-0] (anhy-
drous), monohydrate [6106-90-5], 2-diethyl-
aminoethoxy-N-(2,6-dimethylphenyl)acetamide monohydrochloride monohy-
drate, C₁₀H₁₆N₂O·HCl·H₂O, M, 208.8.

Meipacaine hydrochloride [1722-62-9], N-
(2,6-dimethylphenyl)-1-methyl-2-piperidino-
BOXe hydrochloride, C₁₇H₂₃N₂O·HCl, M, 
262.8.

Pilocarpine hydrochloride [7789-81-8], N-2-me-
ethylphenyl-2-piperidinoacetophenone monohy-
androchloride, C₁₅H₂₃N₂O·HCl, M, 256.8.

Procaine hydrochloride [51-05-8], 2-diethyl-
aminoethoxy 4-aminobenzoate hydrochloride, 
C₁₇H₂₅N₂O₂·HCl, M, 272.8.

Tetracaine hydrochloride (see Section 1.1).
2. Antimicrobial Agents

2.1. Antibacterial Agents

Successful therapy for bacterial infection with antibiotics relies upon five considerations:
1) Appropriate indications for use
2) Isolation and identification of the infective agent
3) Efficacy of the antibiotic for the infective agent
4) Adequate dosage of the antibiotic at the site of infection
5) Low toxicity of the antibiotic for the host [5]

Antibiotics act upon bacteria through a variety of mechanisms. The penicillins, cephalosporins, vancomycin, and bacitracin inhibit development of the bacterial cell wall. Tetracycline, erythromycin, clindamycin, chloramphenicol, and the aminoglycosides inhibit protein synthesis.

2.1.1. Sulfonamides

See also → Chemotherapeutics, A.6, pp. 186-192.

Although the use of sulfonamides for the treatment of major bacterial infections has been largely supplanted by antibiotics, they are still prescribed for the topical treatment of minor ocular infections. They exhibit broad-spectrum bacteriostatic activity against many gram-positive and gram-negative organisms, and are useful against the gram-negative Proteus. gonidia and Plasmodium falciparum. Some strains of Pneumococcus, Clostridia, and Actinomycetes are also sensitive to these drugs. A major disadvantage is the frequent occurrence of cross-resistant microorganisms. Many side effects have been reported following the topical administration of sulfonamides. These drugs are contraindicated for the treatment of keratoconjunctivitis sicca or penetrating corneal wounds. Sulfacetamide sodium is the most widely used sulfonamide at a concentration of 10%, or in combination with the steroid prednisolone acetate (0.2-0.5%).

The sulfonamides are antimetabolites. Their structural similarities to 4-aminobenzoic acid allow them to act as competitive inhibitors in the folic acid biosynthetic pathway.

Sulfacetamide sodium [212-90-9], N-(4-aminophenyl)sulfonamidomethyl-4-hydroxybenzenesulfonamide, C<sub>13</sub>H<sub>14</sub>N<sub>2</sub>O<sub>6</sub>S, M<sub>r</sub> 347.30, is incorrectly called sulfacetamide. For synthesis see [6].

Sulfadiazine [68-15-9] (sodium [547-17-9], silver [2276608-2]B), 4-amino-N-2-pyrimidinylbenzenesulfonamide, C<sub>13</sub>H<sub>14</sub>N<sub>2</sub>O<sub>6</sub>S, M<sub>r</sub> 350.3, mp 252-256 °C for synthesis, see [7].

Sulfamethazine [27-58-7], 4-amino-N(4-methyl-2-pyrimidinyl)benzenesulfonamide sodium salt, C<sub>13</sub>H<sub>14</sub>N<sub>2</sub>O<sub>6</sub>S, M<sub>r</sub> 286.3. For synthesis, see [3]. Sulfamethazine sodium is a short-acting sulfonamide with action similar to that of sulfanilamide. It is usually administered with other sulfonamides.

Sulfamethizole [144-82-1], 4-aminobenzene-3,5-diamido-1,3,4-isochromanone, C<sub>16</sub>H<sub>10</sub>N<sub>2</sub>O<sub>4</sub>, M<sub>r</sub> 270.3, mp 208 °C. For synthesis, see [8].

Sulfonamido diacetae [2499-60-9], 4-amino-N-(3,4-dimethyl-2-furoyl)-benzenesulfonamide diethylamine, M<sub>r</sub> 372.4. For synthesis, see [9].

Trade names: Genisulf (Optical; Ointment; Solution, Sodium- sulfonamides (Rexis).

2.1.2. β-Lactam Antibiotics

2.1.2.1. Penicillins

Penicillins are effective antimicrobials, although they have two drawbacks: (1) microbeal resistance is relatively common, and (2) penicillins may be antigenic; little stock is therefore a concern when they are administered systemically. See also → Antibiotics, A2, pp. 473-475.
Ampicillin [69-73-4], (sodium derivative [69-52-3], tetrabutylammonium salt [7177-48-2]), C₁₆H₁₇N₂O₄S, M₉₀.42, mp 262°C (decomp). Ampicillin is a semisynthetic derivative of penicillin. For synthesis, see [10]. See also →Antibiotics, A₂, p. 508.

Methicillin sodium [132-93-3], C₁₆H₁₇N₂O₄NaS, M₁₉₂.42, mp 196-197°C. Methicillin sodium is a semisynthetic antibiotic related to penicillin. For synthesis, see [11]. See also →Antibiotics, A₂, p. 507.

2.1.2. Cephalosporins

The cephalosporins originate from a mold of the genus Cephalosporium. Although cephalosporins do not usually cause an allergic reaction in patients sensitized to penicillin, allergy to cephalosporins can also develop. The cephalosporins are not inactivated by penicillin-resistant bacteria and have a broader spectrum of activity than penicillin. See also →Antibiotics, A₂, pp. 474-478.

Carbenicillin [697-76-7] (sodium derivative [4808-64-6], indanyl sodium derivative [2660-69-4], phenyl sodium derivative [21649-37-5]), C₁₉H₁₈N₂O₄S, M₂₃₈.42. For synthesis, see [12]. See also →Antibiotics, A₂, p. 506.

Cefadroxil [28533-19-9] (sodium salt [3764-41-1]), C₁₉H₁₈N₂O₄NaS, M₂₃₈.50. mp 198-200°C. For synthesis, see [13]. For structure see →Antibiotics, A₂, p. 477.

Cephalotin [531-61-7] (cephalothin sodium [567-73-9], C₁₈H₁₇N₂O₃NaS, M₂₃₈, mp 160°C. Cephalothin is a semisynthetic cephalosporin antibiotic. For synthesis, see [14]. For structure see →Antibiotics, A₂, p. 477.

2.1.3. Tetracycline Antibiotics

Tetracyclines reversibly block protein synthesis by specifically binding to the bacterial ribosome. Tetacycline and chloramphenicol were the first broad-spectrum antimicrobials discovered. The tetracycline antibiotics listed below are described in detail elsewhere; see →Antibiotics, A₂, pp. 484, 485, 516.

Chlortetracycline hydrochloride [64-77-7] (chlorotetracycline [35-65-5]), C₂₀H₁₄Cl₁N₂O₆, M₄₉₃.9. Chlortetracycline is isolated from Streptomyces aureofaciens [15].

Trade name: Auromycin (Optulex, USA).

Oxytetracycline [76-57-1] (hydrochloride [205-66-0]), C₁₉H₁₈N₂O₄Cl₂, M₄₆₀.84, is an antibacterial isolated from the fermentation of Streptomyces rimosus [16].

Trade name: Terramycin (sodium) with polymyxin B (Schering Corp., 10000 USP Units). Tetracycline [66-54-8] (hydrochloride [64-75-5], phosphate complex [1336-20-2]), C₁₉H₁₇N₂O₄P, M₄₄₄.43, is an antibiotic produced by Streptomyces spp. [17]. [18].

Trade name: Achromycin and Achromycin Ophthalmic Ointment 1% (Dea.

2.1.4. Aminoglycoside Antibiotics

The aminoglycoside antibiotics exhibit broad-spectrum antimicrobial activity, particularly against gram-negative organisms →Antibiotics, A₂, pp. 485-491. They inhibit protein synthesis and decrease translational efficiency through interaction with the 30S subunit of bacterial ribosomes. Cross resistance exists among the aminoglycosides. Aminoglycosides are generally administered topically because systemic absorption may produce ototoxicity and nephrotoxicity. Aminoglycosides and β-lactam antibiotics are incompatible in the same formulation. Aminoglycosides are not effective under acid conditions, in high sal: concentrations, or against intracellular bacteria.

Furanyllactate sulfate [146-83-9], C₂₀H₂₂O₇S, M₃₉₂.72, the sulfate of neomycin B, C₁₇H₁₇O₆N₃S, 3H₂SO₄, M₉₀₈.9. Neomycin B is isolated from the mixture of neomycins A, B, and C, produced by Streptomyces fradiae; see also →Antibiotics, A₂, p. 520 [19]. Furanyllactate sulfate has broad-spectrum activity similar to that of neomycin but is more efficacious against Pseudomonas spp. Unlike most other aminoglycosides, furanyllactate sulfate can be administered by subconjunctival injection; however, because of its high degree of systemic absorption, extreme caution must be employed to avoid toxicity.

Trade name: Fostyurgan (Favex), Solfamycin (Russia), with 0.5% hydrocortisone acetate in Fostyurgan (Favex), with 100% benzalkonium chloride and 0.005% gramicidin in Solfamycin (Russia).

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Gentamicin sulfate [405-41-0] (gentamycin [403-66-2]) is a complex mixture of the sulfates of gentamicin C₁₇, C₁₈, and C₁₉. This complex is produced by fermentation of *Mycoplasmapharao* [20]; see also --Antibiotics, A2, p. 519.

Gentamicin sulfate is used as a drop, ointment, or buffered preserved solution, generally at a concentration of 0.3%.

Trade names: Akemycin (Akorn); Cedricyna (Ross-Byck); Gentamicin (Kabi-Warner); Gentamicin Ophthalmic Ointment Solution -- Sustained (Shire); Genopt (Allergan); Gentamicin (CooperVision); Gentamicin (Pharmacia); Gentamicin (Solvay); Gentamicin Ophthalmic Solution (Allergan); Genopt S.O.P. Sterile Ophthalmic Ointment (Allergan); Gentamicin Cream and Ointment Solution (Pharmacia); Gentamicin Ointment and Solution (Allergan); Gentamicin Ointment/Solution (RoDail); Gentamicin Ointment/Solution (Bausch & Lomb); Minig Gentamicin Sulfate (Phillips & Neitz); Neo Mycin Sterile Ophthalmic Ointment/Solution (Oxandol); Pedi-G Lipafilin Sterile Ophthalmic Suspension (Allergan); Pred-G S.O.P. Sterile Ophthalmic Gauze (Allergan).

Micromycin sulfate (micromycin [52093-17-7], C₂₃H₁₈N₈O₄·3H₂SO₄·5H₂O·M, 1477.5, mp 360°C). This gentamicin C₁₂ complex antibiotic is produced by *Mycoplasmapharao*; var. microdictum [21].

Trade name: Saganacin (Kowa); Sanyohtecin (Santo-ten).

Neomycin [404-66-2] is an antibiotic complex made up of neomycins A, B, and C from *Streptomyces fradiae* [22]-[24]. See also --Antibiotics, A2, p. 529.

Trade name: Al-Spore (K-C.) Ointment/Solution, Al-Stark Ointment & Suspension (Allergan); Cortisporin Ophthalmic Ointment/Suspension (Burroughs Wellcome); Deso-Acin Ointment/Suspension (RoDail); Desoxapen Ophthalmic Suspension (Pharmacia); Infectol Ointment; Neomycin (Bausch & Lomb); Neo-Desox Ophthalmic Ointment (Merk Sharp & Dohme); Neo-Dex Ophthalmic Solution (Pharmacia); Neomycin Ophthalmic Ointment/Solution (Burroughs Wellcome); Neo-Gel (Burroughs Wellcome); Neo-Sporin Ophthalmic Solution (Burroughs Wellcome); Neo-Sporin Ophthalmic Solution (Bausch & Lomb); Neo-Sporin Ophthalmic Ointment (Burroughs Wellcome); Neo-Sporin Ophthalmic Suspension (Burroughs Wellcome); Neo-Sporin Ophthalmic Solution (Pharmacia); Ocliptic Ophthalmic Suspension (Bausch & Lomb); Ointu-Mycin Ophthalmic Ointment (RoDail); Ointul (Burroughs Wellcome); Pred-Mycin Ophthalmic Ointment (Allergan); Poly-Mycin Ophthalmic Ointment (Allergan).

Soomicin [22855-11-8] (sulfate [3379-09-2], C₂₀H₁₆N₄O₄·M, mp 198–201°C). Soomicin is an antibiotic produced by *Mycoplasmapharao microdictum* [25]. It is usually administered systemically and not commonly used as an ophthalmic antibiotic. See also --Antibiotics, A2, p. 522.

Streptomycin sulfate [810-74-0] (streptomycin [57-92-3], C₁₀H₁₃N₉O₄·M, 1457.60. Streptomycin is produced by *Streptomyces griseus* [26]; see also --Antibiotics, A2, p. 521. Concanal penetration of streptomycin is poor but can be greatly enhanced by iontophoresis.

Tobramycin [32986-36-4] (sulfate [79843-27-5], C₁₃H₂₈N₄O₃·M, 447.5). Tobramycin is produced by *Streptomyces tenuebrasii* [27]. See also --Antibiotics, A2, p. 318. Tobramycin has a broad spectrum of activity similar to that of gentamicin. Cross-resistance of tobramycin and gentamicin has been observed. Tobramycin is four times more effective against *Pseudomonas aeruginosa* and less effective against *Serratia*, than gentamicin. Unlike other aminoglycosides, tobramycin is ineffective against mycobacteria.

Trade name: Tobradex Ophthalmic Ointment and Suspension; Tobradex, Tobrex, Tobrasmin, Tobrnea (Allergan); Tobrex (Gibbons); Tobrex-3T (Osaka).

2.1.5. Polypeptide Antibiotics

Bacitracin [405-87-4], bacitracin A (major component): C₁₃H₁₇N₋O₇S·M, 1422.71. Commercial bacitracin is a mixture of at least nine bacitracins produced by *Bacillus subtilis* and *B. licheniformis* [28],[29]; see also --Antibiotics, A2, p. 528. It is available singly only at an ointment (500 mg/g) and in combination with other antimicrobials (see Table H).

Trade name: All-Poly Bac Ointment, All-Spore (Cex.) Ointment (Allergan); Bacitrax Ophthalmic Ointment Sterile (Pharmacia); Carbimycin Ophthalmic Ointment Sterile, Neosporin Ophthalmic Ointment Sterile (Burroughs Wellcome); Neosporin Ophthalmic Ointment (Burroughs Wellcome); Ointu-Mycin Ophthalmic Ointment (Bausch & Lomb); Ointu-Mycin Ophthalmic Solution (Bausch & Lomb); Pred-G Lipafilin Ophthalmic Suspension (Allergan); Poly-Mycin Ophthalmic Ointment (Allergan).

Colistimethate sodium [8056-28-8], C₁₃H₁₇N₄O₂Na₂·M, 1749.8. Colistimethate sodium is an injectable form of colistin, a cyclopolypeptide produced by *Bacillus colistinus* [30]. See also --Antibiotics, A2, p. 528.

Trade name: Colymycin M (Parke-Davis).

Polymyxin B sulfate [404-20-5] is a mixture of polymyxins B₁ and B₂ produced by *Bacillus polymyxa* [31],[32]. See also --Antibiotics, A2.
### Table 1. Concentration Antibiotic solutions and sources

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**Tray names**: Ak-Chlor Sterile Ointment, Ak-Ontan (H.C.), Oxytetracillin Suspension, Bakt-Ointment Suspension (Acorn); Cortisporin Ointment Suspension (Bathway Wellscome); Doxycyclin Ointment Suspension (PGC); Dicloxacillin Ointment Suspension (Pharmacia); Flarex suspension (Brand & Lamb); Moxifloxacin Ointment Suspension (Novartis); Neosporin Ointment Ophthalmic Solution (Sanofi-Aventis Wellscome); Neosporin Ointment Suspension (Brad & Lamb); Oxyceril Ointment Suspension (Oxford); Oxytetracillin (Oxford); Polysporin Ointment Ophthalmic Solution (Oxford); Toxidol Ointment Suspension (Pharmacia); Toxidol Ointment (Oxford); Oxytetracillin (Oxford). **Polyene**: Polyoxin Ophthalmic Ointment (Burns Wellscome).

### 2.6. Miscellaneous Antimicrobial Agents

**Chloramphenicol** [56-77-7], C<sub>6</sub>H<sub>5</sub>ClN<sub>2</sub>O, M<sub>r</sub> 231.1, mp 150.5–151.5°C, is a broad-spectrum antibiotic produced by *Streptomycetes cacaoae* [33] [35]. Chloramphenicol reversibly blocks the bacterial ribosome, inhibiting protein synthesis. See also **Antibiotics**, A.2. p. 535.

**Trade names**: Ac-Chlor Sterile Ointment (Acorn); Chlortetra Ointment (Pharmacia); Chlorhexidine Ophthalmic Ointment/Solution (Powder: Hydrocortisone Ophthalmic Solution (Parke-Davis)). Chloramphenicol Sodium Ophthalmic Solution (Allergan); Oto-Chlor Sterile Ophthalmic Ointment (Adrian); Oto-Chlor Ophthalmic Solution (Oxorn). **Polyoxin**: Polyoxin B Ophthalmic Solution (Oxford). **Polysporin**: Polysporin Ophthalmic Ointment (Sanofi-Aventis Wellscome).

**Chloramphenicol** [56-77-7], C<sub>6</sub>H<sub>5</sub>ClN<sub>2</sub>O, M<sub>r</sub> 231.1, mp 150.5–151.5°C, is a broad-spectrum antibiotic produced by *Streptomycetes cacaoae* [33] [35]. Chloramphenicol reversibly blocks the bacterial ribosome, inhibiting protein synthesis. See also **Antibiotics**, A.2. p. 535.

**Trade names**: Ac-Chlor Sterile Ointment (Acorn); Chlortetra Ointment (Pharmacia); Chlorhexidine Ophthalmic Ointment/Solution (Powder: Hydrocortisone Ophthalmic Solution (Parke-Davis)). Chloramphenicol Sodium Ophthalmic Solution (Allergan); Oto-Chlor Sterile Ophthalmic Ointment (Adrian); Oto-Chlor Ophthalmic Solution (Oxorn). **Polyoxin**: Polyoxin B Ophthalmic Solution (Oxford). **Polysporin**: Polysporin Ophthalmic Ointment (Sanofi-Aventis Wellscome).

**Chloramphenicol** [56-77-7], C<sub>6</sub>H<sub>5</sub>ClN<sub>2</sub>O, M<sub>r</sub> 231.1, mp 150.5–151.5°C, is a broad-spectrum antibiotic produced by *Streptomycetes cacaoae* [33] [35]. Chloramphenicol reversibly blocks the bacterial ribosome, inhibiting protein synthesis. See also **Antibiotics**, A.2. p. 535.

**Trade names**: Ac-Chlor Sterile Ointment (Acorn); Chlortetra Ointment (Pharmacia); Chlorhexidine Ophthalmic Ointment/Solution (Powder: Hydrocortisone Ophthalmic Solution (Parke-Davis)). Chloramphenicol Sodium Ophthalmic Solution (Allergan); Oto-Chlor Sterile Ophthalmic Ointment (Adrian); Oto-Chlor Ophthalmic Solution (Oxorn). **Polyoxin**: Polyoxin B Ophthalmic Solution (Oxford). **Polysporin**: Polysporin Ophthalmic Ointment (Sanofi-Aventis Wellscome).

**Chloramphenicol** [56-77-7], C<sub>6</sub>H<sub>5</sub>ClN<sub>2</sub>O, M<sub>r</sub> 231.1, mp 150.5–151.5°C, is a broad-spectrum antibiotic produced by *Streptomycetes cacaoae* [33] [35]. Chloramphenicol reversibly blocks the bacterial ribosome, inhibiting protein synthesis. See also **Antibiotics**, A.2. p. 535.

**Trade names**: Ac-Chlor Sterile Ointment (Acorn); Chlortetra Ointment (Pharmacia); Chlorhexidine Ophthalmic Ointment/Solution (Powder: Hydrocortisone Ophthalmic Solution (Parke-Davis)). Chloramphenicol Sodium Ophthalmic Solution (Allergan); Oto-Chlor Sterile Ophthalmic Ointment (Adrian); Oto-Chlor Ophthalmic Solution (Oxorn). **Polyoxin**: Polyoxin B Ophthalmic Solution (Oxford). **Polysporin**: Polysporin Ophthalmic Ointment (Sanofi-Aventis Wellscome).

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**Chloramphenicol** [56-77-7], C<sub>6</sub>H<sub>5</sub>ClN<sub>2</sub>O, M<sub>r</sub> 231.1, mp 150.5–151.5°C, is a broad-spectrum antibiotic produced by *Streptomycetes cacaoae* [33] [35]. Chloramphenicol reversibly blocks the bacterial ribosome, inhibiting protein synthesis. See also **Antibiotics**, A.2. p. 535.
biotics and exerts its effect at the level of protein synthesis by reversibly inhibiting the bacterial ribosome. See also —Antibiotics, A2, pp. 494, 522.

Trade names: Al-Mycin Ointment (Akorn), Erythromycin Ophthalmic Ointment (Pharmacia), Lincocin (Dista).

Lincomycin [154-21-2]. C_{10}H_{18}N_{2}O_{8}, M. 406.6, is an antibiotic produced by Streptomyces lincolnensis var. lincolnensis [38], [39]. Lincomycin reversibly inhibits the bacterial ribosome. See also —Antibiotics, A2, p. 534.

Trade name: Linocin (Upjohn).

Oloframoxin [82410-36-1]. C_{16}H_{17}FN_{2}O_{6}, M. 364.4, mp 250—257° C., is a broad-spectrum, fluoroquinolone antibacterial. See also —Chemotherapeutics, A6, p. 184. For synthesis, see [40]. It is currently in clinical trials by Allergan.

Silver nitrate [775-88-4], AgNO_{3}, M. 169.9, mp 712° C., is used to treat the eyes of newborns. Caution should be used with repeated applications because overutilization of the cornea and blindness may result. Silver nitrate is incompatible with sulfacetamide preparations.

Trade name: Silver Nitrile (Eli Lilly).

Vancomycin [14840-98-6] (hydrochloride [14840-97-5], C_{12}H_{24}ClN_{2}O_{12}, M. 449.2, Vancomycin is an amphoteric glycopeptide produced by Streptomyces orientalis [41]. It inhibits cell wall synthesis. See also —Antibiotics, A2, p. 530.

Trade names: Vancomycin (Eli Lilly), Vanocid (Lehner, Vancocin (Astra)."

2.2. Antifungal Agents

For general information see —Antimycotics. Ocular fungal infection is a rare disease but is increasing in occurrence [42], [44]. Commensal fungi commonly present in the eye include Aspergillus, Penicillium, Candida, Fusarium, and Rhodotorula. These may become opportunistic pathogens if the eye’s defenses are compromised by physical trauma or an underlying disease such as diabetes.

Although natamyacin is the only antifungal agent currently available commercially in the United States as a topical ophthalmic formulation, other antifungal drugs (including polyenes and imidazoles) have been used topically in dilute solution or suspension [45].

The polyene antifungics (amphotericin B, nystatin, natamyacin) are insoluble in water and unstable in oxygen, light, water, heat, and at extreme pH. Their biological specificity for yeast relies on preferential binding to yeast membranes via ergosterol over their affinity for cholesterol, the primary sterol in mammalian cell membranes. Cell death is induced by increasing the permeability of the fungal membrane, allowing depletion of intracellular components.

The imidazoles (miconazole and ketoconazole) have a broad-spectrum antifungal and antimicrobial spectrum, with significantly less toxicity than the polyenes. Antifungal effects may result from the inhibition of ergoster synthesis, leading to cell membrane permeability. Miconazole physically disrupts the membrane, leading to cell lysis. High concentrations of miconazole also increase intracellular concentrations of hydrogen peroxide, presumably through inhibition of cytochrome C peroxidase.

Flucytosine is a widely used pyrimidine antimycotic.

Amphotericin B [1367-89-2]. C_{32}H_{32}N_{2}O_{12}, M. 924.1, is a polyene antibiotic produced by Streptomyces nodosus [46]. Amphotericin can be administered parenterally for systemic mycosis. Topical administration of 0.1 and 0.25% has been effective for the treatment of keratomycoses. See also —Antimycotics, A3, p. 78.

Trade name: Fungizone (Squibb).

Nystatin [14840-6-9] is a polyene antifungal antibiotic complex containing three active components (A_{1}, A_{2}, and A_{3}) produced by several Streptomyces spp. [47]. See also —Antimycotics, A3, p. 78. Nystatin is effective in topical application for ocular infection.

Trade names: Mycostatin (Squibb), Nystat (Lehner), Nysor (Savage), O-V Statin (Squibb).

Natamyacin [766-92-4]. C_{12}H_{18}N_{2}O_{6}, M. 665.75, mp 280—300° C (decomp.), is a polyene antibiotic produced by Streptomyces natamensis and S. natansporus [48]. See also —Antimycotics, A3, p. 79. Natamyacin is the least toxic, least irritating, and most stable polyene. It is only useful, however, for the treatment of super-
ficial keratonyzosis because it penetrates tissue poorly.

Trade name: Natracyn (Alcon).

Miconazole [22896-74-8] (nitrate [22892-
87-7]). C14H11Cl2N2O2. M, 416.12. See also →Antimycotics, A.3, p. 82. For synthesis, see [49].

Trade name: Micatin, Monistat-Derm (Ortho).

Ketoconazole [65777-42-1]. C27H32Cl2N2O4. M, 531.44, mp 146 °C, is an orally active, broad-
spectrum antymycotic. See also →Antimycotics, A.3, pp. 83–84. For synthesis, see [50].

Trade name: Micatin (Janssen).

Flucytosine [30232-85-7]. 5-Fluorocytosine, C7H6F5NO4. M, 129.1, mp 295–297 °C (de-
comp.). For synthesis, see [51]. Flucytosine, a fluorinated pyrimidine, is metabolized to either 5-fluorouracil, an inhibitor of RNA synthesis, or 5-fluoro-2-deoxyuridylic acid, a potent inhibitor of DNA synthesis. Flucytosine has a limited spectrum of activity but is effective in topical application against external infections. It ex-
hibits poor oral penetration but can be admin-
istered orally. See also →Antimycotics, A.3, pp. 84–85.

Trade name: Acicon (Hoffmann-La Roche).

2.3. Antiproliferative Agents

Brodine [496-00-4]. 4-6-(dimethylamino)py-
but-2-yl-2-bromobenzylamine, C17H19BrN2O. M, 722.4, mp 236 °C, is used to treat Acan-
thamyceta keratitis infections [52]. For synthesis, see [53].

Trade name: Brodine Eye Drops (Bausch & Lomb); Brodine Ointment, Brudine (May & Baker).

Sulfadiazine [68-35-9] (sulfer salt, [22199-
68-7]). 4-amino-N2-pyrimidylbenzen sulfa-
amide, C17H16N2O4S, M, 250.3, mp 252–256 °C. For synthesis, see [7]. See also →Chemotherapeutics, A.6, p. 190. This com-
ound is used to treat toxoplasma retino-
choroiditis in triple sulfonamide mixtures with sulfonamide and sulfacetamide.

Trade name: Cosc-Biokinet (Lilly); Euklastone (SKF).

Antibiotic–Corticosteroid Preparations. A variety of opthalmic antibiotic–corticosteroid combination preparations are available for treating protozal infections. Ophthalmic applications of corticosteroids and corticosteroid–antibiotic combination preparations are dis-
cussed in Section 3.1.

2.4. Antiviral Agents

Currently marketed antimalarials are available only as topical applications for the treatment of infection with the herpes simplex virus (HSV). These agents inhibit viral replication at the level of DNA synthesis. The prophylactic use of anti-
virals may reduce the frequency of viral latency [54]. The use of high dosages does not rid the host of latent virus but may reduce the frequency of recurrences during therapy [55].

Acyclovir [150777-09-3]. C21H21N5O5. M, 225.2, mp 256.5–257 °C, is an orally active acylcarnosine used against HSV. It is also used as a 3% ointment in HSV infections of the epithelium. For synthesis, see [56]. See also →Chemotherapeutics, A.6, p. 216.

Trade name: Zovirax (Burroughs Wellcome).

Iodoluridine [54-42-2]. 2-deoxy-5,3'-iodouridi-
n, C21H18N3O5. M, 354.1. Iodoluridine is a functional analogue of the nucleoside thymidine; see →Chemotherapeutics, A.6, p. 217. Incorporation into DNA results in death of the virus particle through DNA base-pair mismatches and mutation. The toxicity of the substance is at-
tributable to its incorporation into the host cell DNA. This agent is used topically on a su-
perficial lesion and is available as a 0.5% solu-
tion or a 0.5% ointment. For synthesis, see [57].

Trade name: Hepol (Adenalin); Soral Ointment, Soral Solution (SKF).

Trifluridine [70-49-4]. 2-deoxy-2-fluorometh-
uluridine, C21H15F3N5O4. M, 296.2, mp 186–189 °C. Trifluridine is a thymidine analogue but unlike iodoviride is rapidly metabolized and thus less toxic. Trifluridine is effective against HSV and, in addition, is compatible with corticosteroids [59]. See also →Chemother-
apeutics, A.6, p. 217. Trifluridine is generally available as a 1% solution or a 3% ointment. For synthesis, see [60].
3. Anti-inflammatory Agents

A variety of agents are available for the treatment of ocular inflammatory conditions, including corticosteroids, nonsteroidal anti-inflammatory agents that block mediator synthesis or release, and, more rarely, immunosuppressive agents. For general information, see →Anti-inflammatory-Antihistamine Drugs.

3.1. Corticosteroids

For general information, see →Hormones, A13, pp. 154–154.

Corticosteroids are widely used for the treatment of ocular inflammation [62–64]. Prednisolone, hydrocortisone, dexamethasone, medronate, and fluorometholone are available in topical ocular preparations (suspension, ointment, or solution). In certain cases, topical application may be supplemented or replaced by systemic or periocular administration (e.g., severe anterior uveitis and inflammation of the posterior segment, or orbit) [62, 63].

The use of corticosteroids is not without potential ocular and systemic side effects (e.g., elevated intraocular pressure, posterior subcapsular cataracts, and inhibition of epithelial wound healing [60], [61], [64–67]). Because corticosteroids have immunosuppressive properties, resistance to infection is lowered. Accordingly, a number of ophthalmic preparations containing combinations of corticosteroids and antimicrobial agents are available for anti-inflammatory/anti-infective therapy (Tables 2 and 3).

Hydrocortisone [50-21-7], 17-hydroxy cortisol, cortisol, C₂₁H₃₀O₅, M 362.5. See also →Hormones, A13, pp. 137–141.

Hydrocortisone (1%) is available in antimicrobial anti-inflammatory ointment or suspension combination products (Tables 2 and 3).

Trade names: Ak-Supre ointment (Akorn), hydrocortisone, nortriptyline HCl suspension. Cortisporin ointment (Burroughs Wellcome); hydrocortisone, nortriptyline HCl susp (Burroughs Wellcome); hydrocortisone, chlorhexidine, crotamiton (Burroughs Wellcome); hydrocortisone, neomycin, and polymyxin B sulfate; Oxy-Cort ointment (Oxandol: hydrocortisone, polymyxin B sulfate, neomycin sulfate, and bacitracin zinc); Oxacort HC ointment (Pharmacia: hydrocortisone, bacitracin zinc, polymyxin B, and neomycin sulfate); Oxacort HC suspension (Pharmacia: hydrocortisone, neomycin sulfate, and polymyxin B sulfate).

Prednisolone acetate [50-24-1], 1,2-dihydroxyhydrocortisone, C₂₁H₂₂O₅, M 360.5. See also →Hormones, A13, pp. 143–144.

Prednisolone acetate [52-21-1], prednisolone 21-acetate, C₂₁H₂₂O₅, M 402.5.

Prednisolone sodium phosphate [123-0-6], prednisolone 21-(disodium orthophosphate), C₂₁H₂₅Na₂O₁₂P, M 548.4; water soluble and is available as sodobetadine.

Prednisolone [85-05-7], prednisolone phosphate, C₂₁H₂₅Na₂O₁₂P, M 548.4; water soluble and is available as sodobetadine.

Oxy-Cort ointment (Oxandol: hydrocortisone, polymyxin B sulfate, neomycin sulfate, and bacitracin zinc); Oxacort HC ointment (Pharmacia: hydrocortisone, bacitracin zinc, polymyxin B, and neomycin sulfate); Oxacort HC suspension (Pharmacia: hydrocortisone, neomycin sulfate, and polymyxin B sulfate).
### Table 2. Steroid and antibiotic drops

<table>
<thead>
<tr>
<th>Product</th>
<th>Steroid</th>
<th>Antibiotic</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlormadin Hydrocortisone Powder</td>
<td>0.5% hydrocortisone acetate</td>
<td>0.25% chloramphenicol</td>
<td>Parke-Davis</td>
</tr>
<tr>
<td>Neomycin/Bacitracin Suspension</td>
<td>0.5% hydrocortisone acetate</td>
<td>Neomycin sodium equivalent to 0.35% base and 10000 units polymyxin B sulfate. Bacitracin sodium equivalent to 0.35% base and 10000 units polymyxin B sulfate.</td>
<td>Lipps-Rogby</td>
</tr>
<tr>
<td>Triple-Gen Suspension 1% hydrocortisone</td>
<td>1% hydrocortisone</td>
<td>Neomycin sodium sulfate equivalent to 0.35% base and 10000 units polymyxin B sulfate.</td>
<td>Goldfarb</td>
</tr>
<tr>
<td>Cortisporin Suspension 1% hydrocortisone</td>
<td>1% hydrocortisone</td>
<td>Neomycin sodium sulfate equivalent to 0.35% base and 10000 units polymyxin B sulfate.</td>
<td>Barrows/Wellcome</td>
</tr>
<tr>
<td>Ten-Cortisone Suspension 1.5% hydrocortisone</td>
<td>1.5% hydrocortisone</td>
<td>Neomycin sodium sulfate equivalent to 0.35% base and 10000 units polymyxin B sulfate. Bacitracin sodium equivalent to 0.35% base and 10000 units polymyxin B sulfate.</td>
<td>Roening</td>
</tr>
<tr>
<td>Ake-Neor-Cort Suspension</td>
<td>1.5% hydrocortisone acetate</td>
<td>Neomycin sodium sulfate equivalent to 0.35% base and 10000 units polymyxin B sulfate.</td>
<td>Akeen</td>
</tr>
<tr>
<td>Oph-Orbs Suspension 1.5% hydrocortisone acetate</td>
<td>1.5% hydrocortisone acetate</td>
<td>Neomycin sodium sulfate equivalent to 0.35% base and 10000 units polymyxin B sulfate. Bacitracin sodium equivalent to 0.35% base and 10000 units polymyxin B sulfate.</td>
<td>Vennesch, Allergan</td>
</tr>
<tr>
<td>Poly-Tet-Suspension 0.5% prednisolone acetate</td>
<td>0.5% prednisolone acetate</td>
<td>Neomycin sodium sulfate equivalent to 0.35% base and 10000 units polymyxin B sulfate. Bacitracin sodium equivalent to 0.35% base and 10000 units polymyxin B sulfate.</td>
<td>Vennesch, Allergan</td>
</tr>
<tr>
<td>Pred-G Suspension 1% prednisolone acetate</td>
<td>1% prednisolone acetate</td>
<td>Neomycin sodium sulfate equivalent to 0.35% base and 10000 units polymyxin B sulfate. Bacitracin sodium equivalent to 0.35% base and 10000 units polymyxin B sulfate.</td>
<td>Allergan</td>
</tr>
<tr>
<td>NovoCortisol Solution 0.1% dexamethasone phosphate</td>
<td>0.1% dexamethasone phosphate</td>
<td>Neomycin sodium sulfate equivalent to 0.35% base and 10000 units polymyxin B sulfate. Bacitracin sodium equivalent to 0.35% base and 10000 units polymyxin B sulfate.</td>
<td>MSD</td>
</tr>
<tr>
<td>Tablets/Dispersion 0.1% dexamethasone</td>
<td>0.1% dexamethasone acetate</td>
<td>Neomycin sodium sulfate equivalent to 0.35% base and 10000 units polymyxin B sulfate. Bacitracin sodium equivalent to 0.35% base and 10000 units polymyxin B sulfate.</td>
<td>Alcon</td>
</tr>
<tr>
<td>Desonepor Suspension 0.1% dexamethasone acetate</td>
<td>0.1% dexamethasone acetate</td>
<td>Neomycin sodium sulfate equivalent to 0.35% base and 10000 units polymyxin B sulfate. Bacitracin sodium equivalent to 0.35% base and 10000 units polymyxin B sulfate.</td>
<td>IOLAB</td>
</tr>
<tr>
<td>Ake-Tol Suspension 0.1% dexamethasone acetate</td>
<td>0.1% dexamethasone acetate</td>
<td>Neomycin sodium sulfate equivalent to 0.35% base and 10000 units polymyxin B sulfate. Bacitracin sodium equivalent to 0.35% base and 10000 units polymyxin B sulfate.</td>
<td>Alcon</td>
</tr>
<tr>
<td>Desonatide Suspension 0.01% dexamethasone acetate</td>
<td>0.01% dexamethasone acetate</td>
<td>Neomycin sodium sulfate equivalent to 0.35% base and 10000 units polymyxin B sulfate. Bacitracin sodium equivalent to 0.35% base and 10000 units polymyxin B sulfate.</td>
<td>Alcon</td>
</tr>
<tr>
<td>Mestrol Suspension 0.01% dexamethasone acetate</td>
<td>0.01% dexamethasone acetate</td>
<td>Neomycin sodium sulfate equivalent to 0.35% base and 10000 units polymyxin B sulfate. Bacitracin sodium equivalent to 0.35% base and 10000 units polymyxin B sulfate.</td>
<td>Alcon</td>
</tr>
</tbody>
</table>

### Table 3. Steroid and antibiotic contents

<table>
<thead>
<tr>
<th>Product</th>
<th>Steroid</th>
<th>Antibiotic</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orhidrocort 0.5% hydrocortisone acetate</td>
<td>0.5% hydrocortisone acetate</td>
<td>Neomycin sodium sulfate equivalent to 0.35% base and 10000 units polymyxin B sulfate</td>
<td>Parke-Davis</td>
</tr>
<tr>
<td>Cortisporin 1% hydrocortisone</td>
<td>1% hydrocortisone acetate</td>
<td>Neomycin sodium sulfate equivalent to 0.35% base and 10000 units polymyxin B sulfate</td>
<td>95% Barrows, Welcomes</td>
</tr>
<tr>
<td>Corac 1% hydrocortisone acetate</td>
<td>1% hydrocortisone acetate</td>
<td>Neomycin sodium sulfate equivalent to 0.35% base and 10000 units polymyxin B sulfate</td>
<td>Coractin</td>
</tr>
<tr>
<td>Neosoral 0.05% dexamethasone phosphate</td>
<td>0.05% dexamethasone phosphate</td>
<td>Neomycin sodium sulfate equivalent to 0.35% base and 10000 units polymyxin B sulfate</td>
<td>MSD</td>
</tr>
<tr>
<td>AK-Test 0.1% dexamethasone acetate</td>
<td>0.1% dexamethasone acetate</td>
<td>Neomycin sodium sulfate equivalent to 0.35% base and 10000 units polymyxin B sulfate</td>
<td>Alcon</td>
</tr>
<tr>
<td>Desoacrin 0.1% dexamethasone acetate</td>
<td>0.1% dexamethasone acetate</td>
<td>Neomycin sodium sulfate equivalent to 0.35% base and 10000 units polymyxin B sulfate</td>
<td>IOLAB</td>
</tr>
<tr>
<td>Desacrin 0.1% dexamethasone acetate</td>
<td>0.1% dexamethasone acetate</td>
<td>Neomycin sodium sulfate equivalent to 0.35% base and 10000 units polymyxin B sulfate</td>
<td>Pharmaceutical, Alcon</td>
</tr>
<tr>
<td>Mastrol 0.1% dexamethasone acetate</td>
<td>0.1% dexamethasone acetate</td>
<td>Neomycin sodium sulfate equivalent to 0.35% base and 10000 units polymyxin B sulfate</td>
<td>Alcon</td>
</tr>
</tbody>
</table>

### Dexmethasone \([30-02-2]\), 9a-fluoro-16α-methylprednisolone, \(C_{21}H_{27}O_{3}, M = 392.5\). See also Hormones, A15, pp. 9-7 to 9-14.

\[
\begin{align*}
\text{OH} & \quad \text{OH} \\
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{O} \\
\text{C} & \quad \text{C} \\
\text{H} & \quad \text{H} \\
\text{C} & \quad \text{C} \\
\end{align*}
\]

Trade names: Ak-Dex, AK-Test (Alcon), Radex (Beach & Lofland), Desoacrin (IOLAB), Desoxon (Pharmacai), Desoacrin (Pharmacia), Desomed (Beach & Lofland), Maxamed, Mastrol (Alcon), I-Methasone (Amersham), Oksold (Beach & Lofland), Tobradex (Alcon); see also Tables 2 and 3.

### Mefloquine \([2660-66-3]\), 11β-hydroxy-9α-methylprogesterone, \(C_{27}H_{34}O_{6}, M = 445.5\).
The prostaglandins mediate certain steps of the inflammatory process. The role of arachidonic acid metabolites in ocular inflammation and pressure elevation continues to emerge [62]. Oral administration of NSAIDs has been approached as an alternative to corticosteroids anti-inflammatory therapy [62], [63]. Oral administration of classical cyclooxygenase inhibitors (e.g., acetylsalicylic acid and indomethacin) has met with mixed success in the treatment of ocular inflammation, partially due to systemic intolerance (e.g., gastrointestinal side effects). A number of more recently developed NSAIDs such as diflunisal (Dolobid) and naproxen (Naprosyn) may be better tolerated orally.

Flurbiprofen [5104-40-4], 2-fluoro-a-methyl-(1,1'-biphenyl)-acetic acid, C₁₃H₁₁FO₂, М₀ 244.3. The sodium salt dehydrate of flurbiprofen is available as an ophthalmic solution (0.03%) for topical application (Ocufen Liquifilm, Aller-gan) for inhibition of intraocular mucus.

Ectracecyline (see Section 2.1.3) is used to treat ocular rosacea [69].

Immunosuppressive agents, including alkylating agents such as cyclophosphamide, the folic acid antimetabolite methotrexate, and the antibiotic cyclosporin A, are systemically cytotoxic and dangerous drugs. Although their use in ocular therapy is rare, some of them have been used to treat intractable and progressively destructive ocular conditions [65].

4. Antiglaucomatous Agents

Glasicam is a leading cause of blindness and may be defined as a loss of visual function and optic nerve damage associated with an elevated intracocular pressure (IOP). Ocular hypertension alone is not predictive of glaucoma or visual impairment [70]. In a healthy eye, the IOP (ca. 2 - 2.6 kPa, 15 - 20 mm Hg) [71] is maintained by a balance of aqueous humor formation and outflow. Glaucoma therapy often involves a reduction in IOP by increasing outflow or decreasing production. A variety of therapeutic agents have ocular hypotensive effects [86] - [84] and include adrenergic agents, miotics, carbonic anhydrase inhibitors, and hyperosmotic agents. The applications and adverse effects of ocular hypotensives are discussed in [70] - [80].

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the enzyme cyclooxygenase, which is responsible for the first step in the synthesis of prostaglandins from arachidonic acid.

3.2. Miscellaneous Anti-inflammatory Agents

Disodium cromoglycate [15526-37-6], DSGC, cromolyn sodium, sodium cromoglycate, C₁₃H₁₈NaO₄, М₀ 513.3, appears to achieve its antiallergic and anti-inflammatory effects by stabilizing mast cells and inhibiting antigen-induced mast cell degranulation and the associated release of a variety of inflammatory mediators [67], [68]. See also → Anti-allergics, Agents, A2, pp. 429-430. Topical ophthalmic DSGC (Opicrom, Fisons) is available for prophylactic treatment of allergic disorders such as vernal or allergic keratoconjunctivitis. Maintaining DSGC therapy throughout the allergy season may be more advantageous than sporadic treatment of flare-ups [68]. Therapy with DSGC may permit the reduction or elimination of topical corticosteroid treatment [62].

4. Antiglaucomatous Agents

Glasicam is a leading cause of blindness and may be defined as a loss of visual function and optic nerve damage associated with an elevated intracocular pressure (IOP). Ocular hypertension alone is not predictive of glaucoma or visual impairment [70]. In a healthy eye, the IOP (ca. 2 - 2.6 kPa, 15 - 20 mm Hg) [71] is maintained by a balance of aqueous humor formation and outflow. Glaucoma therapy often involves a reduction in IOP by increasing outflow or decreasing production. A variety of therapeutic agents have ocular hypotensive effects [86] - [84] and include adrenergic agents, miotics, carbonic anhydrase inhibitors, and hyperosmotic agents. The applications and adverse effects of ocular hypotensives are discussed in [70] - [80].

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the enzyme cyclooxygenase, which is responsible for the first step in the synthesis of prostaglandins from arachidonic acid. The prostaglandins mediate certain steps of the inflammatory process. The role of arachidonic acid metabolites in ocular inflammation and pressure elevation continues to emerge [62]. Oral administration of NSAIDs has been approached as an alternative to corticosteroids anti-inflammatory therapy [62], [63]. Oral administration of classical cyclooxygenase inhibitors (e.g., acetylsalicylic acid and indomethacin) has met with mixed success in the treatment of ocular inflammation, partially due to systemic intolerance (e.g., gastrointestinal side effects). A number of more recently developed NSAIDs such as diflunisal (Dolobid) and naproxen (Naprosyn) may be better tolerated orally.

Flurbiprofen [5104-40-4], 2-fluoro-a-methyl-(1,1'-biphenyl)-acetic acid, C₁₃H₁₁FO₂, М₀ 244.3. The sodium salt dehydrate of flurbiprofen is available as an ophthalmic solution (0.03%) for topical application (Ocufen Liquifilm, Allergan) for inhibition of intraocular mucus.

Ectracecyline (see Section 2.1.3) is used to treat ocular rosacea [69].

Immunosuppressive agents, including alkylating agents such as cyclophosphamide, the folic acid antimetabolite methotrexate, and the antibiotic cyclosporin A, are systemically cytotoxic and dangerous drugs. Although their use in ocular therapy is rare, some of them have been used to treat intractable and progressively destructive ocular conditions [65].

4. Antiglaucomatous Agents

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Glaucoma associated with congenital ocular abnormalities is treated surgically or with a combination of surgical and medical therapy. Glaucoma may be classified as primary (direct disturbance of the aqueous circulation) or secondary (arising from other disease state). They are also classified as open angle or narrow angle, depending on the anterior chamber angle (the anatomy of the structures within the angle of the eye as visualized by gonioscopy). These classifications are important in determining whether surgery or drug therapy should be employed and which ocular hypertensive drug therapies may be appropriate.

4.1. Sympathomimetic Drugs

Epinephrine [37-45-4, adrenalin, C₇H₁₅NO₃, M: 332.2, is used widely in primary open-angle glaucoma but is contraindicated in narrow-angle glaucoma [36, 71] because of its mydriatic effects (dilation of the pupil). Topically applied epinephrine has mydriatic, vasoconstricting, and ocular hypotensive effects. Although its mechanism of action is not fully understood, it may lower the IOP by reducing aqueous humor production and also increasing outflow [70]; [74]. Epinephrine is often used in combination with other ocular hypotensives (e.g., pilocarpine).

\[
\text{Epinephrine} \quad \struct{\text{C}_7\text{H}_15\text{NO}_3} \quad \text{M: 332.2}
\]

**Trade name:** Timoptic (Smith & Nephew), 1 and 2% solution (Pharmacia); U.S.P. Epinephrine Solution: a solution of epinephrine prepared with hydrochloric acid.

**Epinephrine hydrochloride** [55-11-2], Epinephrine (0.25, 0.5, 1, or 2%, Allergan), Glaucom (1 or 2%, Alcon).

Epinephrine bitartrate [15052-12-9], adrenaline bitartrate, C₁₆H₂₁NO₄, C₆H₆O₇, M: 333.3, Epitrate (Wyeth-Ayerst). Epinephrine bitartrate is also available in combination with pilocarpine hydrochloride (P-Pilo-1-6, IOLAB).

**Epinephrine tartrate** [5579-06-9], EpyN (0.5, 1.0, and 2%, Solco-Barnes, Hind).

**Dipivefrin hydrochloride** [52656-16-6], dipivalylepinephrine hydrochloride, dipivalylepinephrine hydrochloride, C₁₆H₂₁NO₄.HCl, M: 387.9. For synthesis, see [81]. Dipivefrin hydrochloride is a dipivalyl prodrug that is converted to epinephrine by esterase action. It has enhanced corneal penetration and hypotensive potency relative to epinephrine [71, 73]. Dipivefrin 0.1% is about as potent as 2% epinephrine.

**Trade name:** Alphagan (Allergan), Glaucoma (Tahoe), Glaucomit (Costa), Propine (Allergan).

4.2. β-Adrenergic Blocking Agents

Although systemic blockers of the β-adrenergic receptors are not approved for ocular hypotensive indications, some reduce IOP in addition to having cardiovascular activity against arrhythmias, angina, and hypertension. The β-blockers lower the IOP by decreasing aqueous humor production [72]; [74]. Although topical preparations are generally well tolerated, systemic (CNS, cardiovascular, and respiratory) side effects have been observed [71]; [74].

**Timolol maleate** [36072-17-5] (timolol [26639-73-4]), (S)-1-trifluoromethyl-2,5-diethyl-3-[4-[(dimethylamino)-2-hydroxypropyl]-3-ethoxy-2-propanol maleate, C₁₆H₂₇NO₃S.C₂H₅O₂, M: 432.5, is available as 0.25 and 0.5% solutions. For synthesis, see [82]. See also → Blood Pressure Lowering Agents, 4.4, p. 240. Timolol can provide an additive effect when used concurrently with other ocular hypotensive agents such as miotic agents or carbonic anhydrase inhibitors, although the effects with epinephrine are more controversial [72]; [74].

**Trade name:** Timoptic, Timoptol (Merck Sharp & Dohme).

**Levo-β-hydrochloride** [27912-14-7] (levo-β-hydrochloride, [47414-42-4], (+)–levomethadone hydrochloride, C₁₆H₂₁NO₃.HCl, M: 379.9. For synthesis, see [83]. Levo-β-hydrochloride is a dipivalyl prodrug that is converted to epinephrine by esterase action. It has enhanced corneal penetration and hypotensive potency relative to epinephrine [71, 73]. Dipivefrin 0.1% is about as potent as 2% epinephrine.
Betaxolol hydrochloride [63659-19-8] (betaxolol [63659-16-7], 1-[4-[2-cyclopropylmethoxy]ethyl]phenyl]-3-isopropylamino-2-propanol hydrochloride; C$_{22}$H$_{26}$NO$_{3}$S; M, 345.9. For synthesis, see [84].

Peak name: Betaxolol (0.5% Aconit.).

Metipranolol [22664-55-7], 4-(2-hydroxy-3-isopropylaminompropoxy)-3,3,6-trimethylphenyl acetate, C$_{21}$H$_{24}$NO$_{3}$; M, 369.4. For synthesis, see [83], [86].

Peak name: Metipranolol (Marcumar, Beta-Opfelnol; Mast; Glaucine, Minitol Metipranolol (Smith & Nephew); Optipranolol (Karch & Lemb; Normatolone (Mast)).

4.3. Carboxylic Anhydrase Inhibitors

Carboxylic anhydrase inhibitors decrease the IOP by blocking bicarbonate formation in the ciliary process required for aqueous humor production [74], [79]. These agents are administered systemically and are useful in treating glaucoma cases that do not respond to topical therapy [72], [74]. Virtually all (90–99%) of the carboxylic anhydrase activity must be blocked before the IOP is lowered [72], [79], and oral doses are usually administered several times a day. The sulfonamide carboxylic anhydrase inhibitors are diuretics that are readily absorbed from the gastrointestinal tract. Effective oral doses of these agents for glaucoma therapy depend on their pharmacokinetic properties [72], [74], [79]. Systemic side effects [72], [74], [76], [80] may limit the use of oral carboxylic anhydrase inhibitors, especially in the elderly. Unfortunately, no topically effective preparations of these agents are available, possibly due to poor corneal penetration. Orally administered carboxylic anhydrase inhibitors may provide additive effects when used in combination with topically applied antiglaucoma agents (e.g., pilocarpine and timolol) [74], [79].

4.4. Hyperosmotic Agents

Orally (glycerol, isosorbide, urea) or intravenously (mannitol) administered hyperosmotic agents produce a rapid reduction of IOP as a result of migration of water from the eye to ocular blood vessels [72], [75]. These drugs may have significant side effects [72], [75], [76] and are used primarily to treat acute IOP elevation and in ocular surgical procedures [72].

Glycerol [56-81-5]. propane-1,2,3-triol, C$_{3}$H$_{8}$O$_{3}$; M, 92.1.

Peak name: Optifleet (Wexler-Avery), Osmogly (Aconit.).

Isosorbide [637-67-3], 1,4,3,6-dianhydro-sorbitol, C$_{6}$H$_{12}$O$_{6}$; M, 186.1.

Peak name: Isosorbide (Aconit.).

Mannitol [68-68-3]. coryzepic acid, manna, C$_{6}$H$_{12}$O$_{5}$; M, 182.2.

Peak name: Mannitol Injection (Astrai).
4.5. Myotic (Parasympathomimetic) Agents

Miotics are agents that cause constriction of the pupil. Two classes of miotics, cholinergics and anticholinesterases (parasympathomimetic agents), have therapeutic roles in glaucoma. Acetylcholine itself is not generally useful because of its short biological half-life and topical ineffectiveness, although it can induce miosis when applied directly to the iris during surgery [73]. Cholinergic agonists (pilocarpine, carbachol) act directly on cholinergic effector cells to mimic the effects of acetylcholine; anticholinesterases (phystigmine, demecarium benzilate, echothiophate iodide, isoflurane) prolong the action of endogenous acetylcholine by blocking its hydrolysis by cholinesterases. In the eye, miotics appear to reduce IOP through activation of mesorecicular acetylcholine receptors, which contract the ciliary muscle and enhance flow through the trabecular meshwork. Muscarinic activation also constrains the pupilary sphincter and produces miosis, which is sometimes an undesirable side effect of antiglaucoma therapy. Other ocular and systemic side effects may be associated with the use of miotics for antiglaucoma therapy [72], [73], [76], [77], [80].

4.5.1. Cholinergic Agonists

Carbachol [53-88-2]. O-carbamoylcholine chloride, C8H17N3O7, M = 182.7. Carbachol is inherently more potent and longer acting than pilocarpine but has poorer corneal penetration and more severe ocular side effects. Enhancement of corneal penetration may be achieved with 0.3% benzalkonium chloride (BAK) in the formulation, or with lower levels of BAK along with methyl cellulose or hydroxypropyl methyl cellulose to prolong contact with the ocular surface [73]. Carbachol is used when the response to pilocarpine is inadequate or when a pilocarpine allergy develops [73], [76].

\[
\text{O}^+ \text{N}^+ \text{O}^- \text{CH} \text{CH} \text{N}^+ \text{CH} \text{O}^- 
\]

Trade names: Carnobloc (Alcon), also available as 0.1% solution (Alcon) for intravenous injection for miosis during surgery.

Pilocarpine [67-11-7]. 3,3-Dihydroxy-3-ethyl-dihydro-4-[1-ethyl-3-(1-methyl-2-pyridyl)pyridyl] furan-2(3H)-one, C11H15N3O2, M = 208.3. Pilocarpine is one of the most useful drugs for management of glaucoma, including primary open-angle and acute angle-closure glaucomas [72], [73]. Principal ocular side effects of pilocarpine solutions (0.25–10%) include miosis, ciliary spasm, and visual blurring [72], [73], [76]. A sustained-release drug delivery system (Os Qatar) for pilocarpine base is also available [72], [73], [76].

\[
\text{C} \quad \text{H} \quad \text{O} \quad \text{N} \\
\text{3} \quad \text{15} \quad \text{2} \quad \text{2} 
\]

Trade names: Qatarglo, Pilo-20 and Oceanic Pilo-40 Ocular Therapeutic System (OTS) or 40 μg pilocarpine delivery per hour for one eye). Alcon.

Pilocarpine Hydrochloride [54-71-7]. C11H15N3O2.HCl, M = 244.7. Trade name: Alupent (Alcon); Pilocarpine (American); Marzio-Carpine (Alcon), One-Carpine (Kamini), Pylop (Ocular); Pilocarpine (Pharmacal); Pilocarpine (Alcon), and in various combinations with cycloplasmatic inhibitor E-Pilo-1 + (Ocular).


4.5.2. Anticholinesterases

Anticholinesterases may be divided into two classes. The short-acting "inhibitory" inhibitors (e.g., physostigmine and demecarium) transfer a carbamoyl group to the enzyme, which is removed within a few hours to regenerate the enzyme. The long-acting irreversible inhibitors (e.g., edrophonium and neostigmine) phosphorylate the enzyme, and cholinesterase activity is restored only through synthesis of new enzyme. The anticholinesterases are contraindicated for angle-closure glaucoma [72], and their ocular use may produce a variety of systemic and ocular side effects [72], [73], [76]. Anticholinesterases are used primarily when other antiglaucoma medications have failed and are the least commonly used antiglaucoma agents [72].
Phystostigmine [57-47-6], eserine, C₇H₁₂N₂O₄, M, 274.4.

\[
\text{H}_2\text{C}=\text{N} - \text{CH}_3 \quad \text{N} \quad \text{H} \quad \text{CH}_3
\]

Trade names: Eserine sulfate (0.25%) Sterile Ophthalnic Ointment (FOSLAB).

Demecarium bromide [56-94-9], C₃₅H₆₁BrN₂O₄, M, 716.6.

\[
\text{C}_4\text{H}_9\text{Cl}_2\text{N}_2\text{O}_2\text{Br}_2\text{N}
\]

Trade name: Hanocin (Merk Sharp & Dohme).

Echotoxiche iodide [538-71-1] (echotoxin [672-60-3]). mercaptoethyltrimethylammonium iodide C₅H₃NBrI, phosphorothionate, C₆H₅PO₃S, M, 363.2.

\[
\text{CH}_3\text{N} \quad \text{H} \quad \text{CH}_3
\]

Trade names: Echotoxin, Iodone de Iodofor, Phosphorothionate Iodide (Weithner, Promedico, Chronic; Phosphorothionil (Wasser).

Isosulfaphate [55-91-4], diisopropyl fluoro-phosphinate, C₆H₅FO₂P, M, 184.1.

\[
\text{CH}_3\text{CHO} \quad \text{P} \quad \text{OCH}_2\text{CHO}
\]

Trade names: Dilphos (Ishiru), D-P-O (Wistar, Fluproph (Merk Sharp & Dohme).

5. Mydriatics and Cycloplegics

Mydriatic and cycloplegic agents are used routinely in ophthalmic practice for dilating the pupil to facilitate examination of the retina [89]. In addition to dilation, cycloplegics cause paralysis of accommodation for near vision and are used primarily as an aid in refraction and in the treatment of uveitis [97]. They are also used as postoperative agents in cataract and retinal detachment surgery.

Mydriatics and cycloplegics are divided into sympathomimetic and parasympatholytics. They can be used alone or in combination. Sympathomimetic agents imitate (direct acting) or potentiate (indirect acting) the effect of nor-adrenaline at sympathetic nerve terminals and produce mydriasis by stimulating the iris dilator muscle fibers. Parasympatholytic agents block the action of acetylcholine at the neuromuscular junction and produce pupil dilation with loss of accommodation by immobilizing the iris sphincter and ciliary muscle.

Although serious side effects from mydriatics and cycloplegics are rare, individual response to these drugs varies [89]. They should be used with caution in patients with closed-angle glaucoma or in patients with a narrow angle between the iris and the cornea because they may increase the IOP and precipitate an acute attack [88].

5.1. Sympathomimetics

Phospholine hydrochloride [61-76-7], (S)-1-(3-hydroxyphenyl)2-methylaminoethanol hydrochloride, C₆H₁₂N₂O₂.HCl, M, 203.7. Phenylamine hydrochloride is used topically (2.5% and 10% solutions) to dilate the pupil both for ophthalmoscopy in the treatment of uveitis and for cataract surgery [97]. Maximum dilation occurs within 45-60 min and recovery in about 6 h. A 1% solution can be used in the diagnosis of Horner’s syndrome [97].

\[
\text{HO} \quad \text{CH}_3 \quad \text{N} \quad \text{H} \quad \text{CH}_3 \quad \text{Cl}
\]

Trade names: Al-Dilt, Al-Venarex (Alcon); Neuramin (Alcon); Iproan (Amersham); Isonest (Alcon); Minina (Pharmacia); Hydrochloride (Smith & Nephew); Mydine (Nestlé) Neosynephrine (Winston); Opazid (Alcon); Phospholine Hydrochloride (FOSLAB); Proxim (Alcon); Venusol (Cooper Vision); Yotora (Alcon); Zimovia (Alcon).

Hydroxyamphetamine hydrobromide [306-23-8], 1-[3-(aminopropyl)aminomethyl hydrobromide, C₇H₁₉NO₂.HBr, M, 232.1. For synthesis, see [99]. Hydroxyamphetamine hydrobromide is an indirect-acting sympathomimetic agent. It is used in a 1% solution as a mydriatic (effect com-
5.2. Parasympatholytics

Atropine sulfate [5698-96-6] is trichloroacethyldene (15-49-1)], \( \text{C}_7\text{H}_3\text{NO}_2\cdot\text{H}_2\text{SO}_4\cdot\text{H}_2\text{O}, M = 698.49\). See also = Alkaloids, A1, pp. 360-362.

→ Atropine is the most effective cycloplegic agent and has the longest duration of action. It is used to maintain a dilated pupil after intracocular surgery. Pupil dilation occurs within 30-40 min and lasts up to 2 weeks.

Trade name: Atropine Sulfate: Proprietary 1% (or more), Atropine Sulfate Ophthalmic (Aqua), Atropine Sulfate Ophthalmic (Aqua), Atropine Sulfate Ophthalmic (Alcon), Atropine, Meyer, Rogers, Akina, Stivin, Alcon, Fungus, Lilly.

→ Atropine Sulfate: S.A.P. (Allegro), Atropine Sulfate (ROE), Cyclogyl (Pfizer), Insta-Atrone (Alcon), Oftone (Alcon), Minim's Atropine Sulfate (Smith & Nephew), SMF, Atropine (Cooper vision).

Cyclogylate hydrochloride [5970-29-1]. \( \text{C}_7\text{H}_3\text{NO}_2 \cdot \text{HCl}, M = 327.9. \) For synthesis, see [106]. Cycloglycylate hydrochloride has a rapid onset (30-60 min) and a short duration of action (1-24 hr) when used as a cream [97].

Trade name: Alcon-Ophthalmic Cyclogylate (Alcon), Alcon-Pentacaine (Alcon), Cialands (Alcon), Cyklegyl, Cedexan cyclogyl (Alcon/Clencia Cyclogyl/Elizabeth Cerlega, Cyklegyl, Cyclogystrol Cohava, Cyclogyl Aqueous, Cyclogyl, Cyclogyl (Alcon), Cyclogylate, Micat Aqueous, Cyklegyl, Mydlegyl, Mydriatic Cycloglycylate (Alcon, Smith & Nephew). Mydril (Bausch, Bausch), Skiirol (Fun), Zyklogyl (Merck).

Homatropine hydrobromide [51-56-9]. \( \text{C}_11\text{H}_10\text{NO}_2 \cdot \text{HBr}, M = 356.3. \) Homatropine hydrobromide is weaker and less toxic than atropine. The onset of action occurs in about 15-20 min and lasts ca. 3 hr. Complete recovery time is about 36-48 hr. Homatropine is used for the relief of inflammatory conditions of the eye, conjunctivitis, and its pre-surgical preparation. It is also used as an optical aid for visual loss (opacities) [97].

Trade name: Ak-Homatropine (Aqua), Atropin Hydrobromide (Alphapharm), Atropine, Solan Drop (Alstro), Hydrobromide (Arthur), Homatropine (Hibbs, Hibbs Hbr Hydrobromide (Hibbs), Homatropine Hydrobromide (Smith & Nephew).

Scopolamine hydrobromide [114-46-8]. \( \text{C}_14\text{H}_{22}\text{NNO}_2 \cdot \text{HBr}, M = 348.3. \) See also = Alkaloids, A1, p. 261. Scopolamine hydrobromide is an effective cycloplegic and is used in the treatment of uveitis, in retraction of children, postoperatively, and in patients sensitive to atropine. Mydriasis and cycloplegia occur within 20-60 min and last 3-7 days. The duration of action is much shorter in eyes with inflammation.

Trade name: Comar (Allegro), Homn (Richler, Allen, Medofina, Homn Hydrobromide (Smith & Nephew), Mydriatic (Hibbs) & (Smith & Nephew).

1-topiylcaine [508-75-1]. N-ethyl-N-4-pyridylmethylylpropiophenone, \( \text{C}_20\text{H}_23\text{NO}_2, M = 344.4. \) For synthesis, see [101]. 1-Topiylcaine is used as a non-synthetic substituted for atropine or scopolamine when prurigo of mydriasis and cycloplegia are not required. It is an effective mydriatic with weak cycloplegic activity and is, therefore, useful for opthalmoscopes and some postoperative and postoperative uses. Onset of mydriasis takes place within 15-20 min and lasts ca. 7 hr [98]. Mydriasis may be discontinued by local application of pilocarpine. Maximum cycloplegia occurs within 20-25 min; the duration of this peak effect is 3-4 hr. 8-10 hr.
6. Vasoactive (Adrenergic) Agents

In addition to their mydriatic effect, adrenergic agents constrict the vascular system of the conjunctiva within minutes (a adrenergic effect) and are used to treat congestion and relieve minor allergy irritation and itching of the conjunctiva. Commerically available ophthalmic vasoconstrictive agents usually containephedrine, naphazoline, oxymetazoline, phenerenzin, or tetrahydrozoline. Side effects are not typically observed because of the relatively low concentrations used for rebound congestion can occur with extended use [97].

Naphazoline hydrochloride [550-99-2], 2-(4-naphthylmethyl)-2-imidazoline hydrochloride, C₁₅H₁₄N₂.HCl, M, 246.7. For synthesis, see [301]. One or two drops of naphazoline solution (0.01% - 0.1%) are administered in the eye every 3-4 h.

Oxymetazoline hydrochloride [25150-07-8], 2-(4-tert-butyl-3-hydroxy-2,6-dimethylbenzyl)-2-imidazoline hydrochloride, C₁₇H₁₅N·HCl, M, 298.8.

7. Diagnostic Agents

Diagnostic agents are used to examine the eye for signs of systemic disease and to diagnose ocular abnormalities. Dyes used for this purpose include fluorescein, rose bengal, indocyanine green [599-35-4], trypan blue [72-35-7], and alcian blue [72609-44-7]. Methylene blue [61-73-4], and fluorescein. Of these, only fluorescein, rose bengal, and fluorescein are commercially available [104], [105]. Several dyes are also used as ophthalmic diagnostic agents, including edrophonium chloride, methacholine, and pilocarpine.
**Fluorescein C.I. 43:350 [221-07-5] (fluorescein sodium) [58-47-8], C₁₆H₁₈N₂O₇, M₁, 332.3, mp 314 – 316 °C (decomp.). The synthesis, properties, and historical tests of fluorescein have been reviewed [106, 107]. Fluorescein sodium is used typically as a 5 or 2.5% solution or as impregnated filter paper strips for detecting foreign bodies and examination of the corneal surface. During corneal surgery, topical administration of fluorescein can be used to detect leakage from the anterior chamber. In cataract surgery, leaks are detected as bright green rivulets [104, 109]. Fluorescein is used for the fitting and management of hard contact lenses. In the presence of fluorescein the tear layer fluoresces green under a cobalt blue light and contrasts with a blue fluorescence or the absence of fluorescence where the lens comes in contact with the cornea. Fluorescein is not useful for fitting soft contact lenses because it passes through the lens matrix, providing insufficient contrast between the lens and the tissue [104, 109]. Fluorescein is also used intravenously in concentrations of 3–25% for examination of the ophthalmic vasculature and the presence of ocular sciences.

**Trade name:** Alcon (Alcon, Fluorescan (Alcon), Flecta (Akorn), Fluoro-End (Wyeth-Ayerst), FFA (Burns-Hiland), Fudansensi (Cochiseyrk); IV propria- trium hydrochloride Fluorescin (Alcon).)

**Rose bengal, C₁₁₂, 43:440 [111-24-85], (di- sodium salt) [15626-40-9], C₁₀H₁₂Cl₂N₂O₅, M₁, 107.6. The di-sodium or dihydro salt of rose bengal dissolves in water giving a bluish red color [106]. Unlike fluorescein, rose bengal stains degenerated corneal and conjunctival epithelial tissue red. The stain intensity correlates with the state of degeneration, with dead cells staining intensely [108]. The dye is useful in highlighting abnormal epithelial cells in "dry eye" conditions. It is also a useful adjunct in determining the area of epithelial squamous metaplasia in 0.5%.

**Trade name:** Eiron (Anaquen, Tensilas 450Chl).

**Methacholine chloride [62-51-3], acetyl-β-trimethylcholine chloride, C₁₀H₁₆ClNO₃, M₁, 195.5, mp 172 – 173 °C. A 2.5% solution is applied topically to the conjunctival sac to diagnose Adie's pupil (a disruption of cholinergic innervation to the iris). Normal pupils do not respond significantly to methacholine, whereas the Adie's pupil responds with intense miosis.

**Trade name:** Provenzine (Hoffmann-La Roche).

**Pilocarpine, see Section 4.5.1. A 0.1-0.125% solution of pilocarpine can be used to diagnose Adie's pupil. A 0.5- 1% solution can be used in the differential diagnosis of the finer, dilated pupil. The dilated pupil responds to the drug if the dilution is of neurologic origin, where it does not.**
8. Dry Eye Medications

"Dry eye" denotes a number of conditions including insufficiency lacrimation, mucin deficiency, lipid abnormalities, impaired blinking, or primary ocular disorder [13]. The seriousness of dry eye ranges from mild "dry and scratchy" eyes to serious degeneration, and keratinization of corneal tissue, which may lead to blindness. The latter condition is often found in developing countries in areas of malnutrition, (deficiency of protein and vitamin A). However, in highly developed nations, a milder form of dry eye occurs, which is characterized by chronic eye irritation and decreased visual acuity [114]. Symptoms are normally subclinical but become symptomatic in a dry, windy, or dusty atmosphere, in air conditioning, or when contact lenses are worn.

If dietary deficiency is the underlying cause of the dry eye syndrome, a proper diet should be implemented. Beta-carotene and/or vitamin A deficient diet may be applied to counter vitamin A deficiency [115]. In dry eye conditions induced by inferences, treatment with an antimicrobial agent should be initiated.

The most common treatment of non-specific, incipient dry eye is with tear substitutes [116]. Commercial dry eye preparations typically contain at least one demulcens; which lubricates and wets the eye, and a preservative to prevent microbial contamination of the product. Nonpreserved preparations are also available in single-dose containers. Some demulcents serve as emulsifying agents (e.g., substituted cellulose ethers) based on the concept that highly viscous tear substitutes should have a longer retention time in the eye. Because contact lens wearers generally experience improved comfort from the lubricant and wetting properties of demulcents, many lens preparations include one or more of these agents (see Section 9.1).

Other components of dry eye medications include emollients (such as petrolatum, mineral oil, and lanolin), which lubricate and protect the eye from drying, and lipids, which are intended to supplement a deficient superficial lipid layer of tear fluid. Both emollients and lipids may, however, interfere with visual acuity.

The most common demulcants are listed below.

Ophthalmic Preparations: Glycerin Ophthalmic Solution, U.S.P.

Hydroxyethyl cellulose [9004-62-9], nearly odorless, yellowish-white, white, or grayish-white, hygroscopic granules, is an ef-fluent white powder that softens at 130°C, produces aqueous solutions with a wide range of viscosities, and precipitates from solution at 40-45°C.

Hydroxypropyl cellulose [9004-64-3] is an ef-fluent white powder that softens at 130°C, produces aqueous solutions with a wide range of viscosities, and precipitates from solution at 40-45°C.

Hydroxypropyl methyl cellulose [9004-65-5] is a powder that dissolves in cold water (insoluble in hot water) to give solutions with a wide range of viscosities.

References
[104, 112]
9. Miscellaneous Ophthalmic and Contact Lens Preparations

Contact lenses are broadly classified as "hard" or "soft". Hard lenses are typically composed of polymethyl methacrylate (PMMA); they are inflexible and hydrophobic, and retain their shape when removed from the eye. Soft ("hydrophilic") lenses are flexible, hydrophilic (typically with a water content of 30%-79%), and conform to the contour of the supporting surface. They are composed of any one of a wide variety of cross-linked polymers that form a hydrophilic gel network (e.g., polymacon, a copolymer of 2-hydroxyethyl methacrylate with 2-hydroxyethyl-2-methyl-2-propenoate) [116]-[118]. In addition, "semipermeable" or gas-permeable lenses are available. These lenses are commonly made from PMMA and silicone, and are a hybrid of soft and hard lenses.

The advantages and disadvantages of each type of lens are reviewed elsewhere [116]-[118]. The wide range of polymers used for contact lens materials results in a broad spectrum of physicochemical interactions between the lenses, tear film, eye tissue, and contact lens products. For example, 20-30 µg of tear fluid protein is typically deposited on a polymacon soft lens, whereas >50 µg of protein may be deposited on an etafilcon A soft lens during the same period of wear [119]. (Etafilcon A is a copolymer of 2-hydroxyethyl methacrylate, sodium methacrylate, and the methacrylate ester of 3-ethyl-2-hydroxyethyl-1,1-propenediol.) Moreover, the compositions of tear fluid proteins deposited on each lens type differ: the negatively charged etafilcon A lens attracts more positively charged lysozyme than the nonionic polymacon material.

The effectiveness and cytotoxicity of the agents used for contact lens disinfection, cleaning, lubrication, wetting, etc., vary markedly with the properties of the lens material. Many factors may affect product efficacy, safety, and utility. Heat disinfection is unsatisfactory for some hydrophilic lens materials because it reduces lens life and makes deposits more difficult to remove after thermal disinfection. Chemical disinfectants and preservatives are described in Section 9.1. Hydrogen peroxide (3%) is a good antimicrobial agent, but its use requires a neutralization step and has pustulent compliance problems. Thimerosal is also a good antimicrobial agent, but a subcutaneous injection of the popu-
lotion has become sensitized to it. Benzyl alcohol is an effective preservative but tends to irritate the eye [120]. Chlorobutanol is only a fair preser-
vative because it has a slow kill rate, is unstable in solutions above pH 6, and is adsorbed by con-
tainers. Ethylhexadimethynitrone acid is not an effective antimicrobial agent when used alone; it disrupts the integrity of bacterial cell walls and is used in combination with other preservatives.

Boric acid (often used as a buffering agent in ophthalmic and contact lens care solutions) and sorbic acid are preservatives with relatively low cytotoxicity, but they are not as useful as lens disin-
fectants. Quaternary amines such as benzalkoni-
urn chloride are good disinfectants and preserva-
tives but accumulate on negatively charged hy-
drophilic lenses with a high water content, caus-
ing cytotoxic responses [121]–[126]. Polyquaid is the only quaternary amine currently in use for soft lens disinfection.

Bifouicides are both potent disinfectants and good preservatives. Unfortunately, chlorhexi-
dine has been associated with sensitivity re-
actions. In contrast, polyhexamethylenebiguanide (PHMB) has a very low frequency of adverse patient response and is safe for use with soft lens materials. Lens disinfected with PHMB solu-
tion (0.5 ppm) can be placed directly on the eye, without the saline rinse required by most other disinfectants.

Considerable variation exists among individ-
uals in both tear chemistry and tear deposits on contact lenses [127]–[132].

Most lens cleaning agents are used daily or weekly (see Section 9.3). Daily cleaners (e.g., macrogol esters and ethers, sodium laurel sul-
fate, and block copolymers) remove proteinac-
eous and lipidal lens deposits by their surfac-
tant action. However, daily cleaners do not com-
pletely remove protein deposits, and proteins tend to accumulate with time, serving as a pos-
itive site for microbial growth and causing eye irritation and lens clouding. Weekly cleaners are used to remove accumulated protein deposits. They are generally formulations of proteolytic enzymes (e.g., pancreatin, papain, or subtilisin-
A), which cleave the protein into smaller frag-
ments that are more readily rinsed off the lens surface.

In addition to disinfectants, preservatives, and cleaning agents, contact lens preparations may contain lubricants, wetting agents, or stear-
ity adjusters to improve lens comfort. Formu-
lations containing such materials are listed in Chapter 8 contact lens products). Contact lens solutions also contain buffers (e.g., borate, cit-
rate, and phosphate) and osmolarity adjusting agents (usually sodium chloride).

9.1. Disinfectants and Preservatives

9.1.1. Bifouicides

See → Disinfectants, A.8, p. 559.

Chlorhexidine gluconate [15472-51-9], chlo-
rehidine digluconate, C₂₄H₄₇Cl₂N₂O₁₀·2C₇H₆(OH)₄, M, 897.8.

Contact lens products: Bausch & Lomb Syntex Dis-

Polyhexamethylenebiguanide hydrochloride [27056-78-8], polyaminobipropyl biguanide hy-
drochloride [C₆H₁₂N₂HCl for synthesis, see [120].

Contact lens products: ReNu Multi-Purpose Solution; ReNu Multi-Solution (Bausch & Lomb).

9.1.2. Mercurial Preservatives

Phenylmercury(II) acetate [62-58-6], C₁₃H₁₄HgO₂, M, 338.8, mp 140°C.

Trade name: Bils (Ibrest-Hindi).

Phenylmercury(II) nitrate [8603-65-2], C₁₃H₁₄HgNO₃, M, 634.4, mp 187–190°C (de-
comp.).

Contact lens preparation: Clean-N-Sense (Allergan).

Thimerosal [54-64-8], C₁₃H₁₄HgNaO₂S, M, 404.84.

Trade name: Absorbens, Absorbents (Allergan), Col-
linton (Winston): Eye Care 2020 Inc: Drops (Milson); Liquifilm Force, Puffa & Liquifilm (Allergan); M-Rane (Milson); Neo Trans (Kerr-Hindi); Softside (Alcon).

Contact lens products: Adaptiples (Alcon); Clean-
ing:Detergent (Allergan); Clex (Cooper Vision); Dual-Core (Rema: First-Care, Flexicare (Alcon): Gel-
Core (Ibrest-Hindi): LC-60: Lens-Net (Allergan); Penta-
Ven II (Semiart Labs): Sanders (Alcon): Soft Care, Soft-
Ease (Bausch-Hindi): Stay-Brite (Rema): Steinh Disin-
fecting Solution, Sterile Lens Lubricant (Bausch & Lomb).
9.1.3. Quaternary Ammonium Compounds

See → Disinfectants, A.R., p. 559.
See → Microbicides, A.16, p. 566.

Mezalkonium chloride [8901-54-5] is a mixture of alkyl(dimethylbenzyl)trimethylammonium chlorides.

Trade names and contact lens products are too numerous to list.

Benzethonium chloride [121-54-6], C₁₃H₂₄N₂O₂, M₁₃, 488.1, mp 164–166°C.

(C₆H₅CH₂)₆N⁺CH₂CH₂CH₂CH₂CH₂CH₂CH₂CH₂CH₂CH₂O⁻

Cetylpyridinium chloride [121-63-1], 1-hexadecyl-hexadecyltrimethylammonium chloride, C₃₄H₆₈ClN • H₂O, M₂, 539.0, mp 77–83°C.

Cetyltrimethylammonium bromide [505-86-2], cetyltrimethylammonium bromide, is chiefly trimethyltributylacetammonium bromide together with dodecyl- and hexadecyltrimethylammonium bromides.

Trade names: Pilawnums, Denasymex Ophthalmic (Mastis).

Polyquad [25345-27-6], poly(dimethylamino-2-benzene-1,4-dial chloride), polyquaternium-1, pontujet.

H₂C • O • N • Cl • H₂C • CH₂CH₂CH₂CH₂CH₂CH₂CH₂CH₂CH₂

Contact lens products: Opti-Free, Alcon.

9.1.4. Miscellaneous Disinfectants and Preservatives

Benzyl alcohol [100-51-6], C₆H₅CH₂OH, M₁, 106.1, mp 52°C. See also → Benzyl Alcohol.

Boric acid [10043-15-1], orthoboric acid, BH₃O₃, M₂, 61.84, mp ca. 171°C.

Commercial products: Boric acid is used in a variety of topical and contact lens care products.

Chlorobutanol [157-72-5], 1,1,1-trichloro-2-methyl-2-propanol, C₃H₅ClO₂, M₂, 177.5, mp 97°C.

Trade names: Gentamycine Ophthalmic (Mann), Lacril, Lacrilin, Tears, Tears Plus (Allergan).

Ethyleneiminoethoxacetate acid [66-05-4], EDTA, C₁₀H₁₀N₂O₄, M₂, 202.2, mp > 300°C. See also → Ethylenediamineethoxacetate Acid and Related Chelating Agents.

Commercial products: EDTA has widespread use in a variety of ophthalmic and contact lens care products.

Hydrogen peroxide [7722-84-1], H₂O₂, M₂, 34.0. See also → Hydrogen Peroxide.

Contact lens products: Oxyjet (Allergan); Neo-Dex (Bausch & Lomb); Aqueous (Bausch & Lomb); Moistjet (CooperVision); Matrix Pure Sep (Ross).

Sorbic acid [109-44-7], 2,4-hexadienoic acid, M₂, 112.12, mp 134.5°C.

Ophthalmic contact lens products: Sorbic acid is used widely as a preservative in contact lens care products.

9.2. Contact Lens Cleaners and Revesting Agents

Most lens cleaning agents are used daily or weekly (see Section 9.1). Daily cleaners remove proteinaceous and lipoidal deposits by their surfactant action. Weekly cleaners are used to remove accumulated protein deposits.

9.2.1. Surfactant Cleaners

Octylphenoxypolyethoxy ethanol [9002-93-1], poly(ethylene glycol) -isooctylphenyl ether, C₆H₄(OCH₂CH₂O)nH, average M₄, 471.

Contact lens product: Bates-Hand Wetting & Sealing, Soft-Mate (Bausch & Lomb).

Polyoxyl 40 stearate [9004-95-3], poly(ethylene glycol) monostearate.

Contact lens product: Blist-N-Clean (Allergan).

Poly(ethylene glycol) [25322-64-5], typical lens product, M₂, range 190–420; hygroscopic, viscous liquid.

Contact lens product: Blist-N-Clean (Allergan).
Tyloxapol, \( [3,30,6-2,4]-4,1,1,3,3-tetrameth- 
lylarylsphenol polymer with formaldehyde and 
ethylen oxide, tyloxapol.

Telluric acid: Etitunan (Aiken).

Sodium lauryl sulfate \( [55-27-1] \), sodium do- 
decyl sulfate, \( \text{C}_{12}\text{H}_{25}\text{NaSO}_{4}\text{H}, M = 288.4 

Contact lens products: Lent Plus Daily Cleaner, 
ReNu Multi-Purpose Solution (Bausch & Lomb).

Polyoxymethylene \( 407 \) [8003-11-6], ethylene- popylene block copolymer, average \( M \), 4000 with 
78 wt% polyethylene.

Contact lens products: Fiji Vision Lens Drops, 
Microflow Fama-Flow Cleaner (Ciba).

Poloxamine, \( [11087-17-7] \), Tretornic, co-
polymer of ethylene oxide, propylene oxide, and 
terrakis ether of ethylenediamine with 
propylene.

Contact lens products: ReNu Multi-Purpose Solution 
(Bausch & Lomb).

9.2.2. Enzymatic Cleaners

Sec. \( \rightarrow \) Enzymes, A,9, pp. 395–397.

Pancreatin \( [8049-47-6] \) is obtained from hog 
pancreas and has protease, amylase, and lipase 
activity.

Contact lens products: Optizyme (Aiken).

Papain \( [9001-73-4] \) is derived from papaya.

Contact lens products: Allergan Enzymatic, Stetzyme 
(Allergan).

Subtilin \( A \) [9042-01-2] is extracted from 
Bacillus subtiliferus.

Contact lens products: ReNu Efficient Enzymatic 
Contact Lens Cleaner, ReNu TheraLine Enzymatic 
Contact Lens Cleaner (Bausch & Lomb), Ultrasafe (Allergan).

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