## Drugs Used in Dermatological Disorders

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### Drug List

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Although skin diseases only infrequently affect longevity, they significantly influence one’s sense of well-being. The skin functions not simply as a passive barrier but also as an important organ intimately connected to the immune and nervous systems. Furthermore, transdermal drug delivery for systemic therapy and the recognition of the skin as a potential target for gene replacement have enhanced awareness of the skin’s importance.

**SKIN STRUCTURE**

The skin consists of two main compartments, the epidermis, a stratified squamous epithelium, and the underlying dermis, a richly vascularized tissue embedded in a connective tissue matrix (Fig. 41.1). The epidermis consists of multiple layers of keratinocytes, which differentiate into the outermost layer, the stratum corneum. This layer contains the hydrophilic structural

**FIGURE 41.1**
The layers of the epidermis. (Adapted with permission from Montagna W and Parakkal PF. The Structure and Function of Skin [3rd ed.]. New York: Academic, 1974.)
protein keratin surrounded by hydrophobic intercellular lipids, a remarkably effective barrier to many topically applied agents. The differentiation of keratinocytes in the basal layer from proliferative cells to highly differentiated nondividing cells in the stratum corneum is tightly regulated by a variety of intrinsic and extrinsic factors, including cytokines and calcium. The epidermis also contains melanocytes, which synthesize the photoprotective pigment melanin, and Langerhans cells, the dendritic antigen-presenting cells that compose the farthest outpost of the body’s immune system.

The dermis provides a base for the epidermis and contains fibroblasts that elaborate proteins, such as collagens and elastin, which are crucial for the skin’s structural integrity. In addition, mast cells, enriched in a variety of proinflammatory substances, play an important role in tissue remodeling, wound healing, and fibrosis.

### PERCUTANEOUS ABSORPTION

The rate of diffusion of a chemical across the skin is related to these, among other features:

- Its concentration when applied
- The surface area to which it is applied
- Its movement through the epidermis (the diffusion constant)
- The relative tenacity with which it binds to its vehicle compared with epidermis (the partition coefficient)
- The thickness of the stratum corneum (barrier)

The amount of drug absorbed can be enhanced by increasing its applied concentration, increasing the size of the area to which it is applied, decreasing the barrier to its mobility through the layers (generally by hydrating the skin), and increasing its affinity for the skin (usually by increasing its hydrophobic component). Drug absorption is also greater in regions in which the skin is thinner.

### PRACTICAL CONSIDERATIONS IN TOPICAL DRUG THERAPY

For designing effective topical drug therapy it is important to understand the principles of transmembrane transport and the unique structure of the stratum corneum. Some practical factors:

- **Dosage–surface area relationships:** In general, about 2 g of a topical product is required to cover the scalp, face, or hand; 3 g to cover an arm; 4 g to cover a leg; and 30 to 60 g to cover the entire body.

- **Hydration of the stratum corneum:** Hydration enhances the drug’s solubility in and mobility through the skin (and its absorption) as much as tenfold. Hydration is usually achieved by using an occlusive vehicle or covering the treated skin with impermeable plastic film.

- **Type of vehicle:** In addition to their importance for hydration of the skin, vehicles vary in their partition coefficients (i.e., oil–water solubility ratio) for a given drug with respect to the stratum corneum. For example, a lipophilic drug moves more readily into the epidermis if it is in an aqueous vehicle, to which it is less tightly bound. Also, certain vehicles are soothing in various types of skin eruptions; dry, chronic inflammation often improves with drugs administered in lipophilic vehicles, whereas moist acute inflammation is best treated with aqueous preparations. Chemical constituents of vehicles can occasionally cause irritation or allergic sensitization that in turn may enhance penetration of drugs. Remember that for most topical drugs the vehicle constitutes more than 99% of the formulation.

- **Variation in penetration at different anatomical sites:** Drug penetration is inversely related to thickness of the stratum corneum. Thus, permeability (and often toxicity) is greater in areas of thinner skin, such as the face or scrotum.

- **Inflammation:** Permeability to most drugs is greater in inflamed skin.

- **Age:** Systemic toxicity from topically applied drugs is most likely in infants and small children because of their high ratio of surface area to body weight.

### TOPICAL GLUCOCORTICOSTEROIDS

Topical glucocorticosteroids are the most widely prescribed drugs for skin diseases. Like systemic glucocorticosteroids (Chapter 60), topical glucocorticosteroids bind to cytoplasmic receptors that transport the drug to the nucleus, where the complex binds to particular regions of DNA known as the glucocorticoid response element (GRE) and alters gene expression. Such receptors have been identified in both epidermis and dermis.

Drug absorption is enhanced by the use of agents with lipophilic side chains; by application of the drug to larger areas of skin, to inflamed areas, and/or for long periods; and by the use of occlusive dressings. Like their systemic counterparts, topical glucocorticosteroids have myriad pharmacological effects. Especially important in skin diseases are their antiinflammatory and immunosuppressive effects and their catabolic characteristics (hence their usefulness in eczematous dermatitis and their toxicity of dermal atrophy, respectively).
Although their exact mechanism of action is unclear, they are known to inhibit the expression of various cytokines and adhesion molecules and to antagonize the activity of transcription factors, including NF-κB, NF-AT, and AP-1.

Topical corticosteroids are most useful in inflammatory dermatoses, such as eczematous dermatitis and psoriasis; they may also be helpful in other skin diseases that have a prominent inflammatory component, such as autoimmune blistering diseases (e.g., bullous pemphigoid and pemphigus vulgaris) and lupus erythematosus.

Many compounds are available in both proprietary and generic forms, and their bioequivalence is difficult to document. Nonetheless, the drugs are classified into seven categories according to their relative potencies (Table 41.1).

Systemic toxicity from topical corticosteroids can occur, particularly from the more potent agents. Cushing’s syndrome, although rare, has been reported.

Milder suppression of the hypothalamic–pituitary–adrenal axis is more common. Local toxicity is relatively frequent and may not be reversible. Dermal atrophy, appearing as striae or telangiectasias, is especially likely in intertriginous areas, where occlusion occurs naturally and the skin is likely to be thin. Less commonly, steroid-induced acneiform eruptions, rosacea, and perioral dermatitis can occur. Glaucoma and cataracts have been reported from chronic application around the eye. The normal inflammatory response to local infections may be masked by corticosteroids, complicating diagnosis and therapy. Contact allergy to the glucocorticosteroid preparations has been recognized with increasing frequency. This may present as diagnostically confusing eczematous dermatitis or unresponsiveness of the original dermatosis to treatment because the steroid–allergen maintains partial antiinflammatory properties.

**RETINOIDS**

Retinoids are a family of naturally occurring and synthetic analogues of vitamin A. The skin of subjects deficient in vitamin A becomes hyperplastic and keratotic (phrynoderma, or toad skin). While natural vitamin A is occasionally employed therapeutically, synthetic retinoids are more effective and represent a major advance in dermatological pharmacotherapy. Retinoids have myriad effects on cellular differentiation and proliferation; it is likely that nuclear retinoic acid receptors mediate these effects by activating gene expression in a manner analogous to receptors for steroid hormones and thyroid hormones. Despite a common mechanism of action, however, retinoids vary widely in their physiological effects.

Retinoid action depends on binding to both cytosolic and nuclear retinoic acid receptors (RARs). RARs have distinct DNA and retinoid-binding domains, and they function as pairs and bind to the retinoic acid receptor element (RARE) to regulate transcriptional activity.

**Isotretinoin**

Isotretinoin (Accutane) alters keratinization in the acroinfundibulum of sebaceous glands and shrinks them, thereby reducing sebum excretion and comedogenesis. These features underlie its usefulness in acne vulgaris, since sebum secretion is a hallmark of acne-prone skin. Furthermore, the drug has antiinflammatory activity.

Isotretinoin is rapidly absorbed orally, with peak blood concentrations 3 hours after ingestion. It is not stored in tissue, and the elimination half-life is 10 to 20 hours, either after a single dose or during chronic therapy.

Isotretinoin is most useful for the treatment of severe recalcitrant nodular acne vulgaris. It may also be

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**TABLE 41.1 Selected Topical Corticosteroid Preparations**

<table>
<thead>
<tr>
<th>Potency class</th>
<th>Drug</th>
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<tbody>
<tr>
<td>1</td>
<td>Betamethasone dipropionate cream, ointment 0.05%</td>
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<tr>
<td></td>
<td>Clobetasol propionate cream, ointment 0.05%</td>
</tr>
<tr>
<td></td>
<td>Diflorasone diacetate 0.05%</td>
</tr>
<tr>
<td>2</td>
<td>Amincnonide ointment 0.1%</td>
</tr>
<tr>
<td></td>
<td>Desoximetasone cream or ointment 0.25%, gel 0.05%</td>
</tr>
<tr>
<td></td>
<td>Fluocinonide cream, ointment, gel 0.05%</td>
</tr>
<tr>
<td></td>
<td>Halcinonide cream 0.1%</td>
</tr>
<tr>
<td>3</td>
<td>Betamethasone valerate ointment 0.1%</td>
</tr>
<tr>
<td></td>
<td>Diflorasone diacetate cream 0.05%</td>
</tr>
<tr>
<td></td>
<td>Triamcinolone acetonide ointment 0.1%, cream 0.5%</td>
</tr>
<tr>
<td>4</td>
<td>Amincnonide cream 0.1%</td>
</tr>
<tr>
<td></td>
<td>Desoximetasone cream 0.05%</td>
</tr>
<tr>
<td></td>
<td>Fluocinolone acetonide cream 0.2%</td>
</tr>
<tr>
<td></td>
<td>Fluocinolone acetonide ointment 0.025%</td>
</tr>
<tr>
<td></td>
<td>Hydrocortisone valerate ointment 0.2%</td>
</tr>
<tr>
<td>5</td>
<td>Betamethasone dipropionate lotion 0.05%</td>
</tr>
<tr>
<td></td>
<td>Betamethasone valerate cream, lotion 0.1%</td>
</tr>
<tr>
<td></td>
<td>Fluocinolone acetonide cream 0.025%</td>
</tr>
<tr>
<td></td>
<td>Hydrocortisone valerate cream 0.2%</td>
</tr>
<tr>
<td></td>
<td>Triamcinolone acetonide cream 0.1%</td>
</tr>
<tr>
<td></td>
<td>Triamcinolone acetonide cream 0.025%</td>
</tr>
<tr>
<td>6</td>
<td>Aclometasone dipropionate cream 0.05%</td>
</tr>
<tr>
<td></td>
<td>Desonide cream 0.05%</td>
</tr>
<tr>
<td></td>
<td>Hydrocortisone 0.5%, 1.0%, 2.5%</td>
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</tbody>
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*Using the vasoconstrictor bioassay, class 1 is most potent; class 7 is least potent.
helpful in other disorders of keratinization, but it is not useful for psoriasis. High doses of isotretinoin (2mg/kg/day) are effective as cancer chemoprevention agents to reduce the frequency of cutaneous malignancies in patients at increased risk, such as those with xeroderma pigmentosum, an inherited disorder in which DNA repair is deficient, or in immunosuppressed patients.

The most serious toxicity of isotretinoin is teratogenicity. Pregnant women should never receive the drug, and women should not conceive for at least 1 month after its discontinuation. Other toxicities:

- Skin complaints, particularly xerosis, conjunctivitis, and cheilitis.
- Hypertriglyceridemia in about a quarter of patients.
- Elevation of liver function test findings, which is usually reversible.
- Headache, which rarely may be attributable to pseudotumor cerebri.
- Arthralgias, including skeletal changes such as hyperostoses, tendinous calcifications, premature epiphysial closure, and pathological fractures.
- Depression and suicidal ideation may occur, but no mechanism of action for these events has been established.

Acitretin

Unlike isotretinoin, acitretin (Soriatane) is not primarily sebosuppressive. Rather, it promotes normalization of dysregulated keratinocyte proliferative activity in the epidermis and is also antiinflammatory. Oral absorption is optimal when acitretin is taken with a fatty meal; peak levels are reached approximately 3 hours after ingestion, while steady-state plasma levels are achieved after approximately 3 weeks of daily dosing. The mean terminal elimination half-life of the parent compound is 49 hours. However, when consumed with ethanol, acitretin may be transesterified to form etretinate, a retinoid that is stored in adipose tissue, resulting in a much longer half-life (3–4 months or longer).

Acitretin is most useful for the treatment of severe psoriasis, particularly the pustular and erythrodermic variants. Psoriatic nail changes and arthritis also may respond. Combining the drug with ultraviolet light therapy (Re-UVB, in the case of ultraviolet B radiation, or Re-PUVA, with psoralen plus ultraviolet A radiation) permits the use of lower doses of both acitretin and ultraviolet radiation. Other conditions for which the drug may be especially useful include congenital and acquired hyperkeratotic disorders, such as the ichthyoses and palmoplantar keratodermas, and severe lichen planus.

Like other systemic retinoids, acitretin is a serious teratogen and should not be prescribed for women of childbearing potential unless no acceptable alternative is available and the patient has acknowledged in writing that she understands the need to use two effective forms of contraception during therapy and for 3 years following discontinuation of therapy. Because of the much longer half-life of etretinate, which may be formed when ethanol is ingested with acitretin, female patients of childbearing potential must also agree not to ingest alcohol during treatment and for 2 months following its discontinuation. Other toxicities are similar to those of isotretinoin; they include cutaneous irritation and inflammation, bone and joint pain, hyperlipidemia, hepatic enzyme elevation, and tendinous and ligamentous calcifications. Alopecia (hair loss) may also occur in some patients.

Tretinoin

Topical tretinoin (Retin-A, Renova, Avita), like isotretinoin, alters keratinization in the acroinfundibulum. In addition, it reverses certain premalignant and other histological changes associated with the photoaging changes that accompany chronic exposure to ultraviolet radiation. Topically applied tretinoin is indicated in comedogenic and papulopustular acne vulgaris, and its mild exfoliative effects make it sometimes useful in molluscum contagiosum, flat warts, and some ichthyotic disorders. It is often prescribed to lessen the clinical signs of photoaging (wrinkling and hyperpigmented macules).

The major toxic effect of tretinoin is erythema and irritation of the skin to which it is applied, especially if the skin is moist. This toxicity often decreases with continued therapy.

Adapalene

Adapalene (Differin) is a polyaromatic retinoidlike compound that binds to specific retinoic acid nuclear receptors and is thought to normalize the differentiation of keratinocytes in the sebaceous acroinfundibul. Adapalene is indicated for topical treatment of acne. Minor local irritation is a common, usually tolerable side effect. In contrast to other drugs of the retinoid group, adapalene has not been shown to be teratogenic in rodents. However, since adequate human studies are lacking, its use in pregnant women should be discouraged until further information is available.

Tazarotene

Like other retinoids, tazarotene (Tazorac) acts by binding to RARs and altering gene expression. Tazarotene appears to be particularly selective for the retinoid receptors RAR-β and RAR-γ, but the clinical significance of this observation is unknown.
In the United States, tazarotene has been approved for topical treatment of psoriasis (involving up to 20% body surface area) and mild to moderate facial acne. Application site burning, stinging, and desquamation are common side effects, especially with acne. Tazarotene is contraindicated in women who are pregnant.

**Bexarotene**

Bexarotene (Targretin) belongs to a subclass of retinoids that selectively bind to and activates retinoid X receptors (RXRs), which have biological properties distinct from those of RARs. In vitro, bexarotene exerts antiproliferative effects on some tumor lines of hematopoietic and squamous cell origin.

Bexarotene is available in oral and topical formulations. Peak plasma levels are achieved within 2 hours of oral administration, although higher levels are obtained when the drug is ingested with a fatty meal. It is thought to be metabolized primarily by the hepatobiliary system, with a terminal half-life of approximately 7 hours.

Topical and oral bexarotene are approved for early-stage (patch and plaque) cutaneous T-cell lymphoma that is refractory to at least one other therapy. Oral bexarotene is also approved for refractory cases of advanced disease; however, the best response has been noted in early disease.

Local irritation, such as burning, pruritus, and irritant contact dermatitis, is common following topical application. Major side effects seen after systemic administration include dyslipidemia, leukopenia, liver function test abnormalities, and possibly development of cataracts. Unlike other systemic retinoids, oral bexarotene causes thyroid abnormalities in approximately half of patients, which may necessitate treatment for hypothyroidism. Bexarotene is teratogenic and should not be prescribed in topical or oral form to women of childbearing potential unless a negative serum pregnancy test has been obtained and the patient agrees in writing to use two effective forms of contraception from 1 month before to 1 month after treatment.

**Alitretinoin**

Alitretinoin (Panretin) is a naturally occurring endogenous retinoid that binds to and activates all known retinoid receptors (both RARs and RXRs). It is approved for the topical treatment of cutaneous lesions of Kaposi’s sarcoma. Most patients have local irritation while using alitretinoin gel; however, the irritation rarely necessitates discontinuation of therapy.

**β-Carotene**

This naturally occurring retinoid (Solatene), a dimer of vitamin A, reduces free radical formation induced by photosensitizing porphyrins and light. Its major use in dermatology is for decreasing skin photosensitivity in patients with erythropoietic protoporphyria. Its major side effect is a yellow-orange discoloration of skin.

**PHOTOCHEMOTHERAPY**

Photochemotherapy is exposure of the patient to light of an appropriate wavelength after topical application or oral ingestion of a photosensitizing drug. The most common photosensitizing drugs used in dermatology are synthetic psoralens; psoralens also occur naturally in many plants, such as citrus fruits and celery.

**Psoralen and Ultraviolet A Therapy**

Psoralens form covalent linkages with pyrimidine bases in DNA when exposed to light of the appropriate wavelength, and if oxygen is present, reactive oxygen species also are generated. Although inhibition of DNA replication may account for some of the beneficial effects of PUVA therapy in certain hyperproliferative disorders such as psoriasis, PUVA has other important biological effects. It suppresses contact hypersensitivity and may evoke other immunological changes by affecting T lymphocytes and epidermal Langerhans cells. It increases melanin pigmentation in the skin and is useful in treating vitiligo. PUVA also inhibits mast cell release of inflammatory mediators.

Orally administered psoralens are rapidly absorbed (maximum photosensitivity for the most common preparation, 8-methoxypsoralen [Oxsoralen Ultra], is 1–1.5 hours). Although the elimination half-life is 2.2 hours, the skin remains photosensitive for 8 to 12 hours. Most excretion is renal, and the drug does not accumulate. It can be absorbed if applied topically, and after application to the entire body, therapeutic plasma levels can be detected.

PUVA is most useful for the treatment of severe psoriasis. Early (patch and plaque) stage cutaneous T-cell lymphoma (CTCL) also responds to PUVA therapy. In addition, patients in advanced stages of CTCL have been treated with a modification of PUVA known as extracorporeal photopheresis. In this therapy, blood from a CTCL patient who has taken psoralen is exposed to UVA light and returned to the patient. Lymphocytes are altered or destroyed by the treatment, and theoretically, the return of these abnormal cells triggers an immune response directed against certain lymphocyte surface antigens. The effectiveness of this modality appears to be variable.

Both topical and systemic PUVA are useful in some patients with vitiligo, although repigmentation is rarely complete. Other skin diseases for which PUVA may be helpful include atopic dermatitis, dyshidrotic eczema, and polymorphous light eruption.
Nausea is the most common acute side effect. About 36 to 48 hours after therapy, erythema and blistering can occur, especially if the UVA dose is too high or if the patient is exposed to other sources of UVA (such as sunlight). Long-term toxicities include the following:

- **Squamous cell carcinoma of the skin** (especially of the male genitalia). This risk is increased in patients already at risk because of fair skin, a history of skin cancer, and a history of exposure to other cutaneous carcinogens.
- **Melanoma.** After 15 years or more of PUVA (>200 treatments) the risk of melanoma increases approximately fivefold in patients treated with higher doses in the United States.
- **Cataracts.** Patients should wear UVA-absorbing wraparound sunglasses when exposed to ultraviolet light during the 24 hours after taking the drug.
- **Hyperpigmentation and development of discreet dark macules** called PUVA lentigines.

**PHOTODYNAMIC THERAPY**

Porphyrians are potent photosensitizing intermediates in heme synthesis and are thought to accumulate in malignant cells. This feature is used in photodynamic therapy, in which a synthetic porphyrin is administered and the patient is exposed to visible light. This modality has been shown to be effective in treating basal cell and squamous cell skin cancers, although a limiting toxicity has been that patients remain extremely photosensitive for weeks after treatment because of the long elimination half-life of the porphyrin analogues.

**AMINOLEVULINIC ACID**

Aminolevulinic acid (ALA HCl, *Levulan Kerastick*) is indicated for the treatment of nonhyperkeratotic actinic keratoses of the face and scalp. It has two components, an alcohol solution vehicle and ALA HCl as a dry solid. The two are mixed prior to application to the skin. When applied to human skin, ALA is metabolized to protoporphyrin, which accumulates and on exposure to visible light produces a photodynamic reaction that generates reactive oxygen species (ROS). The ROS produce cytotoxic effects that may explain therapeutic efficacy. Local burning and stinging of treated areas of skin due to photosensitization can occur.

**DAPSONE**

Although dapsone (*Avlosulfon*) is most often used as an antimicrobial agent, it has important antiinflammatory properties in many noninfectious skin diseases. Its pharmacology and toxicities are discussed in Chapter 49. The mechanism of action of dapsone in skin disease is not clear. Most of the cutaneous diseases for which it is effective manifest inflammation and are characterized by an infiltration of neutrophils; the drug’s antiinflammatory effect may arise from its inhibition of intracellular neutrophil reactions mediated by myeloperoxidase and hydrogen peroxide or from its scavenging of reactive oxygen species, which inhibits inflammation.

Dapsone is approved for the treatment of an autoimmune blistering skin disease, dermatitis herpetiformis. This intensely pruritic eruption is characterized histologically by a dense dermal infiltration of neutrophils and subepidermal blisters. Other skin diseases in which dapsone is helpful are linear immunoglobulin A (IgA) dermatosis, subcorneal pustular dermatosis, leukocytoclastic vasculitis, and a variety of rarer eruptions in which neutrophils predominate, including some forms of cutaneous lupus erythematous.

**THALIDOMIDE**

Thalidomide (*Thalomid*) is a derivative of glutamic acid that is chemically related to glutethimide. It exerts a number of biological effects as an immunosuppressive, antiinflammatory, and antiangiogenic agent, yet its mechanisms of action have not been fully elucidated. Thalidomide potently inhibits production of tumor necrosis factor (TNF) α and interleukin (IL) 12, and its effect on these and other cytokines may account for some of its clinical effects.

Its absorption from the gastrointestinal tract is slow, with peak plasma levels being reached after 3 to 6 hours. It appears to undergo nonenzymatic hydrolysis in the plasma to a large number of metabolites. The elimination half-life is approximately 9 hours.

Thalidomide is approved for use in the United States for the treatment of cutaneous manifestations of erythema nodosum leprosum, a potentially life-threatening systemic vasculitis that occurs in some patients with leprosy. Although not approved for other indications, thalidomide has also been shown to be very effective in the management of Behçet’s disease, HIV-related mucosal ulceration (aphthosis), and select cases of lupus erythematosus.

Thalidomide is a highly teratogenic drug, characteristically causing phocomelia (aplasia of the midportions of the limbs). Even a single dose may cause fetal malformation. Thalidomide should be prescribed to women of childbearing potential only when no acceptable alternative exists. Because it is not known whether thalidomide is present in the ejaculate of males receiving the drug, male patients must use a latex condom when engaging in sexual activity with women of childbearing potential.
Other side effects of thalidomide may include sedation (in fact, thalidomide was originally marketed in Europe as a sleeping aid), constipation, and peripheral neuropathy, which may be permanent.

**ANTIMALARIAL DRUGS**

Like dapsone, the antimalarial drugs chloroquine, hydroxychloroquine, and quinacrine are useful in some noninfectious skin diseases, although the mechanism of their therapeutic effect is unknown. Their pharmacology is discussed in Chapter 53.

Antimalarial drugs have many effects, including impairment of lysosomal phagosomal activity, inhibition of neutrophilic iodination and locomotion, and diminution of macrophage and T-cell responsiveness in vitro. Chloroquine (Aralen) and hydroxychloroquine (Plaquenil) also form complexes with hepatic porphyrins and can chelate iron, thereby enhancing their urinary excretion. Both drugs have an affinity for melanin, which may at least partially explain their ophthalmological toxicities (retinopathy).

Hydroxychloroquine is approved for the treatment of both systemic and cutaneous lupus erythematosis. Both chloroquine and quinacrine (Atabrine) are also effective in this skin disease. Low-dose chloroquine is used for the therapy of porphyria cutanea tarda in patients in whom phlebotomy has failed or is contraindicated. Other skin diseases in which the drugs are useful (after sunscreens and avoidance of sun exposure) include polymorphous light eruption and solar urticaria.

The duration of treatment for skin diseases is often longer than it is for malaria, and therefore, dose-related toxicities are important. The most serious toxicities are ophthalmological. Reversible alterations include ciliary body dysfunction and corneal changes with edema and deposits. Irreversible retinopathy also occurs; however, it is less common with quinacrine than with the other two drugs. Toxicity may be asymptomatic, but the earliest symptoms are night blindness, scotoma, or tunnel vision.

**ANTIMICROBIAL AGENTS**

**Systemic Antibiotics**

Antibiotics are used in dermatology for both infectious and noninfectious skin eruptions. Noninfectious skin eruptions, such as acne vulgaris and acne rosacea, are often treated with systemic antibiotics. The mechanism of action is not clear, although tetracycline inhibits lipases derived from resident flora in the sebaceous follicle (Staphylococcus epidermidis, Propionibacterium acnes). These lipases cleave irritating fatty acids from triglycerides in sebum, presumably contributing to cutaneous inflammation.

**Topical Antibiotics**

Topical antibiotics are helpful in acne vulgaris and acne rosacea and probably in reducing the frequency of infections related to intravenous catheters. One drug, mupirocin (Bactroban), is effective in treating impetigo contagiosa. Mupirocin binds to bacterial isoleucyltransfer RNA synthetase and prevents the incorporation of isoleucine into protein sequences. Mupirocin is most effective against gram-positive bacteria. Toxicity is uncommon.

Another topical antibiotic, metronidazole, is effective in the treatment of acne rosacea. Metronidazole is a synthetic nitroimidazole derivative that reduces inflammation by an unknown mechanism. Other selected topical antibiotics are listed in Table 41.2.

**DRUGS FOR CUTANEOUS FUNGAL INFECTIONS**

Like bacterial infections of skin, cutaneous fungal infections are treated with either topical or systemic agents. The pharmacology and toxicities of these agents are discussed in Chapter 52.

**Systemic Agents**

**Griseofulvin**

Griseofulvin (Fulvicin, Grifulvin V) has been used safely and effectively for decades for dermatophyte infections of scalp and nails and for more widespread skin eruptions. However, infections in certain sites (e.g., toenails) respond poorly. The drug is generally well tolerated, even in the long-term courses necessary for nail disease.

**Ketoconazole**

Ketoconazole (Nizoral) is approved for treating dermatophyte infections unresponsive to griseofulvin and for patients unable to tolerate that drug. A single oral

<table>
<thead>
<tr>
<th>Drug</th>
<th>Major Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clindamycin</td>
<td>Acne vulgaris</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Acne vulgaris</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Acne rosacea</td>
</tr>
<tr>
<td>Bacitracin</td>
<td>Superficial infection (gram-positive bacteria)</td>
</tr>
<tr>
<td>Polymixin B</td>
<td>Superficial infection (gram-negative bacteria)</td>
</tr>
<tr>
<td>Neomycin</td>
<td>Superficial infection (mainly gram-negative bacteria)</td>
</tr>
</tbody>
</table>
dose is also effective for the treatment of pityriasis versicolor. Other effective drugs that are less hepatotoxic may be preferred, however.

**Fluconazole**

Fluconazole (*Diflucan*) may be better absorbed and is possibly less hepatotoxic than ketoconazole, but it is considerably more expensive, an important consideration given the required length of therapy for most cutaneous fungal diseases.

**Itraconazole**

Itraconazole (*Sporanox*), a triazole, is highly lipophilic and concentrates in skin. It is approved for both cutaneous deep fungal infections and dermatophyte nail disease, for which shorter courses of therapy are probably effective. Pulse therapy, whereby the drug is administered for 1 week and then the patient is off treatment for 3 weeks between pulses, may reduce toxicity without compromising antifungal efficacy.

**Terbinafine**

Terbinafine (*Lamisil*), an antifungal drug, is highly lipophilic and concentrates in stratum corneum and nail plate. It is very effective for many dermatophyte infections, especially those of the nails, with which it may permit shorter courses of therapy than other drugs. Meta-analysis suggests that long-term efficacy of terbinafine is superior to that of the other antifungal drugs used in treating onychomycosis.

**Potassium Iodide**

Potassium iodide is used to treat the cutaneous lymphatic form of sporotrichosis, although newer agents are also effective in this disorder and may be better tolerated. The drug is also used for erythema nodosum and nodular vasculitis.

**Topical Agents**

Many effective topical agents are available both with and without a prescription for treating cutaneous dermatophyte infections and seborrheic dermatitis (Table 41.3); the azole drugs are also active against superficial candidal infections.

**DRUGS FOR CUTANEOUS VIRAL INFECTIONS**

The specific antiviral agents used to treat cutaneous infections caused by herpes simplex and varicella zoster viruses are discussed in Chapter 50.

**Interferons**

Interferons α-2b (*Intron-A*), α-nl, and α-n3 (*Alferon N*) have both intrinsic antiviral effects and antiproliferative and immunomodulatory actions. These interferons are approved for intralesional therapy of refractory or recurrent condylomata (genital warts). Toxicities include flulike symptoms, nausea, depression of the white blood cell count, and mild diminution in hematocrit.

**Podophyllotoxin**

Podophyllotoxin (*Podofilox*) is available alone and as the main cytotoxic ingredient in podophyllin (25% podophyllum resin), a mixture of toxic chemicals derived from May apple plants. The active ingredients inhibit cell mitosis. The drugs are used to treat condylomata acuminata. The most common toxic effects are skin irritation and less commonly, ulceration. Systemic

<table>
<thead>
<tr>
<th>Drug</th>
<th>Availability</th>
<th>Frequency of application</th>
<th>Duration of course to treat tinea pedis (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciclopirox</td>
<td>Rx</td>
<td>bid</td>
<td>4</td>
</tr>
<tr>
<td>Clotrimazole</td>
<td>OTC</td>
<td>bid</td>
<td>4</td>
</tr>
<tr>
<td>Econazole</td>
<td>Rx</td>
<td>qd</td>
<td>4</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Rx</td>
<td>qd</td>
<td>6</td>
</tr>
<tr>
<td>Miconazole</td>
<td>OTC</td>
<td>bid</td>
<td>4</td>
</tr>
<tr>
<td>Natifine</td>
<td>Rx</td>
<td>qd</td>
<td>4</td>
</tr>
<tr>
<td>Oxiconazole</td>
<td>Rx</td>
<td>qd</td>
<td>4</td>
</tr>
<tr>
<td>Terbinafine</td>
<td>Rx</td>
<td>bid</td>
<td>1-4</td>
</tr>
<tr>
<td>Tolnaftate</td>
<td>OTC</td>
<td>bid</td>
<td>4</td>
</tr>
</tbody>
</table>

Durations of therapy and frequency of application are those recommended in the package insert. The weekly dose for drugs applied twice a day is 30 g.

OTC, available over the counter; Rx, available only with a prescription.

absorption of podophyllin can occur (especially if applied to large, inflamed areas or mucosal surfaces), with gastrointestinal, hematological, renal, and hepatotoxic effects. In addition, seizures and peripheral neuropathy have been reported.

DRUGS USED TO TREAT SCABIES AND LICE

Pyrethrins and Pyrethroids

Pyrethrins are naturally occurring pesticides derived from chrysanthemum plants. They are active against many insects and mites. Over-the-counter liquid and gel preparations of pyrethrins with piperonyl butoxide are available for the treatment of pediculosis (piperonyl butoxide inhibits the hydrolytic enzymes that metabolize the pyrethrins in the arthropod). A synthetic pyrethroid, permethrin (Elimite), is available by prescription. A lower concentration of permethrin (Nix) is available without prescription. Pyrethrins and permethrin are quite safe.

CYTOTOXIC AND IMMUNOSUPPRESSIVE AGENTS

Cytotoxic and immunosuppressive drugs, which inhibit the synthesis or action of crucial cellular macromolecules, such as nucleic acids, are used in three broad categories of skin disease: hyperproliferative disorders, such as psoriasis; immunological disorders, such as autoimmune bullous diseases; and skin neoplasms. The pharmacology of these drugs is discussed in Chapter 57.

Methotrexate

Methotrexate is approved for use in severe disabling psoriasis recalcitrant to other less toxic treatments. The standard regimen is similar to low-dose therapy used for the treatment of rheumatoid arthritis (see Chapter 36). Although toxicities are similar to those described in the treatment of other diseases, hepatic cirrhosis and unexpected pancytopenia are of special concern given the chronicity of treatment.

Mycophenolate Mofetil

Mycophenolate mofetil (MMF, CellCept) is an ester prodrug of mycophenolic acid (MPA), a Penicillium-derived immunosuppressive agent (see Chapter 57) that blocks de novo purine synthesis by noncompetitively inhibiting the enzyme inosine monophosphate dehydrogenase. MPA preferentially suppresses the proliferation of cells, such as T and B lymphocytes, that lack the purine salvage pathway and must synthesize de novo the guanosine nucleotides required for DNA and RNA synthesis. MPA has been used for decades as a systemic treatment for moderate to severe psoriasis. MMF was developed to increase the bioavailability of MPA.

MMF is rapidly and completely cleaved to form MPA, the active metabolite, after oral administration. MPA is converted in the liver and kidney to an inactive glucuronide. However, certain tissues, such as the epidermis, express a glucuronidase that converts the inactive glucuronide back to the active agent. The half-life of MPA is approximately 18 hours; 90 to 95% of the mycophenolate dose is excreted in the urine.

MMF is indicated for the prophylaxis of organ rejection in patients receiving renal, hepatic, and cardiac transplants; it is often used in combination with other immunosuppressive agents for this indication. In dermatology, MMF is particularly useful as monotherapy, or as a steroid-sparing agent, for treatment of autoimmune blistering diseases (bullous pemphigoid and pemphigus). It may also be useful for the treatment of inflammatory skin diseases mediated by neutrophilic infiltration, such as pyoderma gangrenosum, and psoriasis.

The principal advantage of MMF over alternative systemic immunosuppressive agents (e.g., methotrexate, cyclosporine) is its relative lack of hepatotoxicity and nephrotoxicity. Adverse effects produced by MMF most commonly include nausea, abdominal cramps, diarrhea, and possibly an increased incidence of viral and bacterial infections. Whether MMF may be associated with an increased long-term risk of lymphoma or other malignancies is controversial; however, any such risk is likely to be lower in patients treated for skin disease with MMF monotherapy than in transplant patients treated with combination immunosuppressive therapy.

6-Thioguanine

6-Thioguanine is a purine analogue structurally related to 6-mercaptopurine and azathioprine. Thioguanine interferes with several enzymes required for de novo purine synthesis, and its metabolites are incorporated into DNA and RNA, further impeding nucleic acid synthesis. The mechanism of action of thioguanine in psoriasis is not clearly understood; it has been hypothesized to affect the proliferation and trafficking of lymphocytes as well as the proliferation of keratinocytes.

Absorption of orally administered 6-thioguanine is slow and incomplete; only approximately 30% of the oral dose is achieved in the plasma, peak levels being reached after 8 hours. Thioguanine is extensively metabolized prior to excretion. The elimination half-life is on the order of 80 minutes.

Although 6-thioguanine is chiefly used in chemotherapy for acute myelocytic leukemia and other marrow-based malignancies, lower doses are very effective for moderate to severe psoriasis, particularly in...
patients who cannot tolerate alternative systemic agents such as methotrexate and cyclosporine.

Dose-related myelosuppression is the major adverse effect produced by 6-thioguanine. Patients deficient in thiopurine methyltransferase (TPMT), a cytosolic enzyme required for metabolism of 6-thioguanine, are at heightened risk. Other adverse effects include gastrointestinal complaints and elevations of liver transaminases. There have been rare reports of more serious hepatotoxicity, including acute hepatitis, acute cholestasis, and hepatic venoocclusive disease.

**TOPICAL IMMUNE-MODULATING AGENTS**

**Tacrolimus**

Tacrolimus is a macrolide lactone originally derived from *Streptomyces tsukubaensis*. Although structurally unrelated to cyclosporine, tacrolimus has a very similar mechanism of action; that is, it blocks the production of proinflammatory cytokines by T lymphocytes by inhibiting calcineurin. Tacrolimus, however, appears to be 10 to 100 times as potent as an immunosuppressive. Oral tacrolimus (FK506) is used for prevention of organ rejection in recipients of renal and hepatic transplants. A topical formulation (*Protopic*) has recently been approved for treatment of moderate to severe atopic dermatitis in children and adults who have not responded to other therapies. Levels of systemic absorption are low even when applied to a relatively large body surface area. Local irritant reactions (burning, stinging, erythema) are a common side effect, but these usually resolve within the first few days of treatment. The major benefit of topical tacrolimus over topical corticosteroids is that tacrolimus does not cause atrophy, striae, or telangiectasia, even with chronic use.

**Pimecrolimus**

Pimecrolimus (SDZ ASM 981, *Elidel*) is another recently approved macrolide immunosuppressant that acts by inhibiting calcineurin and blocking the release of proinflammatory cytokines from T lymphocytes. The parent compound, ascomycin, was originally isolated from *Streptomyces hygroscopicus* var *ascomyceticus*. Like tacrolimus, pimecrolimus is approved for the topical treatment of moderate to severe atopic dermatitis that is refractory to other therapies. Transient local irritation is a common side effect.

**Imiquimod**

Imiquimod (*Aldara*) is a topical immune response modifier approved for the treatment of anogenital warts (condylomata acuminata). The exact mechanism of action is unknown; it has no direct antiviral activity in vitro. It is thought to work in vivo by inducing the production of tumor necrosis factor (TNF α), interferons (IFN α and γ), and other cytokines with antiviral activity. It may also be useful for treatment of other types of warts, molluscum contagiosum, and certain forms of skin cancer. Local irritant reactions related to the frequency of application are common.

**5-Fluorouracil**

5-Fluorouracil (*Efudex, Fluoroplex*) is an antimetabolite used for the topical treatment of actinic keratoses. It is also useful for the treatment of superficial basal cell carcinomas when conventional surgical modalities are impractical. Local inflammatory reactions characterized by erythema, edema, burning, and pain are common (and, some would argue, desirable) but may be minimized by reduced frequency of application or use in combination with a topical corticosteroid.

**Mechlorethamine**

Mechlorethamine (*Mustargen*) is a cytotoxic alkylating agent. Topical application of freshly prepared aqueous solutions are used in patients with early stages of cutaneous T-cell lymphoma. A major disadvantage to the use of this drug is the rapid induction of allergic contact dermatitis in some patients.

**ANTIHISTAMINES**

A large number of oral H1-receptor antagonists (see Chapter 38) are available with and without prescription for the treatment of mast cell–mediated diseases, such as acute and chronic urticaria, angioedema, and cutaneous mastocytosis. Until relatively recently, two major limitations of the available antihistamines, such as diphenhydramine (*Benadryl*), hydroxyzine (*Atarax*), promethazine (*Phenergan*), and cyproheptadine (*Periactin*), were their short half-lives and sedative effects. New-generation long-acting antihistamines pass the blood-brain barrier much less readily and are theoretically less likely to cause somnolence. Examples of these relatively non-sedating drugs are fexofenadine (*Allegra*), cetirizine (*Zyrtec*), and loratadine (*Claritin*).

**DOXEPIN**

The tricyclic tertiary amine doxepin (*Zonalon, Prudox*), a potent H1- and H2-receptor antagonist, is indicated for the short-term relief of pruritus associated with topical eczematous dermatitis. Systemic absorption occurs, and the drug may potentiate or alter the metabolism of a va-
riety of other systemic agents. Drowsiness is the most common adverse side effect.

DRUGS USED TO TREAT DISORDERS OF PIGMENTATION

Hydroquinone
Hydroquinone interferes with the production of the pigment melanin by epidermal melanocytes through at least two mechanisms: it competitively inhibits tyrosinase, one of the principal enzymes responsible for converting tyrosine to melanin, and it selectively damages melanocytes and melanosomes (the organelles within which melanin is stored).

Hydroquinone is applied topically to treat disorders characterized by excessive melanin in the epidermis, such as melasma. In the United States, nonprescription skin-lightening products contain hydroquinone at concentrations of 2% or less; higher concentrations are available by prescription.

The incidence of adverse effects with hydroquinone increases in proportion to its concentration. A relatively common side effect is local irritation, which may actually exacerbate the discoloration of the skin being treated. Allergic contact dermatitis occurs less commonly. A rare but more serious complication is exogenous ochronosis, in which a yellow-brown pigment deposited in the dermis results in blue-black pigmentation of the skin that may be permanent.

Monobenzone
Monobenzone (Benoquin) potently inhibits melanin production and destroys melanocytes. Like hydroquinone, monobenzone was originally introduced for the topical treatment of disorders of excess melanin pigmentation, including melasma. It is now used only to permanently depigment the remaining normally pigmented skin in patients with extensive vitiligo. Irritant and allergic contact dermatitis are common side effects.

RECOMBINANT PROTEINS AND OTHER BIOLOGICALS

Becaplermin
Becaplermin (Regranex) is a recombinant human platelet–derived growth factor (rhPDGF-BB) which is thought to enhance wound healing by stimulating granulation tissue. It is approved for the treatment of lower extremity neuropathic ulcers extending to the subcutaneous tissue in diabetic patients with an adequate blood supply. Local irritant reactions (erythema, burning, pain) occur in a minority of patients.

Etanercept
Etanercept (Enbrel) is a recombinant fusion protein designed to block the action of TNF-α (see Chapter 40). The drug is composed of the extracellular ligand-binding portion of the 75-kilodalton human TNF receptor linked to the Fc portion of human IgG1. TNF-α is a cytokine thought to play a major role in the pathogenesis of a number of inflammatory skin diseases, including psoriasis. Etanercept binds soluble TNF-α, preventing it from binding to and activating receptors for TNF that are present on cell membranes.

Etanercept is administered by subcutaneous injection. The maximum serum concentration is reached after approximately 72 hours. The half-life is approximately 115 hours.

Etanercept is approved in the United States for the treatment of psoriatic arthritis and rheumatoid arthritis. Although etanercept has not been specifically approved for the treatment of the cutaneous manifestations of psoriasis, it significantly improves the skin lesions of patients with moderate to severe cutaneous psoriasis who have used it for psoriatic joint disease.

Injection site reactions characterized by mild to moderate erythema, itching, burning, and/or pain occur in approximately one-third of patients but rarely necessitate drug discontinuation. The impact of etanercept on the host’s response to new or chronic infections is not fully understood. Serious infections and sepsis, including fatalities, have been reported in patients treated with etanercept. Increased levels of autoantibodies, including antinuclear antibodies and anti-double-stranded DNA antibodies, have also been reported, but the clinical significance of this observation is unknown.

Denileukin Diftitox
Denileukin diftitox (DAB 389 IL-2, Ontak) is indicated for treatment of patients with cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the IL-2 receptor. Denileukin diftitox is a recombinant fusion protein composed of IL-2 amino acid sequences joined to sequences of diphtheria toxin. The drug targets and destroys cells expressing the high-affinity (CD25/CD122/CD132) IL-2 receptor, including the malignant cells of cutaneous T-cell lymphoma.

The half-life of the drug is approximately 75 minutes after intravenous infusion. Antibodies directed against the diphtheria domain decrease mean systemic exposure by approximately 75%. Approximately 85% of patients develop such antibodies after a single course of treatment, and nearly all do after 3 cycles.

Most patients using denileukin diftitox have flulike symptoms (fever, chills, myalgias, nausea, diarrhea) within a few hours to days of treatment. Another common adverse effect is an immediate hypersensitivity
syndrome in which hypotension, back pain, dyspnea, chest pain or tightness, and rash may occur. Other notable side effects include a vascular leak syndrome (edema, hypoalbuminemia, hypotension), infections, and elevations of transaminases.

**Botulinum Toxin**

Botulinum toxin purified neurotoxin complex (Botox) is a purified form of botulinum toxin type A, produced from a culture of *Clostridium botulinum*. Injection of botulinum toxin into muscle induces paralysis by inhibiting the release of acetylcholine from motor neurons, thereby blocking neuromuscular conduction. It is approved for the treatment of blepharospasm, strabismus, and excessive sweating. *Botox* is also approved for use in dermatology to induce paralysis of the muscles of facial expression to reverse deep wrinkles. The effect of an individual treatment usually becomes apparent within 3 days and lasts approximately 3 months. The effect may persist for a longer period after a series of treatments because the muscles atrophy. The major adverse effect is temporary loss of function of a muscle required for normal social functioning, as may occur after inadvertent injection of muscles required for smiling or raising the upper eyelids.

**MISCELLANEOUS TOPICAL AGENTS**

**Azelaic Acid**

Azelaic acid (*Azela*lex) is a naturally occurring dicarboxylic acid produced by the yeast *Malassezia furfur*. Azelaic acid inhibits tyrosinase, a rate-limiting enzyme in the synthesis of the pigment melanin. This may explain why diminution of melanin pigmentation occurs in the skin of some patients with pityriasis versicolor, a disease caused by *M. furfur*. Azelaic acid is bacteriostatic against a number of species thought to participate in the pathogenesis of acne, including *Propionibacterium acnes*. The drug may also reduce microcomedo formation by promoting normalization of epidermal keratinocytes. Azelaic acid is used for the treatment of mild to moderate acne, particularly in cases characterized by marked inflammation-associated hyperpigmentation.

**Analgesia Anesthetics**

Topically administered local anesthetics are useful in dermatology for preparation of the skin prior to minor surgical procedures, such as skin biopsies, laser treatment of vascular malformations, and curettage of molluscum contagiosum lesions, particularly in young children and needle-phobic adults. The topical anesthetic may be used alone or may be applied prior to intradermal injection of a local anesthetic to reduce the pain caused by the needle. Two recently approved drugs in this group are ELA-Max, a topical formulation of lidocaine, and EMLA, which contains a mixture of lidocaine and prilocaine.

**Capsaicin**

Capsaicin (*Zostrix*) is approved for the relief of pain following herpes zoster infection (postherpetic neuralgia). The drug depletes neurons of substance P, an endogenous neuropeptide that may mediate cutaneous pain. It is applied to affected skin after open lesions have healed. Local irritation is common.

**Anthralin**

Anthralin (*Anthra-Derm*) is a potent reducing agent whose mechanism of action is unknown. It is approved for the treatment of psoriasis and also may be helpful in alopecia areata. The major toxicities are discoloration of skin, hair, and nails and irritant dermatitis.

**Benzoyl Peroxide**

Benzoyl peroxide is a potent oxidizing agent that has both antimicrobial and comedolytic properties; its primary use is in treating acne vulgaris. It is converted in the skin to benzoic acid; clearance of absorbed drug is rapid, and no systemic toxicity has been observed. The major toxicities are irritation and contact allergy. Outgrowth of bacteria resistant to topical antibiotics used to treat acne can be reduced by the addition of benzoyl peroxide in combination products such as erythromycin (*Benzamycin*) and clindamycin (*Benzaclin*).

**Calcipotriene**

Calcipotriene (*Dovonex*), a synthetic vitamin D₃ derivative, is indicated for the treatment of moderate plaque psoriasis. Its mechanism of action is unknown, although it competes for calcitriol receptors on keratinocytes and normalizes differentiation. It also has a variety of immunomodulatory effects in the skin. Although the drug can cause local irritation, the most serious toxicities are hypercalciuria and hypercalcemia, which are usually reversible.

**KERATOLYTICS**

Drugs that are used to treat hyperkeratosis, a thickening of the stratum corneum, are called keratolytics. Examples of these agents are salicylic acid, urea, lactic acid, and colloidal or precipitated sulfur. The precise mechanisms by which these agents treat hyperkeratosis are not known. Presumably, a common property is the ability to denature keratin, the major structural protein of the epidermis. Other beneficial effects vary among the different drugs. All of them have antimicrobial or
antiparasitic properties. Salicylic acid is a potent antiinflammatory agent. Urea is highly hygroscopic, enhancing the ability of tissue to absorb and retain water. Keratolytics are especially useful for treatment of corns and calluses, warts, palmoplantar keratodermas, ichthyoses, and psoriasis. When used in conjunction with topical steroids for treatment of psoriasis, keratolytics enhance the steroid’s penetration. Urea may also be used for chemical avulsion of dystrophic nails.

**Selenium Sulfide**

Selenium sulfide is a cytostatic and sporicidal agent available without prescription in a variety of shampoos and lotions for treatment of scalp seborrheic dermatitis. Higher concentrations are available by prescription for the treatment of pityriasis versicolor, which is caused by the yeast *M. furfur*, and tinea capitis.

**SUNSCREENS**

Sunscreens absorb ultraviolet radiation before it can be absorbed in the skin. They are recommended to protect the skin from the major toxicities of sun exposure: sunburn and skin cancer. Most available agents primarily absorb UVB, although newer preparations also provide protection against UVA. Physical sunscreens (which are generally opaque, like titanium dioxide and zinc oxide) block all ultraviolet radiation.

The frequency of application of sunscreen is guided by the SPF (sun protection factor) of the preparation. This derived value is the ratio of the time of ultraviolet exposure that causes erythema with the sunscreen to the time that causes erythema without the sunscreen. The higher the SPF, the less frequent the needed application of sunscreen. SPFs of available preparations vary from 2 to 50.

### Study Questions

1. Botulinum toxin is used in dermatology to reverse deep wrinkles. Its pharmacological mechanism of action in this use is
   (A) Blockade of acetylcholine esterase
   (B) Inhibition of release of acetylcholine from motor neurons
   (C) Inhibition of synthesis of acetylcholine by inhibiting choline acetyl transferase
   (D) Inhibition of acetylcholine binding to muscarinic receptors

2. Which one of the following agents is known to be a potent teratogen in humans?
   (A) Levulan Kerastick
   (B) Dapsone
   (C) Thalidomide
   (D) Mupirocin

3. Several very useful dermatological agents are derived directly from plants. A compound occurring in the May apple is
   (A) Interferon-α-2b
   (B) Mycophenolate mofetil
   (C) Methotrexate
   (D) 6-Thioguanine
   (E) Podophyllotoxin

4. Melasma is a condition characterized by excess melanin in the epidermis. A topical agent that is frequently successful in this condition is
   (A) Becaplermin
   (B) Etanercept
   (C) Hydroquinone
   (D) Botulinum toxin

### Answers

1. **B.** Botulinum toxin has no ability to inhibit esterase (A) or inhibit enzymes involved in the acetylcholine synthetic pathways (C), nor does it possess muscarinic receptor blocking properties (D).

2. **C.** Thalidomide caused a high incidence of phocomelia, particularly in Europe, where it was approved as a sedative agent. There is no definitive evidence associating teratogenic activity with the other compounds.

3. **E.** Interferon-α-2b is a recombinant product (A). Mycophenolate mofetil is derived from a *Penicillium* sp. (B). Methotrexate and 6-thioguanine (C and D) are totally synthesized.

4. **C.** Hydroquinone inhibits the enzyme tyrosine kinase, which converts tyrosine to melanin. It also damages melanocytes. Becaplermin (A) is a recombinant human platelet–derived growth factor that is useful in enhancing wound healing. Etanercept (B) is a recombinant fusion protein approved for treatment of psoriatic arthritis and rheumatoid arthritis. Botulinum toxin (D) is a purified form of botulinum toxin type A approved for therapy of blepharospasm and strabismus.

### Supplemental Reading


**Case Study** Treatment May Be Worse Than the Condition

A 35-year-old mother of two has moderate psoriasis. She tells you that her mother had a similar condition 3 years ago and was successfully treated with the agent acitretin. She has come to you because her regular physician refused to write her a prescription for acitretin, and she is very uncomfortable with her skin condition. You tell her that there is a serious risk of teratogenicity if she should become pregnant. She informs you that she is taking oral contraceptives and that the possibility of pregnancy is very low. Do you prescribe the drug she has requested anyway?

**Answer:** Acitretin should not be prescribed for women of childbearing potential unless no acceptable alternative is available and the patient has acknowledged in writing that she understands the need to use two effective forms of contraception during therapy and for 3 years after she discontinues the drug. She has not yet been treated with PUVA. You convince her that this is a more appropriate therapy, considering her age and her childbearing potential. She grudgingly accepts your suggestions and begins a course of PUVA treatment. She responds well to the treatment, and after 6 months the psoriasis is greatly improved and treatment is terminated.