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ESSENTIALS Topical therapy employs a vehicle (ointments, creams, lotions, gels) to deliver an active ingredient to the skin, to provide a protective bar- rier, or to hydrate and moisturize the skin. There are many types of topical treatments, including (1) antipruritics (e.g. calamine), are used to relieve itching; (2) keratolytics (e.g. salicylic acid, urea) are used to remove hyperkeratotic skin; (3) tars act by reducing the thickness of the epidermis; (4) corticosteroids have anti-inflammatory and im- munosuppressive effects that are useful in treating many skin dis- orders; (5) calcipotriol (an analogue of 1,25-dihydroxycholecalciferol) reduces epidermal proliferation and is used in local treatment of plaque psoriasis; (6) calcineurin inhibitors for eczema and other dis- eases; (7) retinoids influence immune function and have some anti- inflammatory activity and are used in acne; (8), immunomodulatory drugs such as imiquimod for some human papillomavirus infections, superficial basal cell carcinomas, and other diseases; (9) medical therapies such as diclofenac cream and inguenol mebutate for ac- tinic keratosis and superficial basal cell carcinoma; (10) antiseptics (e.g. benzoyl peroxide, chlorhexidine); (11) antifungal agents; (12) sunscreens; (13) anaesthetics/analgesics; (14) hair growth promoting agents such as minoxidil and topical prostaglandin analogues such as bimatoprost and stemoxydine. Other dermatological treatments include phototherapy (e.g. for psoriasis), photodynamic therapy (e.g. for actinic keratosis), and cryotherapy (e.g. for viral warts). Systemic therapies include oral ret- inoids, cytotoxics, and immunosuppressants. A major advance in the treatment of skin diseases has been the development of biological therapies as effective interventions for psoriasis, psoriatic arthritis, pemphigus vulgaris, urticaria, atopic dermatitis, and alopecia areata. General principles of therapy Topical therapy employs a vehicle to deliver an active ingredient to the skin, to provide a protective barrier, or to hydrate and moisturize the skin. Compliance and adherence Noncompliance to the clinician’s instructions is an important con- sideration in the treatment of dermatological disease where patients are asked to apply sticky and unpleasant preparations. The incidence has been estimated at around 30%. Helping patients to understand their disease encourages them to follow instructions from their medical attendant. Patient involve- ment in the decision making process can be helpful in building rap- port when dealing with a chronic problem like psoriasis or atopic dermatitis. Compliance is affected by the cost of medication, so a clear

indica- tion of the likely duration, cost, and quantities needed for adequate treatment should be given, especially if the patient is financially disadvantaged. When prescribing topical preparations, it is important to provide patients with sufficient quantities. Full body coverage requires 40 g of a cream and slightly less if applying an ointment. Dermatological vehicles Dermatological vehicles are composed of one or more of the fol- lowing ingredients: powders (e.g. zinc oxide, starch, calamine, or talc); liquids (e.g. water, alcohol, glycerol, or propylene glycol); oils, greases, or waxes (e.g. peanut oil, castor oil, liquid paraffin, white and yellow soft paraffin, wool fat, hard paraffin, beeswax, or poly- ethylene glycols (macrogols)). These ingredients are combined to produce ointments, creams, gels, powders, lotions, paints, tinctures, and pastes. Ointments Ointments consist of oils, greases, or waxes and have little or no water. They are generally greasy, but can be rendered water miscible if an emulsifying agent is included. They have emollient, protective, and occlusive properties. Greasy ointments can be sticky and dif- ficult to remove, and are often not well received by patients. Non- greasy ointments such as macrogol ointment consist of polyethylene glycols and are water-soluble. They spread well on the skin and wash off with water. Ointments are not prone to mould or bacterial growth and therefore do not require the addition of preservatives. 23.17 Management of skin disease Rod Sinclair

section 23 Disorders of the skin 5762 Creams Creams contain ointment and water, stabilized by an emulsifying agent. The stability and the drug-carrying ability of these finely balanced emulsions are dependent on the pH of the creams, the type and amount of emulsifying agents used, and the chemical properties of the active ingredients. Lotions Lotions are liquid preparations. They may be aqueous or alcoholic solutions, suspensions, or emulsions. They are easily spread, have a cooling effect, and a low risk of irritation to the skin. They are often used to deliver a thin layer of powder to the affected surface over a large or hairy area. Shake lotions such as calamine lotion tend to evaporate quickly, providing a cooling effect, but leaving a layer of powder on the skin. Gels Gels are water-miscible, viscous preparations which contain no oil. They contain a gelling agent such as tragacanth, gelatin, or hydroxypropyl cellulose, together with a solvent such as glycerol, propylene glycol, or alcohol, and a preservative. Gels form a durable film which stays on the skin surface longer than a water-miscible cream. They are suitable for the delivery of water-soluble drugs. Additives Preservatives Preservatives are added to products with high water content (e.g. creams, lotions, and shampoos) to inhibit the growth of moulds or bacteria and prevent spoilage. All preservatives are capable of pro- ducing irritant or allergic contact dermatitis. Absorption enhancers Several chemical agents can be added to the vehicle base to enhance percutaneous absorption of certain drugs. These agents include pro- pylene glycol, dimethyl sulfoxide (DMSO), cetrimide, and sodium lauryl sulphate. Antioxidants Antioxidants are sometimes added to topical preparations to in- crease the stability of formulations that are susceptible to oxidation. These agents act either by reacting with free radicals and blocking oxidation by competing for oxidation (reducing agents), or by enhancing the action of other antioxidants. Emulsifiers Emulsifiers are added to stabilize complex ingredients, vehicles, and additives. For water-based preparations, the issue of ion compati- bility must be considered when emulsifiers are selected. Vehicle choice The vehicle is a critical factor in the effectiveness of all topical therapies. Some vehicle-related key factors which may influ- ence therapeutic outcome in topical therapy are water/lipid mis- cibility, occlusive properties, and durability. The following guide can be used in the selection of an appropriate vehicle or base for a particular use. Creams and ointments are the most commonly used bases and the selection usually depends on the degree of hydration of the skin, as well as cosmetic factors. Creams are generally used on normal or moist skin. They are cosmetically

acceptable for use on the face, and are suitable for use in the flexures and for application to large areas. However, some creams can be drying if the skin is already very dry. The preservatives in creams can also cause contact dermatitis in some patients. Ointments are generally used when the skin is dry, when enhanced absorption is required (ointments are generally more effective than creams), and when avoidance of preservatives is desirable. Lotions are generally used on wet surfaces, for example, wet rashes (soaks or wet dressings) and oral mucosa (mouthwashes), or on hairy areas, for example, scalp, axillae, and pubic area. Gels are used as alternatives to lotions in hairy areas and where a drying effect is beneficial; and this applies especially to gels with an alcoholic base such as use in the treatment of acne. Gels or lotions containing alcohol should not be applied to excoriated or abraded skin, as they will sting. Pastes are used for occlusion and protection, and where substan- tive effects are required, allowing the drug to stay in contact with the skin for prolonged periods. They are also used in the application of an irritant drug to a limited area of skin (e.g. dithranol or a high con- centration of salicylic acid). Moisturizers Moisturizers can be categorized into emollient, humectant, and occlusive (see Table 23.17.1). Excessive soaking in water damages the waterproof seal on the skin, allowing a net water loss and dehy- dration. The best time to apply a moisturizer is immediately after a handwash or a bath. Emollients are preparations of emulsified oils and fatty acids, which replace the natural oils in the stratum corneum. These mol- ecules are incorporated into the epidermal structure, repairing the epidermis and providing a humidifying barrier to loss of water from between the cells of the keratin layer, which is the main source of loss, as well as from the skin surface, thereby increasing the water-holding capacity of the skin. Humectants contain chemicals that attract and retain water due to their hygroscopic or osmotic properties. They act by causing a migration of water from the epidermis to the skin surface as well as trapping water on its way out. Occlusive preparations provide an external physical barrier over the skin surface to prevent transepidermal water loss, at the same time replacing the natural oils in the stratum corneum. They are Table 23.17.1 Types of moisturizers Emollient Humectant Occlusive Aqueous cream Urea 10% cream White soft paraffin 50% in liquid paraffin Sorbolene cream Glycerol 10% cream White/yellow soft paraffin Peanut oil 5% cream Olive oil 10% cream

 very effective but are greasy and often not cosmetically acceptable to patients. Topical antipruritics Calamine Calamine is zinc carbonate or zinc oxide powder mixed with a small amount of ferric oxide, which gives it its pink colour. It is a mild astringent and antipruritic, and is used as a soothing and protective application in dusting powders, creams, lotions, and ointments. Camphor This is a white, crystalline ketone, which acts as a mild topical anal- gesic and a counterirritant. It is readily absorbed from all surfaces and systemic adverse effects such as nausea, dizziness, headache, and breathing difficulties may occur. Menthol Menthol is a crystalline substance obtained from mint oils or pre- pared synthetically. When applied topically, it will dilate blood ves- sels and cause a cooling and analgesic effect. It is used in creams and ointments to relieve itching in pruritus. However, it has the potential to cause allergic reactions and contact dermatitis, and may sting if applied to broken skin. Keratolytics Keratolytics are used to remove hyperkeratotic skin in conditions such as dermatitis, seborrhoeic dermatitis, ichthyosis, psoriasis, palmoplantar keratoderma, warts, and acne. Salicylic acid and benzoic acid Salicylic acid and benzoic acid are keratolytic agents with mild bac- teriostatic and antifungal properties. They are both mild irritants and can themselves cause dermatitis. Salicylic acid has been used topically as a 2–10% cream or oint- ment for hyperkeratotic dermatitis, although concentrations as high as 50% have been used in palmoplantar keratoderma. A 2% alcoholic lotion is used in acne to unblock

comedones. It can be combined with liquor picis carbonis (LPC) in the treatment of psoriasis and dermatitis or with sulphur in the treatment of ich- thyosis. Salicylic acid 30% in mineral oil is used to remove scale from the scalp. For warts, a 10–15% paint or a 20–72% paste can be used. Benzoic acid 6% can be used with 3% salicylic acid (Whitfield's ointment) for treating fungal infection of the skin, but specific targeted antifungal treatments are more effective (see Chapter 23.10). Urea Urea is a mild bactericidal keratolytic agent and promotes hydration of the skin by increasing the ability of the epidermis to absorb water. It is used as a 10% cream for moisturizing, or a 20–60% soak solution for the treatment of hyperkeratotic dermatitis. Propylene glycol Propylene glycol is a keratolytic agent with some bactericidal and fungicidal properties. A 40–60% solution applied under occlusion can be used to clear scaling skin in hyperkeratotic eczema. Tars Introduction Tars act by reducing the thickness of the epidermis and are used for the treatment of psoriasis, dermatitis, seborrhoeic dermatitis, and dandruff. Their efficacy is enhanced when ultraviolet B (UVB) therapy is given after application of the tar. Controversies exist in relation to the potential carcinogenic and teratogenic effects, and to the increased risk of carcinogenicity with concurrent use of tar ap- plication and ultraviolet (UV) therapy. Long-term treatment with high concentration tar preparations is not encouraged. Coal tar Coal tar is obtained from bituminous coals at high temperature. It has anti-inflammatory, antipruritic, and mild antiseptic proper- ties. Crude coal tar 0.5–5% is included in creams, ointments, pastes, shampoos, and soaps, often in combination with salicylic acid. Coal tar solution (liquor picis carbonis or LPC), which is a 20% solution of coal tar in alcohol, is used in concentrations of 3–12%. Coal tar may cause skin irritation and photosensitivity, but hypersensitivity reactions are uncommon. Preparations stain clothing and skin and have a mild odour, which may affect compliance. Pine tar Pine tar is obtained from the destructive distillation of the wood of trees belonging to the Pinaceae family. It has antipruritic prop- erties, but does not have the anti-inflammatory properties or photosensitizing potential of coal tar. It is included in a variety of proprietary preparations as solutions, cleansing bars, gels, and bath oils. Ichthammol Ichthammol is a black, viscous liquid with a strong odour, consisting of a destructive distillation product of bituminous schist or shale to- gether with ammonium sulphate. It has a mild antibacterial effect and is used in chronic dermatitis. It is a mild skin irritant. It is in- cluded in proprietary preparations for the treatment of dermatitis, psoriasis, and acne. Ichthammol 2% in glycerol lotion has been used for the treatment of ear psoriasis. Dithranol Dithranol is a yellow to orange powder of synthetic trihydroxy anthracene. When used in topical preparations, its strength starts at 0.05 or 0.1% and gradually increases to 3% as required. Strengths as high as 6% have been used in severe cases. It has anti-inflammatory properties. It stains skin and many fabrics and surfaces. Liquid par- affin may be used to remove dithranol products from the skin. Dithranol reduces proliferation of the epidermis by inhibiting en- zyme metabolism and reducing mitotic turnover. As it is irritant to mucosal surfaces, inflamed skins, and other delicate skin areas, it should not be used on the face, groin, and perilesional skin. Patients with fair skin are more sensitive. Concomitant use of coal tar may reduce its irritating effect. Dithranol can be localized to the plaques by application in Lassar's paste. Application of white soft paraffin to the perilesional areas may provide further protection. Dithranol is better absorbed through plaques of psor- iasis than normal skin. There are two methods of dithranol

 treatment: low-strength, long-contact therapy and high-strength, short-contact therapy. It is also used in the treatment of alopecia areata. While its mode of action is unknown, it is not effective unless skin irritation is produced. Dithranol preparations have many problems with stability, which decreases with the strength of the preparations. Addition

of sali- cylic acid, ascorbic acid, or oxalic acid as an antioxidant stabilizes dithranol products and prevents discolouration and inactivation. White soft paraffin appears to be the most stable base, while cream bases are least stable. Dithranol must be protected from light and should be supplied in appropriate light-occlusive containers. Topical corticosteroids The naturally occurring hydrocortisone has anti-inflammatory and immunosuppressive effects, which are useful in treating many skin disorders. Modifications of the hydrocortisone molecule have pro- duced a large number of agents with varying anti-inflammatory po- tency, which may be used systemically or topically. The potency of topically applied corticosteroids is ranked ac- cording to clinical effectiveness and potential for adverse effects (see Table 23.17.2). Adverse effects consist of loss of dermal collagen (leading to skin atrophy, striae, fragility, and easy bruising), telangi- ectasia, and perioral dermatitis. Penetration of corticosteroid to the dermis is greater on the face, the scrotum, and where conditions mimic application under oc- clusion (i.e. flexures and intertriginous areas). The use of the more potent corticosteroids on these sites therefore carries greater risk of local damage and should be avoided. With greater potency, there is increased risk of rebound on withdrawal and of tachyphylaxis. Absorption of more potent agents applied to large areas might cause suppression of the hypothalamic-pituitary axis and other usual complications associated with systemic corticosteroid administration. Topical corticosteroids should not be used on a patient where the diagnosis is uncertain. For example, patients may use topical cor- ticosteroids for years on a groin rash where the diagnosis is tinea cruris, which is curable with correct treatment. It is common for patients to express reluctance to use topical cor- ticosteroids because of misconceptions about the risks of their use. Suggested potencies and preparations for intermittent use of topical corticosteroids for chronic dermatoses are: • face and flexures (hydrocortisone 1%) • trunk (betamethasone valerate 0.02%, triamcinolone acetonide 0.02%) • elbows/knees and palms/soles (betamethasone dipropionate 0.05%, mometasone 0.1%, methylprednisolone aceponate 0.1%) Potent corticosteroids should be avoided on the face. However, more potent corticosteroids may be used intermittently for up to two weeks. The greater the potency the greater the risk of local adverse effects, particularly perioral dermatitis. Calcipotriol Calcipotriol is an analogue of 1,25-dihydroxycholecalciferol, the active form of vitamin D. It shares with the vitamin affinity for an intracellular receptor, combination with which reduces epidermal proliferation and inhibits interleukin 1 (IL-1) and T-cell function. It is used topically as an ointment or cream in local treatment of plaque psoriasis. Adverse effects include erythema and irritation. The the- oretical possibility of hypercalcaemia, renal calculi, and ectopic cal- cification due to absorption is not a practical problem unless it is applied to large areas of inflamed skin. It should not be used on the face or flexures. Calcineurin inhibitors Both pimecrolimus and tacrolimus can be formulated as topical agents. They have anti-inflammatory activity similar to a class I or class II topical corticosteroid and are used in atopic dermatitis, seborrhoic dermatitis, lichen planus, vitiligo, and psoriasis. Both agents can be used on the face with minimal risk of aggravating ros- acea or inducing perioral dermatitis. The United States Food and Drug Administration (FDA) mandated that topical pimecrolimus packaging would be required to carry a ‘black box’ warning regarding the potential increased risk of lymph node or skin malignancy. Topical tacrolimus is formulated extemporaneously as a 0.1% ointment for use on the body or 0.03% ointment for use on the face. Retinoids The term vitamin A refers to a group of compounds that are neces- sary for cellular differentiation, organ development, and production of the visual pigment in the retina. These compounds also influence immune function and have some anti-inflammatory activity. Tretinoin creams in concentrations ranging from 0.025 to 0.1% can be used for acne and sun damage. Acne sufferers can experi- ence some erythema, dryness, and irritation, which can be managed by

decreasing the frequency of application or discontinuing the preparation. Patients with sun-damaged skin react more vigorously to topical tretinoin, and its use should be titrated for the individual patient, starting with a daily application for 10 min before washing off. The duration of application can be increased until the preparation is eventually left on overnight. The best results in the treatment of sun damage are not seen until the preparation has been used for six months but include improvement in texture, reduction of pigmentation, removal of Table 23.17.2 Classification of potencies of topical corticosteroids Class I—mild Hydrocortisone 0.5–1% Hydrocortisone acetate 0.5–1% Class II—moderate Alclometasone dipropionate 0.05% Betamethasone valerate 0.02, 0.05% Triamcinolone acetonide 0.02, 0.05% Class III—potent Betamethasone dipropionate 0.05% Betamethasone valerate 0.1% Methylprednisolone aceponate 0.1% Mometasone furoate 0.1% Triamcinolone acetonide 0.1% Class IV—very potent Clobetasol 0.05%

23.17 Management of skin disease 5765 superficial solar keratoses, and effacement of small wrinkles. Topical isotretinoin and adapalene are used in acne and may also cause drying, erythema, burning, and photosensitivity, but generally these symptoms would be less than with tretinoin. Tazarotene can be used for acne, psoriasis, and sun-damaged skin. It is available as a cream or gel in concentrations of 0.05% or 0.1%. It is drying on the skin and should be used together with a moisturizer. Antiseptics Benzoyl peroxide Benzoyl peroxide has mild keratolytic, antiseptic, and bleaching properties. It is used in the treatment of acne as a 2.5–10% gel. Its antiseptic properties are probably the result of its oxidizing effect. Bleaching of clothing may occur where it is in contact with the agent. As irritation is common, caution is needed when applying it near the eyes and other mucosal surfaces. The irritation usually resolves on continued use. Chlorhexidine Chlorhexidine is a bisbiguanide antiseptic that is commonly used in topical preparations with or without cetrimide. It is used as the acetate, gluconate, or hydrochloride in sprays, creams, gels, so- lutions, dressings, and powders in concentrations ranging from 0.02 to 5%. Chlorhexidine salts may cause skin reactions, irritate mucosal surfaces, and interrupt wound healing. Discolouration of the teeth, tongue, and the buccal cavity associated with chlorhexidine mouth- wash or oral gel has been reported. Cetrimide Cetrimide is a quaternary ammonium antiseptic with surfactant properties. It has been used alone or with chlorhexidine in topical preparations in concentrations ranging from 0.1 to 3%. Skin sensi- tivity can occur, particularly with repeated and prolonged applica- tions. Application to mucosal surfaces should be avoided. Povidone-iodine Povidone-iodine is an iodine complex which has antibacterial, antifungal, and antiviral properties. It is used in mouthwash/gar- gles, skin cleansers, and antiseptic creams, ointments, solutions, and paints, in concentrations ranging from 5 to 14%. It is also used in some antiseptic swabs and wound dressings. It can cause skin irri- tation and is absorbed via damaged skin. Application over a large, broken skin surface is not recommended. Triclosan Triclosan is a bisphenol antiseptic agent commonly used in medi- cated soaps and topical preparations in concentrations of up to 2%. It is a mild irritant and allergic contact dermatitis has been reported. Antifungal agents Topical application of antifungal agents is effective for superficial cu- taneous infections but is not for those involving hair or nails. There are many agents used in this way. Imidazole derivatives bifonazole, clotrimazole, econazole, miconazole, and ketoconazole have a broad spectrum of antifungal activity achieved by inhibition of ergosterol synthesis and consequent disruption of the fungal mem- brane. After topical application they efficiently reach keratinocytes but there is no appreciable systemic absorption. Topical imidazole preparations can be irritating but local sensitization is uncommon. Tolnaftate is a thiocarbamate active against dermatophytes

but not Candida species. Its mode of action is unknown. Terbinafine is an allylamine, which inhibits ergosterol synthesis at an earlier stage than the azoles. It is fungicidal for dermatophytes, and is also active against pityrosporum species, but less clearly useful against Candida species. Nystatin and amphotericin are polyenes active against Candida species but not dermatophytes. Various other compounds such as undecenoic acid and the keratolytics benzoic acid and sali- cylic acid are used to treat tinea. Amorolfine is a morpholine with a broad spectrum, which inhibits ergosterol synthesis at different sites to other antifungals. It is used as a lacquer painted onto abraded nails once or twice weekly for 6–12 months to treat onychomycosis. Sunscreens Sunscreen active agents work by either absorbing or reflecting UV radiation. Absorbent sunscreen chemicals act mainly in the UV range, whereas reflectants provide a barrier against UV, visible light, and infrared radiation. A list of the commonly used sunscreen agents is included in Table 23.17.3. Most sunscreen products combine agents that absorb in the ultra- violet B (UVB) range (wavelengths 290–320 nm) with agents that absorb in the UVA range (wavelengths 320–360 nm) to provide broad-spectrum coverage. Many products also include a reflectant, such as titanium dioxide, which increases the protection but can give the skin a white appearance. Zinc oxide is used as a physical sun bar- rier for the protection of the ears and nose, which often receive high sun exposure. Primary prevention is an important part of the public approach to management of skin cancer. Reduction of sunlight exposure in child- hood is critical, but protection during adulthood is also important. It has been suggested that the entire spectrum of ultraviolet radiation (UVR) (i.e. 290–400 nm), contributes to risk of skin cancer, so pro- tection should be broad-spectrum in the UVR range. The primary approach is natural protection, involving the use of good quality clothing and hats while outdoors, seeking shade where possible, and avoiding the sun around the middle of the day. Reflected radiation may result in people receiving a high dose of UVR even when they are in the shade, and this needs to be accounted for when a canopy is being designed to reduce UVR exposure. Sunscreens are an adjunct to natural protection, not a substitute for it. Table 23.17.3 Commonly used sunscreen chemicals Physical blockers (reflectants) Zinc oxide, titanium dioxide, talc, red petrolatum UVB absorbers Salicylates—octyl salicylate, homosalate Cinnamates—octyl and isoamyl p-methoxycinnamate Camphor derivatives—4-methylbenzylidene camphor Aminobenzoates—p-aminobenzoic acid (PABA), padimate-O (octyl dimethyl PABA), methyl anthranilate UVA absorbers Benzophenonesa—benzophenone-6, oxybenzonea Dibenzoylmethanes—dibenzoylmethane, avobenzone (butylmethoxydibenzoylmethane) a Benzophenones absorb in the UVB, UVA, and UVC ranges.

 Sun protection factor (SPF) is a laboratory-derived figure classi- fying the relative potency of the different products. Because of the many variables determining the actual dose of UVR received (e.g. time of day, time of year, cloud cover, reflection, adequacy of ap- plication), it is not a figure which can be translated easily into the degree of protection afforded when used under normal conditions outdoors. The SPF number applies to the ability of a sunscreen product to reduce predominantly the UVB range of the solar spectrum. There is relatively little increase in protection for large increases in SPF number after SPF15 (Table 23.17.4). Other topical therapies Antihistamines Topical antihistamines are poorly absorbed and not effective in the treatment of most skin conditions. Systemic H1 receptor antagonists should be considered when indicated. Emulsifying ointment Emulsifying ointment is a mixture of paraffin and emulsifying wax. It can act as a detergent or soap substitute and is particularly useful for patients with contact dermatitis in which the offending chemical is not known. Lanolin Lanolin (wool fat) is a purified anhydrous waxy substance obtained from the wool of sheep. It is used in creams and

ointments to provide skin penetration properties. Lanolin is capable of absorbing about 30% of water, and hydrous lanolin is used as an ointment base. It is known to cause skin sensitivities. However, most lanolin-related sensitivities are found to be caused by residues of pesticide and de- tergent used on sheep. Removal of these impurities reduces the inci- dence of sensitization markedly. Podophyllum Podophyllum has an antimitotic action and is used in the treat- ment of warts. A combination of podophyllum resin and salicylic acid as a paint or ointment is used in the treatment of plantar warts. Podophyllotoxin 0.5% paint is used for anogenital warts. Podophyllum should not be used during pregnancy or in children. Topical anaesthetics and analgesics Most local anaesthetic agents are well absorbed through mucous membranes and damaged skin but absorption through intact skin is poor. However, a eutectic mixture of lidocaine and prilocaine can produce effective surface analgesia of intact skin prior to minor medical or surgical procedures, and this effect is enhanced by occlu- sion. Lidocaine is used in several products for use on oral and other mucosal surfaces and ulcers. Choline salicylate is used as a local an- algesic for oral lesions. Zinc oxide Zinc oxide is a mild astringent used as a soothing and protective ap- plication in dusting powders, pastes, ointments, creams, and lotions, often combined with ingredients such as coal tar, ichthammol, sali- cylic acid, calamine, or castor oil. Common topical preparations containing zinc oxide include cala- mine cream and lotion, zinc cream, ointment, and paste, Burow’s emulsion, and zinc and castor oil ointment. Zinc oxide reflects UV radiation and is used in sunscreen preparations. Fluorouracil Fluorouracil cream is used to remove superficial solar keratoses. It is used for a period of three weeks on the face and on the arms and legs for four to six weeks, although times may vary. It causes severe chemical irritation with erythema and crusting, but heroic patients who complete a course reap significant benefits. Some irritation is needed for the preparation to be effective. It may cause some photosensitivity. If added potency is required, tre- tinoin can be applied along with the fluorouracil, as the two act synergistically. Diclofenac sodium 3% Diclofenac gel is a topical nonsteroidal anti-inflammatory medica- tion that is approved for the topical treatment of actinic keratosis. It is applied twice daily to the affected areas as a field treatment for 60–90 days. In contrast to fluorouracil, diclofenac generally only produces mild skin irritation. Ingenol mebutate Ingenol mebutate is an extract of the Australian milkthistle. Its mech- anism of action involves both direct cell necrosis and immune medi- ated inflammation. It is used in the treatment of actinic keratosis: on the face and scalp in a 0.015% concentration; on the trunk and ex- tremities a 0.05% gel is applied for two consecutive days. Significant erythema swelling, crusting, flaking, and scaling may occur. Imiquimod Imiquimod (1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4- amine) is an immune response modifier that binds to the toll-like receptors 7 and 8. The drug has many actions including modulation of antigen presenting cell function and consequent enhancement of effector T-cell activity. It is used topically in the treatment of external genital warts, but has no direct antiviral activity. It is also used in the treatment of actinic keratosis and superficial basal cell carcinoma (BCC). Inflammatory reactions can be a problem. Complementary medicines in topical therapy Aloe vera Extract from aloe vera has been used in a variety of creams, oint- ments, gels, lotions, and shampoos. It has been suggested that aloe vera gel is useful for the treatment of mild burns and to Table 23.17.4 Erythemal UVB reduction by SPF number SPF number % Reduction % Penetration 2 50 50 4 75 25 8 87.5 12.5 16 93.75 6.25 32 96.88 3.13 64 98.44 1.56

 promote wound healing as a result of antiseptic, anaesthetic, anti- inflammatory, antipruritic, and moisturizing properties. While recent clinical studies have provided mixed findings about its effectiveness in the treatment of frostbite, wound

healing, and cuts, its topical use appears to be nontoxic. Tea tree (melaleuca) oil Oil from the leaves of the tea tree Melaleuca alternifolia has trad- itionally been used for cuts, burns, and insect bites. It contains various terpene oils and sesquiterpenes. It may also contain cineole, which is known to be a skin irritant. The antiseptic effect of tea tree oil is largely due to the presence of terpinen-4-ol. This is added to various commercial preparations. There are many in vitro studies demonstrating the antibacterial and antifungal effects of melaleuca oil. However, its antimicrobial ac- tivity is concentration dependent and clinical studies have not ad- equately demonstrated its effectiveness in the treatment of acne and skin infections such as tinea. Phototherapy Phototherapy involves treating patients with ultraviolet (UV) light of three types. These are shown next. Narrowband UVB (311 nm) The adverse effects of this treatment seem to be few. Carcinogenesis has not so far been demonstrated; however, lag times for the devel- opment of skin cancer are prolonged. Remission seems to be shorter than seen with psoralen ultraviolet A (PUVA) therapy, but the lack of long-term problems indicates that it should be the first-line form of phototherapy in most patients. Broadband UVB (290–320 nm) This is a tried and tested therapy, having been used for more than 80 years. It has not been shown to be carcinogenic. It is often com- bined with tar therapy for added efficacy. Psoralen and ultraviolet A (PUVA) (320–400 nm) Ultraviolet A light source is administered following pretreatment with a psoralen drug, usually methoxypsoralen 0.6 mg/kg orally, 2 h before UVA. Adverse effects include nausea and photosensitivity. Long-term use causes skin atrophy, lentigines and, after cumulative high dose, the incidence of squamous cell carcinoma is greatly in- creased. Long-term studies are still in progress, but it appears to also cause a small but definite increase in the incidence of melanoma. In the management of psoriasis, both PUVA and narrowband UVB are made more efficacious by pretreatment with acitretin. Continuation of acitretin during a course of phototherapy reduces the cumulative dose needed for clearing the psoriasis and lengthens the duration of post-treatment remissions. Patients taking psoralens to photosensitize themselves take the drug 2 h before phototherapy. They remain photosensitive to a decreasing extent for 24 h, so while on these drugs they must protect themselves generally from natural UV light, including the wearing of suitable eye protection. A typical course of photo- therapy, either PUVA or narrowband UVB, for plaque psoriasis may involve three treatments a week for 6–8 weeks. Patients need to stand unaided in the phototherapy apparatus for periods of up to 10 min. Claustrophobia is a relative contraindication for phototherapy. Photodynamic therapy Photodynamic therapy (PDT) is used to treat actinic keratosis, Bowen’s disease, and superficial basal cell carcinoma. It involves the application of a photosensitizing cream to the target lesion fol- lowed after a few hours application of intense red light to the skin. During this time the drug is selectively modified and concentrated in diseased cells while largely clearing from normal tissue. The drug remains inactive until exposed to light. When applied, the light energy, delivered to the cancer site, chemically activates the active metabolite and creates a toxic form of oxygen which destroys the cancerous and precancerous cells with minimal damage to healthy cells. Most PDT treatment can be performed on an outpatient basis. Principal side effects of PDT include a skin sensitivity to light for a few hours following treatment. Inflammation can occur after treat- ment. The reaction can be painful while the light is on (5–10 min) and local anaesthetic may be required in some cases. Cryotherapy Cryotherapy is very useful in the treatment of solar keratoses, super- ficial basal cell carcinoma, viral warts, small seborrhoeic keratoses, and small skin tags (acrochordons). A firm diagnosis is needed prior to consideration of cryotherapy. Liquid nitrogen is the preferred cryogen. The method of appli- cation of the nitrogen is somewhat immaterial as the damage to the tissue is determined by the depth of the resultant ice ball and the thaw time. Nitrogen is usually applied with a cotton-

tipped ap- plicator or sprayed on with a cryotherapy gun. After cryotherapy, patients may be alarmed at the blistering reaction. If they are fore- warned they are less likely to be anxious. Systemic therapy Oral retinoids Isotretinoin (13-cis-retinoic acid) is a stereoisomer of all-trans-retinoic acid, which probably acts by conversion to it but has less toxicity. It is given orally in the treatment of cystic acne. Like all vitamin A analogues it is teratogenic, but in contrast to acitretin relatively rapid elimination permits the safe initiation of pregnancy from one to two months after stopping the drug. Adverse psychiatric events such as mood swings, depression, and suicidal ideation have been reported as idiosyncratic reactions to isotretinoin. Acitretin has been used orally in the treatment of psoriasis and disorders of keratinization such as severe ichthyosis. It is necessary to avoid pregnancy for two years (three years in the United States of America) after stopping acitretin. More recent potent synthetic analogues known as arotinoids (adapalene and tazarotine) differ more markedly in structure from retinoic acid. They bind to retinoic acid receptors with different

 affinities for the different subtypes. Future developments may pro- duce agents with selective activity and consequent reduced toxicity. All systemic retinoids have substantial toxicity potentially manifested as: • cheilitis • dryness of nose, eyes, and face • scaling of palms and soles and softening of nails • loss of hair • joint and muscle pain and headache • hypertriglyceridaemia • hypercholesterolaemia and reduced high-density lipoprotein cholesterol • photosensitivity Most significantly, they are teratogenic and must not be used in women who may conceive. Because of prolonged retention of etretinate in the body, pregnancy should be prevented for two years after the drug is ceased (three years in the United States of America). A similar caution applies to acitretin since it is in part metabolized to etretinate. Comprehensible, practical advice on the need and means for fertility control is essential. Cytotoxics and immunosuppressants Corticosteroids Oral corticosteroids have an important role in management of many skin conditions. They are the mainstay of therapy in autoimmune blistering disease and most life-threatening dermatoses. While ef- fective in atopic dermatitis, most cases can be managed with topical therapy. While also effective in psoriasis, their use in this condition is contraindicated due to the potential for severe rebound on dose reduction. Chronic stable plaque psoriasis may be converted in to generalized pustular psoriasis following discontinuation of oral steroid. Azathioprine Azathioprine is converted in the body to 6-mercaptopurine, an in- hibitor of purine synthesis and an immunosuppressant. It also has potent anti-inflammatory properties. It is used alone or in combin- ation with other agents, usually corticosteroids. Toxicity is mainly due to bone marrow suppression, although this is less than with agents such as cyclophosphamide. Estimation of serum levels of thiopurine methyltransferase (TPMT) help predict the risk of myelotoxicity. Gastrointestinal upset is common and may necessi- tate discontinuation of therapy. Cyclophosphamide Cyclophosphamide is a nitrogen mustard analogue which is con- verted to the active metabolite in the body where it exerts its im- munosuppressant effects by interfering with DNA synthesis and function in B and T cells. It may be a more effective immunosuppres- sant than azathioprine, but this is associated with greater toxicity. Ciclosporin Ciclosporin is a potent inhibitor of T-cell activation and prolifer- ation. It is variably absorbed after oral administration and exten- sively metabolized predominantly by CYP3A4, an isoform of the hepatic cytochrome P450 enzymes. Standard doses for psoriasis are in the range of 3–5 mg/kg. Use of high doses should be guided by monitoring of blood levels. The main toxicity is partially reversible renal impairment and hypertension. Its place in dermatology is in the treatment of a wide variety of inflammatory conditions such as psoriasis, atopic dermatitis, lichen planus, and bullous pemphigoid, but the

difficulties in its use and the reversibility of benefit on ceasing administration markedly limit the circumstances warranting its use. Methotrexate Methotrexate is an inhibitor of dihydrofolate reductase. It is well ab- sorbed after oral dosing of up to 25 mg/m2. It is not metabolized to any extent and elimination depends on renal excretion, so caution and perhaps dosage adjustment is needed in the presence of renal impairment. Toxicity due to bone marrow depression and mucositis is less likely in dermatological applications than when higher doses are used, but regular monitoring with blood counts is necessary. Prolonged intake leads to hepatic fibrosis and this requires liver function to be included in the monitoring. Liver biopsy is neces- sary for early detection and characterization of this complication, but whether this is justified and how often it should be performed is controversial. Methotrexate is valuable in treatment of severe unresponsive psoriasis. Hydroxyurea Hydroxyurea blocks pyrimidine synthesis. It causes much more short-term bone marrow depression than methotrexate, necessitating frequent blood counts. Thalidomide Thalidomide is not generally available but is an inhibitor of tumour necrosis factor and has found a use in several inflammatory condi- tions despite its significant risks. Bleomycin Bleomycin has antitumour, antibacterial, and antiviral activity. It binds to DNA, causing strand scission and elimination of pyridine and purine bases. Intralesional injections are used in the treatment of unresponsive warts, although it can be extremely painful. The mechanism of ac- tion is not known. Biological treatments See Chapter 23.5 for an account of the currently used biological agents in the management of psoriasis. Many other potential uses have emerged and it seems likely that this will continue to develop. Anti-CD20 antibody is currently approved for the management of various forms of B-cell lymphoma, but reports are also appearing of their use in pemphigus vulgaris, paraneoplastic pemphigus, epi- dermolysis bullosa acquisita, dermatomyositis, and graft versus host disease, as well as other disorders. Off-label reported uses of the tumour necrosis factor-α (TNFα) antagonists have included the treatment of hidradenitis suppurativa, pyoderma granulosum, cuta- neous sarcoidoisis, cutaneous Crohn’s disease, Wegener’s vasculitis, autoimmune blistering diseases, Behçet’s disease, graft-versus-host disease, and others, although there appears to be differences in ac- tivity between the specific TNFα antagonists. IL-12/IL-23 pathway inhibition is increasingly being recognized as a potentially useful

 therapy for psoriasis. There are many other emerging biological therapies, resulting in a rapidly progressing and exciting area of therapeutics. Antimicrobial agents Topical administration favours development of resistance in skin flora (particularly if given long term) and is prone to cause hypersensitivity in the patient. It can be an extremely valuable ap- proach, but should thus be cautiously employed with these caveats in mind. Mupirocin Mupirocin is a valuable topical antibiotic which is not used system- ically. It is active mainly against Gram-positive aerobes, including most strains of staphylococci and streptococci. However, the emer- gence of high-level mupirocin resistance in methicillin-resistant Staphylococcus aureus (MRSA) has been reported. Topical mupirocin is used in the treatment of bacterial skin in- fections such as impetigo and infected dermatitis. Nonmacrogol based formulations are used intranasally to eradicate staphylococcal carriage. Tetracyclines Tetracycline itself has a very broad spectrum, but acquired resist- ance is common in many species of organisms. Modifications of the basic molecule has produced many drugs, including doxycycline and minocycline, which have longer half- lives and greater potency on a weight basis but do not differ appre- ciably in spectrum and exhibit cross-resistance. All tetracyclines cause some gastrointestinal symptoms and may lead to photosensitivity. They damage enamel of unerupted teeth and should not be given to children under 12 years. They should be avoided in pregnancy for

the same reason but also because of the rare occurrence of hepatic necrosis in pregnant women. Except for doxycycline and minocycline they are excreted renally, and may accumulate in renal failure and further aggravate renal impairment. Minocycline is particularly prone to cause dizziness and ataxia but such symptoms can occur with others of the group and they can rarely cause benign intracranial hypertension. Minocycline in par- ticular can cause abnormal pigmentation of mucosae and of tissues, including scars. As with all broad-spectrum antibiotics, overgrowth of resistant organisms occurs, particularly fungi in the case of tetracyclines. Tetracyclines are frequently used in the treatment of acne where, like other antibiotics, they probably act by suppressing proliferation of Propionibacterium acnes. The rationale for use in rosacea is uncer- tain. Tetracyclines also have anti-inflammatory effects, mediated by inhibition of neutrophil chemotaxis and phagocytosis and suppres- sion of granuloma formation, and possibly a direct effect on vascular endothelium, which may be beneficial in a variety of skin conditions. Erythromycin Erythromycin is a macrolide active against Gram-positive organ- isms and some anaerobes. It is used both topically (as a 2% gel or solution) and systemically in the treatment of acne and rosacea. This antibiotic is suitable for use in pregnancy. Clindamycin Clindamycin is active against P. acnes. It is used topically as a lotion or gel in acne and rosacea. Oral administration carries a risk of pro- ducing pseudomembranous colitis. Metronidazole Metronidazole is active against anaerobes but not P. acnes. It is ad- ministered topically in rosacea but the mode of its action is un- known, although there is some evidence that metronidazole is effective against the demodex mite. Dapsone and sulphapyridine Dapsone, a sulphone used for the treatment of leprosy, and sulphapyridine, a sulfonamide, are used in dermatology for anti- inflammatory effects in a variety of inflammatory skin conditions. Dapsone is of specific value in dermatitis herpetiformis and is used in such noninfective inflammatory conditions as pyoderma gangrenosum, pemphigus, and bullous pemphigoid. Dapsone, in the doses employed, causes a considerable incidence of haemolysis (especially in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency), methaemoglobinaemia, and rash. Rarer ad- verse consequences are blood dyscrasias, severe skin reactions, hepatitis, fever, and malaise, which may occur alone or as part of a generalized hypersensitivity reaction. Antifungal agents Systemic antifungals are used to treat deep-seated infections and those involving nails and hair. The imidazole, ketoconazole was the first orally active azole but has been largely superseded by the triazoles (itraconazole and fluconazole) due to the rare occurrence of liver damage, inhibition of androgen synthesis, and interactions with many drugs due to inhibition of the cytochrome P450 3A4 pathway. The triazoles are absorbed after oral administration. Both are effective against Candida species, but itraconazole is more active against filamentous fungi. Terbinafine, an allylamine, is well absorbed when given by mouth and concentrates in the stratum corneum, including the nail bed. Gastrointestinal disturbance occurs in approximately 5% of patients and rare adverse effects include hepatitis, toxic epidermal necrolysis, blood disorders, and a reversible loss of taste. Griseofulvin was the first orally effective agent against dermato- phytes. It is less effective than the azoles and allylamines but is much cheaper. It is poorly soluble and absorption is assisted by prepar- ations with very small particle size or by ingestion with a fatty meal. It is taken up by keratinocytes and exerts a fungistatic action in the stratum corneum which continues in hair and nails. It must be given for sufficient time for the quiescent but viable spores in the keratin to be shed. It is inactive against Candida species. Antimalarial agents Chloroquine and hydroxychloroquine are used as immunomodulating agents in lupus erythematosus and other con- nective tissue disorders. Their mode of action in these diseases is unknown. The most alarming adverse effect is a dose-related

section 23 Disorders of the skin 5770 permanent retinopathy, and regular monitoring by an optometrist or ophthalmologist is necessary. They are category D drugs and their use should be avoided in pregnancy. Antiviral agents Aciclovir is an analogue of guanosine that is phosphorylated prefer- entially by herpes simplex viral thymidine kinase to then inhibit the DNA polymerase. It can be administered topically or systemically by oral or intravenous routes. When taken orally, it is poorly and vari- ably absorbed. Its prodrug, valaciclovir, is its L-valyl ester which is much better absorbed after hydrolysis, resulting in higher and more reliable blood levels of aciclovir and permitting less frequent dosing. Famciclovir is a prodrug of penciclovir, which has the same mode of action as aciclovir. Penciclovir is also administered topically. They are all generally well tolerated. Antiandrogens These have a role in hirsutism, androgenic alopecia, and in acne. They should all be avoided in pregnancy. Spironolactone Spironolactone is a potassium-sparing diuretic which, independent of that property, is a weak antagonist of androgen receptor binding and an inhibitor of androgen biosynthesis. Spironolactone should not be administered to patients with renal failure due to the potential for potassium retention. The patient’s potassium status should be checked prior to commencing therapy and on an annual basis thereafter. Cyproterone acetate Cyproterone acetate is a synthetic corticosteroid with progestational and antiandrogen actions. The latter is due to competition at the dehydrotestosterone receptor and, at high doses, to inhibition of an- drogen synthesis. It may be used in the treatment of hirsutism and paradoxically of alopecia of the androgenetic type. Finasteride Finasteride inhibits the conversion of testosterone to dehydrotesto sterone by the type 2 5α-reductase enzyme, which is present on hair follicle cells, thus reducing the influence of androgens. Consequently, it has a role in androgenetic alopecia in men since it does not alter the effect of androgen on the testes and hypothalamic-pituitary function. Minoxidil Minoxidil was initially developed as a vasodilator antihypertensive medication. Its systemic use to treat hypertension is limited by tachycardia, fluid retention, and the undesired stimulation of hair growth. Minoxidil is used as a local application to the scalp where it acts as a nonspecific hair growth stimulant, probably by prolonging the anagen phase. This persists only while treatment is continued. Topical prostaglandin analogues Eye drops used for the treatment of glaucoma containing the pros- taglandin analogue bimatoprost or ophthalmic prostaglandins such as latanoprost and travaprost were unexpectedly found to promote eyelash growth. Bimatoprost was subsequently approved as a cos- metic drug for the darkening and lengthening of eyelashes. It has also been investigated for the treatment of scalp hair loss and other prostaglandin analogues such as stemoxydine are used in shampoos, conditioner, and scalp serums to promote hair growth. Biologics Biologics are medicines extracted from or semi-synthesized from biological sources. Gene based biologics are used to treat a variety of dermatological conditions including psoriasis, psoriatic arth- ritis, pemphigus vulgaris, atopic dermatitis, urticaria, and alopecia areata. Custom-designed monoclonal antibodies and fusion pro- teins to tumour necrosis factor-α, Interleukin 12, Interleukin 23, and Interleukin 17 have become established treatments for psoriasis. Interleukin 2 receptor binders were used to treat metastatic mel- anoma, but have been largely superseded by B-Raf inhibitors such as vemurafenib, debrafenib, and, MEK inhibitors such as trametinib, CTLA-4 inhibitors such as ipilimumab, and phosphatidylserine- targeting immunotherapy agents (anti-PD-1 antibodies) such as bavituximab. The sonic hedgehog signalling pathway targeting agent vismodegib is used to treat advanced basal cell carcinoma, Rituximab, an anti-CD20 antibody has been shown to induce long- term remission in pemphigus vulgaris. Omalizumab, and anti- IgE antibody has been used to treat chronic idiopathic urticaria. Multiple new biologic agents are currently undergoing clinical trials for the treatment of atopic dermatitis, lupus erythematosus, Merkel cell carcinoma, alopecia areata, autoimmune blistering disease, and a host of other

inflammatory and neoplastic skin diseases. Management of skin failure Erythema multiforme, Stevens–Johnson
syndrome, toxic epidermal necrolysis These disorders represent a spectrum ranging in severity from rela- tively benign erythema multiforme to life-threatening toxic epi- dermal necrolysis. Erythema multiforme is usually secondary to infection (mainly herpes simplex) and presents with target lesions particularly on the hands and feet. It can be more generalized, with mucosal involvement. Stevens–Johnson syndrome and toxic epi- dermal necrolysis are both, in most cases, caused by drugs (Box 23.17.1). They are considered to be a continuum, with clinical fea- tures ranging from atypical targetoid lesions with blisters and severe mucosal involvement in Stevens–Johnson syndrome to widespread detachment of full-thickness epidermis, confluent erythema, and skin tenderness in toxic epidermal necrolysis. See also Chapter 23.16. There is a mortality rate of up to 20% even with appropriate man- agement in toxic epidermal necrolysis, but this was much higher several years ago. Most fatalities in patients with toxic epidermal necrolysis are the result of sepsis. If Stevens–Johnson syndrome or toxic epidermal necrolysis is suspected, then hospital admission is essential. Patients with toxic epidermal necrolysis should be ad- mitted to a burns unit. All drugs should be stopped.

23.17 Management of skin disease 5771 Treatment consists of fluid and electrolyte replacement; main- tenance of body temperature; adequate pain relief; early treatment of infection; debridement where needed; and treatment of mucosal surfaces, especially the eye, where there is a 30% long-term mor- bidity. The role of oral corticosteroids is controversial, but if they are to be given they need to be started early, in high doses, and should be given for short periods of time. Ciclosporin and other approaches have been reported in some recent articles to be effective. Some studies have suggested that intravenous immunoglobulin (IVIG) may be of benefit, but others have disputed this. Staphylococcal scalded skin syndrome Children and neonates are most susceptible. They present with ir- ritability and raised temperature, along with skin tenderness and a scarlatiniform eruption, leading to superficial crusting initially in the flexures and around body orifices and then becoming general- ized. Treatment is with supportive measures and di/flucloxacillin 2 g (children: 25–50 mg/kg up to 2 g) orally, six-hourly. Corticosteroids are contraindicated. Meningococcal septicaemia A preceding, viral-like illness is followed by petechial lesions plus transient urticarial, macular, or papular lesions. The petechiae have a ‘smudged’ appearance and are raised with pale greyish centres. There is associated fever and there may be signs of meningitis. For further information on management, see Chapter 8.6.5. Exfoliative dermatitis (erythroderma) These terms are applied to any inflammatory skin disease that affects more than 90% of the body surface. The cause is not found in 10% of patients. The most common causes are dermatitis, psoriasis, drugs, lymphoma, pityriasis rubwra pilaris, and Norwegian (crusted) sca- bies. There are profound metabolic disturbances which mean that rapid diagnosis and inpatient management are needed. These dis- turbances include hypothermia, fluid loss, protein and electrolyte imbalance, and haemodynamic changes. Any suspected drug should be withdrawn. Treatment is directed at the underlying cause but oral corticosteroids are effective for cases due to dermatitis or drugs. FURTHER READING Dermatology Expert Group (2009). Therapeutic guidelines: dermatology version 3, 3rd edition. Therapeutic Guidelines Limited, Melbourne. Lebwohl MG, et al. (eds) (2006). Treatment of skin disease: comprehen- sive therapeutic strategies, 2nd edition. Mosby Elsevier, Philadelphia. Price CJ, Sinclair RD (2008). Fast facts: minor surgery, 2nd edition. Health Press, Oxford. Rakel RE, Bope ET (2009). Conn’s current therapy. Elsevier Science, Philadelphia. Williams HC, et al. (eds) (2008). Evidence-based

dermatology, 2nd edi- tion. BMJ Books, London. Box 23.17.1 Drug-induced rashes Drugs that commonly cause serious reactions • Allopurinol • Anticonvulsants • NSAIDs • Sulfa drugs • Bumetanide • Captopril • Furosemide • Penicillamine • Piroxicam • Thiazide diuretics Drugs less likely to cause skin reactions • Digoxin • Diphenhydramine hydrochloride • Aspirin • Aminophylline • Prochlorperazine • Ferrous sulphate • Prednisone • Codeine • Tetracycline • Morphine • Regular insulin • Warfarin • SSRIs NSAIDs, nonsteroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors.

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ESSENTIALS Clinical neurology uses conversation, detailed questioning, and dis- cussion, observation, structured examination, and selective investi- gation to formulate the patients’ problems into an anatomical and pathological framework. The competent neurologist identifies and probes relevant components of the history, reliably elicits the phys- ical signs, knows which investigations are necessary and relevant, appreciates the most likely underlying diagnosis and mechanism of disease, and communicates relevant information to the patient ac- curately, intelligibly, and sensitively. This system has evolved over sev- eral centuries, during which much knowledge has accumulated on structure and function in health and disease, the reliability of physical signs and laboratory investigations, and the nosology of disease. The neurological history Although patients usually start with an account of what troubles them most, the neurologist prefers a history of the components in the order in which they occurred. However, much can be gleaned from listening to the patient without interruption for a few minutes. It may then take some time to establish the chronology of the symp- tomatology. The first task is to assess the core symptoms and how they cluster. The neurologist asks enough questions to try and determine a likely anatomical localization and aetiology based on the temporal sequence of events. For example: a reported episode of difficulty with speech refers to a disturbance of language (aphasia) or articu- lation (dysarthria); there are motor or sensory deficits in a ‘heavy’ limb; alterations of sensation are positive (tingling and paraesthesia) or negative (numbness) symptoms; a disturbance of bladder func- tion suggests neurological or urological disease; and double vision actually refers to diplopia or altered acuity. Some questions reflect the peculiarities of neurological anatomy; it may surprise the pa- tient complaining of impaired vision on the right that the symptom is in fact unaltered by sequential closure of either eye—because it is hemianopic—or that awareness of temperature and the appreciation of pain may be disturbed in the ‘good’ leg in some forms of spinal cord disease (the Brown–Séquard syndrome). Once the individual symptoms have been accurately defined, they can be grouped; from this follows an interpretation of their anatomical basis, suggesting the involvement of one or more sites. Recognition of these patterns is fundamental to interpretation of the neurological history and this synthesis directs attention to specific components of the subsequent examination. It is easy to conclude that the patient with cognitive impairment has disease of the cere- bral cortex, but a more detailed history will, in addition, indicate whether this is diffuse or focal and reflects involvement of the dom- inant or nondominant hemispheres and the frontal, temporal, or parietal cortices. Incoordination of more than one motor skill (eye movement, speech, the limbs, and balance) necessarily indicates involvement of brainstem–cerebellar

connections. The pathology causing a hemianopic field defect lies above and that resulting in lower cranial nerve palsies below the tentorium. The combination of motor and sensory symptoms in limbs with altered sphincter function indicates spinal cord disease; for the male patient with an unreliable bladder, the significance of linking urgency and fre- quency to impotence and constipation may seem strange. In turn, the coexistence of diffuse distal symmetrical motor and sensory symptoms, shoulder and pelvic girdle weakness, or ocular, bulbar, respiratory, and upper limb weakness steers the thinking towards peripheral nerve, primary muscle, and neuromuscular junction dis- ease, respectively. The time course of the onset of the symptomatology helps to deter- mine the possible underlying pathology. As a generalization, abrupt events are vascular or electrical in origin, subacute symptoms are demyelinating or inflammatory, and symptoms that develop slowly suggest structural deficits or degeneration. The subsequent course of the symptoms also assists in identifying the underlying pro- cess: self-limiting events are often vascular; paroxysmal symptoms tend to be electrical or demyelinating, depending on their duration; and progressive syndromes are compressive or degenerative. The circumstances surrounding the development of the symptoms may be suggestive of a particular pathophysiology: trauma, preceding infection, drug exposure, or pregnancy alerts the observer to struc- tural, demyelinating, toxic, and venous thrombotic mechanisms, respectively. Although it can be dangerous for the beginner, but nevertheless important to recognize, are the inconsistencies of ex- aggeration, mismatch between the severity of symptoms and altered 24.1 Introduction and approach to the patient with neurological disease Alastair Compston and Christopher Kennard

SECTION 24 Neurologica l disorder 5776 function, and the anatomical impossibilities that usually feature in nonorganic neurological disease. Together, these pattern recogni- tions are the stuff of neurological diagnosis. The neurological examination Examination of the patient with neurological disease needs to be structured and organized without exhausting the patient and exam- iner through obsessive attention to irrelevant detail. Conclusions on likely localization from the history are essential to focus the exam- ination to the most likely relevant areas. In fact, the neurological examination is often used to confirm or refute the diagnosis which has been formulated on the basis of the history. However, much can be learned by astute observation without formal assessment. Gross defects of cognition do not need to be confirmed by reciting tele- phone numbers in reverse or assembling lists of former prime minis- ters, defects of speech will usually be evident in conversation, many neurological diagnoses are immediately apparent from the patient’s gait and movement disorders can be observed while taking the his- tory. That said, it is best routinely to adopt a basic core examination and do things in order because the detection of one abnormality will determine the interpretation of another. It takes only a few minutes for the experienced and adequately equipped examiner to confirm that corrected visual acuity is normal in each eye, there is no gross field defect, and the optic fundi are normal. Although more detailed assessment will sometimes be ne- cessary, a full range of smooth following (pursuit) eye movements in the horizontal and vertical planes can rapidly be established: this will detect obvious ophthalmoplegia and can be supplemented by cover testing of each eye during fixation on the examiner’s nose, and rapid gaze refixations from right to left—very few significant defects of eye movement will escape this rapid screen. Movement of the lower face during forced eye closure, voluntary elevation of the palate, and rapid protrusion or side-to-side movement of the tongue take a few seconds to observe and effectively cover all the lower cra- nial nerves. It is rarely necessary to test the sense of smell or hearing, and a tuning fork is most useful for establishing that deafness is con- ductive and therefore probably not relevant. Before moving to the limbs, it is worth testing

neck flexion in patients where the history suggests muscular or neuromuscular disease. A sufficient routine examination of the arms would start with posture (outstretched in supination with the eyes open and then closed): a quick look for selective muscle wasting and fascicula- tions; tone in flexion–extension and supination–pronation at the elbow and wrist, respectively; strength in flexion and extension at the elbow and wrist, spreading the fingers, and abduction of the thumb; coordination during movement between the patient's nose and examiner's finger (or both hands if there is gross incoordination to avoid accidental ocular injury); and the tendon reflexes. This will take the experienced examiner less than a minute. It may be neces- sary to establish specific patterns of muscle weakness: global loss affecting the hand in cortical disease; selective involvement of ex- tensor groups in upper motor neuron disease; the patterns of C5 to T1 nerve root lesions; diffuse distal weakness of both extremities in peripheral neuropathy; and the subtle distinctions between radial, median, and ulnar neuropathies, and C7, C8, and T1 root lesions, re- spectively. Detailed sensory examination of the arms rarely achieves more than can be learned from establishing that crude protective sense (recognition of a sharp pin) or discrimination (position sense and the ability to distinguish two points or perform a simple task such as manipulating a button) is intact. Although this may involve some rearrangement of clothing, it otherwise takes almost no time to swipe the abdominal reflexes in passing, before examining the legs. Here, the structured motor examination is as for the arms, although increased tone is more easily detected by lifting the relaxed leg from the couch at the thigh, and testing internal and external rotation at the hip. Characteristic patterns of weakness are the involvement of flexors at all joints and eversion at the ankle in upper motor neuron lesions, the usual dif- fuse symmetrical distal involvement in peripheral neuropathy at a time when the hands may be normal, and difficulty in distinguishing injury of the lateral popliteal nerve from an L5 to S1 root lesion (in which the ankle jerk is lost) in the context of unilateral foot-drop. Proximal weakness is best detected by watching the patient walk, and the calf muscles are normally so strong as to be untestable ex- cept with the patient standing. As in the arm, coordination can be assessed only once the degree of weakness has been established. Tendon reflexes in the legs may be brisk in isolation and often spread, so that, in an upper motor neuron lesion, when one is tapped several may respond—and in either leg. Even non-neurologists rarely forget to elicit the plantar responses. Sensory examination of the legs tends to be more reliable for protective than for discriminative sensation. In mapping a sensory level, it is best to move from the relatively anaesthetic to the normal zone, noting the band of hypersensitivity that usually exists at the boundary. It is a matter of fact that many patients confuse the exam- ination by exaggeration or elaboration of physical signs; this most commonly affects power, with the usual clues being a mismatch between the ability to walk and findings on formal assessment of muscle strength (or vice versa), and simultaneous contraction of agonist and antagonist muscles. Sensory testing is subjective and so necessarily vulnerable to inaccurate reporting, but confirming that a sensory level is present both on the abdomen and back, and on the same side on each, with a slightly higher level on the trunk, is a simple manoeuvre that may yield surprising discrepancies in the patient with nonorganic deficits. The overall purpose of the history and examination is to assess where and through what mechanism structure and function have been affected. Detection of these patterns becomes routine for the experienced neurologist, but the process represents more than just a ritual of clinical neurology. From anatomical localization follows a formulation of likely mechanisms and pathological conditions underlying the patient's symptoms and signs. Investigation of neurological disease The investigation of patients with neurological disease was revolu- tionized in the early 1970s with the introduction of computed tom- ography. Before then, only the most primitive structural details of the central nervous system could

be detected by demonstrating in- directly the shape and placement of the ventricles and blood vessels, and usually at some discomfort to the patient. Function in the cen- tral nervous system and peripheral nervous system was measured using neurophysiological techniques. Disruption of the blood–brain

 barrier and immunological activity in the central nervous system were assessed through analysis of the cerebrospinal fluid. Investigation still does not replace clinical assessment but, as the chapters that follow make clear, it is now possible to detect structural changes in most parts of the brain and spinal cord at high resolution; to distinguish many pathological appearances at these sites on the basis of differences in the magnetic resonance signals; to map func- tion within regions of interest using changes in blood flow and the use of metabolic substrates; to show variations in efferent and af- ferent electrical activity in the central nervous system and peripheral nervous system; and to detect an increasing range of soluble medi- ators of normal and pathological function in the cerebrospinal fluid. Taken together, these laboratory investigations still do no more than supplement clinical assessments and, in one sense, the high expect- ations of diagnosis make for additional difficulties in interpreting neurological illness when the images are normal, compared with the era when authoritative statements from neurologists could never be validated and necessarily went unchallenged. The value of many routine investigations lies in confirming nor- mality and endorsing abnormalities already strongly suspected on clinical grounds. Given the increasing sensitivity of techniques for brain imaging, altered appearances that are not necessarily of patho- logical significance and genuine lesions that are not relevant in the particular clinical context need to be interpreted with common sense. Overall, the trend has been for the pendulum to swing from diagnosis without adequate laboratory evidence to diagnosis made in defiance of clinical intuition. Even when an imaging abnormality has been identified, its nature may require clinical discussion in order to resolve the most likely pathological substrate—the distinc- tion between ischaemic and inflammatory tissue often proving diffi- cult and not all neoplastic tissue being easily identified as such. The management of neurological disease The first issue that confronts the doctor looking after a person with neurological disease is when to discuss and name the diagnosis. Most wait until there is sufficient clinical or laboratory evidence to rule out misdiagnosis; telling people that they have a condition when they do not is bound to cause distress and has landed some special- ists in the law courts. However, excessive caution and avoidance of discussion can be equally damaging, and there are many more pa- tients who harbour bitterness over delay in learning the true nature of their illness than those who wish that they had not been told so soon, or at all. Most individuals cope extremely well even with the prospect of conditions that are known to be life-threatening or have a poor prognosis for disability. Advice may be needed on alterations in lifestyle resulting from neurological disease (e.g. driving in epi- lepsy, and the use of drugs in pregnancy). There is a basic human need to know why a thing has happened and most patients enquire about causation but, naturally, the uppermost question is whether symptoms can be treated, or the natural history of disease usefully modified. The chapters that follow document specific treatments for par- ticular conditions, but judgement is often required when deciding whether to deploy these remedies, depending on age, significance of the symptoms for the individual, level of disability, security of the diagnosis, adverse effects, and the patient’s own views. Drug treat- ment may be used, on an intermittent or regular basis, to suppress symptoms; for example, intravenous methylprednisolone to reduce inflammation, anticonvulsants to suppress epilepsy, γ-aminobutyric acid agonists to deal with spasticity or anticholinesterases to enhance transmission at the neuromuscular junction. Pharmacological op- tions also exist for interfering with

the mechanism of disease, again on an intermittent or routine basis (e.g. the use of triptans to relieve migraine or the replacement of dopamine in Parkinson’s dis- ease). In other situations, the rationale of treatment is to modify the underlying disease process; for example, by suppressing inflam- matory processes in acute post-infectious polyneuritis using intra- venous γ-globulin, treating patients with multiple sclerosis using β-interferon, and using immunosuppressants such as methotrexate and cyclophosphamide in polymyositis and vasculitis, respectively. Many other illustrations could be given, confirming that the age-old witticism concerning the therapeutic nihilism of clinical neurology is at best now only of historical interest and was always generally rather ill-informed. Beyond the present pharmacological achieve- ments in drug treatment lie many opportunities for improving handicap and disability through the use of rehabilitation, which - increasingly assumes centre stage in the management of neuro- logical disease through attention to the person with impairments in a particular social and cultural setting rather than focusing on the pathophysiology of disease in an individual void. For the future, there is the prospect of enhanced regeneration in the context of dis- eases affecting the central nervous system and peripheral nervous system, restoring structure and function, and thereby both limiting and repairing the damage.

Revision #1
Created 2026-01-22 16:42:59 UTC by Omar Ayman
Updated 2026-01-22 16:42:59 UTC by Omar Ayman