Malignant neoplasms. Retinoids such as isotretinoin have been studied in the treatment of various neoplastic or preneoplastic disorders. Although oral tretinoin is used for remission induction in acute promyelocytic leukaemia (see p.1619), other retinoids do not have an established role in the treatment of cancer. There may, however, be a place for the use of retinoids in the chemoprevention of some malignancies.

There has been particular interest in the potential for retinoids to prevent the formation of skin cancers (p.672) in patients at increased risk. Maintenance immunosuppression may increase the incidence of pre-malignant and malignant skin lesions in solid organ transplant recipients; large numbers of lesions can develop and tend to be more aggressive than those in the general population.1 Although there has been some investigation in cardiac transplant recipients, most case reports and some small studies have involved renal transplant patients. Oral acitretin has been reported to reduce the number of actinic keratoses and reduce the development of new basal and squamous cell carcinomas in these patients. ¹⁻⁴ Other patients at increased risk of skin cancers who may benefit from prophylactic retinoid therapy include those with xeroderma pigmentosum and naevoid basal cell carcinoma syndrome; oral isotretinoin, rather than acitretin, has been tried in such patients.⁵ Retinoids might also be considered in others who have already developed nonmelanoma skin cancers, such as those with conditions requiring maintenance immunosuppression, chronic lymphocytic leukaemia or non-Hodgkin's lymphoma, severe photodamage of the skin, and those with squamous cell carcinoma at high risk of metastasis or that has already metastasised.5

Since retinoids suppress rather than cure skin cancer, rebound occurs when the retinoid is stopped and long-term therapy is needed. There is some concern about the risks of such long-term use, particularly on plasma lipids and bone, and monitoring has been recommended. ^{1,4,5} The mucocutaneous adverse effects that commonly occur can affect patient acceptance during long-term use; mucocutaneous effects may be more severe with isotretinoin, but hair loss may be more extensive with acitretin. 4,5 Gradual dose escalation to an effective dose can be used to minimise these mucocutaneous effects. One example using isotretinoin starts with a dose of 250 micrograms/kg on alternate days for a month, increased to 250 micrograms/kg daily for the second month, then to 500 micrograms/kg daily for the third month; the dose is then adjusted as tolerated.5 As there are risks of teratogenicity with retinoids, isotretinoin is preferred for women of child-bearing potential because of its shorter half-life.4,5 For acitretin doses that have been used, see p.1586

Topical application of retinoids has also been tried for chemoprevention of skin cancers. Topical tretinoin has been used on actinic keratoses in organ transplant recipients, but results have been mixed and may depend on dose. If squamous cell carcinomas are present, however, systemic retinoids should be considered.3

Retinoids have been studied in the chemoprevention of primary disease recurrence and second primary tumours after treatment for squamous cell carcinoma of the head and neck (p.666) but results have been mixed and limited by resistance and toxicity.6 A large placebo-controlled study7 has also reported that lowdose oral isotretinoin (30 mg daily for 3 years with an additional 4 years of follow-up) did not reduce the rate of second primary tumours or death in patients who had been treated for early stage head and neck squamous cell carcinoma. There has also been some interest in the use of retinoids, given orally (isotretinoin) or topically (isotretinoin or tretinoin), in the management of oral leucoplakia, which can be pre-malignant (see under Bleomycin, p.688). However, despite reports of beneficial response, relapse frequently occurs on stopping retinoid therapy.

Oral isotretinoin has been studied as continuation therapy in children with high-risk neuroblastoma that had responded to intensive chemotherapy. One study⁹ found improved survival with 6 cycles of isotretinoin given for 14 days of each 28-day cycle. However, another study¹⁰ using a lower dose given daily for 4 years or until relapse found no additional benefit from isotretinoin.

- Kovach BT, et al. Systemic strategies for chemoprevention of skin cancers in transplant recipients. Clin Transplant 2005; 19: 726-34.
- 2. Chen K, et al. Oral retinoids for the prevention of skin cancers in solid organ transplant recipients: a systematic review of radomized controlled trials. *Br J Dermatol* 2005; **152:** 518–23.
- 3. Neuhaus IM, Tope WD. Practical retinoid chemoprophylaxis in solid organ transplant recipients. *Dermatol Ther* 2005; **18**:
- 4. Campbell RM, DiGiovanna JJ. Skin cancer chemoprevention with systemic retinoids: an adjunct in the management of selected high-risk patients. *Dermatol Ther* 2006; **19:** 306–14.
- Otley CC, et al. Chemoprevention of nonmelanoma skin cancer with systemic retinoids: practical dosing and management of adverse effects. Dermatol Surg 2006; 32: 562–8.
- Smith W, Saba N. Retinoids as chemoprevention for head and neck cancer: where do we go from here? Crit Rev Oncol Hema-tol 2005; 55: 143–52.
- Khuri FR, et al. Randomized phase III trial of low-dose isotretinoin for prevention of second primary tumors in stage I and II head and neck cancer patients. J Natl Cancer Inst 2006; 98: 441-50.
- Gorsky M, Epstein JB. The effect of retinoids on premalignant oral lesions: focus on topical therapy. Cancer 2002; 95:

- Matthay KK, et al. Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis-retinoic acid. N Engl J Med 1999; 341· 1165_73
- 10. Kohler JA, et al. A randomized trial of 13-cis retinoic acid in children with advanced neuroblastoma after high-dose therapy. Br J Cancer 2000; 83: 1124-7.

Skin disorders. Apart from its established role in the treatment of acne (above), isotretinoin has been tried in many other skin disorders not responding to usual therapy. 1,2 Clinical responses to oral isotretinoin have been reported in small numbers of patients with anogenital warts (p.1584), rosacea (p.1583), and lichen planus (p.1580). Benefit has also been reported for keratinisation disorders such as Darier's disease² (p.1578), ichthyosis^{1,2} (p.1580), and pityriasis rubra pilaris.^{1,2} Isotretinoin is less effective than other retinoids for psoriasis¹ (p.1583). Oral isotretinoin may be used for chemoprevention of skin cancers (see Malignant Neoplasms, above).

Topical isotretinoin has been used to reduce some of the signs of photoageing³ (p.1581).

- Akyol M, Özçelik S. Non-acne dermatologic indications for systemic isotretinoin. *Am J Clin Dermatol* 2005; **6:** 175–84.

 2. Sehgal VN, *et al.* Isotretinoin – unapproved indications/uses and
- dosage: a physician's reference. Int J Dermatol 2006; 45: 772-7.
- 3. Stratigos AJ, Katsambas AD. The role of topical retinoids in the treatment of photoaging. Drugs 2005; 65: 1061-72.

Preparations

BP 2008: Isotretinoin Capsules; Isotretinoin Gel; **USP 31:** Isotretinoin Capsules.

Proprietary Preparations (details are given in Part 3)

Arg.: Atlacne; Curacne; Isotrex; Retinide; Roaccutan; Scheritonin†; Zonatian; Austral.: Accure; Isohexal; Isotrex; Oratane; Roaccutane; Austria: Cistian; Austrai.: Accure; isonexa; isotrex; Oratane; Roaccurane; Austrai: Uscutan; Isosuchat; Isosuch; Lurantal; Roaccuran, Belgz; Isosupra Lidose; Roaccutane; Braz.: Acnil; Cecnoin; Isoacne†; Isoface; Isotrex; Lurantal; Roacutan; Canad.: Accutane; Clarus; Isotrex†; Roface; Isotrex; Isotrex†; Roaccutan; Piplex; Roaccutan; Cz.: Aknenomin; Curacne; Isotrexi; Isotrex†; Roaccutane; Stiefel Acne Gel; Denm.: Accutin; Dermaoral†; Isotrex; Roaccutan; Fin.: Roaccutan; Fir.: Contracne; Curacne; Procuta; Roaccutan; Ger. Aknefug Iso; Aknenormin; Isoderm; Isotret; Isotrex; Roaccutan; Gr.: A-Cnotren; Accuran; Acnogen; Aknesil; Curacne; Derminoin; Filtrion; Inotrin; Isoderma; Isogeni†; Isoskin; Isotrori; Lyotret; Nolivori, Noroseptan; Novacne; Opridan; Policano; Reducar; Roaccutane; Stiefotrex; Trecifan; Tretin; Hong Kong, Acnotin; Isotrex; Oratane†; Roaccutane; Hung. Aknenormi; Isotrex; Roaccutane; Isotrex; Tectin; Inl.: Isotrex; Roaccutane; Is Isotrex; Roaccutan; **Malaysia**: Acnotin; Isotrex; Nimegen; Oratane; Roaccutane; **Mex.:** Isoface; Isotrex; Neotrex; Oratane; Roaccutane; **Nex.:** Isoface; Isotrex; Neotrex; Oratane; Roaccutane; **Philipp.:** Acnetrex; Isotrex; Roaccutane; Pol.: Aknenormin; Curacne; Isotrex; Izotek Roaccutane; Tretinex; **Port.**: Isdiben; Isoprotil; Isotrex; Orotrex; Roaccutan†; **S.Afr.**: Acnetane; Isotrex; Oratane; Roaccutane; **Singapore**: Acnotin; Isotrex; Nimegen; Oratane; Roaccutane; **Spain**: Acnemin; Dercutane; Farisoties, Namegen, Oradane, Noaccutaine; Spain: Actienini, De Cutaine; Amanen, Floresan; Isoliben; Iso Estediri; Isotrex; Roaccutan; Switz.: Curakne; Liderma; Roaccutane; Tretinac; Thai.: Acnotin; Isotane; Isotrex; Proacne; Roaccutane; Ostret; Turk.: Roaccutane; UK: Isotrex; Roaccutane; USA: Accutane; Amnesteem; Claravis; Sotret; Venez.: Cuticlin; Isoface; Isotrex†;

Multi-ingredient: Austria: Isotrex; Isotrexin; Braz.: Isotrexin; Isotrexol; Cz.: Isotrexin; Fr.: Antibiotrex: Ger.: Isotrexin; Hung.: Isotrexin; Inl.: Isotrexin; Pol.: Isotrexin; Pol.: Isotrexin; Singapore: Isotrexin; Spain: Isotrex Eritromicina; Thai.: Isotrexin; UK: Isotrexin

Keluamid

Keluamida

Келуамид

Profile

Keluamid has keratolytic properties and has been used in topical preparations for the treatment of seborrhoeic dermatitis and other scaling skin disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Kelual; Fr.: Kelual

Multi-ingredient: Arg.: Kelual Zinc; Fr.: Kelual DS; Kelual Zinc; Kertyol-S.

Kinetin

 N^6 -Furfuryladenine; 6-Furfurylaminopurine.

Кинетин

 $C_{10}H_9N_5O = 215.2.$ CAS - 525-79-1.

NOTE. The name kinetin has also been used as a proprietary name for hyaluronidase (p.2321).

Kinetin is a plant growth hormone that has been promoted in products for the management of photodamaged skin and hyperpigmentation but good evidence of efficacy appears to be lack-

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Kinerase†, Braz.: Kinerase; Hong Kong: Kinerase; Malaysia: Kinerase†, Mex.: Kinerase; Singapore: Kinerase; USA: Kinerase.

Kojic Acid

Kójico, ácido. 5-Hydroxy-2-hydroxymethyl-4-pyrone. Койевая Кислота

 $C_6H_6O_4 = 142.1.$ CAS — 501-30-4.

Kojic acid is reported to inhibit melanin production and is used in topical preparations for the treatment of hyperpigmentation disorders (p.1582). Kojic acid is also used as a food additive.

♦ References.

Lim JT. Treatment of melasma using kojic acid in a gel containing hydroquinone and glycolic acid. Dermatol Surg 1999; 25:

Preparations

Proprietary Preparations (details are given in Part 3) *Chile:* Unitone 4.

Multi-ingredient: Arg.: Cellskinlab Phyto Spot; Melasoft†; Neoquin; Braz.: Melani-D Maos; Chile: Alastik†; D 4†; Neostrata; Phyto Spot; Primacy Phyto +†; Mex.: Nova Derm; Port.: Despigmentante; Fade Cream†.

Liarozole (BAN, rINN)

Liarozol; Liarozolum. (±)-5-(m-Chloro-α-imidazol-I-ylbenzyl)benzimidazole.

Лиарозол

 $C_{17}\dot{H}_{13}CIN_4 = 308.8.$ - 115575-11-6; 145858-51-1.

Liarozole Fumarate (BANM, USAN, rINNM)

Fumarato de liarozol: Liarozole, Fumarate de: Liarozoli Fumaras: R-85246.

Лиарозола Фумарат

 $2C_{17}H_{13}CIN_4, 3C_4H_4O_4 = 965.7.$ - 145858-52-2.

Liarozole Hydrochloride (BANM, USAN, rINNM)

Hidrocloruro de liarozol; Liarozole, Chlorhydrate de; Liarozoli Hydrochloridum; R-7525 I.

Лиарозола Гидрохлорид

 $C_{17}H_{13}CIN_4$, HCI = 345.2. CAS - 145858-50-0.

Profile

Liarozole, an imidazole analogue, increases plasma and cutaneous retinoic acid concentrations through inhibition of cytochrome P450 isoenzymes involved in retinoic acid catabolism. It is under investigation for the management of ichthyoses and pso-

♦ References.

- 1. Bhushan M, et al. Oral liarozole in the treatment of palmoplantar
- nustrial M, et al. Oral macroei in the realment of paintoplanta pustular psoriasis: a randomized, double-blind, placebo-controlled study. Br J Dermatol 2001; 145: 546–53.

 2. Lucker GPH, et al. Topical liarozole in ichthyosis: a double-blind, left-right comparative study followed by a long-term open maintenance study. Br J Dermatol 2005; 152: 566–9.
- Verfaille CI, et al. Oral liarozole vs. acitretin in the treatment of ichthyosis: a phase II/III multicentre, double-blind, randomized, active-controlled study. Br J Dermatol 2007; 156: 965-73.

The symbol † denotes a preparation no longer actively marketed

Lisadimate (USAN, rINN)

Glyceryl Aminobenzoate; Glyceryl PABA; Lisadimato; Lisadimatum. Glyceryl I-(4-aminobenzoate).

Лизадимат $C_{10}H_{13}NO_4 = 211.2.$ CAS — 136-44-7.

Profile

Lisadimate, a substituted aminobenzoate, is a sunscreen (see p.1576) with actions similar to those of aminobenzoic acid (p.1589). It is effective against UVB light (for definitions, see

Preparations

Proprietary Preparations some preparations are listed in Part 3.

Lithium Succinate

Litio, succinato de Лития Сукцинат $C_4H_6O_4.xLi.$ CAS — 16090-09-8. ATC — D11AX04. ATC Vet — QD I I AX04.

Lithium succinate is reported to have anti-inflammatory properties and is used as an 8% cream or ointment, usually with zinc sulfate. It is applied twice daily initially in the treatment of seborrhoeic dermatitis (p.1584). It should be used with caution in patients with psoriasis as it may exacerbate their condition.

◊ References.

- 1. Gould DJ, et al. A double-blind, placebo-controlled, multicenter trial of lithium succinate ointment in the treatment of seborrheic dermatitis. *J Am Acad Dermatol* 1992; **26:** 452–7.
- Cuelenaere C, et al. Use of topical lithium succinate in the treatment of seborrhoeic dermatitis. Dermatology 1992; 184: 194–7.
- Langtry JA, et al. Topical lithium succinate ointment (Efalith) in the treatment of AIDS-related seborrhoeic dermatitis. Clin Exp Dermatol 1997; 22: 216–19.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: Arg.: Litiofarm†; Austria: Efalith; Belg.: Efalith; Ger.: Efadermin; Irl.: Efalith; Switz.: Efalith.

Maggots

Larvas: Sterile Larvae

Profile

Maggots used in wound management are the live sterile larvae of Lucilia sericata, the common greenbottle fly. Larval therapy (sometimes called biosurgery) may be used for debridement of infected or necrotic wounds (p.1585), including diabetic foot ulcers. Maggots produce a mixture of proteolytic enzymes that breaks down the necrotic tissue while leaving the healthy tissue unharmed, and kill or prevent the growth of micro-organisms, particularly Gram-positive bacteria. The movement of the maggots also appears to stimulate the growth of granulation tissue. The maggots are applied to the surface of the wound and kept in place with dressings for up to 3 days. They are removed with the dressing, and the wound is irrigated with sodium chloride solution; any remaining maggots are removed with forceps.

Maggots should not be applied to wounds that have a tendency to bleed easily, or that communicate with a body cavity or any internal organ. Pain has been reported with larval therapy and some patients may require analgesics.

◊ References.

- Courtenay M, et al. Larva therapy in wound management. J R Soc Med 2000; 93: 72–4.
- Jukema GN, et al. Amputation-sparing treatment by nature: "surgical" maggots revisited. Clin Infect Dis 2002; 35: 1566-71.
 Sherman RA, Shimoda KJ. Presurgical maggot debridement of soft tissue wounds is associated with decreased rates of postoperative infection. Clin Infect Dis 2004; 39: 1067-70.
- 4. Armstrong DG, et al. Maggot therapy in "lower-extremity hospice" wound care: fewer amputations and more antibiotic-free days. J Am Podiatr Med Assoc 2005; 95: 524-75.

 5. Steenvoorde P, et al. Maggot debridement therapy: free-range of
- contained? An in-vivo study. Adv Skin Wound Care 2005; 18:

Preparations

Proprietary Preparations (details are given in Part 3)

Melanin

Profile

Melanin is a group of natural pigments found in many plants and animals; they are present in human skin and hair. Natural and synthetic forms of melanin have been used in sunscreen prepara-

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: Arg.: Fotocrem Ultra; Chile: ProZone Face; ProZone Gel; Mex.: ProZone Body, ProZone Face; ProZone Gel; ProZone Ultra; ProZone Ultra Fluido.

Mequinol (USAN, rINN)

BMS-181158; p-Guaiacol; 4-HA; 4-Hidroxianisol; HQMME; Hydroquinone Monomethyl Ether; p-Hydroxyanisole; Hydroxyquinone Methyl Ether; Méquinol; Mequinolum; Metoxifenol; p-Metoxifenol. 4-Methoxyphenol.

 $C_7H_8O_2 = 124.1.$ CAS — 150-76-5. ATC — D11AX06. ATC Vet - QD11AX06

Profile

Mequinol is used similarly to hydroquinone (p.1598), in concentrations of up to 20%, in the treatment of hyperpigmentation (see Pigmentation Disorders, p.1582). A preparation containing mequinol 2% with tretinoin 0.01% is used for the treatment of solar lentigines (liver spots).

Adverse effects. A report of severe reversible irregular hypopigmentation of the hands, arms, neck, and legs in a West Indian woman who applied a bleaching wax containing mequinol for 2 to 3 months to lighten the colour of her skin.1

Boyle J, Kennedy CTC. British cosmetic regulations inadequate. BMJ 1984; 288: 1998–9.

Pigmentation disorders. References.

- 1. Fleischer AB, et al. The combination of 2% 4-hydroxyanisole (mequinol) and 0.01% tretinoin is effective in improving the appearance of solar lentigines and related hyperpigmented lesions in two double-blind multicenter clinical studies. J Am Acad Dermatol 2000; 42: 459-67.
- 2. Njoo MD, et al. Depigmentation therapy in vitiligo universalis with topical 4-methoxyphenol and the Q-switched ruby laser. J Am Acad Dermatol 2000; **42:** 760-9.
- Ortonne JP, et al. Safety and efficacy of combined use of 4-hy-droxyanisole (mequinol) 2%/tretinoin 0.01% solution and sun-screen in solar lentigines. Cutis 2004; 74: 261–4.
- 4. Jarratt M. Mequinol 2%/tretinoin 0.01% solution: an effective and safe alternative to hydroquinone 3% in the treatment of solar lentigines. *Cutis* 2004; **74:** 319–22.

 5. Draelos ZD. The combination of 2% 4-hydroxyanisole (mequi-
- nol) and 0.01% tretinoin effectively improves the appearance of solar lentigines in ethnic groups. *J Cosmet Dermatol* 2006; 5:

Preparations

Proprietary Preparations (details are given in Part 3) Austria: Leucobasal; Braz.: Leucodin; Fr.: Any; Leucodinine B; Gr.: Leucodinine-M; Spain: Novo Dermoquinona.

Multi-ingredient: Canad.: Solage†; USA: Solage.

Meradimate (USAN, rINN)

Menthyl O-Aminobenzoate; Menthyl Anthranilate; Méradimate; Meradimato; Meradimatum. 5-Methyl-2-(1-methylethyl)-cyclohexyl 2-aminobenzoate.

Мерадимат $C_{17}H_{25}NO_2 = 275.4$ CAS - 134-09-8.

NOTE. Do not confuse with methyl anthranilate (p.1607). Neo-Heliopan MA is a trade name that has been used for meradiPharmacopoeias. In US.

USP 31 (Meradimate). Store in airtight containers.

Meradimate is used as a sunscreen (p.1576). It is effective against UVA light (for definitions, see p.1580).

Preparations

Proprietary Preparations some preparations are listed in Part 3.

Ammoniated Mercury

Aminomercuric Chloride; Hydrargyri Aminochloridum; Hydrargyrum Amidochloratum; Hydrargyrum Ammoniatum; Hydrargyrum Praecipitatum Album; Mercuric Amidochloride; Mercuric Ammonium Chloride; Mercurio amoniacal; Mercury Amide Chloride; Mercury Aminochloride; Precipitado blanco (de mercurio); White Precipitate.

Хлористый Меркураммоний

 $NH_2HgCI = 252.1.$ CAS — 10124-48-8. ATC — D08AK01.

ATC Vet - QD08AK01.

NOTE. 'White Precipitate' has also been used as a name for Precipitated Mercurous Chloride.

Pharmacopoeias. In US.

USP 31 (Ammoniated Mercury). A white amorphous powder or pulverulent pieces; odourless. It is stable in air, but darkens on exposure to light. Insoluble in water and in alcohol; readily soluble in warm hydrochloric, nitric, and acetic acids. Protect from light.

Profile

Ammoniated mercury was formerly used topically in the treatment of skin infections and psoriasis but the use of such mercurial preparations is generally deprecated. Frequent or prolonged application to large areas or to broken skin or mucous membranes can cause mercury poisoning (see p.2341) and use on infants has produced acrodynia (pink disease). Ammoniated mercury is also a potent sensitiser and can produce allergic reactions.

Effects on the kidneys. Of 60 patients who were found to have nephrotic syndrome, 32 had used skin-lightening creams containing 5 to 10% of ammoniated mercury.1 Concentrations of mercury in the urine of these patients were up to 250 nanograms/mL compared with a usual upper limit of 80 nanograms/mL. Of 26 patients followed up for up to 2 years, 13 had no remission or response to treatment; 6 of these had used

Barr RD, et al. Nephrotic syndrome in adult Africans in Nairobi. BMJ 1972; 2: 131–4.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: Cz.: Homeovox; Hung.: Dermaforine†.

Mesulphen (BAN)

Mesulfen (pINN); Dimethyldiphenylene Disulphide; Dimethylthianthrene; Mesulfeeni; Mésulfène; Mesulfeno; Mesulfenum. It consists mainly of 2,7-dimethylthianthrene.

Месульфен

 $C_{14}H_{12}S_2 = 244.4.$ CAS — 135-58-0.

ATC — D10AB05; P03AA03.

ATC Vet - QDIOABO5; QP53AA01.

Pharmacopoeias. Jpn includes thianthol, a mixture of 2,7dimethylthianthrene and ditolyl disulfide.

Mesulphen has been used as a parasiticide and antipruritic in a range of skin disorders including acne, scabies, and seborrhoea. Sensitivity to mesulphen has occasionally been reported.

Preparations

Proprietary Preparations (details are given in Part 3) Ger.: Citemul S†; Switz.: Soufrol.

Multi-ingredient: India: Polyderm†.