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ESSENTIALS Normal human skin is photosensitive in that it reddens following acute sunlight exposure and tans and thickens following chronic sun- light exposure. Skin cancer, particularly nonmelanoma skin cancer, is also a consequence of high cumulative sun exposure in genetically predisposed normal individuals (predominantly those with fair skin). Outside the range of normal photosensitivity, there are several conditions in which patients exhibit diverse abnormal cutaneous reactions to sunlight. These are broadly described together as the photosensitivity disorders, but in fact they comprise a very heteroge- neous group of skin conditions. Abnormal cutaneous photosensitive responses range from easy sunburn (as in drug phototoxicity and the DNA repair photodermatoses) and pain (erythropoietic protoporphyria), through to complex inflammatory responses such as urticaria, ec- zema, or epidermal necrosis induced by specific wavelengths of sun- light, the so-called idiopathic photodermatoses. Introduction The sun emits a spectrum of electromagnetic radiation from high frequency γ rays to low frequency radio waves. Terrestrial solar radiation, or sunlight, is a portion of this electromagnetic radiation, not absorbed or scattered by the atmosphere, which reaches the Earth's surface and is essential for life. It is made up of ultraviolet radiation (UVR) (290–400 nm) which is responsible for vitamin D synthesis, visible light (400–800 nm) required for photosynthesis, and infrared (800 nm–1 mm) which provides warmth. Ultraviolet radiation is divided into UVC (which does not reach the Earth's surface), UVB (290–320 nm), and UVA (320–400 nm). Apart from vitamin D synthesis, it is broadly held that exposure of the skin to UVR is otherwise deleterious, causing sunburn and skin cancer. UVR and visible light also play a role in several photosensitivity disorders, a very heterogenous group of skin conditions (Table 23.9.1). Acute effects of sunlight on normal skin The main acute effects of UVR on normal human skin are erythema (sunburn), pigmentation (tanning), and immunosuppression. Sensitivity of the skin to sunlight is genetically determined and used to define the Fitzpatrick skin type classification for white-skinned individuals ranging from Celtic to Mediterranean: • Skin type

I/II—sunburns, tans with difficulty • Skin type III/IV—sometimes sunburns, usually tans Sunburn Sunburn is acute inflammation following sun exposure with ery- thema, heat, pain, and swelling of the skin, associated with systemic upset when severe. The erythema begins 3–6 hours after exposure, peaks by 12–24 hours, and resolves after 48 hours or so. UVB is 1000 times more effective at inducing sunburn than UVA. The standard photobiological measure of photosensitivity is the minimal ery- thema dose (MED), which is generally defined as that dose of UVB required to produce 'just perceptible erythema 12 hours following skin irradiation'. The pathophysiological changes that induce erythema have not been fully established. Many cytokines are released after UVR ex- posure of which TNFα is an important mediator of inflammation. Histologically keratinocytes appear to undergo apoptosis (sunburn cells), probably triggered by UVR-induced DNA damage. Pigmentation Pigmentation of the skin following UVR occurs in two distinct phases: immediate pigment darkening and delayed tanning. Immediate pigmentation occurs during irradiation with UVA, and is transient. It is maximal immediately after exposure and lasts only a few hours. This results from oxidation and redistribution of melanin within the epidermis. Delayed tanning occurs predominantly with UVB and is maximal 72 hours after irradiation. It is the result of new melanin production by melanocytes in the epidermis. UVR triggers melanocytes to become 23.9 Photosensitivity Hiva Fassihi and Jane McGregor

23.9 Photosensitivity 5689 more metabolically active with increased dendritic branching, tyro- sinase activity, and transfer of melanosomes to keratinocytes. Immune suppression There is evidence in animals and humans that T-lymphocyte-mediated immune responses are suppressed from about 24 hours after exposure of the skin to UVR, lasting a few days. Experimentally this can be demonstrated by reduction in both the sensitization and elicitation phase of contact hypersensitivity following UVR irradiation at the site of application on the skin. It is because of immunosuppression that UVR can be used as phototherapy to treat some inflammatory skin diseases, such as eczema an psoriasis. Clinically, it is evidenced by the reactivation of herpes simplex infection on acutely sun-exposed sites. UVB is a more potent immunosuppressor, but there is a syner- gistic effect between UVA and UVB in solar radiation. Low doses of UVR only immunosuppress the skin at the site of irradiation, but higher doses at one site lead to immune suppression of distant non- irradiated parts of the skin. The physiological function of UVR-induced immune suppression is unknown. The major clinical significance is probably in detection and elimination of skin cancer cells, as evidenced by the high in- cidence of skin cancer in people on immunosuppressive drugs fol- lowing transplantation. Chronic effects of sunlight exposure Photoageing Ultraviolet radiation causes the long-term skin changes known as 'photoageing'. Chronically exposed skin, particularly in skin types I/II, becomes wrinkled, furrowed, fragile, inelastic (solar elastosis), dry, and rough, with irregular pigmentation (lentigines) and broken blood vessels (telangiectasia). These changes are different and often superimposed on changes in the skin that occur as a result of chronological ageing. At the molecular level, photoageing reflects ultraviolet radiation- generated reactive oxygen species causing damage. The action spec- trum for photoageing has not been fully determined in humans and the relative contribution of UVB vs. UVA in this process is unknown. However, UVA penetrates deeper into the dermis than UVB, so UVB damage predominates in the epidermis and UVA in the dermis. Photo-carcinogenesis UVB irradiation and UVA, to a lesser degree, result in DNA damage through the formation of DNA photoproducts in skin cells. This damage, if not repaired, can result in UV 'signature mutations' re- ported in tumour suppressor genes (such as p53) of skin cancer cells. Epidemiological evidence indicates two patterns of risk for ma- lignant change; acute intense sunburn (for basal cell

carcinoma and melanoma), and chronic exposure (for actinic keratoses, squamous cell, and basal cell carcinoma). Both melanoma and nonmelanoma skin cancers are more common in sun-sensitive skin types I/II (see Chapter 23.14). Idiopathic photodermatoses The idiopathic photosensitivity disorders comprise a heterogeneous group of skin conditions in which patients exhibit abnormal im- munological responses to UVR. They include polymorphic light eruption (PLE), chronic actinic dermatitis (CAD), actinic prurigo (AP), hydroa vacciniforme (HV), and solar urticaria (SU). Diagnosis relies on an accurate and detailed history, particularly of the onset and offset time of the eruption in relation to sun exposure, as well as a description of the eruption, since the transient nature of the acute photodermatoses means there may be nothing to see on the skin at the time of consultation. Routine investigations include lupus serology (antinuclear anti- body (ANA) and extractable nuclear antigen (ENA)), porphyrin analysis where relevant, HLA class II typing (if a diagnosis of ac- tinic prurigo is considered), and biochemistry and haematinics if systemic medication is to be employed. Skin biopsy is not routinely undertaken but might help in selected cases where the diagnosis is in doubt, or if lupus needs to be excluded. Monochromatic phototesting is useful in some instances to confirm a diagnosis of photosensitivity and to define the provoca- tion spectrum, particularly for solar urticaria and chronic actinic dermatitis. Polymorphic light eruption (PLE) This is the most common of the photosensitivity disorders, with approximately 12% of the UK population affected. The prevalence increases with increasing latitude. Severity varies greatly between patients; some develop the rash only occasionally on sunny for- eign holidays, others repeatedly throughout summer in the United Kingdom. All skin types and all ages are susceptible, but it is more common in skin types I–II and the median age of onset is 25 years. Table 23.9.1 Photosensitivity disorders Idiopathic Polymorphic light eruptiona Chronic actinic dermatitisa Actinic prurigo Hydroa vacciniforme Solar urticaria Exogenous Drugs (oral ingestion or topical sensitization) Metabolic Congenital erythropoietic porphyria or Gunther’s disease Porphyria cutanea tarda Variegate porphyria Erythropoietic protoporphyria Genetic Xeroderma pigmentosum Cockayne syndrome Trichothiodystrophy Bloom syndrome Photo-aggravated skin conditions Lupus erythematosus Dermatomyositits Darier’s disease Bullous pemphigoid and pemphigus Atopic/seborrhoeic dermatitisa Psoriasisa Rosaceaa Actinic lichen planus Melasmaa a Most common conditions

 The female:male ratio is 4:1 and there is a possible association with lupus erythematosus. Evidence suggests a genetic basis for polymorphic light eruption, but the pathogenesis of this condition is not otherwise established. A type IV hypersensitivity reaction to autologous photo-induced antigens in individuals who are defective in UVR-induced immuno- suppression has been suggested. Both UVB and UVA (and occasion- ally visible light) can trigger the eruption, but UVA appears to be more common. Polymorphic light eruption typically presents during the spring and summer months in susceptible individuals. A few days of ex- posure might be required in spring before the eruption develops and thereafter it appears between 30 minutes and several hours after sun exposure as an itchy erythematous papular rash, which resolves within a few days without scarring. The ‘V’ of the chest and the arms are the most frequently affected sites (Fig. 23.9.1). Sparing of some areas (such as the face and backs of the hands) despite exposure to sunlight is common and occurs as a result of the ‘hardening’ phe- nomenon. As a result of this, many patients describe gradual im- provement as summer progresses. Diagnosis is usually made from the history, sometimes in asso- ciation with examination findings or photographs. Serum tests for antinuclear antibody and extractable nuclear antigen are required to exclude lupus erythematosus. For milder cases, sun avoidance and

judicious use of sunblock is all that is required to suppress the condition but, for others, short courses of oral prednisolone and/or prophylactic phototherapy are used. Chronic actinic dermatitis (CAD) Chronic actinic dermatitis is a relatively common condition in the context of the photosensitivity disorders. It occurs almost exclu- sively in older patients (usually more than 60 years) with a male pre- dominance. Patients are typically chronically sun exposed and many are keen gardeners. A variant of chronic actinic dermatitis has been described in younger patients with human immunodeficiency virus (HIV) disease and also, very rarely, in young atopics. Chronic actinic dermatitis presents as a chronic eczema on sun- exposed sites, notably on the face, dorsum of the hands and the neck (Fig. 23.9.2). Although it can worsen over the summer months, it persists throughout the year and patients might not notice its re- lationship to sun exposure. Patch testing often reveals multiple contact allergens, many to airborne antigens, such as colophony and compositae oleoresins (sesquiterpene lactone). Contact allergy to sunscreens is also common in this population. Confirmation of the diagnosis is by monochromatic phototesting, which typically demonstrates extreme photosensitivity (markedly reduced minimal erythema dose responses) to UVB in particular, sometimes extending into the UVA range. Skin biopsy might occa- sionally be required to distinguish chronic actinic dermatitis from photosensitive mycosis fungoides or Sézary's syndrome (cutaneous lymphoma), which it can mimic. Treatment includes general sun avoidance measures, topical ster- oids, and sunblock, but systemic therapy is usually also required to control the symptoms. Prednisolone, azathioprine, ciclosporin, and mycophenolate mofetil have all been used. Actinic prurigo (AP) This is a rare condition which typically presents for the first time in childhood (3–10 years), with a female bias, often improving with age. It is more common in North American Indians and in the Mestizo populations of Central and South America. A diagnosis of actinic prurigo is made on clinical grounds, sup- ported by HLA-DR4 Class II typing which is found in 90% of indi- viduals (compared with 30% of the general population). The subtype DRB1*0407 is frequently present. Patients with the condition present with itchy excoriated papules and nodules, predominantly on sun-exposed sites (Fig. 23.9.3) but also covered areas, typically the buttocks and backs of legs, during the summer months. Occasionally there is also cheilitis and con- junctivitis, more common in American Indians. Actinic prurigo leaves hypopigmented and atrophic scars at affected sites. There is an association with atopy, especially eczema, and it has a significant impact on quality of life, at least in children. Treatment includes sun protection and avoidance. For milder cases desensitization phototherapy, as for polymorphic light eruption, can Fig. 23.9.1 Polymorphic light eruption. Fig. 23.9.2 Chronic actinic dermatitis.

 help reduce the severity of the eruption during the summer, but for most individuals systemic therapy is required. Oral prednisolone will clear the acute eruption but is not an option for maintenance. Thalidomide is routinely used for actinic prurigo and is highly effective. Hydroa vacciniforme (HV) Hydroa vacciniforme is a very rare but severe photodermatosis which presents in childhood as a papulovesicular eruption on sun- exposed sites. The lesions classically resolve over several weeks to leave varioliform scarring, hence the name (Fig. 23.9.4). Recent studies have shown that hydroa vacciniforme and the Epstein–Barr virus (EBV) are strongly associated. EBV levels in the blood are very high and correlate with disease severity. Histology from hydroa vacciniforme skin lesions shows a dermal infiltrate made up of a significant number of lymphocytes (γ- δ- T cells) containing EBV encoded small nuclear RNA (EBER). In addition, there is notable intraepidermal vesicle formation and focal epidermal keratinocyte necrosis which, in the appropriate clinical setting, is diagnostic. Managements is by vigilant sun avoidance. Antiviral therapy for hydroa vacciniforme has been tried, but objective trials of re- sponse to therapy have

not been carried out. There is no systemic treatment that is of proven value. The literature suggests that most cases show spontaneous remission during adolescence. However, patients should be monitored long-term because of the risk of EBV- associated lymphoma, particularly in those with severe hydroa vacciniforme-like eruptions. Solar urticaria (SU) Solar urticaria is a rare and sometimes disabling condition in which urticaria (erythema and weals) occurs on exposed sites, often fol- lowing just a few minutes of sunlight. The wealing characteristically resolves within hours, although solar urticarial vasculitis has been described in which lesions persist for more than 24 hours, and re- solves with bruising. It can occur at any age, but is unusual in children. Like other physical urticarias, it appears to be a transient problem occurring over several years and then spontaneously resolving. There are no studies describing the demographics of this condition. Monochromatic phototesting shows that urtication can occur in susceptible individuals across various wavelengths, including UVR and visible light. Porphyrins should be checked since erythropoietic protoporphyria can, albeit rarely, present with solar urticaria. Treatment in milder cases involves general measures of sun avoid- ance and antihistamines, often in supranormal doses. Desensitization phototherapy can be helpful in selected patients, but is not suitable when the condition is severe. There are published small case series showing the potential benefits of ciclosporin, omalizumab (anti-IgE), intravenous immunoglobulin, and plasmapheresis in severe cases. Drug-induced photosensitivity (oral and topical) Many drugs can cause photosensitization in predisposed individ- uals, meaning that the presence of the drug in the skin of some patients alters their cutaneous response to sunlight. Table 23.9.2 demonstrates some of the important and common drug photosensi- tivity reactions. Other exogenous photosensitizers include topical agents, such as sunscreens and plants which contain psoralens. Fig. 23.9.3 Actinic prurigo. Fig. 23.9.4 Hydroa vacciniforma.

 The most common mechanism of photosensitivity caused by drugs is phototoxicity. Clinically this may present in a variety of ways, including immediate erythema or pain, but more com- monly it presents as an increased tendency to sunburn. A small number of phototoxic drugs cause pseudoporphyria in which the photosensitizing effect is of skin fragility and blistering. Photoallergy is an uncommon cutaneous reaction to sunlight in which, often following an acute phototoxic (erythemal) response, dermatitis occurs on the sun-exposed skin some days or weeks later. This has been reported with the use of phenothiazines and also with musk ambrette, once widely used in fragrances, but which has now been withdrawn in most countries. Para-aminobenzoic acid (PABA) and benzophenones (both used in sunscreens) have also been re- ported as causing photoallergy, although the incidence of this re- action is low. Calcium channel antagonists can cause progressive exposed site telangiectasia. Evidence suggests that some phototoxic drugs can also be photocarcinogenic, although this work has been done in vitro and with animal models and might not be clinically relevant to humans. Azathioprine and the fluoroquinolone antibiotics are two examples. Cutaneous porphyrias A detailed discussion of all aspects of porphyrias is presented in Chapter 12.5. Here we focus on the cutaneous manifestations. The cutaneous porphyrias are a group of inherited disorders of haem biosynthesis and include congenital erythropoietic por- phyria (CEP or Gunther’s disease), sporadic and familial porphyria cutanea tarda (PCT), variegate porphyria (VP), and erythropoietic protoporphyria (EPP) (Table 23.9.3). Identical skin signs can be seen where there is an acquired alteration of porphyrins (e.g. associ- ated with porphyrin-producing hepatic tumours, or in patients with sideroblastic or myeloproliferative anaemia). Photosensitivity, which includes pain, skin fragility, blistering (Fig. 23.9.5) and scarring, derives from the interaction of porphy- rins at various levels within the skin

and penetrating wavelengths of visible light at around 400 nm. Excess hair growth and pigmentation are also seen. The genes for all the enzymes in the human haem biosynthetic pathway have now been characterized, affording a better under- standing of the genetic basis of the porphyrias. Decreased enzyme activity is compensated by an increase in substrate in an attempt to maintain haem synthesis. Such accumulation of substrate character- izes each of the porphyrias, but the clinical presentation, even within families, is very variable. Diagnosis is by analysis of urine, blood, and faeces for porphyrins. Associated pathologies should be sought, including iron overload, haemochromatosis, liver pathology (hepatitis, cirrhosis, and hepa- toma), and HIV in selected patients. Treatment, where possible, includes sun avoidance (particularly for erythropoietic protoporphyria where the pain following sun exposure may be excruciating), venesection (to reduce iron load) and low dose chloroquine (both for porphyria cutanea tarda, but Table 23.9.2 Common photosensitizing drug reactions Skin reactions following exposure to sunlight Exogenous photosensitizers Easy sunburn (phototoxicity) Fluoroquinolone antibiotics, tetracyclines, chlorpromazine, thiazide diuretics, quinine, amiodarone Immediate pain or burning sensation (phototoxicity) amiodarone, chlorpromazine, coal tar Skin fragility and blistering (pseudoporphyria) Nalidixic acid, tetracycline, naproxen, amiodarone, furosemide Dermatitis (photoallergy) Chlorpromazine, PABA (para- aminobenzoic acid), benzophenones Progressive exposed site telangectasia Calcium channel antagonists (amlodipine, diltiazem) Delayed redness, blistering, and hyperpigmentation Psoralens, phytophotodermatitis (plant psoralens, e.g. in cow parseley) Photocarcinogenic (not established in humans) Fluoroquinolone antibiotics, azathioprine
Table 23.9.3 Characterization and clinical features in the cutaneous porphyrias Defective enzyme in haeme biosynthetic pathway Disorder Cutaneous features Other features Uroporphrinogen III synthasw Congenital erythropoietic porphyria (CEP or Gunther’s disease) Blistering and skin fragility, with mutilating scarring of eyelids, earlobes, and scalp. Keratoconjunctivitis may lead to blindness. Rare condition of variable severity. Many present in infancy with red staining of nappy due to urinary porphyrins. Haemolytic anaemia and splenomegaly. Erythrodontia and pathological fractures. Uroporphyrinogen decarboxylase Porphyria cutanea tarda (PCT)—familial and sporadic Blistering, skin fragility, and milia. Skin thickening, hyperpigmentation, and hypertrichosis. Usually presents in adulthood. Investigate for underlying liver pathology, hepatitis, and HIV where indicated. Look for haemochromatosis. Increased risk of hepatocellular carcinoma. Protoporphyrinogen oxidase Variegate porphyria (VP) Skin fragility, blistering, and scarring with milia as for PCT. May be associated with neurovisceral attacks: – acute abdominal pain – confusion – convulsions – hyponatraemia Increased risk of hepatocellular carcinoma. Ferrochelatase Erythropoietic protoporphyria (EPP) Painful skin (and oedema when severe) following sun exposure. Hepatic necrosis and liver failure reported.

 with monitoring for ocular toxicity), and bone marrow transplant- ation in selected cases (for congenital erythropoietic porphyria). The DNA repair photodermatoses Cellular organisms have evolved a complex set of DNA damage repair enzymes, many of which, as a consequence of life on Earth and chronic sun exposure, are directed towards the repair of UVR-induced DNA damage. The best characterized of these are the seven nucleotide excision repair (NER) enzymes, one of which is defective in each of the complementation groups A–G of the rare autosomal recessive disorder known as xeroderma pigmentosum (XP). This is characterized by severe and exaggerated sunburn on minimal ex- posure and early onset of skin cancer. There is also a variant form of XP, with a later onset of phenotypic features of pigmentary change and skin cancers. In the XP variant, there is defective postreplicative translesional DNA synthesis as a result

of a mutation in the human polymerase eta gene. The genetics of inherited cancers are further discussed in Chapter 5.3. Other related DNA repair-defective disorders include Cockayne's syndrome, trichothiodystrophy, and Bloom syndrome which exhibit a variable degree of acute photosensitivity to UVR, but skin cancer is not a feature (Table 23.9.4). Fig. 23.9.5 Skin fragility and blistering seen in porphyria cutanea
tarda. Table 23.9.4 DNA repair photodermatoses DNA repair disorder Molecular defect Diagnostic test Clinical features Comments Xeroderma pigmentosum (XP) complementation group A to G (XP-A
to XP-G) Mutations in any one of seven of genes (XPA through to XPG) involved in the repair of UVR- induced photoproducts in DNA by the process of nucleotide excision repair (NER). Reduction in post UVR DNA repair in cultured skin fibroblasts through measurement of unscheduled DNA synthesis (UDS). Analysis of DNA for the defective gene confirming complementation groups and causative mutation(s). Progressive pigmentary changes at exposed sites, significant increased risk of UVR-induced skin and mucous membrane cancers, ocular disease, severe and exaggerated sunburn in about 60% of cases, neurodegeneration in approximately 30% of affected cases. Rigorous sun avoidance to prevent skin cancer. No effective treatment for neurological disorder. XP variant (XP-V) Mutations in the POLH (XPV) gene encoding DNA polymerase eta, required for replication past UVR damaged sites. UDS is normal. Specific sensitivity to UVR in the presence of caffeine. Analysis of DNA for causative mutation(s). Multiple skin cancers from 30s onward. No neurological manifestations, severe sunburn, or ocular disease are observed. Rigorous sun avoidance to prevent skin cancers. Cockayne syndrome (CS) Mutations in one of two genes, ERCC8 (CSA) and ERCC6 (CSB). involved in NER. Defective post UVR recovery of RNA synthesis in cultured skin fibroblasts. Analysis of DNA for causative mutation(s). Progressive postnatal growth failure, short stature, microcephaly, cachexia, abnormal development, photosensitivity, premature ageing, retinal degeneration, and sensorineural deafness. No specific treatment available. Trichothiodystrophy (TTD) Mutations ERCC2 (XPD), ERCC3 (XPB) or GTF2H5 in photosensitive cases. These three genes encode the XPD, XPB and p8/TTDA subunits of the TFIIH in NER pathway respectively. Mutations in a gene of unknown function, MPLKIP (TTDN1), have been found in a few cases of nonphotosensitive TTD. Amino acid hair analysis shows reduction in cysteine concentration. Reduction in post UVR DNA repair in cultured skin fibroblasts through measurement UDS. Analysis of DNA for causative mutation(s). Short, brittle, sulphur-deficient hair with a pattern of alternating light and dark 'tiger-tail' bands under polarized light microscopy, photosensitivity, ichthyosis, developmental delay, short stature, haematological abnormalities, skeletal abnormalities, and maternal pregnancy complications. No specific treatment available. Bloom syndrome Mutation in BS gene which encodes a DNA helicase. High frequency sister chromatid exchange and high spontaneous mutation rate in cultured cells. Easy sunburn, growth retardation, internal malignancies prevail at young age (e.g. gastro-intestinal and breast). No specific treatment available.

 Photo-aggravated dermatoses These comprise a heterogeneous group of skin disorders which are aggravated by exposure to sunlight, although the mechanism by which they occur is not known (Table 23.9.1). These photo- aggravated dermatoses differ from true photodermatoses in that they can occur without UVR and visible light exposure. Those conditions characteristically worsened by sun exposure in- clude lupus erythematosus, dermatomyositis, bullous pemphigoid and pemphigus, and Darier's disease. For others, exacerbation oc- curs in only a few patients, for example: • Photoaggravation is described in about 10% of people with atopic dermatitis. Photoaggravation has also been noted in seborrhoeic

dermatitis. It is important to differentiate this from chronic actinic dermatitis, a photodermatosis caused by UVR exposure. • In psoriasis, photosensitivity is thought to be secondary to poly- morphic light eruption or sunburn in an individual with pre- existing psoriasis who exhibits Kobner phenomenon. • Rosacea is often exacerbated by sunlight exposure with increasing erythema, papules, and pustules on the cheeks, chin, nose, and forehead. • Actinic lichen planus has been reported mainly in people from the Middle East, East Africa, and India. Nonpruritic grey mac- ules appear on the face, neck, and dorsum of hands. • Melasma is a common in women and presents with sharply de- marcated, hypermelanosis of forehead, upper lip, cheeks, and chin. It becomes more apparent after sunlight exposure. FURTHER READING Beattie PE, et al. (2003). Characteristics and prognosis of idiopathic solar urticaria: a cohort of 87 cases. Arch Dermatol, 139, 1149–54. Chew AL, et al. (2010). Contact and photocontact sensitization in chronic actinic dermatitis: a changing picture. Contact Dermatitis, 62, 42–6. Cleaver JE, Lam ET, Revet I (2009). Disorders of nucleotide excision repair: the genetic and molecular basis of heterogeneity. Nat Rev Genet, 10, 756–68. Dawe RS, Crombie IK, Ferguson J (2000). The natural history of chronic actinic dermatitis. Arch Dermatol, 136, 1215–20. Dawe RS, Ibbotson SH (2014). Drug-induced photosensitivity. Dermatol Clin, 32, 363–8. Faghri S, et al. (2008). Trichothiodystrophy: a systematic review of 112 published cases characterises a wide spectrum of clinical manifest- ations. J Med Genet, 45, 609–21. Fassihi H, et al. (2016). Deep phenotyping of 89 xeroderma pigmentosum patients reveals unexpected heterogeneity dependent on the precise molecular defect. Proc Natl Acad Sci U S A, 113, E1236–45. Ferguson J, Dover JS (eds) (2010). Photodermatology. Manson Publishing Ltd, London. Grabczynska SA, et al. (1999). Actinic prurigo and polymorphic light eruption: common pathogenesis and the importance of HLA-DR4/ DRB1*0407. Br J Dermatol, 140, 232–6. Gupta G, Man I, Kemmett D (2000). Hydroa vacciniforme: a clinical and follow-up study of 17 cases. J Acad Dermatol, 42 part 2, 208–13. Murphy GM (2004). Investigation of photosensitive disorders. Photodermatol Photoimmunol Photomed, 20, 305–11. Murphy GM (2009). Ultraviolet radiation and immunosuppression. Br J Dermatol, 161 Suppl 3, 90–5. Nance MA, Berry SA (1992). Cockayne syndrome: review of 140 cases. Am J Med Genet, 42, 68–84. O’Donovan P, et al. (2005). Azathioprine and UVA light generate mu- tagenic oxidative DNA damage. Science, 309, 1871–74. O’Gorman SM, Murphy GM (2014). Photoaggravated disorders. Dermatol Clin, 32, 385–98. Pleasance ED, et al. (2010). A comprehensive catalogue of somatic mu- tations from a human cancer genome. Nature, 463, 191–6. Sarkany RPE (2016). The cutaneous porphyrias. In: Griffiths CEM, et al. (eds) Rook’s textbook of dermatology, 9th edition, Chapter 60, pp. 60.1–60.20. Blackwell, Oxford.

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