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Dermatology

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Legal category: P **MA holder:** Dermal Laboratories, Tatmore Place, Gosmore, Hitchin, Herts, SG4 7QR. **Date of preparation:** November 2012. 'Doublebase' and 'Dayleve' are trademarks.

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Published by

Hayward Medical Communications

a division of Hayward Group Ltd

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Newmarket CB8 7LG, UK.
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Publisher Mary Read.
Editorial Director Robin Jones.
Senior Sub Editor Anne-Claire Bouzanne.
Sub Editor Josie Mitchell.
Art Editor Richard Seymour.
Publications Manager Andrea Bucceri.

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London WC2E 9NA.
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Fax: +44 (0)207 2404479.
email: edit@hayward.co.uk

ISSN 0262-5504 (Print).
ISSN 2049-8446 (Online).

Printed by Williams Press Ltd.

Cover picture
PETER DAZELEY/GETTY IMAGES

HYBRID IMAGES/CULTURA/SCIENCE PHOTO LIBRARY

Dermatologists now have real engagement with oncologists and radiologists, as team discussions have become more complex

The changing work of the dermatologist

At school I really enjoyed woodwork, such that I hoped to become a joiner – an ambition thwarted by my mother, who had other ideas! I have always enjoyed doing things with my hands and, indeed, built a kit car a few years ago. It's not surprising, therefore, that skin surgery has always been an enjoyable part of my work. I like the visual aspects of working out how to remove the tumour and, more challengingly, how to reconstruct the defect. I like the 'feel' of the tissues and get satisfaction in seeing the results. Barry Monk's article on the changing nature of the work we do as dermatologists is poignant. Many of the boys I shared a bench with at school went on to the highly regarded craft apprenticeships, working as tool makers and so on. I wonder what has happened to them. As the economy was 'rebalanced' in the 1980s, much of the manufacturing industry moved abroad and those trades were lost. Dermatology is starting to go through a similar transition. Although teledermatology seemed to be the threat a decade ago, it is now becoming more mainstream and, in limited situations, rather useful. What is more surprising is how the physical treatments are changing.

In this issue, Nicholas Collier, Faisal Ali and John Lear outline the new genetics of basal cell carcinoma, which are leading to new treatment possibilities. My days spent cutting out basal cell carcinomas may be approaching their end. Our skin cancer multidisciplinary team meetings have changed from simply ensuring patients followed pathways involving excision, or re-excision for melanoma; were counselled appropriately; and then underwent appropriate follow-up. We now consider a whole variety of therapeutic agents and have real engagement with oncologists, and even radiologists, as the discussions have become more complex. Similarly, Colin Morton *et al* describe new treatment options for actinic keratoses. I am aware that I now use much less liquid nitrogen in the clinic and spend much more time explaining to patients how to use the new topical agents. The actinic keratosis information sheet I use has increased from a single page to two pages in length. In my regular visits out to primary care teams I am always asked about actinic keratoses! All this seemed quite remote five years ago.

There are always new opportunities coming along. While health and safety legislation and awareness have dramatically reduced the number of patients we see with industrial contact dermatitis, the rise in reactions to self-care products keeps the patch-test clinics going. Laura Cuddy and Ian Coulson describe some of the hazards patients encounter on the high street. Detecting the culprit in the patch-test clinic can often be challenging, but it's good to have to do a little detective work, if only to keep the brain working. Perhaps that is why dermatology is such fun – it offers a fantastic balance of doing and thinking.

Neill Hepburn, Editor

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Common skin allergens: hazards on the high street

The high street has taken a pounding since the start of the recession, but the hair and beauty sector has flourished and is estimated to be worth billions of pounds. Many people feel that they are not blessed with natural beauty and need a little helping hand. This may be simply purchasing moisturisers or cosmetics over the counter or visiting the hairdresser or beauty salon. However, they may not fully appreciate the risks that they are exposing their skin to. The British Association of Dermatologists estimates that contact dermatitis accounts for between 4 and 7% of dermatological consultations and about 1–3% of the population are allergic to ingredients in cosmetics.[1] Even when a contact allergy has been identified, shoppers need eagle-like vision to interrogate the ingredients' lists of cosmetics, or be persistent and peel back one layer of label to reveal the list lurking below! The list of allergens commonly used in high-street products or services is surprisingly large, and the consequences wide-ranging.

Methylchoroisothiazolinone and methylisothiazolinone

Methylchoroisothiazolinone (MCI) and methylisothiazolinone (MI) have recently attracted growing media interest. They are common biocides in household products such as detergents and cleaners, as well as in personal care items like shampoos, moisturisers, shower gels and wet wipes. They were first used in the 1970s and, during the 1980s, there was an 'epidemic' of MCI- and MI-related contact dermatitis in Europe. As a result, the concentrations of these drugs in personal care items were restricted.[2] Since the early 2000s, MCI has been used in isolation in popular body care products. In 2004, a report by the European Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers concluded that 'the proposed use of Methylisothiazolinone as a preservative at a maximum concentration of 0.01% (100 ppm [parts per million]) in the finished cosmetic product does not pose a risk to the health of the consumer'.[3]

However, MCI and MI appear to be responsible for an increasing number of cases of allergic contact dermatitis. Data gathered between January 2011 and June 2012 revealed that 6.2% of patch-test patients had a reaction to MCI/MI at any concentration.[2] With rising levels of sensitisation in the general population, consideration needs to be given as to whether their widespread use in everyday products should be restricted or even banned.

■ **Figure 1.** On this bottle of sunscreen, the label has to be peeled back to see ingredients, making it difficult for shoppers to identify allergens

Even when individuals are aware of their sensitisation, identifying the allergens within the ingredients' list is not always easy, as in some unboxed products that list may be obscured by a peel-back label (see Figure 1). The careful shopper must be very persistent and inquisitive when on an allergen hunt!

Paraphenylenediamine

Hair dyes are another common cause of allergic contact dermatitis and individuals are frequently referred to a dermatologist for patch testing, the presumed culprit being paraphenylenediamine (PPD). PPD is an organic compound frequently used in permanent hair dyes, textiles, dark cosmetics and inks. PPD requires oxidisation to become coloured and it is the partial oxidised state that may cause sensitisation and an allergic contact dermatitis. It may cause eyelid or ear dermatitis, but in more extreme cases there may be extensive erythema and oedema of the scalp and face. Sensitisation will often have occurred in childhood or adolescence and be long forgotten by the time grey hairs make their unwelcome debut. The first application of PPD to hide these grey hairs may then result in a severe allergic reaction. Hairdressers may also become sensitised and develop hand eczema due to regular contact.

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Contra-indications, warnings, side-effects etc: Please refer to SPC for full details before prescribing. Do not use if sensitive to any of the ingredients. In the unlikely event of a reaction stop treatment. Keep away from the eyes. Take care not to slip in the bath or shower. **Package quantities, NHS prices and MA numbers:** Dermol Wash: 200ml pump dispenser £3.55, PL00173/0407. Dermol 200 Shower Emollient: 200ml shower pack £3.55, PL00173/0156. Dermol 500 Lotion: 500ml pump dispenser £6.04, PL00173/0051. Dermol Cream: 100g tube £2.86, 500g pump dispenser £6.63, PL00173/0171. Dermol 600 Bath Emollient: 600ml bottle £7.55, PL00173/0155. **Legal category:** P **MA holder:** Dermal Laboratories, Tatmore Place, Gosmore, Hitchin, Herts, SG4 7QR. **Date of preparation:** February 2012. 'Dermol' is a registered trademark.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Dermal.

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2. Dermol Range – Total Unit Sales since launch. Dermal Laboratories Ltd. Data on file.

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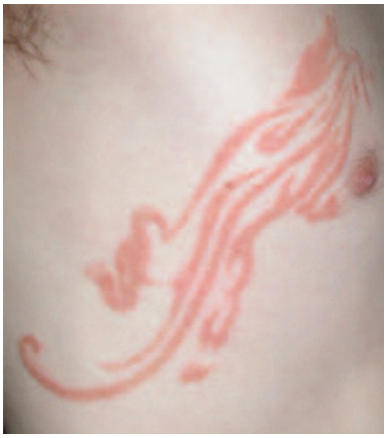
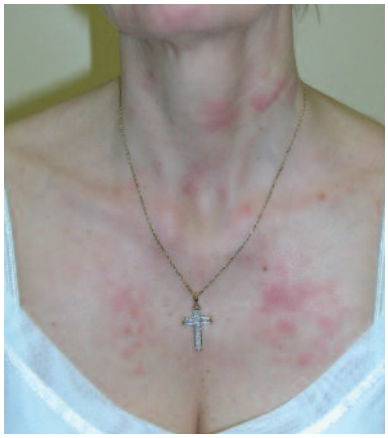
It is important to remember that other ingredients in hair dyes, such as paratoluenediamine (PTD), p-aminophenol, m-aminophenol and resorcinol, may also lead to sensitisation.[4] Patients should be told that it is essential to do a patch test before proceeding with dyeing their hair on every occasion, whether at home or at the hairdresser's.

An increasing problem is sensitisation to PPD in temporary or beach tattoos (see Figure 2). Advertised as 'henna', these tattoos often contain large amounts of PPD, minuscule amounts of (or even no) henna and an organic solvent – the perfect storm for sensitisation.



■ **Figure 2.** A young man has developed allergic contact dermatitis to a 'henna' tattoo containing paraphenylenediamine



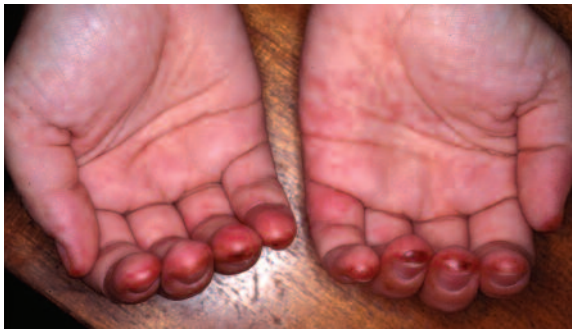
■ **Figure 3.** Neck and chest eczema due to an allergic reaction to both nail varnish and nickel

Acrylates

Nail salons have been thriving on the high street in recent years. According to Local Data Company, a UK retail consultancy, there has been a 16.5% increase in the number of nail salons since 2008.[5] Artificial nails are an increasingly common cosmetic enhancement. These, along with other nail cosmetics such as nail lacquer, nail polish remover and cuticle remover, come with their own potential problems. Most nail varnish contains toluene sulfonamide formaldehyde resin (TSFR), which often causes an allergic eczema distant from the hands, most notably a streaky eczema on the neck (see Figure 3), around the mouth and on the eyelids. Individuals who are allergic to nickel may paint varnish on to their favourite earrings or jean studs and compound their nickel dermatitis with nail varnish allergy!

Data from Kwok *et al* collected between 1996 and 2011 looked at occupational disease in beauticians and found that out of 257 cases of allergic contact dermatitis, acrylates were the most common source, affecting 64.1% of patients.[6] Acrylates are contained in acrylic glue (usually methyl methacrylate), which is used to fix both artificial nails and eyelashes in place. In salons, 'gel nails' are popular with clients due to their durability. The gel is sculptured to produce an attractive shape before ultraviolet (UV) light is used to polymerise the acrylate and set the nail. If a coloured nail is desired, then a coloured acrylate or a conventional varnish (which may contain TSFR) is applied. Nail technicians may develop allergic contact dermatitis on the hand from the filings, and in more severe cases airborne particles can lead to dermatitis affecting the face and neck area as well. Filing dust extraction systems are recommended to minimise allergen exposure. Client sensitisation is less common but can produce severe finger pulp eczema (see Figure 4) and severe nail dystrophy. Women regularly having gel backfills should be warned that increased exposure to UV light can lead to photodamage. Removal of these artificial nails requires them to be soaked in acetone for 10–15 minutes, which can cause nail brittleness. In addition, they can also obscure other dermatological conditions, such as fungal nail infections or acral malignancies.

■ **Figure 4.** A nail bar client with finger pulp eczema



Ultraviolet radiation

In the UK, a golden-brown tan is seen as desirable, especially among young women. A sample of young women surveyed in Northern Ireland reported that a tan would make them feel more attractive (47%) and healthier (42%).[7] Yet the consequences of 'the electric beach' are often ignored. The Sunbeds (Regulation) Act 2010 came into effect on 8 April 2011 and states that no person under the age of 18 years may use a sunbed, be offered the use of a sunbed or be present in the restricted zone (that is, the area where a sunbed is located). Failure to comply with the Act is a criminal offence and may incur a penalty of up to £20,000.[8] However, this has had limited impact on adolescents determined to get a tan. Sixty-nine young women aged 15–18 years who regularly used sunbeds were surveyed about the implications of the aforementioned legislation. While they did acknowledge some risks of sunbed use, they admitted to trying to circumvent the restrictions.[9]

Exposure to ultraviolet (UV) radiation from sunbeds is one of the potential causes of malignant melanoma. As long as sunbed users, particularly young women, do not change their attitudes

and habits, then rates of malignant melanoma will continue to be affected. Since the 1970s, these have quadrupled and malignant melanoma is now the fifth most common cancer in the UK.[10]

Unusually high melanoma rates are reported among young women in the north-west of England, whereas traditionally they have been higher in the south, where the days are longer and there are more hours of sunshine. This change has been attributed to the fact that young women in the north-west have increased their use of sunbeds and take more holidays abroad.[11]

Even more alarming is the fact that most tanning booths in England do not comply with European standards. Research published earlier this year found that nine out of 10 sunbeds examined in England emitted levels of UV radiation that exceed the maximum permitted.[12] Untold damage is being done to sunbed users' skin as vanity is put before health.

Waxing

Whether done at home or in a beauty parlour, waxing is popular as a semi-permanent form of hair removal. But the risks related to having one's legs waxed should not be underestimated. Complications include burns, folliculitis, pseudofolliculitis, spreading mollusca, cellulitis and contact dermatitis. Allergenic ingredients in the wax itself can include modified-colophonium derivatives.[13] There are even reported cases of granuloma annulare appearing on lines of trauma (Koebner phenomenon). Recent trends in the waxing industry include extensive removal of pubic hair, including partial pubic ('Brazilian') or complete anogenital ('full Hollywood') waxing. This can lead to genital injury as well as the aforementioned complications. An unfortunate 20-year-old Australian woman with poorly controlled type I diabetes developed life-threatening *Streptococcus pyogenes* and herpes simplex infection of her external genitalia following a routine perineal Brazilian bikini waxing session.[14] On a more positive note, it has been hypothesised that the popularisation of this type of extreme hair removal has resulted in rates of pubic lice falling.[15]

Dermal fillers

Regulation of the non-surgical cosmetic procedures such as dermal fillers is a hot topic at the moment, in part due to the Keogh report which was a government commissioned report including a review of cosmetic treatment procedures released earlier this year.[16] Dermal fillers involve injecting substances such as hyaluronic acid into the skin to smooth out wrinkles, scars or depressions. This area of cosmetic enhancement is largely unregulated and procedures can be carried out by individuals who are not suitably qualified, leaving patients vulnerable to complications. These complications range from erythema, swelling, bruising, infection and incorrect or superficial placement of the filler to skin necrosis, late-onset allergy and granulomatous reactions.[17] The Department of Health in England has made recommendations to protect clients, including: new legislation to classify fillers as prescription only; formal qualifications for anyone who injects hyaluronic acid or botulinum toxin; and a register of individuals who perform non-surgical cosmetic procedures.[16]

Nickel

Even the money handed over to purchase these various products and services can cause allergic contact dermatitis. Contact allergy to nickel is estimated to affect about 4.5% of the population.[1] The UK Royal Mint began circulating new 5p and 10p coins in January 2012. Prior to this, the coins were a metal alloy known as cupro-nickel, which contains 75% copper and 25% nickel. The newer coins are made of nickel-plated steel and were introduced as a money-saving measure. A small study by Julander *et al* found that the amount of nickel deposited on to the skin when handling these new nickel-plated coins for one hour was four times higher than with the previous cupro-nickel coins. The authors suggest that, due to exposure to higher levels of nickel, these new coins are a public health concern.[18]

Concerned consumers can purchase a tool to test objects, such as jewellery or coins, they suspect of containing nickel. The dimethylglyoxime test is available commercially and can be used on objects that come into contact with the skin. It involves combining a few drops of 1% dimethylglyoxime in alcohol with 10% ammonium chloride solution. This mixture is then applied to a cotton wool tip, which is rubbed for 30 seconds against

Key points

- The British Association of Dermatologists estimates that about 1–3% of the population are allergic to ingredients in cosmetics.
- Methylchoroisothiazolinone and methylisothiazolinone are common ingredients in household cleaners as well as beauty products. They appear to be an increasing cause of allergic contact dermatitis.
- Paraphenylenediamine, toluene sulfonamide formaldehyde resin and nickel can cause allergic reactions.
- Research published earlier this year found that nine out of 10 sunbeds examined in England emitted levels of ultraviolet radiation that exceed the maximum permitted.

■ **Figure 5.** Dimethylglyoxime test on a new five pence coin

the object being tested. A pink-red colour on the cotton tip indicates the presence of nickel (see Figure 5). [19]

Conclusion

It is vital that people be informed of the risks incurred by their skin when they use products and services that are available on the high street. If they present in primary or secondary care with dermatological complications, patients must be advised and treated appropriately. In cases of suspected allergic contact dermatitis, patients should be advised to avoid the suspected allergen and be referred for patch testing to confirm suspicions ■

Declaration of interest
None declared.

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The Primary Care Dermatology Society (PCDS) held its annual Scottish meeting over the weekend of the 9–10 November 2013. There was a very full and varied programme. Professor Chris Bunker gave two outstanding lectures: one on 'HIV and the skin' and the other on 'Penile and perianal dermatology'. Professor Bunker gave a very strong take-home message that we should have a much lower threshold to suspect HIV might be implicated in the aetiology of many dermatological conditions. He also believes that we should be doing more HIV testing because, if cases can be picked up earlier, it will help reduce transmission of the virus. He spoke about the importance of highlighting patients with HIV who are symptomatic with dermatological diseases, and might benefit from initiating early antiviral treatment. This would be preferable to decisions being made based solely on laboratory data.

Dr John English delivered a very informative and entertaining lecture on 'Allergy testing,' including information about drug allergies. He spoke about a balanced approach when dealing with consultations focused on allergy. Other lectures included 'Facial rashes', 'Pyoderma gangrenosum', 'The role of the dermatology liaison nurse' and a host of other useful topics.

Workshops were also held, including: 'Update on contact dermatitis', 'Toenails and foot infections,' and 'Moh's surgery'. There were also sessions on minor surgery delivered by Dr Christy Chou and his colleagues. Dr Chou's superb teaching is definitely not to be missed by the budding skin surgeon, or the established GP wanting to improve their surgical technique.

On the Saturday morning, the PCDS piloted a session entitled 'Dermatology tips for GP registrars,' with the hope of inspiring GPs about dermatology at an early stage in their career. If the evaluations from this meeting are positive, we plan to run such sessions again. So if you have a registrar in your practice who might be interested in future dermatology educational sessions, please get them to contact the PCDS.

Here is provisional list of some of the PCDS meetings planned for early 2014:

- Top Tips in Dermatology, 8 February, Leicester
- Top Tips in Dermatology, 1 March, Winchester
- Spring Meeting, 14–16 March, Kenilworth
- Advanced Dermoscopy, 27 March, Manchester
- Essential Dermatology, 3 April, Crewe
- Essential Dermatology, 1 May, Newcastle
- Essential Dermatology, 14 May, Hemel Hempstead
- Essential Dermatology, 21 May, Northampton

Please visit the PCDS website (address below) for a list of all the future meetings taking place and for more information ■

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Tom Poyner, Former GP, Stockton-on-Tees; Vice Chair of the Executive Committee and Trustee of the PCDS

The genetics of basal cell carcinoma

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Basal cell carcinoma (BCC) is the most common human cancer, with a 30% lifetime risk in those of European descent.[1] Incidence is increasing by 3–10% per annum worldwide[2] and it is expected that, soon, the prevalence will equal that of all other cancers combined.[3] While mortality is rare, BCC causes considerable morbidity and burden on health services. BCCs are slow-growing, locally invasive, malignant epidermal tumours which rarely metastasise (<0.1%).[4] The underlying causal mechanism is a genetic aberration, which may be inherited or acquired.

Primary risk factors are ultraviolet (UV) light exposure and genetic predisposition. Other significant risk factors include Fitzpatrick skin types I and II, immunosuppression, advanced age, male sex, previous BCCs and chronic arsenic exposure.

Research into the molecular genetics of BCCs in the past two decades has uncovered many of the pathways fundamental to their pathogenesis, leading to potential therapeutic targets. Several targeted agents are currently being trialled; one, vismodegib, is licensed in the UK for use in advanced BCC. Studies to date demonstrate efficacy of these targeted agents, albeit with frequent and considerable side-effects, and evidence of resistance and recurrence, which currently limit their use to a select group of patients.[5]

Pathway inhibitors, though in their infancy, offer a novel and exciting avenue for the targeted treatment of BCC.

Link to genetics

Insight into the molecular pathogenesis of BCC was derived from the study of patients with hereditary basal cell naevus syndrome (HBCNS, or Gorlin–Goltz syndrome), first described in 1960 by Gorlin and Goltz.[6] HBCNS is an autosomal dominant condition with mutation of the patched homologue 1 (*PTCH1*) gene located on chromosome 9q22.3. *PTCH1* encodes a 12-span transmembrane protein, Patched-1 (Ptch-1), which acts as the receptor for the hedgehog proteins and functions as a tumour suppressor. HBCNS has variable expression and incomplete penetrance, and 25% of cases arise from *de novo* mutations.[7]

Clinical features of HBCNS include the development of multiple BCCs, with a mean age of onset of 25 years. Other common features include palmoplantar pits, odontogenic cysts, calcification of the falx cerebri, skeletal abnormalities and the development of medulloblastomas.

Hedgehog pathway

Investigations into body segmentation in fruit flies (*Drosophila melanogaster*) in the 1980s produced embryos covered with small pointy projections resembling a hedgehog.[8] This led to the discovery of the hedgehog pathway. The mammalian hedgehog family includes three orthologs: sonic hedgehog (*SHH*), which was described first, Indian hedgehog (*IHH*) and desert hedgehog (*DHH*). The hedgehog pathway is well preserved throughout many species.

SHH encodes a pro-protein, which undergoes cleavage and lipidation producing the sonic hedgehog ligand (Shh). Shh is intrinsic to early embryonic development, acting as a morphogen in neural tube formation, and is involved in musculoskeletal and integumentary system development. Germ-line mutations to *SHH* can cause severe congenital malformations such as holoprosencephaly. In adult tissues, the SHH pathway is largely quiescent except in hair, skin and stem cells.

Key components of the SHH pathway include Shh, Ptch-1, Smoothened (Smo), glioma-associated oncogene transcription factors (Gli) and suppressor of fused protein (Sufu) (see Figure 1).

In the absence of Shh, Ptch-1 is located on the primary cilium and acts as a tumour suppressor, constitutively repressing the G-coupled receptor protein Smo. On binding of Shh, Ptch-1 moves intracellularly and Smo is translocated towards the primary cilium, removing the repression of Smo. Uninhibited Smo promotes the importation of Gli transcription factors into the nucleus. Gli proteins

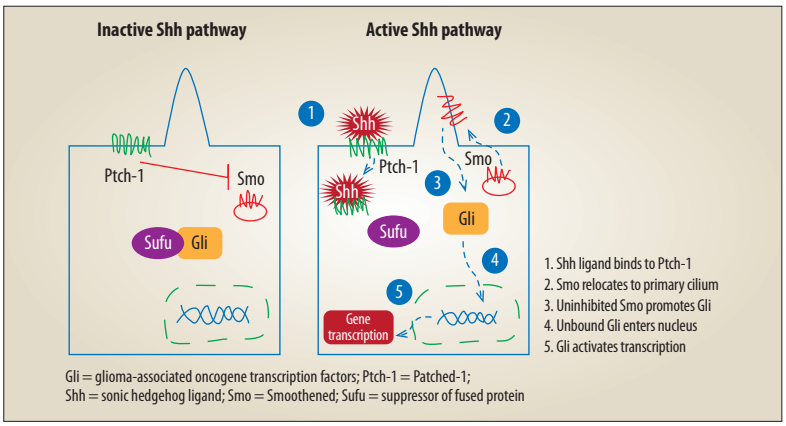
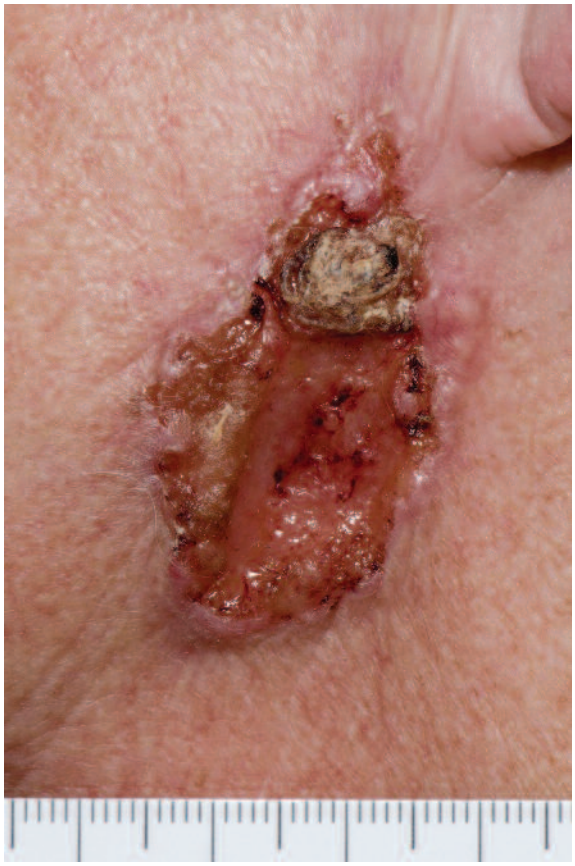
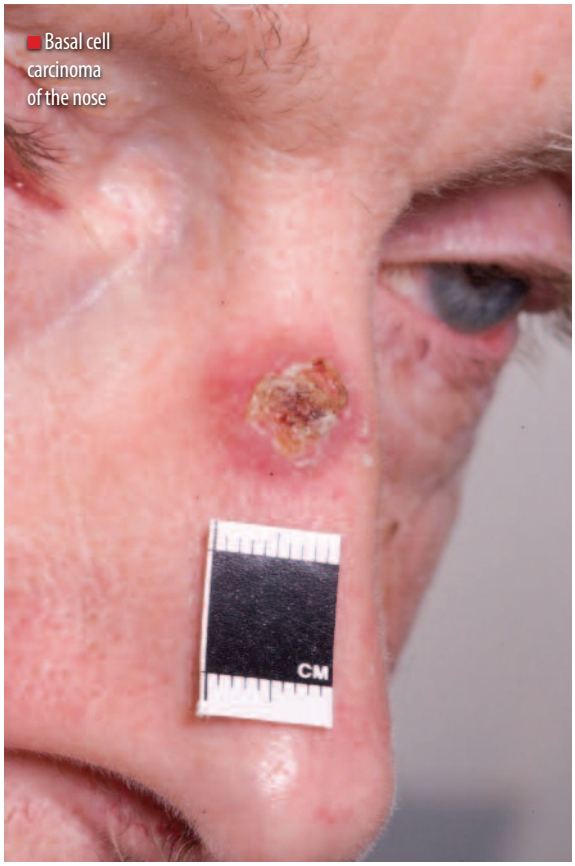


Figure 1. The sonic hedgehog pathway



■ Basal cell carcinoma of the neck



■ Basal cell carcinoma of the nose

are bound by Sufu, the loss of which produces constitutive activation of Gli.

The Gli proteins are effectors of the hedgehog pathway, possessing DNA-binding, zinc-finger domains which bind to consensus sequences on target genes, thus regulating transcription. Gli activates multiple target genes which are key regulators in cell cycle progression and differentiation.

Sporadic BCC tumours demonstrate loss of function of *PTCH1* in 80–90% and *SMO* in 10–20% of cases.[5] BCCs have also been demonstrated to result from constitutive activation of the SHH pathway in both murine skin and human skin grafted to mice.[9] These findings underline the significance of the SHH pathway in BCC tumorigenesis.

Support for the central role of *PTCH1* mutations in BCC tumorigenesis comes from a recent whole-exome sequencing study where only *PTCH1* was found to have a significant functional mutation burden.[10]

Genome-wide association studies (GWASs) are now allowing the identification of novel alleles associated with a risk of BCC.[11] Combining GWASs and gene expression genetics to identify biological pathways associated with BCC has identified the JAK-STAT signalling pathway as plausibly being involved in BCC pathogenesis.[12]

Cellular origins of BCCs

The cellular origins of BCCs have long been uncertain. In 1900, Krompecher first proposed that these tumours arise from the basal cells of the epidermis, though this was contested.[13] More recently, studies using murine stem cells with constitutively active Smo demonstrated BCC formation following interfollicular epidermal progenitor (IFE) cells being rapidly reprogrammed into embryonic hair follicle progenitor (EHFP)-like cells, prior to rapid up-regulation and tumorigenesis. During experiments, temporal up-regulation of the Wnt signalling pathway during tumorigenesis was noted and, importantly, deletion of β-catenin prevented tumour formation.[14,15]

Canonical Wnt/beta-catenin pathway

Many similarities exist between the hedgehog and Wnt signal transduction pathways, both being highly conserved, influential in embryogenesis, inactivated in most cells following development, and key drivers in oncogenesis when hyperactive.

β-catenin promotes transcriptional activation and has a central role in the Wnt pathway. The level of β-catenin is tightly regulated in the cytosol, by being constitutively broken down via the β-catenin destruction complex (BCDC).

Activation of the pathway is triggered by attachment of the Wnt protein to Frizzled (Fz,) a G-coupled receptor protein. Binding promotes BCDC inactivation via Dishevelled (Dsh), allowing β-catenin accumulation and gene transcription.

Genetic damage from solar radiation

UV light is a class 1 carcinogen and the primary aetiological agent in the development of sporadic BCCs. Whole-exome sequencing has demonstrated proportionately increased levels of UV signature mutations in *PTCH1* and *TP53*.[10]

UVB damage occurs through a photochemical reaction following direct UV absorption by DNA. Damage to adjacent pyrimidines may produce cyclobutane dimers (CBDs) and (6-4) pyrimidone-pyrimidine (64PP) adducts. These photolesions cause UV signature mutations, with cytosine being changed to thymine, either singly or in tandem.[16]

UVA photons are less energetic and damage DNA indirectly by the generation of reactive oxygen species (ROS). ROS cause DNA strand breaks and produce oxidative base damage.[16]

Recent whole-exome sequencing has shown BCC to be the most mutated cancer, squamous cell carcinoma (SCC) being the second most mutated (75.8 and 33.3 mutations per megabit of coding DNA, respectively). This has led to the hypothesis that a greater mutational burden increases the antitumour immunological response, leading to a less aggressive phenotype.[10]

Whole exome sequencing has shown BCC to be the most mutated cancer

UV-induced DNA damage normally results in DNA repair (error-free and error-prone) or apoptosis; only very rarely does it lead to tumorigenesis. Where DNA repair mechanisms are impaired in conditions such as the rare autosomal recessive xeroderma pigmentosum (XP), skin cancer rates are greatly increased, with a 2,000-fold increased risk in homozygotic patients.[17]

Pathway inhibitors

Inhibition of the hedgehog pathway provides an attractive therapeutic avenue as BCCs have been shown to originate from its activation.

What is now recognised as hedgehog pathway inhibition was first observed in sheep in Idaho in the 1950s. During a time of drought, sheep grazed on higher ground, ingesting the abundantly growing California corn lily (*Veratrum californicum*). Subsequent progeny were observed to develop craniofacial abnormalities ranging from mild micrognathia to severe cyclopia and holoprosencephaly. Extraction methods later established cyclopamine (11-deoxojervine) as the teratogen, which was subsequently discovered to act as a Smo receptor antagonist.

Vismodegib is a first-in-class, orally bioavailable inhibitor of Smo, which was licensed in August 2013 in the UK for the treatment of metastatic BCC (mBCC) and locally advanced BCC (laBCC). LaBCCs are tumours which have penetrated deeply, have recurred, or are sited where conventional treatments would be unfeasible or cause considerable morbidity.

In the Phase II trial of a multicentre, international, two-cohort non-randomised study, patients with laBCC (n=63) and mBCC (n=33) were treated with 150 mg vismodegib daily until the objective response rate of a 30% reduction in size was obtained. Results demonstrated significant response in 43%, with complete response in 21% in the laBCC group and a significant response rate of 30% in the mBCC group.[5]

All patients described side effects, with over 30% describing myalgia, dysgeusia, alopecia, weight loss and fatigue, which are considered to be class effects of Smo antagonism. Grade 3 and 4 adverse effects were reported in 43%, including fatigue, dyspnoea, muscle spasm, QT prolongation and asymptomatic hyponatraemia. A subsequent trial in HBCNS again demonstrated significant response, but 54% of patients discontinued therapy due to side effects.[5]

In laBCC, 5% of patients demonstrated regrowth during treatment.[5] Elucidation of resistance mechanisms remains sparse; however, a case report documented secondary resistance due to an *SMO* mutation (D473) which decreased binding affinity.[18]

Rebound of tumour growth following cessation of treatment has been documented.[5] This may occur as a fraction of cells remain quiescent and evade apoptosis during treatment. Whether cell destruction occurs concentrically or in a scattered manner requires further investigation, as this will affect its utility as a neoadjuvant treatment.

Further Smo inhibitors are currently being trialled including LDE225 (erismodegib), IPI-926 (saridegib), LEQ506 and PF-04449913.

Upstream blocking of the hedgehog pathway has been investigated with robotnikinin being developed as a macrocyclic molecule able to bind to Shh protein. More recent developments starting

Key points

- Constitutive activation of the sonic hedgehog pathway is central to basal cell tumorigenesis and may occur congenitally (as in basal cell naevus syndrome) or be acquired later in life.
- Recent whole-exome sequencing has shown basal cell carcinoma (BCC) to be the most mutated cancer, squamous cell carcinoma (SCC) being the second most mutated.
- Vismodegib is a first-in-class, orally bioavailable inhibitor of Smo, which was licensed in August 2013 in the UK for the treatment of metastatic BCC and locally advanced BCC.

from robotnikinin's structure found BRD-6851 to be the most promising macromolecule; this was, however, found to act as a Smo antagonist. 5E1, an antibody targeting the epitope close to Shh–Ptch-1 interaction, has been developed.[18]

Downstream blockade provides an exciting avenue of current interest. Treatments being investigated include Gli antagonists (GANT 58 and 61) and agents impairing Gli acetylation and primary cilial function. Inhibition of the Wnt pathway via β-catenin is also being studied, but this may be challenging due to the molecule's flat polar surface, which engages in multiple protein–protein interactions.

Conclusion

Advances in molecular genetics have given substantial insights into the pathophysiology of, and risk factors associated with, BCC. The centrality of the SHH pathway in BCC development is apparent, but understanding downstream pathways and crosstalk between pathways remains complex and incomplete. Novel targeted pathway treatments are emerging, but currently their clinical use remains limited because they are associated with frequent and considerable side effects ■

Declaration of interest
John T Lear has accepted honoraria for speaking at meetings by Leo, Galderma, Almirall, Astellas and GSK. Nicholas J Collier and Faisal R Ali have nothing to declare.

Acknowledgement
The authors acknowledge the support of the Clinical Photography Department, Salford Royal NHS Foundation Trust.

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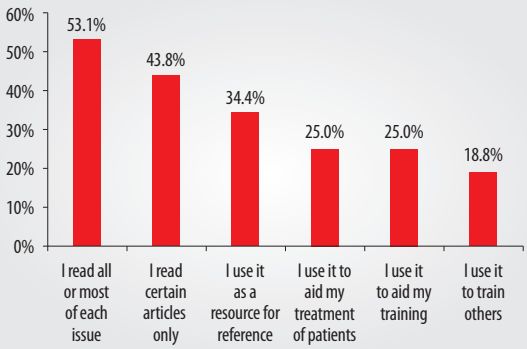
➜ Your views on *Dermatology in practice*

Here, we report on the results of the reader survey we ran earlier this year.

The majority of responses were from GPs (27.3%), closely followed by nurse specialists (24.2%). The rest of the respondents were made up of other nurses (12.1%), dermatologists (9.1%) and GPs with a special interest in dermatology (6.1%).

Over half of respondents read all or most of each issue and it is also used for reference and to aid training (see Figure 1).

■ **Figure 1.** Reading habits



Informative and influential

DIP is considered by 46% of respondents to be 'very useful', with a further 25% finding it 'extremely useful'. The journal is therefore considered a more useful source of information than other medical journals or colleagues, which were rated as 'very useful' by 43% and 36% respectively.

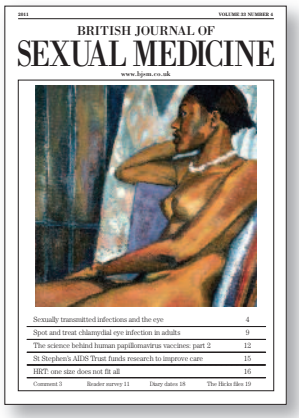
Everyone who took the survey agreed that *DIP* was of some, or great, benefit. Over 74% agreed or strongly agreed that the journal may sometimes influence the way in which they care for their patients.

Over half of respondents are happy to access the journal online as a PDF, but 62% would also like a full text version and 39% would like to read *DIP* in an app.

Additionally, a large proportion of the respondents – 71.4% – would be interested in completing online CPD modules if they were offered on the *DIP* website ■

Congratulations to **Marie Retzback**, Nurse Specialist in West Suffolk, who was the lucky winner of a Kindle Fire in the prize draw.

well written beneficial in practice excellent reviews clear and well presented very helpful and informative good range of articles easy to read topical I like the format practical advice on management interesting and informative nice clear summaries very relevant materials excellent good layout concise very useful I learnt something new today spot on



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Update on the treatment of actinic keratosis

Several new therapy options have recently become available for the management of actinic keratosis (AK). Most of these treatments are intended to treat small, or large, areas of sun-damaged skin – recognising the importance of field cancerisation, where skin adjacent to AK may contain dysplastic cells, while other therapies are best suited for individual lesions. It is impossible to predict which AK might develop into invasive squamous cell carcinoma (SCC), so guidelines recommend widespread treatment of AK. As approximately 20% of the UK population over 60 years of age will have at least one AK, with prevalence increasing with age, this represents a considerable therapeutic challenge in an era of restricted healthcare budgets. In this article, we briefly review the therapies now available and propose a practical approach to treatment choice.

Appearance and prevalence

AKs are common skin lesions, typically presenting as reddish-brown macules or plaques, with a varying amount of hyperkeratotic scale (see Figure 1). They arise in areas of chronic sun exposure – on the face, forehead, scalp, ears, neck, upper chest, arms and dorsum of hands, and are more common in individuals with fair skin. They can range from a few millimetres to 2 cm in diameter and may be solitary or multiple (see Figure 2). AK usually develops as a consequence of cumulative sun exposure, although it can be induced by iatrogenic phototherapy, X-rays and radioisotopes. In the UK and Ireland, 19–23% of individuals over 60 years have at least one AK.[1]

AK usually develops as a consequence of cumulative sun exposure

AKs are typically divided into three subtypes, reflecting thickness: thin/mild (better felt than seen); moderate (easily seen and felt); and thick.[2] There are a few differential diagnoses for AK, including seborrhoeic keratoses, but the most important one is SCC.[3] The diagnosis is usually made on clinical appearance although a biopsy should be considered where there is diagnostic doubt.

Why treat AK?

Recently updated European guidelines encourage us to classify AK as early *in-situ* SCCs in view of the recognition of the genetic similarities between AK and SCC and the observation that 60–80% of SCCs arise within, or close to, existing AKs.[4] As it is currently not possible to determine which lesions may transform, strategies to promote treatment of all lesions are recommended.

Although often observed as occurring as single lesions or in small clusters, AKs are increasingly recognised as arising in a setting of field cancerisation, where adjacent skin may also contain dysplastic skin cells, with increased potential for the development of more AKs and other non-melanoma skin cancers (see Figure 3).[5] Fortunately, for immunocompetent individuals, the risk of an individual AK transforming into an SCC is small, with 15–25% spontaneously clearing over a one-year period – although 15% of regressed lesions have been observed to recur after 12 months.[6,7] Many AKs persist without progression. It is estimated that an individual with an average of 7.7 AKs has a 10% probability of at least one transforming within a ten-year period.[8] The risk of developing AK is around 250-fold higher for patients on long-term immunosuppressants, with a higher proportion of these AKs developing into SCCs.[9] In addition to the risk of progression, AK can cause considerable cosmetic concern to patients, as well as discomfort.

Who to treat?

Guidelines from the British Association of Dermatologists (BAD) indicate that treatment of AK is not

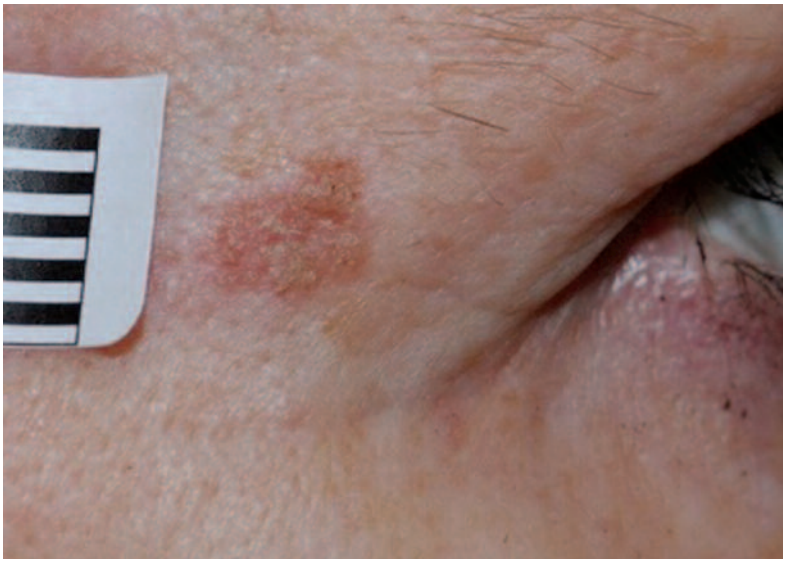

Figure 1. Solitary moderately thick actinic keratosis

universally required[1] (guidance from the Primary Care Dermatology Society is in agreement with this[10]), advising that patients with a small number of lesions might not benefit from treatment, especially if life expectancy is reduced. BAD recommends clinical judgement to discern lesions and patients at increased risk, with the option of no treatment, or palliation with emollient to reduce discomfort when appropriate. In the most recent guidelines, issued by the European Dermatology Forum, a stronger recommendation for treatment is made, with the decision influenced by site of the disease, extent of the disease, the patient's age, comorbidities, evidence of previous skin cancer and presence of immunosuppression.[4]

Who should treat?

Management pathways developed by NHS Scotland and the Scottish Dermatological Society recommend treating AK in primary care, except where there is diagnostic doubt; if the lesions are painful or rapidly growing; if there is extensive solar damage; or in immunosuppressed patients.[11] The National Institute for Health and Care Excellence guidance states that all GPs are expected to recognise, and make management decisions on, patients with pre-cancerous skin lesions.[12]

Treatment options

Therapies are either lesion-specific, for single and/or few lesions, or field-directed, to manage patients with multiple lesions where field cancerisation is more likely to be present. There is a shift from viewing AK as low-risk, individual lesions, to considering them akin to icebergs, indicative of an area of surrounding sun-damaged skin at increased risk of cancer – with a strong focus on field therapies in a European consensus treatment algorithm.[13] Treatments are either ablative (such as curettage, surgical excision and cryosurgery) or topical (such as 5% fluorouracil, 5% imiquimod, 3% diclofenac in hyaluronic acid and methyl aminolevulinate photodynamic therapy). We focus on the therapies most accessible to practitioners in the UK, with brief discussion of new therapies; for example, ingenol mebutate, 0.5% fluorouracil combined with 10% salicylic acid, 3.75% imiquimod and nanoemulsion aminolevunic photodynamic therapy. Therapies such as chemical peels, topical retinoids and laser therapy are not commonly used as primary treatments for AK in the UK.

Surgical excision of AK is not usually required and is only performed if invasive SCC is suspected. Curettage or cryotherapy are commonly performed for AK, although they are now less commonly practised in primary care. Curettage remains a useful option for thick, hyperkeratotic lesions, while cryotherapy is a useful option if there are only a few lesions, or if they have failed to respond to topical therapy. However, patients need to be warned of the risk of pigmentary change and scarring.

A detailed comparison of therapies is beyond the scope of this article, but a recent Cochrane

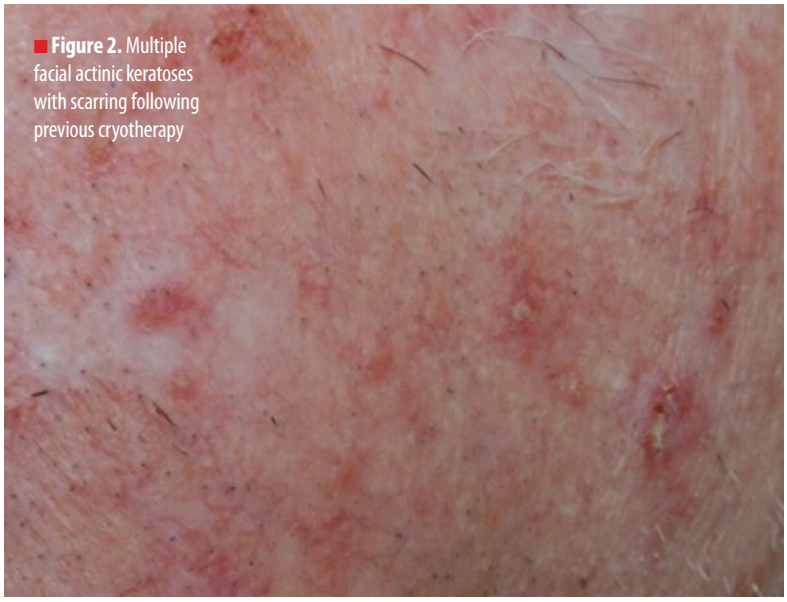

Figure 2. Multiple facial actinic keratoses with scarring following previous cryotherapy

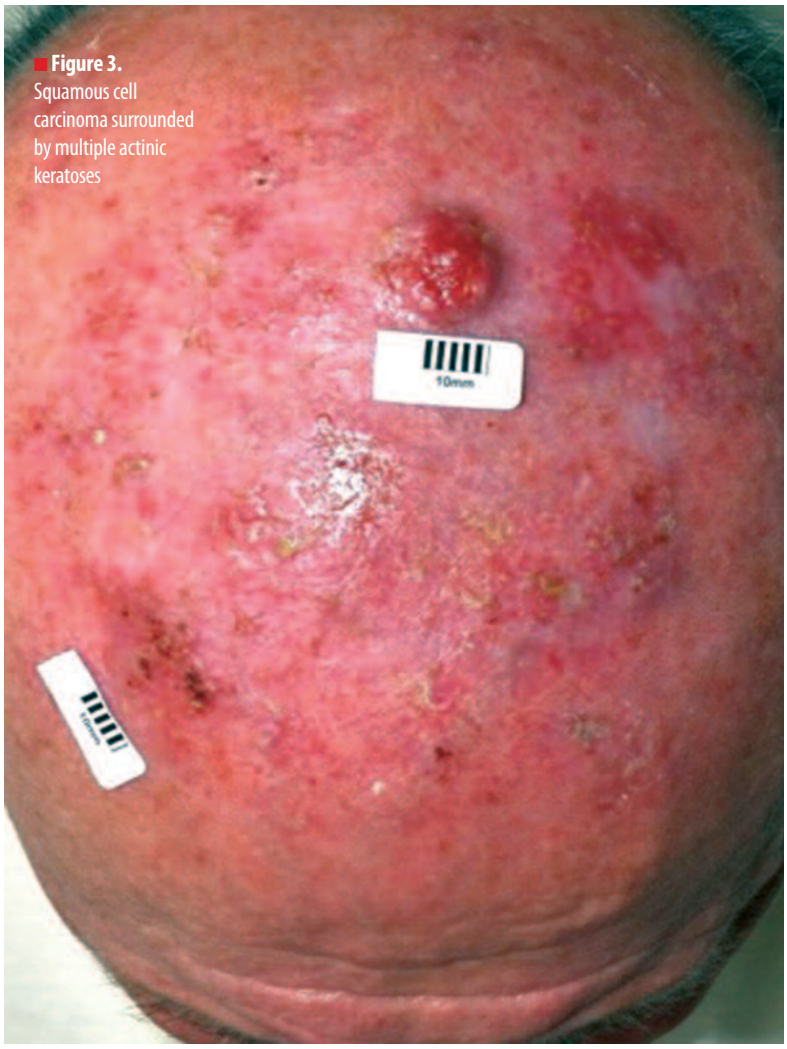

Figure 3. Squamous cell carcinoma surrounded by multiple actinic keratoses

Table 1. Topical therapies for AK – recommended protocols, precautions and field use[15,16]

Therapy	Protocol	Precautions	Field limit
Diclofenac 3% gel (Solaraze®, Almirall)	Twice daily for 60–90 days	Usually well-tolerated, occasionally causes a rash	Max 4 g/application (as 0.5 g covers 5 x 5 cm, max area 200 cm^2)
5% fluorouracil (Efudix®, Meda)	Once or twice daily for 3–4 weeks. Facial lesions usually respond quicker than those on trunk/legs. Lesions on hands/forearms respond more slowly	Normal response is an early and severe inflammatory phase (usually in the second week of application), then necrotic phase, followed by healing	Total area of skin being treated at any one time should not exceed 500 cm^2
0.5% fluorouracil combined with10% salicylic acid (Actikerall®, Almirall)	Once daily to slightly palpable and/or moderately thick hyperkeratotic AK. Response can be seen from 6 weeks. Optimal effect may not be evident for up to 8 weeks after cessation (only experience of use on face/scalp)	Peel off existing coating before re-application. Apply with brush applicator	Total area of skin being treated at any one time should not exceed 25 cm^2
Imiquimod 5% (Aldara®, Meda)	Apply three times a week to AK on face or scalp for 4 weeks. Assess after a 4-week interval, repeat cycle if required	Apply prior to normal sleeping hours, wash off after approximately 8 hours. Local inflammatory reactions are common. There is an association between clearance and intensity of reaction. Advise rest period of several days if inflammation severe. Flu-like symptoms are uncommon	Max recommended is 1 sachet, limit to ~25 cm^2
Imiquimod 3.75% (Zyclara®, Meda)	Apply once daily before bedtime for two treatment cycles of 2 weeks, each separated by a 2-week interval	Local inflammatory reaction common. Rest period if required. Flu-like symptoms are uncommon	Up to 2 sachets, approximately 200 cm^2 (whole face or scalp)
Ingenol mebutate (Picato®, LEO Pharma) 150 µg/g gel	Once daily for 3 consecutive days to AK on face and scalp (store in refrigerator at 2–8˚C)	Local skin responses are common. Erythema, flaking/scaling and crusting typically occur within 1 day of treatment initiation and peak in intensity up to 1 week following completion, resolving within 2 weeks	1 tube covers 25 cm^2
Ingenol mebutate (Picato®, LEO Pharma) 500 µg/g gel	Once daily for 2 consecutive days to AK on trunk and extremities (store in refrigerator at 2–8˚C)	Local skin responses are common, as with 150 µg/g, but can take up to 4 weeks to resolve	1 tube covers 25 cm^2
PDT (Ameluz®, Biofrontera or Metvix®, Galderma)	Ameluz is new nanoemulsion of 5-ALA, Metvix is methylester of 5-ALA	Single treatment, repeat at 3 months if required, to AK on face/scalp (applied under occlusion for 3 hours before illumination with red light). Only to be administered by healthcare professionals trained in PDT. Pain/burning sensation is common during PDT. Erythema common after treatment and scab formation	Apply to lesions and 5–10 mm of surrounding skin

5-ALA = 5-aminolevulinic acid; AK = actinic keratosis; PDT = photodynamic therapy

review of interventions in AK concluded that, for individual lesions, photodynamic therapy appears more effective and has a better cosmetic outcome than cryotherapy. For field-directed treatments, diclofenac, fluorouracil, imiquimod and ingenol mebutate had similar efficacy, but their associated adverse events and cosmetic outcomes are different.[14] Key information about the topical therapies currently available in the UK is shown in Table 1.[15,16]

Patient preference should drive the final choice

Recently approved topical treatments

Ingenol mebutate

Ingenol mebutate (Picato® [LEO Pharma]), derived from the white sticky sap from the plant *Euphorbia peplus*, appears to work both by rapid cell necrosis and specific neutrophil-mediated antibody-dependent cellular cytotoxicity. Two strengths of this fast-acting product are available: a 0.015% gel, for use once daily on the face and scalp for three consecutive days, and a 0.05% gel to be applied once daily on the trunk and extremities for two consecutive days. Pooled results from four pivotal trials show that the 0.015% gel cleared all face/scalp AK in 42% of patients (83% of all lesions).[17] The 0.05% gel cleared all trunk/limb lesions in 34% of patients (75% of all lesions). Local skin responses (namely, erythema, flaking/scaling, crusting, swelling, blistering or ulceration) are commonly observed, peaking after completion of therapy.

Imiquimod 3.75%

A new 3.75% formulation of imiquimod (Zyclara® [Meda]) offers the advantage that it can be applied to larger areas of the skin, such as the complete face, in a simplified application protocol. Complete clearance of all AKs was achieved in 36% of patients (82% of baseline lesions) in a pivotal trial, with subclinical lesions becoming visible during application and also responding to treatment.[18] The treatment appears generally well tolerated, although erythema and scaling/crusting are commonly seen, with about 10% of patients likely to require a rest period during treatment.

0.5% fluorouracil plus 10% salicylic acid

Compared with 5% fluorouracil, the new 0.5% formulation, combined with 10% salicylic acid (Actikerall® [Almirall]) is associated with fewer side effects. It has been shown to achieve superior clearance of AK compared with diclofenac gel (in 74% versus 55% of lesions, respectively), with complete clearance of all treated AKs (4–10 per patient) in 55% versus 32%, respectively.[19] However, it should only be used in small fields, unlike diclofenac gel. It offers a useful alternative to cryotherapy for patients with few, or solitary, hyperkeratotic AKs. The product comes in a bottle with a brush applicator, so patients need to be clear about which sites require treatment and must be able to apply the product at home.

Choosing the correct therapy

In view of the increase in treatment options and the emphasis on AK usually being viewed as a field disease, in Table 2 we divide therapy choice by lesion site and whether the practitioner is seeking to treat only a single or few scattered lesions, or a small (up to 25 cm^2) or large therapy field. Compliance is likely to be improved when treatments with a short duration of application are used, but patient preference should drive the final choice between the options most suitable for a given presentation ■

Table 2. A practical approach to treatment, reflecting current approvals and common practice in the UK

	Face/scalp AK	Trunk/limb AK
Lesional (1–3 non-clustered)	• Cryotherapy (curettage for thick AK)* • 0.5% fluorouracil/10% salicylic acid (Actikerall®)	• Cryotherapy (curettage for thick AK)* • 0.5% fluorouracil/10% salicylic acid (Actikerall®)†
Small field (clusters: ~ 4–8 in single area < 25 cm^2)	• 5% fluorouracil (Efudix®) • 0.5% 5-fluorouracil/10% salicylic acid (Actikerall®) • Imiquimod 5% (Aldara®) • Ingenol (Picato®, 0.015%) • PDT (Ameluz®/Metvix®)‡	• 5% fluorouracil (Efudix®) • 0.5% 5-fluorouracil/10% salicylic acid (Actikerall®, Almirall)† • Imiquimod 5% (Aldara®)† • Ingenol (Picato® 0.05%) • ALA or MAL-PDT†
Large field (25–200 cm^2)	• Diclofenac 3% (Solaraze®) • 5% fluorouracil (Efudix®) • Imiquimod 3.75% (Zyclara®) • PDT‡	• Diclofenac 3% (Solaraze®) • 5% fluorouracil (Efudix®) • Imiquimod 3.75% (Zyclara®)† • PDT†

* By experienced practitioners. † Topical therapy without specific licence for this indication. ‡ Usually initiated in specialist dermatology department. ALA = aminolevulinic acid; AK = actinic keratosis; MAL-PDT = methyl aminolevulinate photodynamic therapy; PDT = photodynamic therapy

Key points

- Actinic keratosis (AK) is a manifestation of field change in which the surrounding skin is dysplastic.
- Several new treatments are available for AK, offering new options to primary care physicians.
- The best choice of treatment depends on the number of lesions, their site, size, the amount of hyperkeratosis and patient preference.

Declaration of interest

Colin Morton has advisory board membership with Leo, Meda and Almirall; he has also received speaker honoraria from Leo, Galderma and Spirit Healthcare within the past three years. Megan Mowbray has received speaker honoraria from Leo. Colin Clark has accepted travel honoraria from Galderma. Girish Gupta has advisory board membership with Leo, Meda and Almirall; he has also received speaker honoraria from Leo and Meda within the past three years. Robert Herd has advisory board membership with Leo and Meda. Colin Fleming has given consultancy at Almirall and is co-investigator on Leo studies.

The outline for this article was discussed at a clinical guideline review meeting supported by an educational grant from Leo.

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Occupational health

In times gone by, it was often possible to tell what a patient's job was by the occupational marks on their skin – the coal dust tattooed into the skin (colliers' stripes) of the miner or the presternal bursa of the bootmaker, for example. Many traditional industries have vanished and are now remembered by surnames such as Fuller, Fletcher, Wainwright and Salter. Towns and cities also used to be identifiable by their traditional trades but are now recalled by the old nicknames of their football teams: The Cobblers (Northampton Town) and The Hatters (Luton Town); incidentally, the term 'mad as a hatter' derives from chronic mercury poisoning, which was a notorious hazard of preparing felt for use in hat-making.

Medicine, of course, is not immune to changes in working practices. The traditional general surgeon, capable of turning his hand to anything, or the general physician, able to take a holistic overview of the undiagnosed case, are now but nostalgic memories. Cardiac surgery has all but vanished, thanks to the remarkable skills of interventional cardiologists and to the general decline in coronary artery disease. Ear, nose and throat surgeons now twiddle their thumbs looking for work, having lost their stock in trade of tonsils, adenoids and grommets. Neurosurgery has had to cope with a dramatic decline in head injury resulting from crash helmets, better car design and safety at work. It is not of course a one-way process; infectious disease medicine, which had all but vanished by the 1970s, suddenly underwent an enormous resurgence with the appearance of AIDS just a few years later.

So what about dermatology? Surely there will always be enough work to keep us busy, especially given the broad spectrum that we cover. When talking to trainees, a surprising number of them want to become dermatological surgeons, sometimes to the complete exclusion of general dermatology. Faced with the present avalanche of skin cancers, there would certainly seem to be plenty for them to do, but how long will this work come pouring in? We now recognise that non-melanoma skin cancer results from a 'field change' and it is therefore much more logical to treat cancers and pre-cancers with non-surgical therapies, which can treat the entire 'at risk' area. Our presently available agents – photodynamic therapy, imiquimod and others – are clearly not the complete answer. But the recent development of a systemic agent, vismodegib, used for difficult basal cell carcinomas, means that pharmaceutical companies are applying their brains and money to this challenging area.

In medicine, as in life, one never knows what will happen next, but it could well be that, in ten years, a dermatological surgeon will be as obsolete as a scrivener or a cursitor (who would deliver messages for lawyers, like a 19th century version of email). I can only suggest that dermatology trainees of today don't get too focused on one small part of our wonderful subject ■

IMAGES/SUPERSTOCK

■ Neurosurgeons have had to cope with a dramatic decline in work. Will dermatological surgeons find themselves in the same position?

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Declaration of interest
None declared

What is 'Breslow thickness' in melanoma?

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First described by pathologist Alexander Breslow in 1970, 'Breslow thickness' is a measurement of the depth of invasion of melanoma into the skin tissue, and remains the most reliable indicator of disease prognosis.

The Breslow thickness is defined as the maximum vertical depth, in millimetres, of melanoma cancer cell infiltration below the granular cell layer, which is the most superficial layer of living skin cells in the epidermis (see Figure 1). It is measured from excisional biopsies in the laboratory using an ocular micrometer. This measurement must include any smaller satellites of cancer cells that may be deeper than the main tumour mass.

When a diagnosis of melanoma is made, the Breslow thickness is routinely included in the pathology report, due to its significant correlation with disease outcome. A Breslow thickness greater than 1.5 mm is generally considered to be high-risk with a significantly poorer prognosis (see Table 1).

Other important prognostic indicators in melanoma skin cancer are the presence of ulceration; lymph node involvement; and evidence of metastatic disease. These features are used together to stage the disease.

In addition to being used directly as a prognostic indicator, the Breslow thickness of a melanoma also determines the re-excision margins ■

Table 1. Approximate re-excision margins and five-year survival

Breslow thickness (mm)	Surgical re-excision margin (cm)	5-year survival (%)
<1.0	1	95–100
1.01–2.0	1–2	80–96
2.01–4.0	2–3	60–75
>4.0	>3	37–50

Declaration of interest
The authors declare that there is no conflict of interest.

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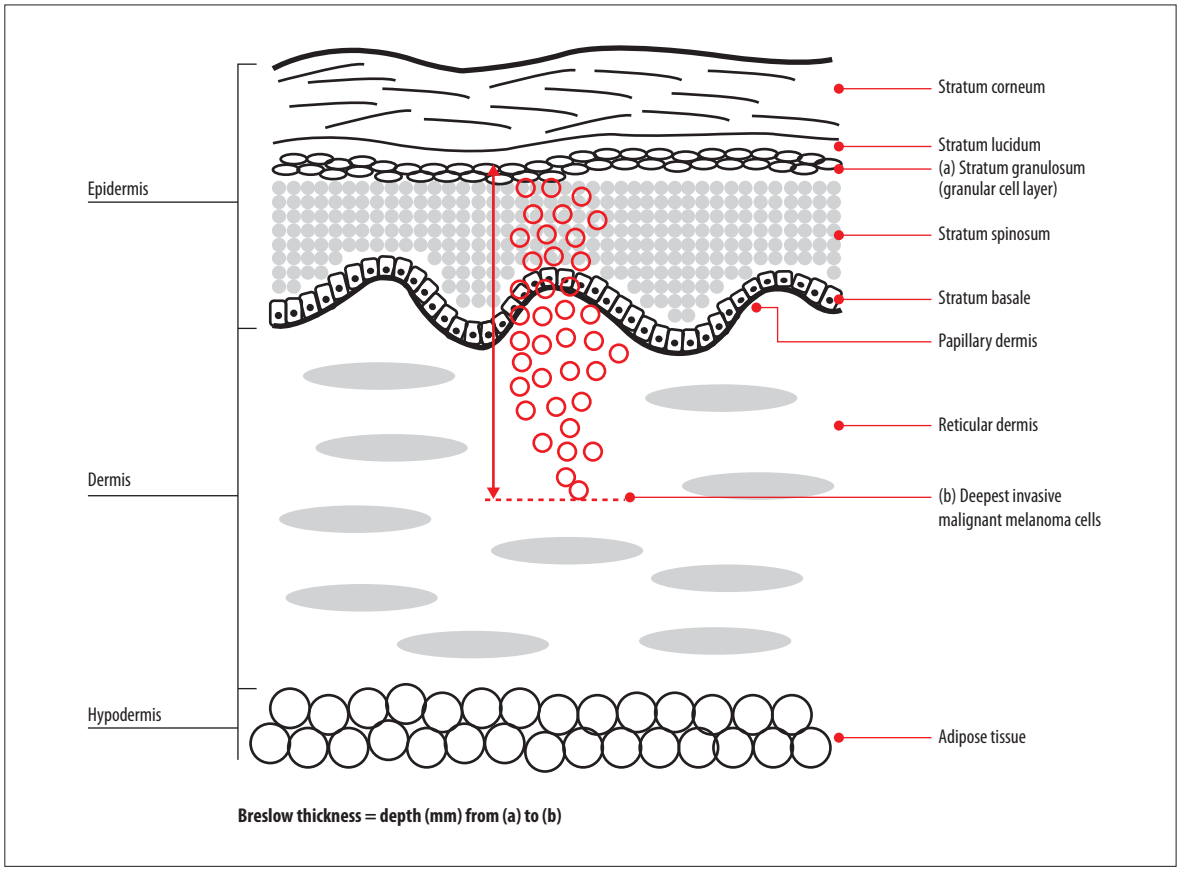

■ **Figure 1.** How to measure Breslow thickness

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