The ageing skin

By Professor Gregory Peterson

Case study

Mrs HL is a 63-year-old lady who has presented to the pharmacy seeking advice on products to prevent and minimise wrinkles. She is quite active, playing tennis twice-weekly. She and her retired husband spend three months of each year at their unit in Cairns. She is a non-smoker and only drinks alcohol occasionally. She does not take any prescribed medications, but takes garlic and echinacea regularly.

As people age, their chances of developing skin-related disorders increase. Skin, which constitutes about one-sixth of the total body weight, forms the most visible indicator of age.[1] Although skin is incredibly durable, it is affected, like other organ systems, by ageing.[2,3] Skin ageing can be separated into two components.[2-7] The first component, intrinsic ageing, occurs as a consequence of chronological ageing in all individuals. Changes over time occur at variable yet unalterable genetically determined rates and are influenced by gender, race and skin colour. The inevitable facial fine lines and wrinkles that accompany ageing occur because the skin atrophies and loses its elasticity, allowing the skin to sag.

It is, however, estimated that 90% of what is perceived as skin ageing is not due to intrinsic ageing, but due to extrinsic ageing – produced by factors that are, to varying degrees, controllable and include ultraviolet (UV) light exposure ('photo-ageing'), cigarette smoking, alcohol abuse, poor nutrition, environmental pollutants, and repetitive muscle movements like squinting or frowning.[4,8] Decreased mobility, drug-induced disorders, and the increased incidence of many chronic diseases (e.g. cardiovascular disease and diabetes mellitus) are among the reasons the elderly are at heightened risk for skin diseases. These diseases tend to impede vascular efficiency and decrease immune responses, thereby reducing the body's ability to heal.

Physiological differences with the ageing of skin include biochemical changes as well as a range of changes in neurosensory perception, permeability, response to injury, repair ability, and an increased incidence of some skin disorders (Tables 1 and 2).[2,3] An increase in cutaneous pH, as well as impairment of immune function, increase susceptibility to infection. Decreases in neurosensory capacity increase the risk of serious morbidity. Increasing disorganisation of the vasculature diminishes circulation, as well as thermoregulatory function. With ageing, wound repair and re-epithelisation slows dramatically.

Skin ageing is a complex, multifactorial process whose baseline rate is genetically determined but that may be accelerated by environmental, mechanical, or socioeconomic factors.[9]

The synergistic effects of intrinsic and extrinsic ageing factors over the human lifespan produce deterioration of the cutaneous barrier. Aged skin is more susceptible to chronic dryness and itching, infection, autoimmune disorders, vascular complications (e.g. stasis dermatitis), decubitus ulcers (pressure ulcers) and increased risk of malignancy. In fact, most people over 65 years of age have at least one skin disorder, and many have two or more.[2,3]

As indicated above, many of the skin changes commonly associated with ageing – changes in pigmentation, sallowness, and deep wrinkling – are actually the result of sun exposure (photo-ageing).[5,8] Sun-exposed areas of the skin, such as the face, neck, upper chest, hands, and forearms, are the sites where these changes occur most often. Chronological (intrinsic) ageing, in contrast, is characterised by laxity and fine wrinkling, as well as development of benign growths such as seborrheic keratoses, but is not associated with increased pigmentation or the deep wrinkles that characterise photo-ageing.[4,6,10,11]

Table 1. Changes in skin function with ageing (modified from Farage *et al.*[2,9])

Skin function	Change with ageing
Barrier	Impaired; slowdown in turnover rate of epidermis, renewal time of stratum corneum increased 50%, thinning of epidermis and dermis, reduced lipid content, decreased chemical clearance
Sensory and pain perception	Loss in sensitivity, especially after age 50 Increased itching
Thermoregulation	Impaired; decreased sweat production, atrophy of sweat glands
Response to injury	Decrease in inflammatory response (erythema and oedema) Decreased wound healing Reduced re-epithelisation Increased vulnerability to mechanical trauma
Permeability	Decreased percutaneous absorption Decreased vascularisation, blood vessels fragile
Immune function	Diminished; decreased number of epidermal Langerhan's cells, decreased number of circulating thymus-derived lymphocytes Impaired delayed hypersensitivity reactions
Other	Decreased vitamin D production Elasticity decreases (loss of collagen and elastin fibres)

Table 2. Key clinical implications of changes in skin with ageing (modified from Norman[16])

Loss of elasticity and thinning of the skin
Clinical results: dry skin, pruritus, laxity, wrinkling, uneven pigmentation, easy tearing, traumatic purpura, neoplasia
Photo-ageing
Clinical results: actinic keratoses, fine and coarse wrinkling, telangiectasia, blotchiness and pigmentary changes

The skin, which thickens over the first 20 years, thins progressively over adult life at a rate that accelerates with age. The epidermis decreases in thickness and cell numbers in the epidermis are reduced with ageing; this change is most pronounced in exposed areas, including the face, neck, upper part of the chest, and the extensor surface of the hands and forearms. Dermal thickness also decreases.[8] Chronologically aged skin is thin, relatively flattened, dry and unblemished with some loss of elasticity and age-related loss of architectural regularity. There are reduced levels of dermal collagen and elastin, and their organisation is impaired. The common signs of intrinsic ageing are:

- Fine wrinkles
- Thin and transparent skin
- Loss of underlying fat leading to hollowed cheeks and eye sockets, with noticeable loss of firmness on the hands and neck
- Bone loss, which causes sagging skin
- Dry skin with pruritus
- Inability to sweat sufficiently to cool the skin
- Greying hair, eventually turning white
- Hair loss.

Photo-ageing is the result of a combination of short wavelength (UV-B) injury to the outer layer of the skin (epidermis) and long wavelength (UV-A) injury to the middle layer (dermis). Photo-aged skin appears deeply wrinkled, flaccid, and rough with uneven pigmentation, with an increased epidermal thickness and alterations of connective tissue organisation.[6,10]

A clear dose-response relationship between wrinkling and smoking has been identified, with smoking being a greater contributor to facial wrinkling than even sun exposure. Smoking increases keratinocyte dysplasia and skin roughness. Smoking has been demonstrated to be an independent risk factor for premature wrinkling, even when the influence of age, sun exposure and pigmentation are controlled:[7]

- Tobacco smoke has a drying effect on the skin's surface
- Blood flow to the skin is reduced, thus depleting the skin of oxygen and essential nutrients
- Squinting in response to the irritating nature of smoke and puckering of the mouth when drawing on a cigarette
- Increased production of collagenase.

The relative risk for moderate-to-severe wrinkling for current smokers compared to that of life-long non-smokers is almost three-fold.[7] Smokers' skin can be prematurely aged by between 10 and 20 years, and although the damaging effects of cigarette smoke on the skin are irreversible, further deterioration can be avoided by cessation of smoking.[7]

Treatment of ageing skin includes (a) measures to prevent against damage and (b) medications and procedures to reverse existing damage.[4,5,8] While it is impossible to halt or reverse the genetic processes responsible for intrinsic ageing, the skin changes associated with photo-ageing are largely preventable. The most effective preventive measures for skin ageing include avoiding sun exposure, using physical blocks such as thicker white and light-coloured cotton clothing and wide-brimmed hats, and regular use of a broad-spectrum (protects against both UV-A and UV-B) sunscreen with a sun-protection factor (SPF) of at least 15. Avoiding

the insults of environmental pollutants and smoking is also important to delay the onset of skin ageing.

Strategies aimed at preventing photo-ageing include sun avoidance, using sunscreens to block or reduce skin exposure to UV radiation, and using retinoids to inhibit collagenase synthesis and to promote collagen production.[12]

According to *Clinical Evidence*,[13,14] there is evidence that topical tretinoin (e.g. *ReTrieve* cream) and tazarotene (*Zorac* cream) can improve fine wrinkles compared with placebo in patients with mild to moderate photo-damage. However, both can cause skin irritation, burning, dryness, peeling and redness. Similarly, isotretinoin cream improves fine and coarse wrinkles compared with vehicle cream in people with mild to severe photo-damage, but causes severe irritation of the face in 5-10% of people. There is insufficient evidence to determine the clinical effectiveness of the following:

- Carbon dioxide laser
- Chemical peel
- Dermabrasion
- Facelift
- Topical glycolic acid or lactic acid
- Oral natural cartilage polysaccharides
- Topical natural cartilage polysaccharides
- Topical vitamin C or E.

A patient leaflet on the review's findings is available at: http://clinicalevidence.bmj.com.ezproxy.utas.edu.au/ceweb/conditions/skd/1711/wrinkles-standard-ce_patient_leaflet.pdf

A Cochrane review also concluded:[15]

'There is conclusive evidence that topical tretinoin improves the appearance of mild to moderate photo-damage on the face and forearms, in the short term. However, erythema, scaling/dryness, burning/stinging and irritation may be experienced initially. There is limited evidence that tazarotene and isotretinoin benefit patients with moderate photo-damage on the face; both are associated with skin irritation and erythema. The effectiveness of other interventions remains uncertain.'

ReTrieve cream (tretinoin 0.05%), a derivative of vitamin A, is the only topical prescription medication approved by the Therapeutic Goods Administration for the adjunctive treatment of dry photo-aged skin. Daily application of topical tretinoin improves fine wrinkling, surface roughness, hyperpigmentation, and sallowness.[8] Progressive improvement is seen over a period of six to 12 months that slowly regresses once treatment is discontinued. The beneficial effect of tretinoin in decreasing fine wrinkles is thought to be due to an increase in dermal collagen produced by both a stimulation of new collagen synthesis and an inhibition of collagenase, and a boost of epidermal growth resulting in a thicker epidermis. Tretinoin also appears to stimulate the formation of new blood vessels.[8] The adverse effects of tretinoin include mild-to-moderate skin irritation, dryness and peeling, as well as an increase in sun sensitivity. Tolerance to irritation can develop in some patients with continued therapy.

Botulinum toxin (botox) is purified botulinum toxin type A, a neurotoxin used to reversibly paralyse small facial muscles when injected in small quantities subcutaneously.[5,8] It is mainly used for treating glabellar wrinkles (between the eyebrows just above the nose), and frown lines near the central brow, forehead, and crows feet. This form of treatment is safe when used by a skilled practitioner, with only temporary bruising or pain at the injection site. Adverse effects of botulinum toxin injections can include pain and bruising, and paralysis of the nerves that control eyelid function (ptosis) is a risk when botulinum toxin is injected into the muscles of the forehead. The ptosis is temporary but could last for several weeks. The results of the botulinum toxin treatment are seen within three to seven days and desired effects last three to six months.

Various soft tissue fillers can be injected into the skin to fill wrinkles and deep creases. Bovine (e.g. *Zyderm*) or human-based (e.g. *CosmoDerm*) collagen extracts and non-animal stabilised hyaluronic acid implants (*Juvederm Ultra* and *Juvederm Ultra Plus*) are injected into the skin to decrease facial lines and wrinkles and fill in furrows. The most common side effects include redness and bruising at the injection site that may last for several days. These treatments are only temporary, lasting about six months before the filler is broken down.[5,8] The soft tissue fillers are

often used in combination with purified botulinum toxin type A for maximal effect.[5]

Of course, apart from the pharmaceutical approaches, there are a multitude of procedures available to treat aged skin. Briefly, these include the following:

- Dermabrasion (using high-speed rotating brushes to buff off the epidermis and superficial dermis, allowing regeneration of new reorganised collagen and regeneration of a new epidermis from the underlying pilosebaceous units). Dermabrasion is painful and usually requires intravenous sedation. The postoperative healing is prolonged, requiring two to four weeks before the redness and swelling disappear. The treatment results can last for up to five years. As with any type of skin resurfacing, there are potential complications including infection, irregular pigmentation, and hypertrophic scars.
- Ablative laser resurfacing, generally with a carbon dioxide laser producing beams of concentrated light that are absorbed by water molecules in the superficial layers of the skin and converted to heat that can selectively ablate or destroy unwanted tissue. It can improve fine and some coarse wrinkles and overall dyspigmentation, lightens dark under-eye circles, and generally improves the texture of skin. The potential risks of laser ablation include transient erythema, post-inflammatory hyper and hypopigmentation, scarring, and infection. Redness may persist for several weeks to several months. Laser resurfacing is not effective for deep wrinkles and cannot achieve the lifting results of cosmetic surgery.
- Cosmetic surgery – a face lift differs from laser resurfacing and chemical peels in that the top layers of the skin are not removed. A face lift pulls the skin up, producing a tightening and smoothing of the skin. With deeper dissection of nerves and blood vessels, surgical approaches involve more risks including bleeding, infection, and scarring. As expected, there is a longer recovery period for the more aggressive surgeries. Face lifts leave the face swollen and bruised lasting up to six weeks. The advantage is that the surgical procedures can improve more severe wrinkles and the effects can last five to seven years.

'The current trend is to address skin ageing before cosmetic surgery is required. This is accomplished by combining available ageing prevention and treatment options including daily sun protection and use of topical products, such as retinoids and moisturisers; regular-interval treatments (e.g. botulinum toxin, fillers, and light-based treatments); and only occasional major surgical procedures, as necessary. Implementation of skin protection and anti-ageing treatment regimens should begin as early as possible and continue throughout life to counteract the effects of intrinsic and extrinsic skin ageing.'[8]

Wrinkles should merely indicate where smiles have been.
Mark Twain

To return to our case, the avoidance of sun exposure through physical means and using a broad-spectrum sunscreen should be emphasised to Mrs HL. She could be advised that there are several topical products available on prescription that can improve fine wrinkles, although they can cause significant irritation.

The water content of the epidermis is reduced in the elderly. Two of the most common dermatological problems found in older patients are dry skin (xerosis) and pruritus.[1,16-22] Dry skin is the most common underlying problem associated with pruritus in the elderly.[16] Dry skin occurs most often on the legs of elderly patients, but may be present on the hands and trunk. It may be exacerbated by exposure to environmental factors such as cold, dry atmospheres and irritation through excessive bathing, washing in water that is too hot, and using soaps and harsh detergents, leading to the development of eczematous changes. Winters often exacerbate pruritus secondary to dry skin. Treatment with topical corticosteroid ointment (e.g. betamethasone valerate 0.02% or 1% hydrocortisone) will rapidly settle eczematous changes, but indefinite treatment of the underlying dry skin is essential to avoid subsequent flare-ups.[17,18,20] Simple measures may alleviate the problem:

- Frequently applying moisturisers (e.g. sorbolene cream) - they are most effective when applied to recently washed or damp skin
- Avoiding long hot baths (use lukewarm water) and overheating in centrally heated environments

- Minimising the use of soap, and using a soap substitute (e.g. aqueous cream) or non-irritating soap, such as *Cetaphil*
- Avoiding friction from washcloths, rough clothing and abrasives
- Using a humidifier in dry environments.

The addition of 10% coal tar, 0.25% phenol, or 0.25% menthol to a moisturising lotion can be a good adjunct in resistant itch.[19] Sedative antihistamines may be helpful in pruritus due to dry skin, but they should be used with extreme caution in the elderly, as confusion can be a side-effect.[17,20,21] If symptoms do not respond to conservative therapy it may indicate underlying disease such as liver and renal disease, anaemia, diabetes, hyperthyroidism or malignancy.[20,21]

Gregory Peterson is Professor and Head of School, Unit for Medication Outcomes Research and Education (UMORE), School of Pharmacy, University of Tasmania

References

1. Norman RA. Geriatric dermatology. Dermatol Ther 2003;16:260-8.
2. Farage MA, Miller KW, Elsner P, Maibach HI. Intrinsic and extrinsic factors in skin ageing: a review. Int J Cosmet Sci 2008;30:87-95.
3. Farage MA, Miller KW, Elsner P, Maibach HI. Functional and physiological characteristics of the aging skin. Aging Clin Exp Res 2008;20195-200.
4. Puizina-Ivic N. Skin aging. Acta Dermatovenerol Alp Panonica Adriat 200817:47-54.
5. Helfrich YR, Sachs DL, Voorhees JJ. Overview of skin aging and photoaging. Dermatol Nurs 2008;20177-83.
6. Callaghan TM, Wilhelm KP. A review of ageing and an examination of clinical methods in the assessment of ageing skin. Part 2: Clinical perspectives and clinical methods in the evaluation of ageing skin. Int J Cosmet Sci 2008;30:323-32.
7. Callaghan TM, Wilhelm KP. A review of ageing and an examination of clinical methods in the assessment of ageing skin. Part I: Cellular and molecular perspectives of skin ageing. Int J Cosmet Sci 2008;30:313-22.
8. McCullough JL, Kelly KM. Prevention and treatment of skin aging. Ann N Y Acad Sci 2006; 1067:323-31.
9. Farage MA, Miller KW, Elsner P, Maibach HI. Structural characteristics of the aging skin: a review. Cutan Ocul Toxicol 2007;26:343-57.
10. Makrantonaki E, Zouboulis CC. Molecular mechanisms of skin aging: state of the art. Ann N Y Acad Sci 2007;1119:40-50.
11. Hashizume H. Skin aging and dry skin. J Dermatol 200431:603-9.
12. Baumann L. Skin ageing and its treatment. J Pathol 2007;211:241-51.
13. Samuel M, Brooke R, Griffiths C. Wrinkles. Clin Evid 2005:2104-16.
14. Manriquez J, Grinberg DM, Diaz CN. Wrinkles. Clin Evid 2008:1711-29.
15. Samuel M, Brooke RC, Hollis S, Griffiths CE. Interventions for photodamaged skin. Cochrane Database Syst Rev 2005:CD001782.
16. Norman RA. Xerosis and pruritus in the elderly: recognition and management. Dermatol Ther 2003;16:254-9.
17. Lim SP, Abdullah A. Managing skin disease in elderly patients. Practitioner 2004;248(1655):100-9.
18. Martin JA, Finlay A. Skin disease in the elderly. Practitioner 2006;250(1683):6-12.
19. Webster GF. Common skin disorders in the elderly. Clin Cornerstone 2001;4:39-44.
20. Australian Medicines Handbook Pty Ltd. Australian Medicines Handbook Drug Choice Companion: Aged Care, 2003:177.
21. Pruritus. In: Beers MH (ed.) Merck Manual of Geriatrics, 3rd ed. Online version. At: www.merck.com/mkgr/mmg/sec15/ch123/ch123b.jsp
22. Xerosis. In: Beers MH (ed.) Merck Manual of Geriatrics, 3rd ed. Online version. At: www.merck.com/mkgr/mmg/sec15/ch123/ch123c.jsp