ATOPIC ECZEMA

Predisposition to sensitive skin and atopic eczema

Genes that control the thickness of our skin and its vulnerability to chemicals in the environment play a role in the development of contact dermatitis and atopic eczema. Sensitive skin manifests itself as a burning, stinging or itching sensation following the application of topical products such as soap, bubble baths and cosmetics. The skin may become red and dry after repeated application of these products. New insights into the skin barrier can help us improve treatment of the skin and prevent problems associated with atopic eczema and sensitive skin

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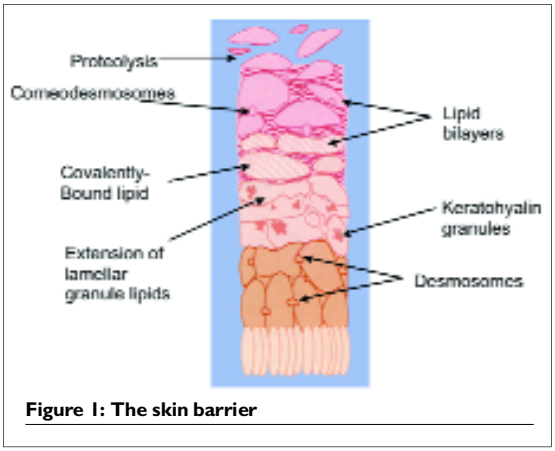

Figure 1: The skin barrier

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Skin sensitivity is on a spectrum with perfect skin at one end and severe eczema at the other. Perfect skin never has rashes, is never dry and never reacts to creams or wash products that are put onto it. In reality, perfect skin is only found in the air-brushed pages of women's interest and baby magazines. Some children and adults have near-perfect skin that appears to be very resistant to damage and reaction to topical products. This has been referred to as 'stainless-steel skin'.[1]

Approximately 50 per cent of adults complain of a condition called sensitive skin.[2] Sensitive skin manifests itself as burning, stinging and/or itching, following the application of products such as soap, some bubble baths and cosmetics. The skin may become red and dry after the repeated application of these products, at which point sensitive skin is starting to overlap with irritant contact dermatitis. In individuals with sensitive skin the skin is delicate and vulnerable to develop dermatitis after repeated washing with soap. Sensitive skin in adults is common, affecting 55 per cent of women and 45 per cent of men in the UK.[2]

In individuals with irritant contact dermatitis the skin is very sensitive and products such as soap can cause redness, severe dryness and fissuring. The most common sites for irritant contact dermatitis are the hands because they are often exposed to excessive washing with soap, particularly in healthcare professionals.

A large proportion of adults with sensitive skin and/or irritant contact dermatitis had atopic eczema when they were children.[3,4] This suggests that there are common factors between sensitive skin, irritant contact dermatitis and atopic eczema. An individual may have atopic eczema as a child and then appear to 'grow out of it'. Later in life they may develop irritant contact dermatitis and/or sensitive skin.

Intrinsic atopic eczema

Atopic eczema has been thought of as principally an allergic 'atopic' disease. Atopy is defined as the tendency to produce 'allergic' IgE antibodies instead of IgM antibodies. These antibodies may be non-specific or a specific reaction against particular allergens such as grasses and pets.

Two forms of atopic eczema have been recognised. In the allergic form, called 'extrinsic' atopic eczema, there are raised levels of both non-specific IgE and specific IgE antibodies. The 'intrinsic' form of atopic eczema is not associated with a raised non-specific or specific IgE. It had previously been thought that the majority of children with atopic eczema (about 80 per cent) had extrinsic allergic atopic eczema and the remaining 20 per cent had intrinsic non-allergic atopic eczema. However, a recent systematic review of all studies of IgE levels in children with atopic eczema demonstrated that in children from the community up to 66 per cent had the intrinsic non-allergic form.[5] The majority of children with intrinsic atopic eczema have mild/moderate disease.

Understanding the skin barrier

If the majority of children with mild/moderate atopic eczema do not have raised IgE levels, why do they have eczema? Although the majority of scientists studying atopic eczema have thought that the main cause was raised allergic IgE antibodies, a couple of groups have suggested that the primary problem is in the skin barrier.[6]

The structure of the epidermis is illustrated in Figure 1. Skin cells (keratinocytes) divide at the bottom of the epidermis in order to produce a supply of new skin cells. The new skin cells then start to mature (differentiate) as they move up through the skin. At the top of the skin the skin barrier (stratum corneum) is formed. This barrier

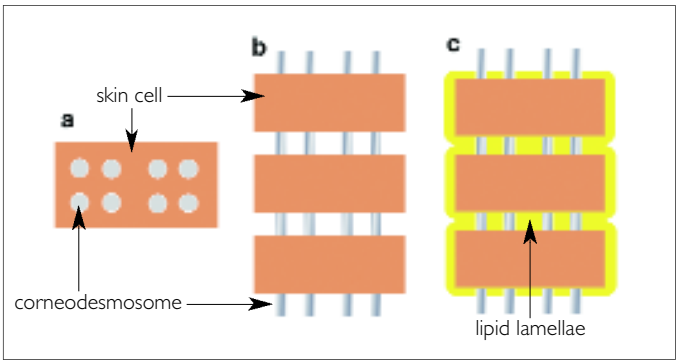

Figure 2: Brick wall model of the skin barrier. Skin cells are analogous to the bricks and lipid layers are analogous to the cement. In tall brick walls, iron rods are passed down through holes in the bricks to give the wall greater strength. These iron rods are analogous to the corneodesmosomes that lock the skin cells together

protects the body from the environment and normally prevents the penetration of irritants and allergens through the skin. The skin cells in the stratum corneum are locked together by structures called corneodesmosomes and the skin cells are surrounded by lipid bilayers.

The stratum corneum has been visualised as being similar to a brick wall, with the skin cells analogous to the bricks and the lipid lamellae analogous to the cement (Figure 2).[7] The stability of tall brick walls is maintained by passing iron rods through holes in the bricks. These iron rods are are analogous to corneodesmosomes, which hold the skin cells together and allow the skin to resist shearing forces. The lipid lamellae protect the skin cells and the corneodesmosomes from the environment (Figure 2). A strong skin barrier is essential to protect the body from the penetration of irritants and allergens.

In order to maintain a constant thickness of the stratum corneum barrier, skin cells must be shed from the surface of the skin. The skin cells can only be shed after the corneodesmosomes (iron rods) have been broken down (rusted) by proteases (Figure 3). This process is called proteolysis and leads to shedding of the skin cells near the surface (desquamation). In normal skin the breakdown of the corneodesmosomes only occurs near the skin surface (Figure 3a). As a result a thick skin barrier is maintained and this prevents the penetration of irritants and allergens.

In a child predisposed to atopic eczema the corneodesmosomes are 'rusted' all the way down through the skin barrier (Figure 3b) as a result of increased skin protease activity. If this child is then exposed to soap or surfactants the rusting process is enhanced and the brick wall falls apart (Figure 3c). This then allows the penetration of other irritants and allergens (Figure 3d), which triggers a flare of the eczema. The lipid lamellae are incomplete in atopic eczema which contributes further to barrier breakdown.

The skin barrier is thinnest at skin sites that are most vulnerable to atopic eczema (Figure 4). The face and the flexures have the thinnest skin barrier and are most often affected by atopic eczema. In areas where the stratum corneum is very thin there is very little barrier reserve. This means that if the barrier is damaged then it will be easy for irritants and allergens to penetrate through the further thinned skin barrier and trigger a flare of the eczema.

Gene-environment interaction

The prevalence of atopic eczema has increased relentlessly over the past 50 years from 4 per cent in the 1940s to more than 25 per cent today (Figure 5).[9] The genes that predispose to atopic eczema have not changed over the past 60 years, but our personal environment has changed considerably.[10] One example is the use of soap and surfactants such as bubble baths to wash babies, which has increased substantially over the past 60 years.[10] Surfactants are used to solubilise dirt and allow it to be washed off the skin. Soap and surfactants have been shown to cause a reduction in the thickness of the stratum corneum by 40 per cent.[8] Soap and surfactants also break down the lipid lamellae.

Atopic eczema has a strong genetic component. If a child has one parent with atopic eczema then they have a 20 per cent chance of developing eczema, but if both parents have/had atopic eczema the risk increases to 50 per cent. Several genes that predispose to atopic eczema have been identified but they are most relevant to extrinsic (allergic) rather than intrinsic (non allergic) eczema.[11,12]

In view of the evidence implicating breakdown of the skin barrier as an important event in the development of atopic eczema, research was undertaken into genes that regulated the strength of the skin barrier in normal controls and children with atopic eczema.[13] Corneodesmosomes in the upper part of the skin barrier are broken down by proteases such as stratum corneum chymotryptic enzyme (SCCE). These proteases are inhibited by inhibitors such as SKALP. In normal skin there are low levels of proteases and so the skin barrier is thick and can resist the penetration of irritants and allergens.

It was found that, in children with intrinsic atopic eczema, there was a change in the SCCE protease gene. The most likely consequence of this change in the gene is the production of higher levels of SCCE.[13] This would lead to premature breakdown of the corneodesmosomes as shown in the brick wall model in Figure 3.

The normal pH of the skin is 5.5; exposure to soap and surfactants will raise this to 7.5 and higher. SCCE is pH sensitive and works best at a pH of 7.5. If the skin pH is raised from 5.5 to 7.5 this will result in a 50 per cent increase in the activity of SCCE, resulting in a greater weakening of the skin barrier and enhanced penetration of irritants and allergens. This is a good example of a gene-environment interaction leading to the development of atopic eczema.

Common mechanisms across the skin sensitivity spectrum

The sensitivity of the skin barrier to damage by environmental agents such as soap and surfactants has been appreciated for over 50 years. We are now starting to understand why these agents damage the skin barrier and trigger flares of atopic eczema. Skin sensitivity can occur in the context of atopic eczema as a child. It may also manifest itself later in life as irritant contact dermatitis or isolated skin sensitivity. The reason that the prevalence of sensitive skin is higher in adults than the prevalence of atopic eczema is that the problem of skin sensitivity has not been formally studied in children and it is difficult to obtain a history of these types of reactions from children.

There is some evidence that suggests that the defect in corneodesmosomes that occurs in

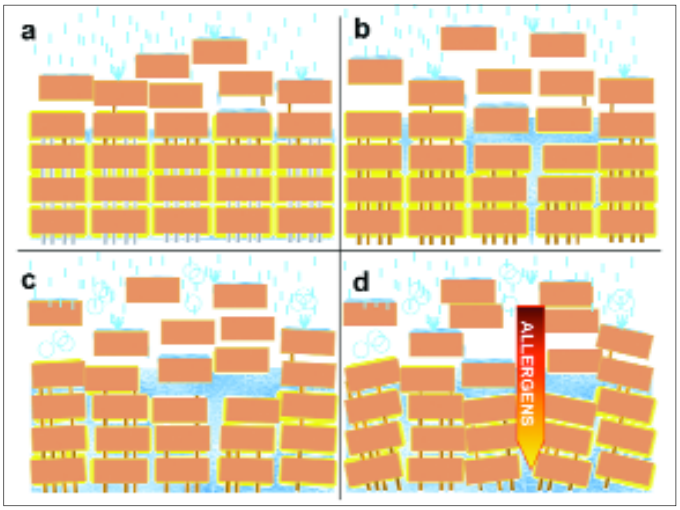

Figure 3: In normal skin (3a) the corneodesmosomes are normal throughout the stratum corneum. At the surface of the skin the corneodesmosomes start to break down as part of the normal process of shedding skin cells (desquamation). Breakdown is enhanced by washing with soap as this increases the activity of proteases. In a child predisposed to atopic eczema the corneodesmosomes are broken down all the way through the skin barrier (3b) as a result of increased levels of proteases. If this child is then exposed to soap the breakdown process is further enhanced and the 'brick wall' falls apart (3c). This allows other irritants and allergens to penetrate, triggering a flare of the eczema (3d)

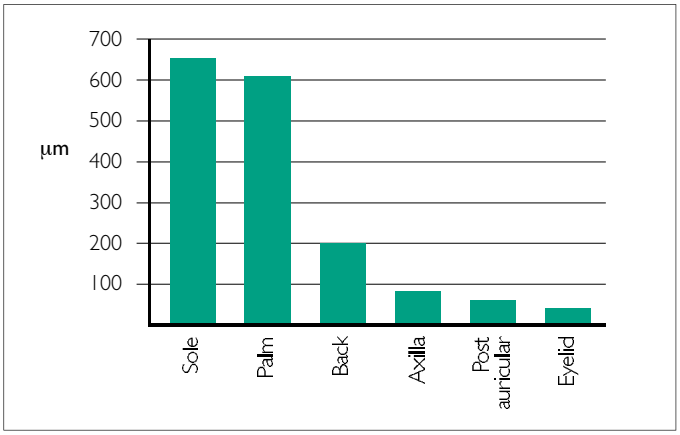

Figure 4: Graph showing variations in skin thickness at diffe rent sites

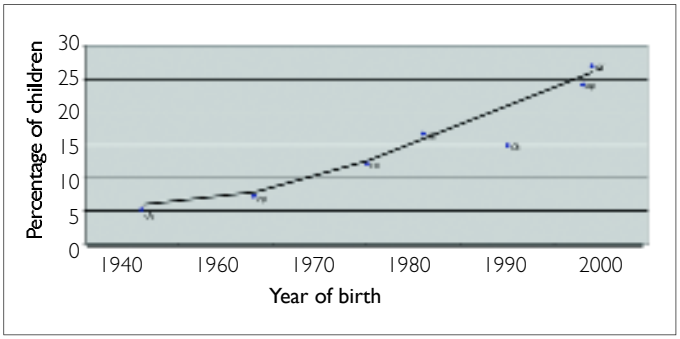

Figure 5: Rising prevalence of atopic eczema over the past 50 years

atopic eczema is also present in isolated skin sensitivity in adults.[14] This suggests a common mechanism through which agents such as soap damage the skin barrier by, for example, damaging the corneodesmosomes. This also helps to explain why soap is a very common trigger for flares of atopic eczema in children.

Identifying and treating babies and children at risk

There is increasing interest in identifying babies and children at high risk of developing atopic eczema. The personal environment of the children could then be modified to reduce the chance of developing atopic eczema or at least reduce its severity. In the future we will probably have a simple diagnostic test that will predict which babies are at highest risk of developing atopic eczema; currently we can predict those at highest risk on the basis of their family history. In babies and children with a sibling who already has atopic eczema, the simplest advice is to use the same emollient bath oils and emollient soap substitute to wash the baby that are used for treating the sibling with atopic eczema.[15]

Emollient soap substitutes, bath oils and creams contain no soap or surfactants (or at very low levels) and so do not have a damaging effect on the skin barrier. The oils in these products can partially repair the damaged lipid lamellae in children with atopic eczema. Current best practice is to use a complete emollient therapy regimen, which replaces all soap and surfactant based bathing products with emollient products.[16,17] On its own this regimen can, particularly in mild atopic eczema, produce very good control for most of the time.[18] Emollients do not repair the corneodesmosomes, and the development of products with this property would be a significant advance in treatment.

The key to the management of atopic eczema (and any skin problem) is to take time to listen, time to teach and time to demonstrate how to use treatments such as emollients. The delivery of this type of education programme to children with atopic eczema and their parents by specialist dermatology nurses produces a substantial improvement in the control of the eczema.[18] We have developed a series of cartoons called 'Skin Wars', to explain to children with eczema (and their parents!) how eczema develops and how to treat it.[15] Figure 6 is one of our cartoons from 'Skin Wars: Episode I', which explains to the child that soap and surfactants can breakdown their skin barrier and can be thought of as 'baddies'. What they need to do is get rid of all the 'baddies' and replace them with the 'goodies'; emollients that help to repair the skin barrier. The skin's response to topical products varies between individuals; a particular emollient may cause a sensitive skin reaction in some children. We let the child and parent pick the emollients that suit their skin best from a tray of all those in the *British National Formulary*.

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Resources

Further information on atopic eczema and sensitive skin can be obtained from Allergy UK (www.allergyuk.org) and the National Eczema Society (www.eczema.org)

Figure 6: 'Skin Wars' cartoon to explain to children with eczema (and their parents) how eczema develops and how to treat it