No. 67
Published August 2004

Karger Gazette

skin [skɪn]

sb. [ME, *fr* ON *skinn* akin to OE *scinn* skin MHG *schint* fruit peel] the flexible continuous covering of a human or other animal body

c. **1384** CHAUCER *The hous of fame* Marcia that lost her skyn Bothe in face, body and chyn.
1611 *Authorized Bible* Job 19:20 I am escaped with the skin of my teeth.
1922 JOYCE *Ulysses* I in my skin hopping around.

Textiles and the Skin

Peter Elsner

Friedrich-Schiller-University
Jena, Germany

According to modern anthropology, humans are the 'unfinished beings.' In contrast to other animals, we construct not only our environments, but also ourselves. Our ability to live in conditions as extreme as the Saharan desert or the Canadian arctic ice has only been possible through the creation of garments which surround the body with a microenvironment in which we can exist and function under physiological conditions. Textiles have, then, the function of a 'second skin,' substituting for the biological properties that other animals have evolved to cope with specific environments on this planet. Thanks to textiles, humans have even been able to enter the most extreme and inhospitable environments, such as interplanetary space.

For millennia, textiles have been continuously developed to improve their physiological tasks. The recent past has seen the advent of completely new technologies that may make textiles of everyday use 'intelligent' (fig. 1). They may have integrated sensors, for example, to diagnose conditions such as heart arrhythmia, or they may be equipped with carrier molecules to absorb substances from the skin and to release therapeutic or cosmetic compounds. While wet dressings have been used by generations of dermatologists to treat their patients, 'therapeutic suits' and the 'cream to wear' or 'cosmetotextiles' are within reach.

At the same time, however, dermatologists and consumers have become increasingly aware of the risks garments may cause to human health. Irritant dermatitis is one concern, but allergic contact dermatitis especially to certain colors used in textiles and to textile finishers even more so. The treatment of textiles or their raw materials with insecticides has alarmed authorities and prompted the industry to set safety standards known as 'eco seals.'

Before discussing in more detail the interactions between textiles and the skin, a few brief comments about the skin itself (see panel on the left for more details). It is the largest organ in the human body, in an adult having a surface area of about 1.8 m² and a weight of 10 kg. It can be differentiated into three components: the outer protective epidermis, the corium or dermis which provides mechanical stability and contains important functional structures such as blood and lymph vessels, nerves and appendages, and the subcutis which is mainly composed of adipose tissue and provides the connection between the dermis and deeper structures of the body, i.e. fascia and muscles.

Clothing as a thermal barrier

Textiles act as a barrier for heat and vapor transport between the skin and the environment [1]. The fabric itself, the air it encloses and the still air on its surface act as insulators preventing heat transfer by conduction and radiation. Since the volume of air enclosed is much higher than the volume of the fibers, the insulation is dependent more on the thickness of the material than on the fiber type. Clothing comfort is closely related to thermal comfort. The skin has no wetness sensors, but temperature sensors reacting to cool wet clothing produce a sensation of discomfort. That is why early nylon shirts which had a low air permeability and trapped moisture on the skin gave the wearer a 'wet-towel' feeling when sweating. In contrast, fabrics which buffer heat and moisture by having well-absorbing fibers or special fiber structures, such as open canals within the fibers, and which are manufactured by appropriate spinning and weaving techniques, keep moisture away from the skin

---

The skin can be divided into three layers: the external epidermis, the dermis below, itself subdivided into two layers, and the subcutis.

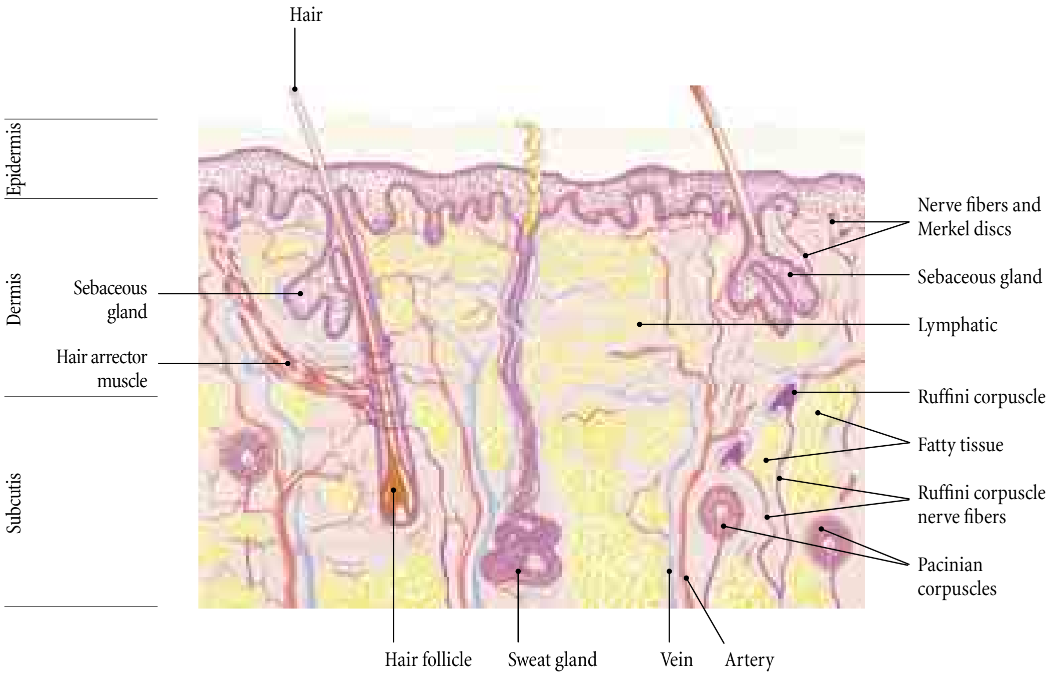


Figure adapted from: G. Thews, E. Mutschler, P. Vaupel: Anatomie, Physiologie und Pathophysiologie des Menschen. Stuttgart, Wissenschaftliche Verlagsgesellschaft, 1999

The epidermis varies in thickness between 0.1 and 1 mm. It consists primarily of epithelial cells – mainly keratinocytes which are increasingly differentiated as they migrate from the basement membrane (separating dermis and epidermis) to replace lost cells, a process taking 2–3 weeks. Melanocytes are also found in the basal layer of the epidermis. The epidermis has no blood vessels and must receive nutrients via diffusion from the dermis. The keratin in the outer epidermal cells forms an effective barrier against desiccation and bacterial and toxin entry. It is also a neurosensory and social-interactive surface.

The dermis is a dynamic layer of thick connective tissue, also in constant turnover. The elasticity and durability of the dermis provide the body protection against trauma. The thinner outer papillary dermis contains capillaries, elastic and reticular fibers and some collagen. The connective tissue in the reticular dermis is thicker; it contains larger blood vessels, elastic fibers and collagen. The primary dermal cell is the fibroblast, which produces collagen, elastin and the extracellular matrix of mucopolysaccharides, chondroitin sulfate and glycoproteins. Mast cells are also present as are most nerve endings (e.g. the pressure- and temperature-sensitive Ruffini corpuscles, and the pressure-sensitive pacinian corpuscles), lymphatics and skin appendages.

The subcutis is essentially a layer of fatty tissue containing vascular and neural structures. It serves for insulation and energy storage.

Important skin appendages are: sebaceous glands which secrete sebum to lubricate the skin and make it more impermeable to moisture; sweat glands producing sweat to cool the body by evaporation; apocrine glands which produce odor, and hair follicles. All these appendages are lined with epithelial cells which can be recruited for repair when the epithelium is damaged.

Skin is thickest on the palms and soles of the feet, thinnest on the eyelids and behind the ear. Male skin is characteristically thicker than female's and children's thin skin thickens progressively until the 4th or 5th decades of life when it begins to atrophy with loss of elastic fibers, skin appendages and matrix.

Fig. 1.
Functional or smart textiles are treated in such a way that they protect the user from adverse conditions while remaining comfortable to wear. **a** Special UV-absorbers increase the sun protection factor of garments (Photo: BASF). **b** Modern sportswear is made from synthetic materials that direct sweat away from the body so that it evaporates quickly (Photo: Keystone).

and thus lead to a feeling of comfort even under exercise conditions. Currently, test standards are only available for the thermoinsulating properties of materials used in clothing, but the complex demands of protective clothing and its effect on human thermoregulation require evaluation by human subject tests.

Clothing as UV protection

Due to the increase in UV-related skin problems, especially melanoma and nonmelanoma skin cancer, considerable attention has been paid over the last 20 years to the use of fabrics as photoprotective materials [2]. An ultraviolet protection factor (UPF) has been defined based on the wavelength-dependent transmission of the fabric, the solar UV spectrum and the erythemal (capillary dilation) action spectrum in the wavelength region 290–400 nm. Standardized test methods have been developed for Australia/New Zealand, the USA and Great Britain. UPF values range from 2 (poor protection) to several thousand (high protection). Nevertheless, two factors which have an influence on the UPF are not currently considered in the calculation: fabric moisture content and tension. Cotton and other cellulose fabrics show great differences in UPF when they are wet (lower values) and dry (higher values). Elastane-containing 'stretch fabrics' also show considerable differences in transmission, with a reduction in UPF when the fabric is stretched because 'holes' develop in it.

While the UPF is calculated for protection from sunburn, further work is needed on fabric protection from other endpoints such as photosensitization and (pre)malignant lesions.

Use of textiles in medicine

The use of textiles in medicine has a long tradition. In phlebology, that branch of medicine concerned with the anatomy and diseases of the veins, compression bandages were mentioned in the Greek Corpus Hippocraticum more than 2000 years ago. Compression therapy is an important option in the treatment of patients with chronic venous insufficiency, especially when a surgical intervention is not possible (fig. 2) [3]. Elastic compression is active under all circumstances, but such bandages must be removed at night to prevent complications of reduced arterial influx. Nonelastic compression bandages on the other hand can be worn at night, but they work only in the upright position. Two types of medical elastic compression stockings are available: flat-knitted stockings with a seam and round-knitted seamless ones. The latter are generally thinner and better accepted by patients for cosmetic reasons.

Another important field of application of textiles in the medical setting is in wound care and the prevention of chronic wounds, for which bandages and wound dressings are used. A new development in this field are spacer fabrics, composed of textile sheets interconnected by distance fibers, which may be polyamides, polyesters, viscose or even natural fibers like cotton (fig. 3) [4]. With these fabrics, a more even distribution of pressure becomes possible, and, depending on the selection of capillary or surface-modified fibers, fluid transport through the fabric is enhanced. Spacer fabrics have been used in bandages for lymphedema. They were shown to be as effective as classical bandaging, but much more comfortable for the patient due to their microclimatic quality.

Absorbant textile devices are usually based on superabsorbers such as acrylic acid polymerized with compounds such as tri-allylamine. They are used for napkins for small children, incontinence devices and as soaking pads in wound care.

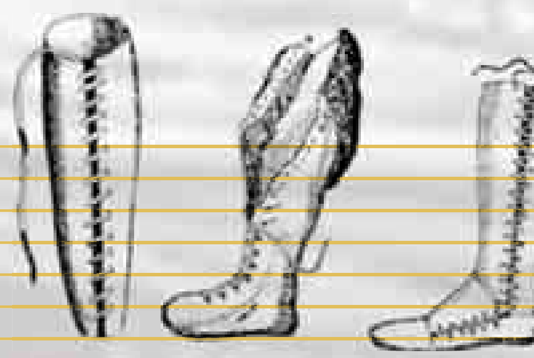


Fig. 2.
Gaiters and laced stockings between 1790 and 1849 [source: V. Weinert, Textbook 'Compression Therapy'].

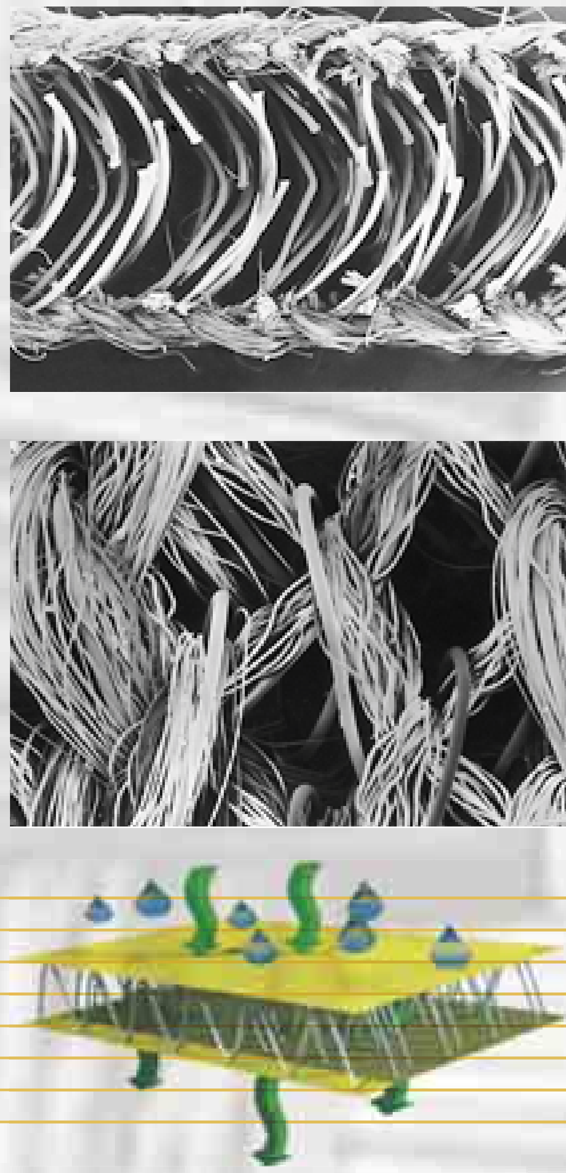


Fig. 3.
Spacer fabrics – two textile areas are interconnected by polyester filaments encouraging directed liquid and heat transport. **a** Scanning microscopy of a spacer fabric demonstrating the monofil filaments interconnecting the textile areas. **b** Details of the polyester filament construction. **c** Schematic presentation.

Antimicrobial textiles

Textiles can be endowed with antibacterial activity in a variety of ways. Soil-repellent fluoropolymers have hydrophobic properties which reduce soiling on textiles and, secondarily, microbial growth. Small molecules such as silver, zinc, copper and quarternary ammonium compounds show antibacterial activity. Silver-coated dressings have been used in wound care [see also the article on burns in this issue], and silver-coated pyjamas have been shown to reduce staphylococcal growth on the skin of patients with atopic dermatitis, reducing recurrences of this chronic disease. Antibacterial agents may be added to synthetic fibers in the spinning process, but they can also be fixated to supramolecular compounds on the textile surface. Cyclodextrins are ring-like carbohydrates which form complexes with 'guest' substances. They can be used as transdermal collector systems in toxicology monitoring, but also to diminish bacterial contamination at sweat-prone sites (so-called odor-controlling textiles) or as antibacterial textiles. The efficacy of antimicrobial textiles may be very diverse and much careful testing is still required to identify those clinical settings where they may be used effectively [5].

Barrier textiles and tissue engineering

Barrier textiles are used widely in medicine, especially for infectious diseases and in surgery to protect both patients and staff from contamination by infectious materials. An important field of textile barrier technology is the encasing of mattresses and pillows to protect allergic patients from house dust mite allergens.

Finally, textiles are used for organ replacement and grafting, as in the case of prosthetic arterial grafts or hernia repair. In the future, textiles may offer interesting properties as biodegradable scaffolds in tissue engineering, which seeks to create functional substitutes for damaged tissues. These scaffold materials provide structural integrity and mechanical stability while the cellular components generate new tissue through production of extracellular matrix. Spacer fabrics have been used to scaffold human and rodent cells such as keratinocytes and hepatocytes (fig. 4). Various approaches to creating artificial skin, chimeric skin substitutes and hybrid technology have used living and nonliving components to substitute lost organ functions. Such use of textiles in skin substitutes is discussed further in the article on burns.

Irritant textile dermatitis

Textiles, on the other hand, may also exert unwanted effects on the human skin. Among the most significant problems are irritant dermatitis, allergic contact dermatitis and immediate-type reactions.

Irritant reactions to textiles may be due to the fibers themselves. One clinical study showed that patients with atopic skin diathesis, characterized by a sensitive skin, reacted more intensely to synthetic textiles than to cotton textiles, and the reaction was linked to the surface structure and diameter of the fibers under investigation. Detergents in textiles are a frequent concern of patients with supposedly textile-induced dermatitis and, indeed, detergents can be shown to be present on the surface of new and repeatedly washed textiles in small amounts. With repeated washings, cotton textiles in particular may accumulate anionic and nonionic surfactants and soap. However, wearing tests both in adults and children performed under practical conditions showed no development of any skin problems.

Fabric softeners are also frequently suspected to cause skin problems, although since these substances modify the surface of textiles, they should reduce the potential of mechanical irritation from fibers. Nevertheless, human repeated-insult patch tests (HRIPTs) and use tests with fabric softeners showed no potential for sensitization and very low, if any, irritation.

Functional treatments for antibacterial or antifungal activity, however, may cause skin problems under stress conditions [6]. New clothes should therefore be rinsed carefully before wearing.

Allergic contact dermatitis to textiles

When considering allergic contact dermatitis to textiles, dyes and textile resins have attracted particular attention from dermatologists. Parameters influencing the risk of sensitization to textile dyes include the allergenicity of the dye molecule, but also the fastness of the dye, i.e. how well it is bound to the fabric, and the percutaneous absorption. The prevalence of textile dye dermatitis in the general population is unknown, but patch testing in unselected populations reveals prevalence rates between 0.0 and 1.0% for nondisperse dyes and 1.4–5.8% for disperse dyes. Among those suspected of suffering from textile dermatitis, positive reactions to textile dyes may be detected in up to 72.9% [7]. Both animal tests and human patch test studies have shown a significant potential for sensitization to disperse blue 35, 106 and 124. There is evidence that at least 15 disperse dyes are contact allergens, while it is difficult to say whether any nondisperse dye is a contact allergen. However, whether and how often positive patch test results to textile dyes mean clinically relevant intolerance still remains unclear.

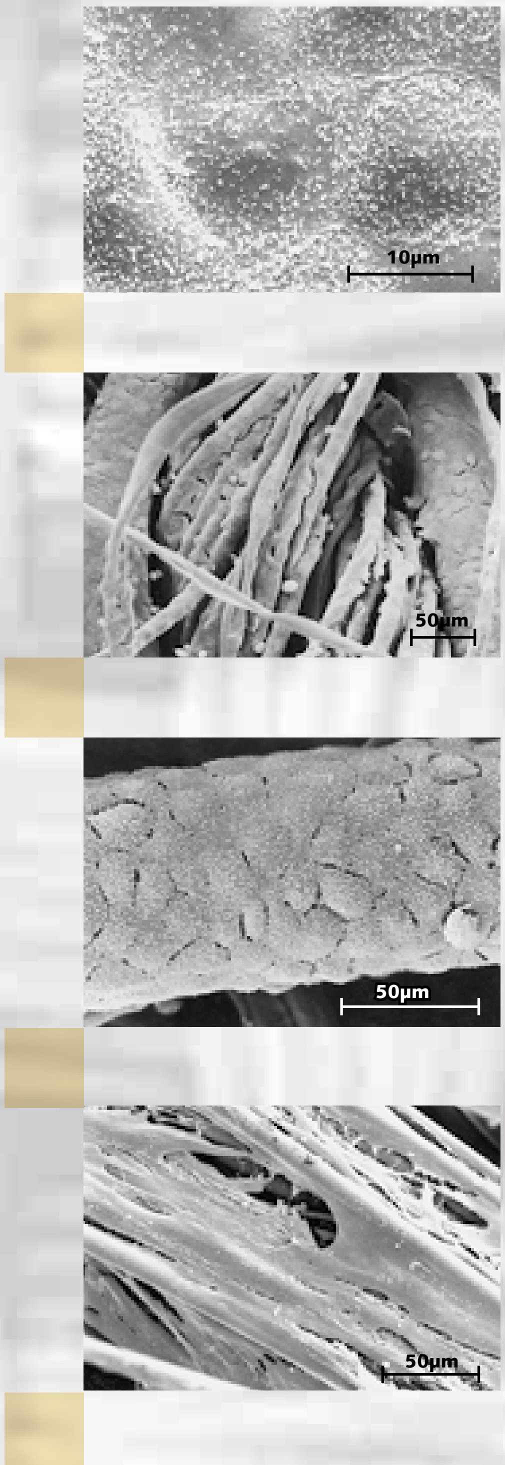
To improve the appearance of textiles, permanent press finishes which may contain formaldehyde-releasing resins are used. In the 1930s, N-methylol (formaldehyde) compounds derived from urea and melamine formaldehyde were used, which released significant amounts of formaldehyde, but gradually cyclic ethylene and propylene urea compounds with lower formaldehyde release were introduced. Some years ago, Fowler and colleagues [8] reported an increase in cases of textile dermatitis due to formaldehyde-releasing permanent press finishes in the USA. The authors theorized that a trend toward using imported textiles, even if the finished garment is made in the United States, may account for this upsurge of cases. It has to be remembered, however, that formaldehyde is a ubiquitous allergen that may be present in leather, but also in cosmetics, disinfectants and occupational chemicals.

Immediate-type allergy to textiles

Immediate-type reactions that manifest as stinging, itching, erythema, angioedema, urticaria and anaphylaxis are rare manifestations of textile allergy. Fibers, formaldehyde, dyes, latex and plant contaminants have been shown to be causes of immediate-type textile allergy [9].

An intimate relationship

As this brief review has shown, the interaction between textiles and the skin is a close and reciprocal one. As more new and innovative textiles come onto the market for both strictly medical as well as more purely aesthetic or recreational (as in sports clothing for example) purposes, a mutual exchange must also be established and maintained between those who create textiles and those who apply them in clinical settings and/or treat the skin: textile engineers must understand basic skin anatomy, physiology and microbiology, and the pathogenesis of skin reactions; dermatologists need to know about the structure and characteristics of fiber and fabric types, dyes and finishes and clothing physiology. As in many other areas of life and the sciences, an interdisciplinary approach to the skin and textiles will provide the basis for the development of both more sophisticated and more sensitive textiles for the benefit of human health, comfort, and pleasure.



a b c d

Fig. 4. The use of spacer fabrics in tissue engineering. **a–c** Scanning electron microscopy of rat liver cells after 9 days culture on sulfated polystyrol (tissue culture chamber) (**a**) and polyester-based spacer fabrics (**b**, **c**). Note the confluent growth of cells on these filaments. **d** Skin fibroblasts on polyester-based spacer fabrics after 6 days of culture.

References

1 Havenith G: Clothing and thermoregulation. Curr Prob Dermatol 2003;31:35–49.
2 Menter JM, Hatch KL: Clothing as solar radiation protection. Curr Prob Dermatol 2003;31:50–63.
3 Geest AJ van, Franken CP, Neumann HA: Medical elastic compression stockings in the treatment of venous insufficiency. Curr Prob Dermatol 2003;31:98–107.
4 Wollina U, Heide M, Müller-Litz W, Obenauf D, Ash J: Functional textiles in prevention of chronic wounds, wound healing and tissue engineering. Curr Prob Dermatol 2003; 31:82–97.
5 Takai K, Ohtsuka T, Senda Y, Nakao M, Yamamoto K, Matsuoka J, Hirai Y: Antibacterial properties of antimicrobial-finished textile products. Microbiol Immunol 2002;46:75–81.
6 Matthies W: Irritant dermatitis to detergents in textiles. Curr Prob Dermatol 2003;31:123–138.
7 Hatch KL, Maibach HI: Textile dye allergic contact dermatitis prevalence. Contact Dermatitis 2000;42:187–195.
8 Fowler JF, Skinner SM, Belsito DV: Allergic contact dermatitis from formaldehyde resins in permanent press clothing: an underdiagnosed cause of generalized dermatitis. J Am Acad Dermatol 1992;27:962–968.
9 Bircher AJ: Cutaneous immediate-type reactions to textiles. Curr Prob Dermatol 2003;31:166–170.

About the author

Peter Elsner, MD, studied medicine at Julius-Maximilians-University, Würzburg, Germany, and trained as a dermatologist and allergologist at the Dept. of Dermatology, Würzburg University. He received his doctoral degree in 1981, his lectureship in dermatology in 1987, and has taught at universities in San Francisco and Zürich. He has been Professor and Chairman, Dept. of Dermatology and Allergology, Friedrich Schiller University of Jena, Germany since 1997. Dr. Elsner has published more than 250 original papers and 20 books. He is a member of many scientific societies and his positions have included chairmanship of the International Society for Bioengineering and the Skin (ISBS). He is editor of the new Karger journal Exogenous Dermatology *and has edited several volumes in the series* Current Problems in Dermatology.

Skin Substitutes in Burn Care

Robert L. Sheridan

Shriners Hospital for Children
Massachusetts General Hospital
Boston, Mass.

Until we actually lose or damage it, we may take the skin, our body's largest organ, and its crucial activities somewhat for granted: the protective functions of the fragile epidermis, providing a barrier against vapor loss and bacterial entry, the strength and elasticity, temperature control, lubrication and extensive neural network of the tougher dermis. Burns, to various degrees, strip the body of its outer layers, exposing it to the risks of infection, desiccation and other functional deficits.

Burns are generally classified into four categories based on the depth of the wound. First-degree burns (e.g. sunburn) do not extend below the basal cell layer of the epidermis, while in second-degree burns, various amounts of the dermis are also destroyed. Both first- and second-degree burns leave behind remnants of the epithelium and can reepithelialize. In first-degree burns, the basal cell layer of keratinocytes persists and so it simply differentiates to recreate the multiple epidermal layers. This process is usually complete within 3–4 days and little treatment other than perhaps a moisturizer is required.

Once the burn extends into the dermis, the entire epidermis has to be reconstructed from the skin appendages like sebaceous glands, sweat glands and hair follicles which are located deep in the dermis and are lined with epithelial cells. Stimulated by the loss of basal cell-cell contacts and growth factors released by the wound, keratinocytes and appendage epithelial cells migrate to the wound surface. Once the wound is covered by a layer of keratinocytes, they differentiate to form all the layers of the epidermis. Wounds with the highest concentration of skin appendages heal the fastest, so the scalp, for example, can heal within 4–5 days, while areas lacking hair take longer – up to 3 weeks. Keeping the wound moist optimizes healing.

Third-degree burns destroy the full thickness of the skin, and fourth-degree burns penetrate to underlying muscle and bone. These wounds will not heal of their own accord and, together with some very deep second-degree burns, require surgical closure with replacement material – grafts and flaps.

Skin substitutes, the subject of this article, have applications in both the short- and long-term care of burn patients. Losing the skin barrier has several immediate, and sometimes life-threatening, consequences. Loss of fluid, both directly and by evaporation, can be rapid and may lead, if wounds are very large, to dehydration and shock. Dry wounds do not heal well, and if deep tissues become desiccated, there may be secondary cell death and concomitant deepening of the wound. Protein losses can also be substantial, and the risks of infection by microorganisms are dramatically elevated. Prompt wound covering is an essential first step in treating burns.

There are two classes of skin substitutes: temporary and permanent. The former provide a temporary barrier function while the underlying skin heals, or are employed at various times during grafting procedures. Permanent skin substitutes are meant to replace the skin when it is irrevocably damaged. The ideal characteristics of skin substitutes are listed in table 1. As yet we have no product that meets all these criteria. When one does become available, it will have a dramatic impact on the care of patients with serious burns.

Fig. 1.
Porcine xenograft showing good coverage of a partial-thickness wound.

Temporary skin substitutes

The role of temporary skin substitutes is to provide a barrier against excessive vapor loss and bacterial invasion while damaged skin heals. They also absorb wound exudate and protect against mechanical traumas. The moist wound environment below the membranes – which may be natural or synthetic – facilitates epithelial migration and helps to control pain.

Temporary skin substitutes are employed in a variety of clinical settings:

- To dress graft donor sites, facilitating pain control and epithelialization from appendages
- To dress clean superficial wounds for the same reasons
- To temporarily close deep dermal and full-thickness wounds while they wait for autografts
- To cover underlying autografts while they heal
- As 'test' grafts on questionable wound beds

Human amniotic membrane is used in many parts of the world to dress clean superficial wounds, donor sites and wounds awaiting grafts. It is usually used either fresh or after brief refrigeration. Although it does not vascularize, it provides effective temporary wound closure. However, amnion is difficult to screen for viral contamination, and this has limited its application in developed countries.

Animal skins, or xenografts, have a long history as skin substitutes. In the 16th and 17th centuries, frog and lizard skins were applied as skin substitutes, while from the 1900s, the skins of a variety of animal species, including rabbit and dog, were tested. Porcine xenograft gained in popularity in the 1960s and is the only form of xenograft still used extensively today (fig. 1). It may be employed fresh or cryopreserved, but its most common form is as a homogenized dermis which is then fashioned into meshed sheets. It is most frequently applied to cover clean wounds such as superficial second-degree burns or in patients with toxic epidermal necrolysis. Like amnion, xenografts do not vascularize, but they adhere well to clean wounds and provide excellent pain control while a wound heals.

Fig. 2.
A variety of composite skin substitutes are in clinical trials, such as the one shown here, a combination of autologous epithelium and allogenic dermis.

A number of single- or double-layer synthetic semipermeable membranes provide vapor and bacterial barriers over healing wounds. A typical two-layer membrane consists of an inner layer of nylon mesh that allows fibrovascular ingrowth, and an outer layer of silastic that provides the vapor and bacterial barrier. Hydrocolloid membranes have a three-layer structure: a porous, gently adherent inner layer, a methyl cellulose absorbent middle layer and a semipermeable outer layer. They foster a moist wound environment and absorb wound exudate. The principal drawback to these membranes is that they are occlusive and can foster infection if placed over contaminated tissue. Their use has to be monitored very carefully.

Table 1.
Characteristics of the ideal skin substitute

- Inexpensive
- Has a long shelf life
- Can be used off the shelf
- Nonantigenic
- Durable
- Flexible
- Prevents water loss
- Bacterial barrier
- Drapes well
- Easy to secure
- Grows with a child
- Can be applied in one operation
- Does not become hypertrophic

Growth factors such as epidermal growth factor, insulin-like growth factor and platelet-derived growth factor are believed to help speed the healing process [1]. Topical preparations of pure growth factors are very expensive, so they are most commonly provided by incorporating allogeneic cells, such as keratinocytes and fibroblasts, into membrane dressings. The application of the concept to treat burns is still relatively new, but the efficacy of several different systems is currently being evaluated. The cells in the membranes can persist for no more than 14 days, but the factors they release both while alive and upon their death and breakdown may enhance wound healing. Keratinocytes transformed to overproduce certain growth factors are now available, and we may see their incorporation into membrane dressings in the next few years.

As already mentioned, infection is a serious threat to a patient with burns. Silver is a very effective antiseptic, and the active ingredient of common topical wound agents. A number of membranes have also been developed that release silver into the wounds to which they are applied. The basic membrane in these products varies: it can be a nonadherent dressing, a hydrofiber dressing, a reconstituted porcine xenograft or a fine nylon mesh. Low-voltage electrical current has also been used to drive silver from these membranes into the wound. Though such membranes have been applied to several types of wound, no consensus has yet emerged for their optimal application.

The current 'gold standard' of temporary skin substitutes is split-thickness human allograft (see box 1). It can be used after brief refrigeration (up to 7 days) or after cryopreservation. Human allograft is still the only temporary skin substitute that will vascularize and can be relied upon to provide biologic cover until it is rejected after 3–4 weeks. Attempts have been made to prolong this interval by application of antirejection drugs, but there is serious concern that these might increase the risk of infection and additional immunosuppression. In general, human skin allografts are frozen while laboratory tests for viruses are undertaken. With modern

Fig. 3.
Even after successful engraftment, cultured epithelial cells may not adhere well to the dermis.

Fig. 4.
Integra showing good vascularization prior to the removal of the outer silastic membrane.

Fig. 5.
Alloderm just prior to placement of an overlying thin autograft.

screening techniques, however, the risks of viral transmission are exceedingly small.

Permanent skin substitutes

When the skin is irreversibly damaged, we still have no materials that will replace it perfectly, and an inexpensive, reliable and durable permanent skin substitute will revolutionize burn care [2]. The split-thickness autograft is still the best current solution. There are, however, a number of membranes that provide some degree of permanent skin replacement. These membranes can be classified as epidermal, dermal and composite substitutes (fig. 2).

The technology for epidermal replacement was developed in the 1970s. Epithelial cells are procured from a full-thickness skin biopsy and cultured in a medium containing growth factors over a layer of mouse fibroblasts. Colonies of epithelial cells expand into broad sheets which are recultured until confluent thin layers of undifferentiated cells are obtained. These sheets are then attached to a petroleum gauze carrier for easier handling.

There were high hopes in the beginning that such epidermal replacements would provide the definite solution for extensive burns but, unfortunately, engraftment rates are suboptimal and, when successful, the epithelium is fragile and shows a lack of durability (fig. 3) [3]. Nevertheless, if a wound is very large, such epithelia are still a useful adjunct to split-thickness autografts.

Many of the imperfections associated with epithelial wound closure may be attributable to the absence of a dermal element, hence the attempts to develop dermal analogues. Results were mixed with the first effort which involved leaving behind from a split-thickness allograft the vascularized allogenic dermis after mechanical excision of the epidermis and upper dermis. The first synthetic dermal analogue was probably a biodegradable polygalactin mesh seeded with allogenic fibroblasts, but it was not successful in clinical trials.

Two dermal analogues have been approved by the Food and Drug Administration. Integra (Integra LifeSciences Corporation, Plainsboro, N.J.), which was originally called 'artificial skin,' is a two-layer membrane intended to provide both a vapor and bacterial barrier and a scaffold for dermal regeneration. The inner layer is a 2-mm-thick combination of collagen fibers and chondroitin-6-sulfate with a 70- to 200-μm pore size to allow fibrovascular ingrowth, after which it will slowly biodegrade. The outer layer is a 0.23-mm-thick polysiloxane polymer with vapor transmission characteristics similar to normal epithelium. Integra is placed on freshly excised full-thickness burns. Fluids will quickly invade the matrix so that it adheres to the wound. Between days 7–14, dermal cells migrate into the matrix and establish a new vascular network. As healing progresses, the collagen in the template is replaced by collagen produced by the new dermal skin cells. After about 3 weeks, when a new dermal layer is formed, the outer silicone membrane is replaced with a thin split-thickness autograft (fig. 4). Clinical reports have in general been favorable, although life-threatening submembrane infection is a problem that must be monitored [4].

Processed allogenic split-thickness dermis – Alloderm (LifeCell Corporation, The Woodlands, Tex.) – has been approved for use in acute-burn resurfacing and reconstruction. It is used at the time of initial wound closure together with a thin epithelial autograft. The allograft skin is obtained from cadavers and screened for transmissible diseases. The epithelium is removed and the remaining dermis treated with detergent to inactivate viruses before being freeze-dried. The result is a nonantigenic scaffold with the basement membrane (particularly laminin and collagen types IV and VII) intact. For use, the material is rehydrated, placed on the wound and covered with an ultrathin epithelial autograft (fig. 5). As with Integra, by days 7–10, fibroblasts will have responded to the transplantation and will begin to initiate the revascularization and normal tissue-remodeling processes. After 7–8 weeks, normal connective tissue forms through host collagen deposition, and by 3 months, the Alloderm is repopulated with the patient's own cells while fibroblasts continue to lay down autologous collagen. Since Alloderm has only recently been introduced into burn care, conclusions about its usefulness must be tentative, but the clinical experience has, so far, been positive [5].

Integra and Alloderm can be used in both children and adults. The experience in children is more limited, and these materials do seem slightly more difficult to contour around the tight curvature of small children's extremities. As with skin grafts, patients with substitute skins do not initially have sensation, but this develops after several months as nerves grow into the replacement material. Sweating, however, only returns with a full-thickness skin graft.

The future

Experience and common sense reinforce the notion that ideally we must replace the epidermis and dermis at the same time. Both elements are required for normal function and appearance, and the cellular interactions between dermal and epidermal elements enhance the maturation of the epithelium. The future seems to be in an autologous laboratory-derived composite skin replacement.

One promising technology is the culture of autologous fibroblasts and epithelial cells into a collagen-glucosaminoglycan membrane. This composite has been successfully engrafted in a nude mouse model, and early clinical trials have been encouraging [6]. There are exciting possibilities here and the technology is being refined in laboratory and clinical investigations. Another autologous composite under active development comprises autologous keratinocytes grown into allogenic split-thickness dermis from which all cellular elements have been removed. This membrane was successful in a nude mouse model and has shown some success in early human pilot trials [7]. In a subsequent study, fibroblasts were added to the composite and improved its function. In the third composite being developed, epithelial cells are centrifuged into the underside of Integra. This composite engrafted successfully in a porcine model.

The lives of patients with massive burns can now be saved and they can anticipate a satisfying quality of life [8], but as burn resuscitation and critical care improve, our need for a durable and reliable skin substitute becomes increasingly acute. We need it both to close wounds more quickly and to provide more effective, more definitive reconstructive operations. The solution lies in the future as we wait for the results of the ongoing clinical trials with the materials described in this article. But, in whatever form, the successful replacement will have a dramatic and long-lasting impact on burn care.

Box 1.

Classification of grafts

Grafts can be autologous (donor and recipient are the same person) or allogenic (donor and recipient are different). Skin grafts generally consist of the entire epidermis and a dermal component of variable thickness. If the entire dermis is taken, the graft is termed full-thickness. If less than the entire dermis is taken, it is termed a split-thickness (or partial) graft. Split-thickness grafts are further classified as thin, intermediate or thick, depending on the amount of dermis taken. The thicker the graft, the closer its resemblance to normal skin in terms of collagen content, vascular plexuses and epithelial appendages. However, thicker grafts require more optimal conditions for survival because more tissue must be revascularized. The choice of graft depends on the condition of the wound, its location and size, and aesthetic considerations.

References

1. Greenhalgh DG: The role of growth factors in wound healing. J Trauma 1996;41:159–167.
2. Sheridan RL, Tompkins RG: Skin substitutes in burns. Burns 1999;25:97–103.
3. Sheridan RL, Tompkins RG: Cultured autologous epithelium in patients with burns of ninety percent or more of the body surface. J Trauma 1995;38:48–50.
4. Heimbach DM, Warden GD, Luterman A, Jordan MH, Ozobia N, Ryan CM, et al: Multicenter postapproval clinical trial of Integra dermal regeneration template for burn treatment. J Burn Care Rehabil 2003;24:42–48.
5. Sheridan RL, Choucair RJ: Acellular allodermis in burn surgery: 1-year results of a pilot trial. J Burn Care Rehabil 1998;19:528–530.
6. Boyce ST, Kagan RJ, Yakuboff KP, Meyer NA, Reiman MT, Greenhalgh DG, et al: Cultured skin substitutes reduce donor skin harvesting for closure of excised, full-thickness burns. Ann Surg 2002;235:269–279.
7. Sheridan R, Morgan JR, Cusick J, Petras L, Lydon M, Tompkins R: Initial experience with an autologous composite skin replacement. J Burn Care Rehabil 2000;21:s214.
8. Sheridan RL, Hinson MI, Liang MH, Nackel AF, Schoenfeld DA, Ryan CM, et al: Long-term outcome of children surviving massive burns. JAMA 2000;283:69–73.

About the author

Robert L. Sheridan is Chief of the Burn Surgery Service at the Shriners Hospital for Children in Boston, Mass., and is Co-Director of the Adult Burn Service at the Massachusetts General Hospital. Dr. Sheridan is also an assistant professor of surgery at Harvard Medical School. His principal research interests are clinical, and include pediatric burns, skin replacement technologies, techniques of wound excision, critical care technologies and the metabolic response to illness.

Atopic Eczema

Johannes Ring
Johannes Huss-Marp
Technical University Munich, Germany

Fig. 2.
Atopic eczema in infancy [from ref. 3].

Fig. 3.
Atopic eczema in childhood [from ref. 3].

Fig. 4.
Eczematous skin lesions in flexural folds [from ref. 3].

Atopic eczema (also called atopic dermatitis) is a noninfectious, chronically relapsing, inflammatory skin disease accompanied by intense pruritus (itching). The disease usually starts in early infancy and childhood, and is often associated with elevated levels of serum immunoglobulin E (IgE) and a personal or family history of asthma and/or allergic rhinitis (see box 1 for a definition of terms used in this article). A diagnosis of atopic eczema is based on clinical findings and made if at least four of the six simple criteria established in 1982 are found (see table 1).

Epidemiology

Atopic eczema occurs throughout the world and is a major health problem. In industrialized countries today, an estimated 10–20% of children and 1–3% of adults are affected. In 60% of the cases, atopic eczema begins in the first year of life (usually after the first month), in 30% in the following 4 years. Atopic eczema tends to be more severe in young children, with periods of remission appearing more frequently as the patient grows older. The outcome of atopic eczema is difficult to predict, but in about one-third of patients the disease will resolve during childhood, while in the remaining two-thirds it tends to persist or will reoccur in adolescence (fig. 1).

There is clear epidemiological evidence that the prevalence of atopic eczema has increased at least two- to threefold in the past few decades. The reasons remain unclear, but hypotheses include increased awareness of the disease, improved diagnostics, increased genetic susceptibility, psychosocial influences, allergen exposure, decreased immune system stimulation, increased prevalence of an underlying disease, antiallergic therapy and environmental pollution [2].

There seems to be good evidence that factors characteristic of a 'modern western society' now play an important role in the development of allergy. With improved hygiene, the immature immune system of the young is less stimulated and, in particular, less challenged by severe parasitic infections. This may mean that the IgE present as a major defense mechanism is now directed against harmless environmental substances such as pollen, house dust mite or animal dander. Investigations in Swiss, Austrian, German, Australian and Finnish children who grew up in farmhouses with heavy exposure to farm animals and endotoxin showed less allergies than in children living in the same area but not in a farmhouse. Gastrointestinal infections also seem to play an important role: studies from Italy with military recruits showed lower rates of gastrointestinal infections in allergic individuals.

Another environmental factor may be pollution. For the indoor environment, tobacco smoke has been shown to increase the risk of developing atopic diseases, especially when women smoke during pregnancy and lactation. For atmospheric pollutants such as diesel exhaust particles, in vitro studies with different cell populations showed a shift of the T cell response towards the T helper 2 (Th2) secretion pattern. Epidemiological studies comparing similar ethnic groups living under different conditions (e.g. people in East and West Germany after reunification who had lived in different air pollution profiles) have given further support to this idea, but the precise mechanisms underlying the rise in prevalence are still not known and are the subject of intense investigations.

Other changes in recent decades that have altered our exposure to allergens include the energy-saving insulation of houses, wall-to-wall carpeting and new and 'exotic' foods.

Nevertheless, we still cannot satisfactorily answer the question as to why allergies are on the increase, and further research is needed not only to identify the most important factors, but also to distinguish between causal and adjuvant/enhancing factors, and to identify protective influences. We must know what the causative factors are to both counteract the rising prevalence of atopic diseases and inform the population of effective measures of prevention. Whereas atopic eczema was once a disease of childhood, in many cases it now continues into adulthood, and at the beginning of the new millennium we are faced with the prospect of increasing numbers of adults needing treatment for this disease.

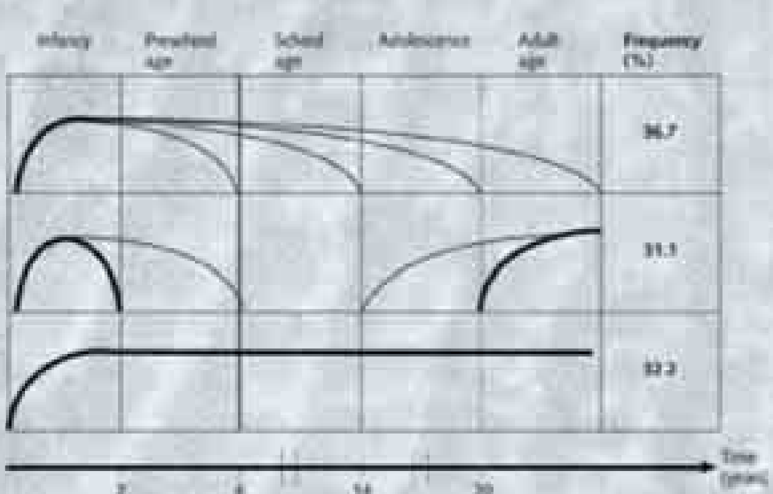


Fig. 1.
The occurrence and evolution of atopic eczema in different age groups [adapted from ref. 1].

Clinical manifestations

In atopic eczema, typical patterns of skin reactions occur in the different age groups, in all cases accompanied by intense pruritus. In infants, atopic eczema involves mainly the scalp, face and extensoral sides of the arms and legs (fig. 2) whereas in older children (fig. 3, 4) and adults, it is primarily found in the flexural folds of the extremities as well as on the skin of hands, feet and neck. In infancy, the disease tends to be more acute, with vesicles over erythematous skin and a serous exudate. As the children get older, the eczema turns dry and the skin shows lichenification, the epidermis turning leathery and thick as a response to scratching. The dominant feature in adults is often excoriated prurigo nodules, i.e. persistently erupting, highly itchy papules that the sufferer scratches. Patients with long-standing atopic eczema frequently display a chronic form of the disease with a dry, lichenificated skin and eczematous lesions localized to the flexural folds. The skin barrier is permanently impaired and exposure to exogenous irritants or allergens can trigger acute exacerbations of the disease. As these descriptions imply, many of the skin lesions seen in atopic eczema, such as erythema, papules or vesicles, can be explained as the consequence of intensive pruritus followed by scratching [4].

Atopic eczema is accompanied by a number of typical stigmata which are summarized in table 2.

Diagnostic criteria for atopic eczema were first published by Hanifin and Rajka in 1980 [5] and included four major features and many associated findings. The major features are (1) pruritus, (2) facial and extensor eczema in infants and children or flexural eczema in adults, (3) chronic or relapsing dermatitis, (4) a personal or family history of atopic diseases. Other diagnostic criteria for atopic eczema are the 'UK Refined Criteria,' the 'Millennium Criteria' and the criteria mentioned above (table 1).

The SCORAD index (severity scoring of atopic dermatitis) was developed by the Task Force on Atopic Dermatitis to assess the intensity of atopic eczema [6]. This method enables the clinician to calculate an intensity index taking into account the extent of the disease as well as the characteristics and prominence of the skin lesions. Subjective symptoms such as pruritus and loss of sleep are also included.

Patients with atopic eczema are prone to bacterial, fungal and viral infections of the skin which can significantly exacerbate the disease [7]. *Staphylococcus aureus* is particularly frequent on atopic skin, and can cause pyoderma, folliculitis and honey-colored crusting accompanied by regional lymphadenopathy (fig. 5). Common superficial fungal infections are mostly caused by *Trichophyton rubrum* and *Malassezia furfur*. Infections with herpes simplex virus are also seen frequently and can lead to the serious complication of eczema herpeticum, a febrile condition which occurs when the virus disseminates cutaneously. Similar skin eruptions can be seen after smallpox vaccination, and are called eczema vaccinatum.

A rare but potentially life-threatening complication is exfoliative dermatitis which can occur

Table 1.
Diagnostic criteria for atopic eczema published in 1982

- Eczematous skin lesions
- Pruritus
- Typical localization (according to age)
- Stigmata of atopic constitution
- Personal or family history of atopic diseases
- IgE-mediated allergic sensitization

in patients with extensive skin involvement and is usually caused by bacterial or viral superinfection leading to generalized redness, scaling, crusting, lymphadenopathy and fever.

Complications are not limited to the skin but can also affect other organs like the eye where chronic blepharitis and atopic keratoconjunctivitis are frequently seen. More severe ocular complications include atopic keratoconus and cataracts.

Fig. 5.
Atopic eczema superinfected with *Staphylococcus aureus* [from ref. 3].

Fig. 7.
Itching child with atopic eczema [from ref. 3].

Fig. 6.
Atopy patch test [from ref. 3].

Pathophysiology

Atopic eczema is closely linked genetically to allergic asthma and allergic rhinoconjunctivitis. The disease occurs in families, with a marked maternal influence on susceptibility. In 60% of patients with atopic eczema, the family history for atopic diseases is positive. A gene likely to be associated with atopic eczema of early infancy is localized on chromosome 3q21. This region encodes the costimulatory molecules CD80 and CD86. Further searching for candidate genes has revealed a linkage to loci on chromosomes 1q21, 17q25 and 20p which were not known to be related to the development of atopic diseases but had been linked to psoriasis. Thus these genes may influence skin inflammation independently of allergic mechanisms.

Total and specific serum IgE are often highly elevated in patients with atopic eczema, as revealed in a recent study which found antibodies to house dust mites in the serum of 95% of patients with atopic eczema compared to 42% for asthmatic subjects. Beside house dust mite, specific IgE antibodies are frequently directed against common aeroallergens such as cat dander, pollen or, in childhood, against foods like hen's egg and cow's milk. The degree of sensitization to aeroallergens is related to the severity of atopic eczema. Nevertheless, sensitization is not always of clinical relevance, and provocation tests are needed to confirm their importance for the development of atopic eczema. Here, the atopy patch test is a valuable tool to identify allergens able to elicit eczematous skin lesions in the individual patient (fig. 6) [8]. In this test, type I allergens are applied epicutaneously to uninvolved skin of patients with atopic eczema for 48 h and the skin reaction is evaluated at the time of their removal and again 24 h later. In healthy individuals or patients with solely respiratory allergies, the atopy patch test is rarely positive. The patch test is proof of the concept that aeroallergens can trigger and maintain atopic eczema, and the finding of IgE and IgE receptors on epidermal Langerhans cells casts new light on the pathogenesis of the disease.

In patients with atopic eczema, activated T cells infiltrate the skin and induce apoptosis of keratinocytes which leads to spongiosis, an intercellular edema of the epidermis and a typical histopathological finding of the disease. The pattern of T cell activation is biphasic: early in the development of eczematous skin lesions, Th2 cells dominate with increased interleukin (IL)-4 and IL-13 expression, with a shift to Th1 in more chronic disease, and a cytokine profile comprising IL-5, IL-12, interferon-γ and granulocyte-macrophage colony-stimulating factor.

Although IgE-mediated allergies are important in the majority of patients with atopic eczema (extrinsic atopic eczema), in some patients, no increased serum IgE levels or type I allergies can be found. The term intrinsic atopic eczema was coined for this group. Recently, IgE autoantibodies against human epidermal proteins (Hom s 1) were found in some patients with atopic eczema. Thus one hypothesis for the evolution of atopic eczema over time could be (1) a Th2 reaction responsible for the initial triggering, (2) Th1-mediated inflammation for chronic lesions leading to finally (3) an autoimmune pathomechanism for perpetuation of severe cases which are therapy resistant and in which allergen avoidance strategies no longer help.

In atopic eczema the skin is dry and rough with reduced levels of surface lipids and ceramides. Transepidermal water loss is increased as the barrier function in eczema patients is impaired in noninvolved and, even more, in eczematous skin. These changes are likely to increase the permeability of the skin to exogeneous substances such as allergens, leading to elevated cutaneous sensitization rates and subsequently to an enhanced Th2 response.

The interaction between dryness of the skin and pruritus which in turn leads to scratching and further skin lesions is complex (fig. 7). The disturbed barrier function renders the skin more vulnerable to irritants which can cause inflammation and enhance pruritus. Investigations into the quality of pruritus using a component analysis of atopic itch in the 'Eppendorf Itch Questionnaire' identified specific patterns of a 'compulsive' character to atopic pruritus. Many patients taking action against the itching sensation, e.g. by scratching, describe it as a pleasurable experience. To break this itch-scratch cycle, an effective antipruritogenic therapy needs to be combined with patient education. Studies to visualize the perception of itch in the central nervous system have been performed by positron emission tomography (fig. 8) and showed activation patterns of sensory and large motor areas in the cortex reflecting movements to counteract the pruritus; the activation of further areas showed involvement of the limbic cortex, perhaps suggesting emotional processing of itch sensations. In the skin, new receptor systems such as vanilloid, opioid and cannabinoid receptors have been identified on sensory nerve fibers. These receptors may modulate itch and therefore represent future targets for antipruritic agents.

Therapy, patient education and prevention

The efficient treatment of atopic eczema must include attempts to restore the disturbed epidermal barrier by cutaneous hydration. Effective skin moisturizers are available in the form of creams, lotions and ointments and should be used on a regular basis by a patient, especially during disease-free intervals when the skin appears to be unaffected. Oil baths can also be used to improve the condition of the skin and preserve epidermal integrity. Eczematous skin lesions are treated with topical or systemic antiinflammatory, antipruritic and antimicrobial drugs. Other therapeutic options include phototherapy and climatherapy (fig. 9).

Less direct but no less important aspects of treatment include the identification and avoidance of triggering factors (i.e. following an accurate allergy diagnosis), and the psychological guidance and education of the patient.

In acute exacerbations of the disease, topical glucocorticoids are

Table 2.
Stigmata of atopic constitution

- Xerosis – pathologic dryness of the skin, conjunctiva, or mucous membranes
- Hyperlinearity of palms and soles ('ichthyosis palms')
- Linear grooves on fingertips
- Dennie-Morgan infraorbital folds – a line below both lower eyelids caused by edema
- Thinning of lateral eyebrows (Hertoghe's sign)
- Low hairline ('fur hat-like')
- Facial pallor and orbital darkening
- Delayed blanch responses to acetylcholine
- White dermatographism – a whitening of the skin in the site and configuration of applied stroking by pressure or friction

Box 1.
Definition of some terms

Allergic rhinitis
Rhinitis is an inflammation of the mucous membranes of the nose; in allergic rhinitis this inflammation is caused by exposure to allergens such as pollen, house dust mites or animal dander.

Atopy
A genetically determined predisposition to develop certain diseases (asthma, allergic rhinitis, atopic eczema) on the basis of a hypersensitivity of the skin and mucous membranes to environmental substances. Atopy is associated with increased IgE production and an altered nonspecific reactivity.

Eczema
A generic term for an inflammatory condition of the skin.

Erythema
Redness due to capillary dilation.

Folliculitis
An inflammatory reaction of the hair follicles.

Papule
A circumscribed, solid elevation on the skin.

Pyoderma
A pus-forming infection of the skin.

Stigma
Generally means visible evidence of disease.

Vesicle
A small circumscribed skin elevation containing fluid.

usually employed. However, two topical immunomodulators, tacrolimus and pimecrolimus, were recently put on the market. These substances inhibit calcineurin phosphatase, lower intracellular signaling and inhibit transcription of multiple proinflammatory cytokines. Both agents have been used successfully to treat atopic eczema without the side-effects, such as skin atrophy, associated with topical glucocorticoids. It is still too early to say, though, what position these new drugs will ultimately occupy in the management of atopic eczema.

Since eczematous skin is prone to bacterial, fungal and viral infections, antimicrobial agents (especially against *S. aureus*) are often needed in the therapy of exacerbated atopic eczema. To achieve control of the atopic itch, systemic antihistamines can be helpful.

For the patient to carry out useful avoidance strategies and improve his or her ability to deal with the disease, new approaches in patient education have been introduced. In Germany, a special education program has been initiated to increase the patients' understanding of the disease so that they can achieve a higher level of independence and self-determination. Physicians, nurses, psychologists and dieticians are also trained within the program to meet the special needs of patients with atopic eczema. Efforts are also underway to spread information about measures of allergy prevention at a population-based level: in Germany, for example, the Government has encouraged the formation of a network of organizations working in the field. This interdisciplinary group is generating evidence-based guidelines for allergy prevention which will be distributed on a national and international level to increase awareness and ensure that the right steps will be taken in the prevention of allergic diseases. If these guidelines are followed, effective prevention, which will decrease the number of allergic individuals, may be within reach.

To identify susceptible individuals who will especially benefit from preventive measures, epidemiological and experimental studies are underway with the long-term aim of delivering tailor-made prevention. One promising approach in the field of diagnosis is the use of the atopy patch test to confirm the clinical relevance of individual allergens and thus customize the therapeutic concept to the patient's needs.

Despite new developments in pathophysiology, treatment and prophylaxis, some of which have been outlined here, atopic eczema continues to seriously impair the quality of life of millions of people, and remains a major challenge for modern medicine requiring further epidemiological, experimental and clinical research.

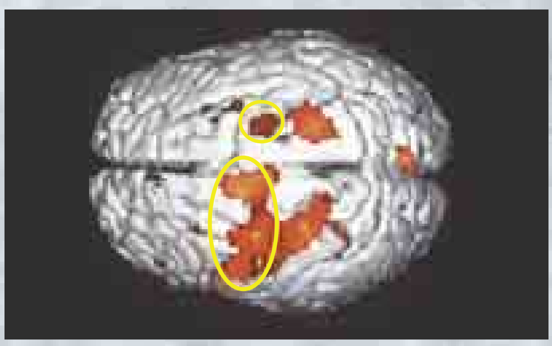


Fig. 8.
Visualization of itch in the central nervous system by positron emission tomography after histamine stimulus. Red areas are significantly activated. Motor-associated areas (yellow circles) are additionally activated [from ref. 9].

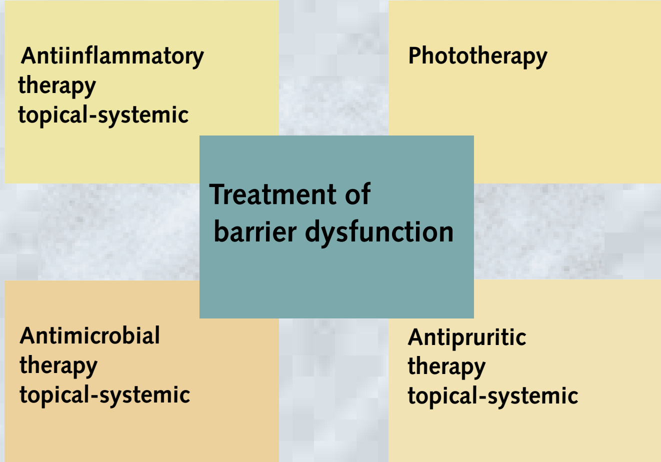


Fig. 9.
The therapeutic concept for atopic eczema [adapted from ref. 10].

References

1 Kissling S, Wüthrich B: Sites, types of manifestations and micromanifestations of atopic dermatitis in young adults: a personal follow-up 20 years after diagnosis in childhood. Hautarzt 1994;45:368–371.
2 Ring J, Kraemer U, Schäfer T, Behrendt H: Why are allergies increasing? Curr Opin Immunol 2001;13:701–708.
3 Ring J: Angewandte Allergologie, 3rd ed. Urban & Vogel, Munich, 2004.
4 Ruzicka T, Ring J, Pryzbilla B (eds): Handbook of Atopic Eczema. Springer, Berlin, 1991.
5 Hanifin JM, Rajka G: Diagnostic features of atopic dermatitis. Acta Dermatol Venereol 1980;92(Suppl):44–47.
6 European Task Force on Atopic Dermatitis: Severity scoring of atopic dermatitis: the SCORAD index. Consensus report of the European Task Force on Atopic Dermatitis. Dermatology 1993;186:23–31.
7 Leung DYM, Eichenfield LF, Boguniewicz M: Atopic dermatitis. In Fitzpatrick TB, Freedberg IM, Eisen AZ (eds): Fitzpatrick's Dermatology in General Medicine. McGraw-Hill Professional, New York, 2003, pp. 1180–1194.
8 Ring J, Darsow U, Behrendt H: Role of aeroallergens in atopic eczema: proof of concept with the atopy patch test. J Am Acad Dermatol 2001;45:S49–S52.
9 Darsow U, Drzezga A, Frisch M, Munz F, Weilke F, Bartenstein P, Schwaiger M, Ring J: Processing of histamine-induced itch in the human cerebral cortex: a correlation analysis with dermal reactions. J Invest Dermatol 2000;115:1029–1033.
10 Schnopp C, Ring J, Abeck D: Wie man kranke Haut stabilisiert. Allgemeinarzt 2000;8:606–612.

About the authors

Johannes Ring, MD, PhD, is director and chairman of the Department of Dermatology and Allergy Biederstein of the Technical University Munich, Germany. He is also President of the Collegium Internationale Allergologicum (CIA) and President-Elect of the European Academy of Dermatology and Venereology (EADV). He is involved in basic, clinical and epidemiological research programs concerning atopic diseases, and has published several textbooks on allergy and atopic eczema, while also being editor of the Karger book series Chemical Immunology and Allergy.

Johannes Huss-Marp, MD, is a Research Fellow in the Center for Allergy and Environment (ZAUM – Zentrum Allergie und Umwelt GSF/TUM) at the Department of Dermatology and Allergy Biederstein of the Technical University Munich. He undertakes research on atopic eczema and skin physiology, with a particular focus on the role of environmental factors.

The Importance of Touch


Photo by G. Schmid

Tiffany Field

University of Miami School of Medicine, Miami, Fla.

Touch is the first sensory system to develop, and it will continue to function even after sight and hearing have failed [1]. Some 1.6 m² of skin surround an adult body, making skin the largest sense organ. Because it cannot be 'shut off,' it is in a constant state of readiness to receive messages. The first sensory input in life comes from the sense of touch while the fetus is in the womb, and touch continues to be the primary means of experiencing the world through infancy and well into childhood, indeed playing a major sensory role right through to old age.

Touch appears to be important for survival and well-being in all species with this sense. For example, rat pups do not survive without their mothers' tongue-licking touch, and mother goats abandon their young if the baby goat is touched by another animal or a human. Monkeys become extremely aggressive when they are touch deprived. The power of touch in young children was demonstrated in a study in which one group of preschool children in a pediatric ward was given only verbal comfort when they showed distress, while the other was given simultaneous verbal and tactile comfort, including holding, patting, rocking, stroking and being offered a pacifier. Only 7 of the 40 verbal comforts succeeded in quieting the children, but 53 of the 60 tactile-verbal comforts were successful [2].

Messages to the brain

The term touch includes several tactile senses: pressure, pain, temperature and muscle movement. Many sensory receptors at different levels in the skin are responsible for conveying the nerve signals from thermal, mechanical, chemical and electrical stimuli. Meissner's corpuscles, located between the epidermis and the dermis on the hairless parts of the body – fingertips, palms, soles of the feet, tongue, sexual organs and so on – respond to the lightest form of stimulation. The pacinian corpuscles, located near the joints and deep tissues and in the genitals and mammary glands, respond to pressure, vibrations and high-frequency sounds. Merkel's disks, located just beneath the skin, respond to constant pressure. Ruffini endings, located deep in skin, can also register pressure and temperature.

Information from touch-sensitive nerve cells ultimately crosses the sensory cortex to the opposite side of the brain where it is processed. The amount of space needed by the cortex is related not to the size of the body part but to the nerve density: areas with more nerve endings, such as fingertips, lips and genitals, require more space in the cortex than the back, which has fewer nerve endings (fig. 1) [3]. Cortical nerve cells may be highly specialized: some, for example, will respond only to stroking the surface of a body part in one single direction, others to stroking at a specific frequency. Those areas of the body with a high density of nerve endings are also most sensitive to pain.

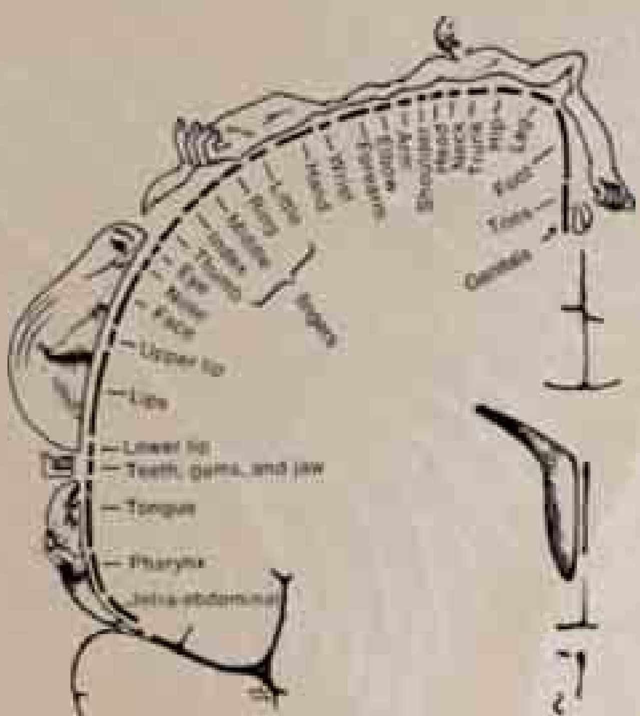


Fig. 1.
'Sensory homunculus,' illustrating the projection of various body regions on the sensory cortex. The length of each line represents the proportion of the somatosensory cortex devoted to the part indicated by the adjacent label. The diagram shows that the size of the body part is less important than the density of innervation in determining how much space is needed in the cortex [from ref. 3].

Touch in culture

Some cultures touch more than others. For example, in African cultures, babies are passed from person to person for many years, and the French are known to touch people more than Americans and certainly more than the British. People touch each other more during the preschool years than across the lifespan. In a recent study we noted, for example, that French mothers touched their preschoolers more at McDonald's in Paris than American mothers did at McDonald's in Miami (fig. 2) [4]. The French children, in turn, were less aggressive toward each other on the playground. French teenagers touched each other more at McDonald's in Paris while teenagers touched themselves (like self-hugging and playing with their hair) more at McDonald's in Miami. The French teenagers were also less aggressive with each other than were the American adolescents.

Young children depend on touch for learning about the world including the qualities of temperature, texture, shape, softness, sharpness, elasticity and resilience. Children also learn safety from touch such as avoiding stoves, sharp objects or frostbite, and they may learn how to write through touch if given hand-over-hand assistance in handwriting classes.

Touch is not only critical for growth, development, communication and learning but also serves for comfort, reassurance and self-esteem. The first emotional bonds are based on physical contact, and they form the foundation for emotional and intellectual development (fig. 3). Despite these critical functions of touch, most children

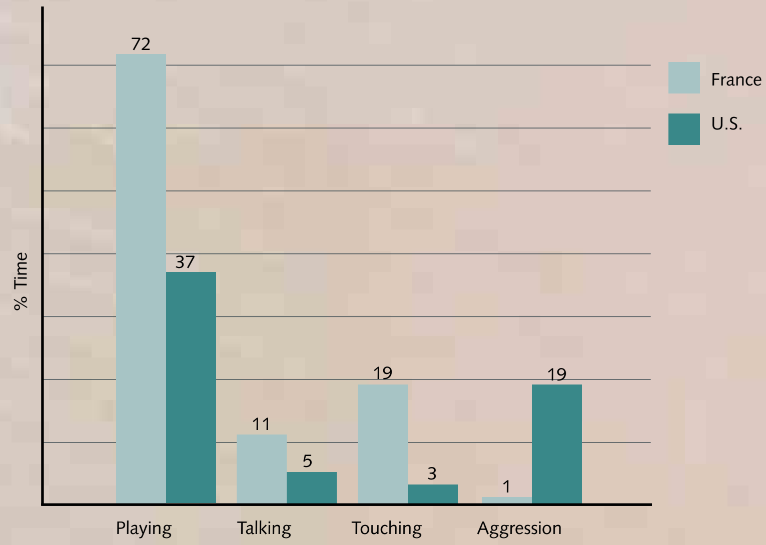


Fig. 2.
Interaction between preschoolers and their parents in Paris and Miami.

in the United States are socialized from a very early age to limited touch. They are punished for touching their own body parts and learn not to touch the bodies of others. They learn by adolescence that they should be cautious about physical intimacy. As adults they may talk about touch in many personal and sentimental ways, but in America's litigious landscape, they have become afraid of touching others because of potential lawsuits.

In the USA, mothers spend about 60% of their interaction time touching their infants. Soothing stimulation by parents is replaced by peer play (rough-and-tumble play at the preschool stage and contact sports during high school). But as children grow older, physical contact from parents becomes more taboo. As children reach high school, they receive about half the touch that they did in primary school. The nature of the touching also changes: there is more shoulder-to-shoulder and elbow-to-elbow rather than hand contact. The American adolescent typically treats family members as if they had some dread disease. Given the American touch taboos it is not surprising that touch-deprived adolescents might be drawn to touch-dancing, skinny-dipping, nude beaches, long showers, sunbathing marathons, applying lots of makeup and peer backrubs. These adolescent touch habits seem to have evolved at around the same time that schools mandated that teachers could no longer hug or touch children.

Some go so far as to say that touch is our strongest contact. In the words of Saul Schanberg: "Touch is ten times stronger than verbal or emotional contact, and it affects damned near everything we do. No other sense can arouse you like touch. We always knew that, but we never realized that it had a biological basis. If touch did not feel good, there would be no species, parenthood or survival. The mother would not touch her baby in the right way unless the mother felt pleasure in doing it. If we did not like the feel of touching and patting one another we would not have had sex. Those animals that did more touching instinctively produced offspring, which survived and had more energy, and so passed on their tendency to touch which became even stronger. We forget that touch is not only basic to our species but the key to it." [5]. Dr Schanberg has isolated a gene for growth that can only be "turned-on" by touch. In his rat model, the pups deprived of touch had significantly reduced growth hormone resulting in zero growth [6].

Touch in health

The 'laying-on of hands' has a long tradition, and the Ebers Papyrus dated to 1553 BC provides evidence of the early practice of healing by touch. In Hippocrates' Greece, around 400 BC, there were hand healers called kheirourgos. This is the origin of the word 'surgeon,' though the Greeks used the palm and their fingers, not surgical methods, to heal. One of the most famous Roman healers, Galen (130 AD), used massage as a medical treatment. There is ample evidence for healing via the hands throughout the Bible and, in the West, the laying-on of hands continued right through to the 18th century.

But then it fell out of favor, possibly because of an increase in sexual taboos as well as the development of drugs and treatment technologies that have dramatically changed the field of medicine.

Nevertheless, many of the touch therapies which have been practiced for thousands of years throughout the world, together with Western massage techniques, are now gaining acceptance by both the general public, medical practitioners and, importantly, insurance companies. Touch therapies can be classified into three groups – energy methods, manipulative therapies and amalgams (combinations of the first two) – examples and brief descriptions are given in table 1.

Although the underlying mechanisms for the effects of touch are unknown, positive effects have been noted for many growth, development and health phenomena as the following few examples will show.

Children with autism are often described as being extremely sensitive and averse to touch. But they seem to accept massage, perhaps because it is predictable. In one study on preschool children with autism, their disruptive behavior in the classroom decreased and their ability to relate to their teachers increased after a 10-day period of massage. In a second study, parents massaged their autistic children every night. The children experienced the same benefits as in the first study, but their sleep also improved [7]. Massage could well be a fundamental way to reach out to these children who appear to reject adult attention and affection.

Massage can also facilitate alertness. In a job-stress study, the staff and faculty of a medical school were massaged for 15 minutes a day for a month, during their lunch breaks. We recorded their EEG patterns before, during and after the massage sessions. Their alpha and beta wave levels decreased, while the theta increased, supporting the feelings of heightened awareness reported by the subjects. We also tested their performance on math computations. After massage, they took significantly less time to do the tasks and their accuracy increased [8]. Perhaps massage breaks should become as institutional as coffee breaks!

Massage therapy has been noted to reduce pain in various pain syndromes. Children with juvenile rheumatoid arthritis experience chronic pain because their antiinflammatory medication is often only partially effective and they cannot be prescribed narcotics because of the risks of addiction. A 1-month study in which parents gave daily massages to their children with rheumatoid arthritis noted several positive effects: anxiety and stress levels decreased, as did the pain. There are several possible explanations for the reduced pain. The pressure nerves stimulated by the massage may transmit their messages faster to the brain than the pain receptors, thus closing a 'gate' and preventing the reception of the pain message. Another possi-

Table 1.
Touch-related therapies

Energy methods

Tai Chi Chuan and yoga
These practices are based on the belief that health depends on the movement of energy through meridians or channels in the body. Research has shown that both tai chi and yoga can reduce pain and counter stress. In stimulating pressure receptors when, for example, limbs are pressed against each other, these techniques do, to some extent, resemble massage therapy.

Acupressure and acupuncture
The channels or meridians through which energy passes in the Eastern systems have corresponding points on the surface of the skin which can be pressed or punctured to affect the workings of internal organs or to enhance pain tolerance. The Japanese version of acupressure is called shiatsu, and involves long and heavy pressure usually with the balls of the thumbs and sometimes the palms and elbows.

Reflexology
Although an energy method, this could also be considered a massage therapy because it involves kneading, stroking, rubbing and other massage procedures centered on particular points of the ears, feet or hands from which energy is transmitted across a network to other parts of the body.

Manipulative therapies

Massage therapy
Western massage was initiated by Peter Lind, an athlete and educator from 19th-century Sweden, and his Swedish massage technique is one of the most popular touch therapies in Western countries. Swedish massage is usually given on a table, the floor or in a special chair, and often with an oil which is stroked and kneaded into all parts of the body. There are basically six types of massage in order of increasing pressure:
(1) stroking or effleurage; (2) friction, moving the hands over the body with more pressure than stroking; (3) pressure without movement; (4) kneading or petrissage, where the hands are stationary, but the fingers move, working their way into sore muscles; (5) vibration, in which a machine is generally used instead of human touch, and (6) percussion, a combination of slapping, pounding and tapping.

The Trager method
A very gentle form of body work which involves gently holding and rocking different body parts and is particularly appropriate for people with generalized pain.

Osteopathy
Osteopaths manipulate soft and connective tissues to balance the tendons, muscles and ligaments attached to bones. Their general approach is prevention oriented and they may also treat with some medication and focus on lifestyle habits such as nutrition.

Chiropractic
The major concern of chiropractors, who also focus on lifestyle, exercise and diet, is adjustment and realignment through various techniques of the 33 vertebrae of the spinal column.

Amalgams

Chinese massage
This combines massage, and acupressure along the meridians.

Polarity therapy
A technique combining energy, manipulation, massage and postural techniques based on energy flows between the positively charged top and right sides of the body and the negatively charged lower body and left side. The therapy involves deep pressure and stretching.

Reichian massage
Wilhelm Reich, an early psychoanalyst, wanted a therapy that worked on both the mind and body simultaneously. Many psychological and physical disorders, he believed, were due to energy blockage, with each region of the body being associated with a different emotion. So, in addition to the verbal therapy, the Reichian therapist kneads, pokes and sometimes strokes body parts where emotion is blocked.

Feldenkrais
The aim of the Feldenkrais technique is to improve posture and the individual's awareness of body movements and gestures. Various gentle manipulative techniques are used, along with small subtle movements, often repeated over and over.

Applied kinesiology
Kinesiologists combine several of the above techniques with a focus on the muscles and their attachments to restore muscle strength. Many people, like athletes and dancers, who need to keep their muscles in top condition use kinesiology.


Fig. 3.
Young people love touching.

Fig. 4.
Father caring for infant.

bility is increased production of serotonin, which has both antidepressant and antipain properties.

In addition, massage therapy has been noted to decrease symptoms in immune disorders such as asthma, diabetes and dermatitis and to enhance immune function, most particularly the production of natural killer cells that ward off cancer and viral cells [1].

We have noted in a recent study that moderate-pressure touch is necessary for these effects to occur. Moderate-pressure touch stimulates pressure receptors which in turn stimulate the vagus (one of the 12 cranial nerves) and increase vagal activity. This leads to a slowed heart rate and lower blood pressure, and the general behavioral effect is a relaxed, more attentive state. Other touch effects we have noted include a reduction in stress hormones (cortisol is a primary example), which could improve immune function, since cortisol normally kills natural killer cells. We also see an increase in activating neurotransmitters including serotonin and dopamine, and the alterations in EEG patterns which I have already mentioned.

Infant massage

Other than studying the physiological effects of touch and its critical importance for growth, development and health, my colleagues and I have been actively exploring ways to reintroduce touch into North American culture. One of the most promising ways may be teaching parents infant massage. Parents who are taught to massage their newborns continue to massage their children into adolescence. Infant massage training groups are now located in many parts of the United States, and the therapists claim that massage helps parent-infant bonding and warm, positive relationships, eases distress following painful procedures such as inoculations, reduces pain in teething and constipation, decreases colic and sleep problems and, importantly, reduces stress in the parents who are giving the massages.

The techniques we teach are based on Indian infant massage, a daily routine beginning at birth, in which the infants are laid on their stomach on their mothers' outstretched legs. Each body part is stretched as warm water and soap are applied. The massage is quite rigorous, and afterwards the children are swaddled and sleep for prolonged periods.

In one study, we taught depressed mothers to massage their infants, with the aim of both decreasing their depression and reducing the infants' associated distress behavior and disturbed sleep patterns. The mothers performed a 15-minute massage daily for 2 weeks. After 2 weeks, the infants were able to fall asleep faster, they slept longer and were less fussy, and the mothers played more easily with them.

Studies have been undertaken in both Australia and the US on fathers' involvement in childcare. In the Australian study, fathers with first-born babies were given a 1-month training program in baby massage, including a bathing massage technique. In comparison with 'control' fathers, after 3 months, they showed greater involvement with their infants and the infants greeted their fathers with more eye contact, more smiling, more vocalization and reaching responses, and less avoidance behavior. In our American study, too, the fathers became more interactive with their infants after massaging them for 1 month (fig. 4).

One of the greatest deterrents to delivering massage to preterm infants is the cost of providing the massage. We have found that teaching 'grandparent' volunteers is a no-cost means to deliver massage therapy (fig. 5). And it's not only the children who benefit. In a study designed to measure massage effects on sexually and physically abused infants, we trained elderly volunteers to massage these children, and they themselves also received massage. The volunteers reported fewer depressive symptoms, an improved mood, and lower anxiety after both giving and receiving massage, and their stress hormone levels decreased. Their lifestyles showed other general improvements: they made more social contacts, fewer trips to the doctor's office and drank fewer cups of coffee, changes which probably helped to improve their sleep and self-esteem [9]. Interestingly, these improvements were greater after a month of giving infants massage than they were after a month of receiving massages.

Other ways that researchers and therapists have tried to introduce touch have included teaching 'good touch-bad touch' in classrooms and showing preschool and grade school-age children to give each other backrubs. These are small attempts in a still highly touch-inhibited western nation, but every effort adds to the knowledge base on the importance of touch for growth, development and health.

Fig. 5.
Volunteer 'grandparent' massaging infant.

References

1 Field T: Touch. MIT Press, Cambridge, Mass., 2003.
2 Triplett J, Arneson S: The use of verbal and tactile comfort to alleviate distress in young hospitalized children. Res Nurs Health 1979; 126:101–110.
3 Schiffman HR: Sensation and Perception: An Integrated Approach. Wiley, New York, 1990.
4 Field T: Preschoolers in America are touched less and are more aggressive than preschoolers in France. Early Child Dev Care1999;151: 11–17.
5 Schanberg S: The genetic basis for touch effects. In: Field T (ed): Touch in Early Development. Erlbaum, Mahwah, 1995, pp 67–79.
6 Schanberg S, Field T: Sensory deprivation stress and supplemental stimulation in the rat pup and preterm human neonate. Child Dev 1987;58:1431–1447.
7 Escalona A, Field TM, Singer-Strunck R, Cullen C, Hartshorn K: Improvements in the behavior of children with autism following massage therapy. J Autism Dev Disord 2001; 31:513–516.
8 Field TM, Ironson G, Pickens J, Nawrocki T, Fox N, Scafadi F, Burman I, Schanberg S, Kuhn C: Massage therapy reduces anxiety and enhances EEG patterns of altertness and math computations. Int J Neurosci 1996;86:197–205.
9 Field TM, Hernandez-Reif M, Quintino O, Schanberg S, Kuhn C: Elder retired volunteers benefit from giving massage therapy to infants. J Appl Gerontol 1998;17:229–239.

About the author

Tiffany Field has been an active researcher in touch for the last 20 years and, in 1992, founded and currently directs the Touch Research Institutes at the University of Miami School of Medicine. She is also deeply involved in community research on child development, and is holder of the Chair Program and Past President of the International Society on Infant Studies (ICIS).

A personal view

lamellar ichthyosis: a form of autosomal recessive primary ichthyosis; incidence, 1:50,000 to 1:300,000 live births, depending on severity and statistics used; cause: defect in transglutaminase gene; histology: massively thick stratum corneum.

The arrival of our grandchild Aïcha in January 2001, with a severe case of lamellar ichthyosis, created a hiatus in the family. She was a collodion baby, her skin at birth so hard and shiny she looked as if she were wrapped in cellophane. She was immediately put in a high-humidity, oxygen-enriched incubator at the hospital. The first evening there her grandfather stood by the incubator with her father, who sang to his sick little newborn daughter. Within hours her skin developed deep and bleeding crevasses. For a week we did not know if she would survive. Sometimes Fatoumata, who turned two, 4 days after Aïcha's birth, accompanied her parents and reached into the incubator to caress her little sister. After a few days our daughter took Aïcha out of the incubator once or twice a day to breast-feed her. Aïcha came home at 3 weeks.

It was frightening that she could never close her eyelids, which turned inside out (ectropion), and that her carapace-like skin kept her almost immobile. And meanwhile the parents searched frantically for information and competent doctors who knew something about this very rare skin disorder (but were, nonetheless, for the most part oblivious to the burdens and sudden wrenching adjustments in family life). There have been many tears and times of despair and depression. Our daughter and son-in-law found themselves with a full-time job for which they were unprepared.

Aïcha was quite passive for the first six months, as if her little body were using all its energy to survive. Fatoumata wanted to proudly show everyone her baby sister and was perplexed by people's strange reactions. Still small herself, it was difficult having a sister who needed so much of their mother's care and attention.

For two years Aïcha was bathed twice a day; one bath is now often replaced by a quick shower. She took to bathing and swimming (tub, pool, lake) as a duck to water. And we all try our best to let the stares of strangers run off us like water off a duck's back. Her skin has to be treated immediately, so that the moisture is as far as possible 'locked in.' Rough over most of her body and extremely dry, it desquamates constantly, sometimes like cornflakes, sometimes smaller, like fish scales. The nape of her neck is dark, with the appearance and texture of a turtle's neck. If her skin itches, she peels it off; if it bleeds, she needs special bandages without adhesive tape. Once a week her mother smears her scalp with ointment, wraps it in plastic foil (occlusive dressing), then a scarf, and after half a day shampoos her hair to comb the thick scales from her head.

Aïcha's arrival had not only emotional, but also logistical consequences: inordinate quantities of laundry, hot-washing her greasy clothes and bedding almost daily; getting a car with air-conditioning because she cannot perspire (danger of hyperpyrexia); keeping her mostly inside in very hot weather and having a cooling spray handy when outside; installing humidifiers in all the rooms in winter, when the air is dry.

Despite her severe skin handicap, the goal has been to let Aïcha lead a normal life – sandbox, swing, tricycle, and all activities typical of a young child. It is now hard to believe she is the same girl who was born almost 3 years ago. The first year she was unable to use her thumbs (the skin so taut she could not stretch them); her mother patiently did exercises with her, so that she is now as skillful with her hands as any other child. She is bright, lively, loves to sing, and radiates such an inner joy and has such a contagious sense of humor, the family find her just as charming outside as in. However, other children can be cruel, pointing and shouting comments, so that Aïcha now frequently says things like "Mama, I'm not ugly, am I?" or "Mama, I'm not disgusting, am I?" Or they refuse to hold her hand in playing games. It tears one's heart out. Adults may either stare mutely, offer inappropriate advice or ask if she has been burned, so we are all constantly faced with quite a pedagogic task.

Among friends and the large extended family, Aïcha is a cheerful, clownish little extrovert. But the minute anyone stares at her, she sticks out her tongue, or does as she recently did in a supermarket, saying to her mother, "Mama, I'm staring back!", or she withdraws into herself. Aïcha and her sister, like any siblings, can get in terrific tiffs with one another. But if Fatoumata notices that Aïcha is being insulted or hurt in any way, she is immediately protective and puts her arms around her. Aïcha is always accompanied by a small pharmacy of salves, ointments, oils and lotions (she knows all their names and what they are for), which are used depending on several factors: which part of the body, the time of day or night, the season, the weather, etc., treatment done mostly by her mother and father, sometimes her grandparents, and now also with the help of Aïcha herself and her sister.

Having a grandchild with a permanent, genetically caused health problem that will always necessitate intensive care has made so many of our former personally focussed concerns seem trivial. We have become more aware than ever of inner worth versus outward appearance. We hope that Aïcha's obvious innate stamina and her outgoing personality will pull her courageously through adolescence and into a rewarding adulthood.

Mary Staehelin, Brugg, Switzerland

The History and Biology of Parchment

Robert Fuchs

University of Applied Sciences, Cologne, Germany

Fig. 1.
Wall painting in the church of St. Georg, Reichenau, Germany.

Throughout the entire Middle Ages, parchment, alongside papyrus, was the predominant writing material in Europe, the Near and Middle East. Only with the invention of paper and the dissemination of bookmaking did this highly efficient and effective product disappear from general use.

Parchment is the dehaired, untanned skin of various animals such as calves, sheep and goats dried under tension on frames. A terminological distinction is sometimes made between vellum, made from calfskins, and parchment, from all other skins; but the words are often used interchangeably. Although parchment has largely been replaced by paper – to say nothing of the computer screen! – it still finds many uses today. As a writing material it is employed for all kinds of 'quality' documents, from wedding invitations to diplomas, from retirement scrolls to limited-edition and artist's books. The copies of acts of the British Parliament signed by the queen are on vellum, and a special white vellum called Kelmscott is used for painted botanical drawings kept at Kew Gardens and libraries in Oxford. This was first produced in 1891 by William Morris for the Kelmscott Press, the high whiteness being obtained with a coating of parchment glue and chalk. Nonliterary uses include the membranes of percussion instruments such as tambourines and drums, and translucent forms of parchment are used to make lampshades, although for this purpose the skin is also tanned with alum.

A brief history of parchment manufacture

The Ancient Egyptians employed three writing materials: rolls of tanned leather were almost exclusively reserved for architectural plans, papyrus was used for cultic documents, while for a long time, private letters and calculations were solely inscribed on 'ostraka,' sherds of pottery or limestone. The Greeks were the first to use papyrus for more everyday purposes, but it remained a relatively expensive material. The oldest surviving written texts on parchment have come down to us in the form of scrolls. The script was written mostly left to right in adjacent columns. For deeds in the Middle Ages, however, the text is commonly vertical, i.e. from the top to the bottom of the scroll in the direction that it unwinds.

The development of the *codex*, i.e. text bound in book form, from the 4th century onward gradually replaced the scrolls, until these were used almost only for deeds and similar official documents. The introduction of parchment codices, whose structure and binding resembles that of today's books, brought many advantages, not least that bound pages are simpler to handle than scrolls. It is much easier to find a section of text flipping through the pages of a codex than by unwinding a scroll that might be up to 25 m long. Furthermore, writing on both sides of a scroll is awkward and difficult, while both sides of the page can be used in a codex. Nevertheless, scrolls with writing on both sides are known and are called opisthographs (from the Greek *opistho* = behind and *graph* = written).

The production of codices benefitted greatly from the availability of parchment. Parchment is smooth, both sides can be used for writing because it is opaque, and it doesn't split when folded. Papyrus, in contrast, is much more brittle, and this tendency to break renders it almost totally unsuitable for a codex.

According to the reports of various Classical authors, parchment was 'invented' by Eumenes II of Pergamon (197–159 BC). To perpetuate his memory and fame, he wanted to establish a library in Pergamon that would rival the most famous library of the time, that in Alexandria. This required the copying of enormous numbers of scrolls and, thus, the acquisition of enormous quantities of papyrus. However, not only did the Ptolemaic ruler in Egypt have a monopoly on papyrus production, the material was in short supply as a result of wars, and so Eumenes had to search for alternatives. Contracts written on parchment from circa 258 BC are known to us from Dura-Europos, in the border region between what are today Syria and Iraq, and Eumenes seems to have returned to this earlier technology and reintroduced the production of parchment scrolls. These thin sheep's skins were also given as gifts to the Romans who called them *membrana pergamena* (Latin for 'skins from Pergamon'). Sadly, none of the scrolls from the libraries of either Alexandria or Pergamon have survived the vicissitudes of time.

The origins of a saying still current in German, "das geht auf

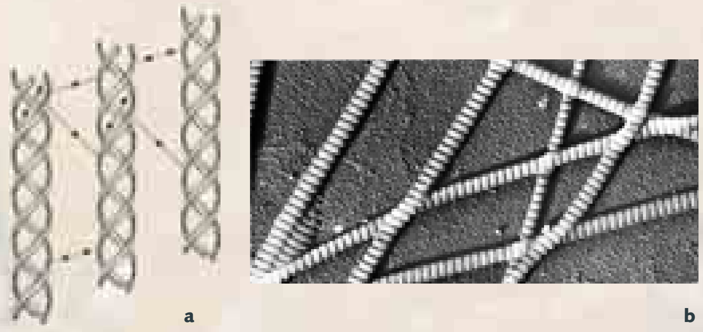


Fig. 2.
a Intermolecular bonds between the triple helices of collagen fibers. **b** Scanning electron micrograph of collagen.

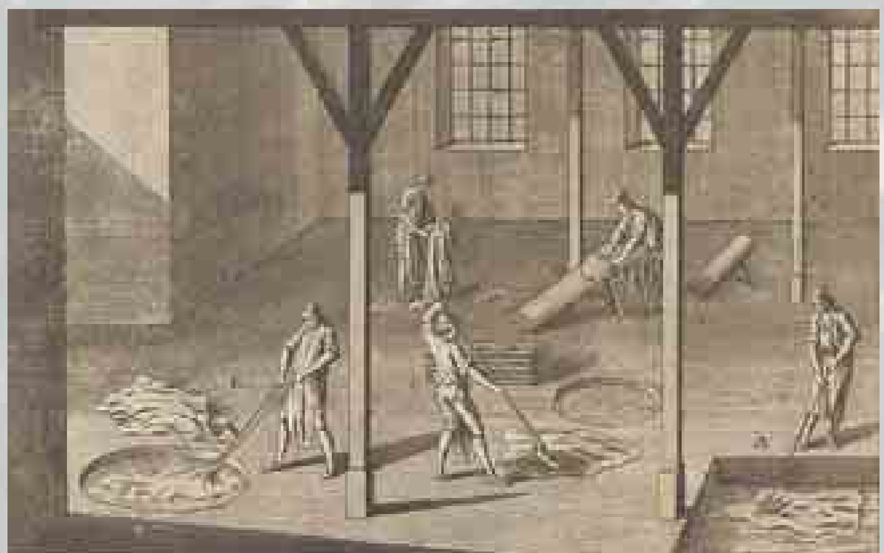


Fig. 3.
The manufacture of parchment. From J.H.G. von Justi, *Die Kunst, Pergament zu machen*, Berlin, 1763.

Fig. 4.
A skin being removed after 3 weeks from the lime bath for dehairing.

a

Fig. 5.
After liming, the hairs and fat layers are removed with a blunt blade from the skin draped over a beam.

b

Fig. 6.
Pouncing of stretched parchment with the lunelarium.
a Yesterday: Fritz Pyrmenter, 73rd brother of the Nuremberg 'Mendelschen Zwölfbrüderstiftung,' 1425.
b Today.

keine Kuhhaut" [literally, 'that won't fit on any cowhide,' in other words, 'it's absolutely beyond belief'], lie in the use of parchment from the skin of a cow or calf as a writing material. This saying is illustrated, and dramatically, in a 14th-century decoration on the north wall to the left of the pulpit in the Church of St. Georg in Oberzell on the island of Reichenau (Lake Constance) (fig. 1): four devils hold out a cowhide, three pulling at it, one biting it, with, above, the figures of two women in conversation and a hanging church lamp. Another devil has written the following text on the skin:

Ich wil hie schribvn von diesen tvmben wibvn was hie wirt plapla gvsprochvn vppigs in der wochvn was wirt all-vs wol gvdaht so es w-irt für den richtvr braht	I will write here of these silly women what is spoken here blablabla cockily during the week. All this will be considered when it is brought before the judge.

The allusion to gossiping women is directed toward the church, not the community. Being displayed on the wall near the pulpit, its role is to exhort the preacher to keep the sermon short.

The biochemical structure of parchment

The essential components of parchment from animal skins are the fibers of the connective tissue. This extracellular matrix in the skin is composed of bundles of long-chained fibrils of the scleroproteins collagen and elastin. In living skin, the intercellular spaces are filled with fluid or plasma.

The basic unit of collagen is tropocollagen (MW 300 kD), a right-handed helix of three polypeptide chains. A single tropocollagen molecule is a microfibril 280 nm long and 1.4 nm wide. Packed together by hydrogen bonds, salt bridges and covalent intermolecular bonding, these microfibrils form fibrils with a diameter of circa 250–500 nm. Adjacent intertwining molecules in the fibrils are displaced relative to one another by a quarter of their length, giving rise to a periodicity of about 70 nm visible as dark bands in the electron microscope (fig. 2).

In contrast to the relative rigidity of collagen, elastin stretches and recoils. It is assembled from tropoelastin monomers, and hydrophobic domains alternate with intramolecular cross-linking (at lysine residues) domains which confer the elasticity on the randomly coiled molecules.

The production of parchment

The preparation of parchment for writing showed very little alteration between antiquity and the Middle Ages, and indeed remained fairly unchanged right into modern times (fig. 3). Though we know little about how early parchment was produced at Dura-Europos or Pergamon, many medieval recipes have come down to us. Only with the introduction of industrialized technology and modern chemistry has the process changed significantly.

The first step involves immersing the fresh animal skin for 2–6 weeks in a 5–10% solution of slaked lime (a process called liming). The different layers of the skin swell at different rates and gradually begin to break up (fig. 4). The epidermis reacts most quickly. Because the hairs have their roots here, after the immersion process, the hairs along with the roots are easily removed by draping the skin over a beam and shaving with a dull blade (fig. 5). The skin is then reversed and the remains of fat, muscle and loose flesh are likewise removed from the flesh side. After washing, the transparent skin is stretched and dried on a frame. These physical and chemical processes orient the fibers in sheets and open up the inner structure of the collagen so that air penetrates between the layers causing the parchment to become opaque, and thus suitable for writing or decoration on both sides.

To enhance the properties of the surface for writing, both sides of the dried parchment are carefully polished so that they are neither too rough nor too smooth. Polishing (also known as pouncing) is done while the skin is still stretched on the frame, either with a crescent-moon-shaped (semilunar) knife (Latin *lunelarium*) (fig. 6), with pumice or with a specially prepared sanding bread. For the latter, bread dough is mixed with glass splinters, formed into small rolls and baked. The parchment surface can be treated far more sensitively with such sanding bread than with pumice or a knife. With inattentive use of the knife, the skin can be damaged quite quickly; pumices are not completely homogenous and contain hard stone-like nodules which leave scratches on the parchment surface. Cuts and tears that occur before the stretching procedure are usually sewn before the skin is put into the frame, so that they don't stretch or expand during drying. They can be cut out after drying, but often they are left in the parchment and can be seen today in the old manuscripts (fig. 7).

From antiquity onward, the Jewish practice was to use a fermenting flour or bran paste to prepare the fresh skin, creating a very fine high-quality product. The parchment of the Dead Sea Scrolls was apparently produced this way. The enzymes that built up during fermentation facilitated the removal of the hair. The rotting paste mass was spread directly on the skins which were piled one on top of the other and left for several hours or days. Because heat also builds up during the process of decay, the decomposition can run out of control, eating holes into the skin. The enzymes attack not only the epidermis but can also penetrate to deeper layers, and may ruin the entire skin. These drawbacks have led to the increasing replacement of fermentation by liming in the Jewish manufacture of parchment. Nevertheless, special laws of cleanliness still have to be observed in preparing parchment for Jewish writings.

a

b

Fig. 7.
a In the early Middle Ages, even parchment with holes was used for manuscripts.
b Old stitched repair in a manuscript in the Berlin Staatsarchiv.

Fig. 9.
Folchart psalter, 9th century AD (Stiftsbibliothek, St. Gallen). The purple coloring of the text columns was achieved using berry and plant juices.

In the modern manufacture of parchment, sodium sulfide and enzymes are used for dehairing. The result is a product differing significantly in durability and quality from historic parchment, which can cause problems if modern material is used in parchment restoration.

Goldbeater's skin

One rather special parchment product is goldbeater's skin, made from the appendix of calves (fig. 8a). After a short lime bath, the outer skin layer of the 40- to 80-cm-long appendix is stripped off and stretched. The result is a very thin (0.05–0.01 mm), elastic and long-lasting skin. The fibrous structure is clearly revealed in the scanning electron microscope. These thin skins were used to beat out gold leaf, hence the name. Small sheets of gold were laid between the pages of a book made of goldbeater's skin. The book was beaten with a hammer until the gold leaves had spread out to the size of the book's pages. The gold sheets were cut into four pieces which were put back into the book which was beaten again. The process was repeated until the gold leaf was a mere 0.001 mm thick (fig. 8b). The goldbeater's skins were so elastic that even under very heavy beating they did not tear, and were so thin that up to 120 sheets of gold could be beaten at one time.

Parchment manuscripts

For over 1000 years, parchment was used not only for de luxe manuscripts but also for everyday documents and texts. Because of its unique, durable structure, surviving manuscripts even from the 4th century AD can give the impression that they were written only yesterday.

Particularly valuable parchment manuscripts were produced with imperial purple coloring. However, the purple dye produced by the mollusc species *Murex brandaris* L., *M. trunculus* L. and *M. erinaceae*, and used for dyeing cloth for example, was not used. Instead, the dyes employed for painting were extracted from plant materials such as berries, lichens, roots and resins (fig. 9). The mollusc purple extract, 6,6'-dibromoindigo, could not be used on parchment because, as in indigo dyeing, the development of the color proceeds via a redox reaction. If parchment gets very wet it shrinks and has to be dried by restretching on a frame, and acidic chemicals, like those that must be used in the reduction process, keratinize and destroy the collagenous material. Instead, plant dyes such as litmus from the *Rocella* lichen, madder from *Rubia tinctorum* L. or lac dye from shellac seem to have been used as the purple coloring on old manuscripts. Berries – bilberries, elderberries and privet berries – also appear to have been a source of color. Analysis of these means of coloring is one of the active areas of research at the Laboratory for the Nondestructive Analysis of Artworks at the University of Applied Sciences, Cologne.

Fig. 8.
a Calf appendix, ca 40 cm long. **b** Thin gold sheet after beating between the pages of a book made from goldbeater's skin.

a

b

The conservation of parchment

The biochemical structure of parchment influences its response to the environment, to aging and during restoration. The collagen fibers are heat sensitive. Above 70°C, they begin to shrink irreversibly and denaturation sets in. The fibers also respond to changes in humidity by continuous shrinking and stretching. This is known as the climatic reflex because it is an automatic response which can only be prevented by keeping the parchment in a constant environment. This is one of the most important basic conditions for the preservation of painted parchment manuscripts. The pigment layers in Byzantine illustrated books, in particular, have a tendency to peel off if heat and humidity keep changing because the parchment surface was treated with size or gum arabic prior to being painted. While the ground material shrinks and stretches, the paint layers cannot; a tension develops between them and the paint layers steadily peel from their base (fig. 10). Originally, the parchment was sometimes coated with a medium to improve the adhesion of the paints. In the long-term, though, this can also have disastrous consequences, threatening the total destruction of the entire manuscript. To preserve such documents, they have to be completely protected from all climatic variations, whether in storage, in the reading room, in exhibitions or during transport.

High humidity or water are hostile to all parchments: they encourage molds or cause the parchment to become transparent and to decompose. In high heat, parchment shrinks to an unredeemable lump. Thus, one of the major tasks of archives and libraries is to protect parchment documents and manuscripts from heat and water – a major undertaking in the event of floods and fire! The threats posed by water and heat also have to be taken into account during any restoration procedure.

To ensure that any piece of parchment will not wrinkle after it has been glued or repaired, it is important to know exactly how the parchment will respond to the adhesive. Research has shown that isinglass, a gelatin obtained from the air bladders of the sturgeon (*Acipenser sturi* L.), is one of the most suitable adhesives for parchment. The sturgeon uses the air bladder to regulate its depth position in the water: filled with air, the fish rises to the surface; emptied, the fish descends. The bladder, therefore, needs to be highly elastic, and is in fact comprised predominantly of collagen fibers with a high proportion of elastin. While an animal skin will contain anything from 2 to 5% elastin depending on age, the sturgeon's air bladder can contain up to 20% elastin. Hence the bladder's special elasticity which can be put to good use if extracted and prepared correctly. The glue is used today not only to repair parchment but also in furniture restoration, because no other modern artificial resin can achieve such elasticity at the adhesion site. Preparing the glue, the bladder must not be heated above 42°C. It is soaked overnight in water and the following morning, slowly melted at 40°C. The resultant glue is fluid only when warm and gelatinizes at room temperature. Addition of a small amount of tragacanth, the water-soluble gum resin from *Astragalus tragacantha* L., improves the distribution of the proteins in the glue, forestalling its premature gelatinization such that it can also be used at room temperature.

Another problem encountered in parchment restoration are folds and wrinkles, which may be centuries old in some documents. Creases can be eased out with the careful use of moisture, but if they have existed for a long time, the structural changes will be imprinted in the inner collagen structure, and will tend to reassert themselves again over time. In such cases, the sheets of parchment must be weighted down for more than 2 months so that the new form is imprinted in the fibers and persists.

Collagen also has a 'memory' for environmental air pollutants. Traces of the bombing of Dresden with phosphorus bombs during World War II can be detected in the parchments kept in the Sächsische Landesbibliothek in Dresden, along with evidence for the sulfur dioxide emitted from the burning of lignite in factories and houses in East Germany in the ensuing 40 years.

Parchment is a material of outstanding stability that can survive for many centuries; archived correctly it can theoretically be preserved, in an unchanging state, indefinitely. Nevertheless, it has certain innate properties requiring of the restorer special knowledge, skills and 'a feeling for the skin' (fig. 11).

Fig. 10.
Because the parchment surface of this Byzantine manuscript was sized before painting, the paint is peeling away. Further degradation can only be prevented by storing the parchment in a controlled environment.

Fig. 11.
The parchment maker and his client. 1255 Hamburg Bible (Royal Library, Copenhagen).

Further reading

Robert Fuchs: Pergament: Geschichte, Material, Konservierung, Restaurierung. Kölner Beiträge zur Restaurierung und Konservierung von Kunst- und Kulturgut, vol 12. Munich, 2001.

Robert Fuchs: Old restorations and repairs in manuscripts. In: Care and Conservation of Books, Copenhagen, 2002, pp 224–241.

Robert Fuchs: Umweltfraß in Innenräumen – Schäden in Bibliotheken durch anthropogen erzeugte Gase aus Braunkohleabbrand und Tierhaltung: In: Preprints zur Tagung der Arbeitsgruppe Archäometrie, Dresden, 29 March–1 April 2000.

Robert Fuchs: New consolidation techniques for fixing brittle paint layers in mediaeval book illuminations. Consolidation of brittle book illumination – development of a micro-dosage device for fixing brittle paint layers. In: Care and Conservation 4, Copenhagen 1999, pp 140–159, plates XXI–XXVI.

Peter Rück (ed): Pergament, Geschichte, Struktur, Restaurierung, Herstellung. Historische Hilfswissenschaften, vol 2, Sigmaringen, 1991.

Mary Dempsey: Hide, Skin and Leather Defects: A Guide to their Microscopy. Palmerston North, New Zealand, 1984.

H. Saxl: An Investigation of Qualities: The Methods of Manufacture and the Preservation of Historic Parchment and Vellum with a View to Identifying the Animal Species Used. MSc thesis, Department of Leather Industries, University of Leeds, December 1954.

About the author

Robert Fuchs obtained his PhD in chemistry at the University of Tübingen, with Egyptology as a subsidiary subject. From 1984 to 1989 he was scientific coordinator of the 'Forschungsstelle für Technik mittelalterlicher Buchmalerei' at the University of Göttingen. Since 1989, he has held a chair for the Restoration and Conservation of Archives, Graphics and Book Illumination at the University of Applied Sciences, Cologne. He is also Head of the Laboratory for the Nondestructive Analysis of Works of Art in the North-Rhine-Westfalia Research Center for Restoration and Cultural Heritage, and since 2003 has been President of the Group of Archeometry in the German Society of Chemists.

Karger Gazette

Don't miss the next issue!

The Karger Gazette appears once a year and highlights a specially selected topic in biomedicine. S. Karger is pleased to continue to provide the biomedical community with an annual free issue of the Karger Gazette – informative and enjoyable reading in an attractive format.

For your free subscription please write to:
S. Karger AG, P.O. Box
CH–4009 Basel, Switzerland
Fax +41 61 306 12 34
Email: gazette@karger.ch

Published by S. Karger AG, Basel
Edited by Dagmar Horn and Anne Blonstein
Design by Erich Gschwind

Printed on recycled paper

Cover photo and background photo page 10–12 by Volker Dietze and Elisabeth Ajtay

The Karger Gazette is also available online:
www.karger.com/gazette