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EDF White Book

Skin diseases in Europe

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This work was a joint enterprise bringing together many European dermatologists, chosen to obtain a broad representation from across Europe and according to their expertise. Although the content of the "White Book" was primarily intended for non-dermatologists it is felt that it will also prove valuable to all our colleagues.

In this second part, the EDF presents two further chapters from "**The many faces of dermatology**" – "**Environmental hazards and the skin**" and "**Occupational skin diseases".**

Environmental hazards and the skin

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Introduction

The skin plays many roles important for life. One of the most vital is its barrier function between a constant internal milieu and the potentially hostile outside environment. Many other major professional groups, including toxicologists, internists, environmental scientists, pharmacologists, oncologists and microbiologists have joined with dermatologists to study this interplay.

The major impetus to study various environmental effects has been the dramatic rise in incidence in disorders resulting from interaction between the environment and the skin. Skin cancers, various forms of dermatitis and exotic infections are forcing their attention on physicians. This has generated a general concern particularly in Europe. Alterations in the earth's atmosphere and in the range and nature of chemical substances and microorganisms that contact human skin appear responsible. Most of these alterations are man-made and in part due to changed changing social and economic patterns.

Two major types of threats to the skin can be distinguished. Physical damage includes trauma and electromagnetic radiation including ultraviolet light. The other category includes chemical insults by exogenous compounds called xenobiotics. The uppermost part of the skin – the stratum corneum – is the main barrier against xenobiotics. Dermatologists have long studied the barrier function of the stratum corneum.

Skin barrier structure and function

Forming the interface with a desiccating external environment, the stratum corneum retards evaporative water loss from the internal milieu of the body. The stratum corneum also protects against mechanical insults and the ingress of xenobiotics and microorganisms. It also provides the first line of defense against ultraviolet light, screening out most ultraviolet B irradiation. The stratum corneum is about 10 μm thick and consists of flattened, dead keratinocytes, called corneocytes, each of them surrounded by lipid layers. It has been likened to a brick wall, with its cells as bricks and the lipids as mortar. The stratum corneum is critical for maintaining the water balance. When it is completely removed, there is free evaporation, identical to that from an open water surface, while under normal circumstances the skin barrier only allows a limited, controlled evaporation. The rate of evaporation from the skin, commonly termed trans-epidermal water loss (TEWL), is a sensitive indicator of the skin barrier function, which can be measured in a non-invasive, objective and standardized way.

The intercellular lipids, rather than the cells, play the crucial rule in the water-retaining function of the skin barrier. Selectively removing only the lipids from the stratum corneum leads to free evaporation. The composition of the barrier lipids is unique and quite different from the lipid composition found in membranes elsewhere in the body. Three main types of fatty substances (cholesterol, ceramides and free fatty acids) make up 90% of the total amount of barrier lipids. These lipids are produced in lamellar bodies, small intracellular organelles within keratinocytes, which discharge their contents into the intercellular spaces to establish the barrier. Skin barrier problems are a feature of many common skin disorders and may actually be the

critical stimulus initiating the inflammatory response. Damage to the skin barrier in itself results in release of pro-inflammatory cytokines, but as the damage also leads to increased penetration of allergens and irritants, a deficient skin barrier also sustains an ongoing inflammatory process. Consequently, skin barrier problems are a critical factor in many kinds of dermatitis.

The skin barrier is continuously maintained through homeostatic processes. Everyday wear-and-tear, such as frequent washing of hands, and wet work may damage the barrier. The resulting increase in TEWL stimulates the skin to initiate barrier repair, which consists of release of the lipid content of preformed lamellar bodies and acceleration of the lipid synthesis. The result is a gradual normalization of TEWL, provided there are not problems with the synthesis of the lipids. If the necessary lipids cannot be synthesized, TEWL remains continuously elevated, and the result is chronic dry skin. This can be due either to an inborn defect in the synthesis of one or more of the crucial lipids, a dietary disturbance or even a temporary phenomenon, such as the typical dry skin during winter.

There are two main types of cutaneous reactions to environmental challenges. Both can appear clinically similar. Irritant contact dermatitis (ICD) results from direct damage to the skin caused by exogenous agents. Every person who encounters a toxic substance in a high enough concentration experiences some damage. Examples from daily life might include harsh soaps, acid added to swimming pools or many industrial exposures. In contrast, allergic contact dermatitis (ACD) only involves a limited number of individuals, is not concentration-dependent, and requires a period of sensitization.

Every day the skin is exposed to hundreds of xenobiotics. These include both naturally- occurring and synthetic substances in the environment, workplace and home. Skin exposure to xenobiotics may be accidental or deliberate, but in most cases, normal everyday skin exposures do not present a toxicological risk. Some chemicals are local irritants, while others are more often allergens. Some substances elicit first an irritant dermatitis and then later an allergic form.

Irritant contact dermatitis. Two different pathways may be involved in ICD. Acute ICD is characterized by an inflammatory reaction that mimics the typical expression of ACD, and is associated with the release of inflammatory mediators and cytokines. Chronic ICD is characterized by disturbed barrier function, associated with increased epidermal turnover leading clinically to lichenification (thickening of the epidermis). Irritation normally starts at the level of the stratum corneum and later involves the dermis, whereas the inflammation of sensitization starts in the dermis.

The variations in the skin reactions are dependent on the degree of injury induced, as well as on the effect of an irritant substance on different cell populations. The physicochemical characteristics, the concentration, volume and contact time of the irritant influence the skin response. Furthermore, inter-individual differences exist based on age, gender, skin typology, previous skin disease and a range of genetic factors. In a given individual, reactivity differs according to the skin thickness and body region. Subjects suffering from atopic dermatitis, seborrheic dermatitis, or with sensitive skin are reported to be more susceptible to irritants. Testing for skin irritation can be helpful in monitoring these conditions and identifying patients at risk for irritant contact dermatitis and/or with sensitive skin.

Allergic contact dermatitis. ACD is a form of delayed Type IV T-cell-mediated hypersensitivity. This condition follows skin contact with small allergens that penetrate into the skin. The skin response is a two-step reaction. The first or sensitization phase occurs when the body generates a circulating population of antigen-specific memory T cells following exposure to a substance. The second or elicitation phase occurs 48-72 hours after subsequent re-exposure to the same substance, but only in sensitized individuals. Elicitation involves cellular infiltration into the epidermis that results into a cutaneous inflammatory reaction characterized by erythema, edema and vesiculation.

Occupational contact dermatitis. Both ICD and ACD combine to account for 90% of occupational dermatoses. Occupational contact dermatitis is the most prevalent of all occupational diseases in many countries. In western Europe, occupational contact dermatitis represents about one-third of all registered occupational diseases.

Surfactants and the consumer. Surfactants are potentially irritant agents that each of us encounters daily. Because of their detergent and foaming properties, surfactants find broad use in many domestic products (cosmetics and toiletries, cleansing products, laundry products). Many surfactants are classified, according to the Dangerous Substance Directive (DSD), as irritant for the skin and for the eyes [53]. It is not always clear why ingredients identified as "irritants" are incorporated into consumer products. Such a classification of surfactants is based on the hazards linked to the individual substances (intrinsic irritation properties), and does not take into account the interaction between the ingredients of the product. The rules about informing consumers about potential risks of irritation differ with the product type, with substantial differences between cosmetics as compared to household cleansers and detergents.

Different solutions exist to develop non-irritating surfactant-based products. Careful selection of the mildest surfactants is important. Combination of several adequate surfactants may also be effective. Nonionic surfactants are generally considered as the mildest, even if several of them are classified as skin or eye irritant by the DSD, and are usual ingredients in body cleansing products for babies, for sensitive skin or for face-cleansing products. They are also the usual ingredients in dishwashing liquids for sensitive skin or in all-purpose cleaners for hard surfaces.

Several anionic surfactants are also well-tolerated by the skin. They are also regularly used in facial cleansers or products for baby care. These very mild anionic surfactants are rarely used in household cleansers, as they clean poorly. Amphoteric surfactants are never used alone, but rather in combination, and they play no role in determining the irritation potential of the finished product. Cationic surfactants are usually used for their antibacterial properties rather than their surface tension properties. While some are quite irritating, there are others which are mild and well-tolerated.

The best way to reduce the irritant effects of surfactants is to combine several different agents with varying properties. Thus the consumer should not be dismayed by long lists of surfactants on package labels. Other additives are possible, but usually less desirable, because of factors such as increased costs or reduced consumer acceptance.

Consumers and cosmetic products. The European Cosmetic Directive (76/768/EEC) [54] states that the manufacturer or the person responsible of marketing of a cosmetic product must keep readily accessible to the competent authorities, for control purposes, the information concerning the assessment of the safety for human health of the said finished product. Existing data, if any, on undesirable effects on human health resulting from use of the cosmetic products must also be accessible to the authority. This means that the information regarding the safety of the product exists but is not directly accessible to the consumer. Nevertheless, many cosmetic products make label claims of mildness, skin compatibility or similar virtues; these must be scientifically proven. With the seventh amendment of the Cosmetic Directive [51], the situation in Europe will change. After 11 September 2004, product information will have to be readily accessible to the public, but it will not have to be present on the label.

Consumers and household cleansers. Whenever a household cleanser or laundry detergent is a potential skin irritant, the consumer should be informed on the product label about such a health hazard. This is done by printing a Saint –Andrew cross, and a "R-38 skin irritant" symbol on the label or package. The Dangerous Preparation Directive (DPD, 1999/45/EC) [52] indicates which products must carry such warnings and defines two basic procedures for assessing health hazard, and in this case skin irritation hazard:

1) Conventional calculation method which states that if 20% or more of ingredients of a finished product are classified as skin irritants, the product should be classified as "skin irritant.";

2) Toxicological determination of the skin irritation properties of the product by testing.

In addition the DPD requires that if data on humans are available (*e.g.* epidemiological surveys, Poison Center data, human studies), they should be taken into account for the classification, especially if the data are different from those generated by one of the two former methods. This requirement is especially important since toxicological studies on animals are out of favor and do not always reflect the skin responsiveness in man. In addition, the calculation method sums all classified ingredients without taking into account interactions between surfactants which reduces their irritation potential. The calculation rule often leads to an over-labeling of finished products as skin irritants.

The absence of the warning label on the product does not exclude the possibility that some transitory discomfort may occur in consumers with sensitive skin or after repetitive use. Products that are not "skin irritants" may also display different levels of mildness. Well- substantiated skin compatibility claims and personal experience should allow consumers to choose the most appropriate products.

Skin and toxic hazards

The percutaneous resorption of xenobiotics results from the transfer of a chemical from the environment to the blood. Understanding intoxication following skin contamination calls for knowledge of the modalities of resorption and diffusion of xenobiotics through the skin. The ingress of xenobiotics through the stratum corneum is a passive diffusion process. Two main routes of penetration can be followed. One way follows the cutaneous appendages including the hair follicles and the sweat glands. The other way is transepidermal penetration, either through the hydrophilic corneocytes or the lipophilic intercellular layers. Once below the stratum corneum barrier, any toxic compound finds its way through the living epidermis and in the dermis where it is resorbed by blood and lymph. The same process occurs with any kind of topically applied drug.

The percutaneous resorption varies according to a series of parameters depending upon the size and the physicochemical properties of the xenobiotic. It also depends on the quality of skin. Regional differences in absorption are recognized over the body. The integrity and degree of hydration of the stratum corneum are also of importance. The coefficient of partition of the compound between its vehicle, if any, and the stratum corneum, as well as the time contact of the compound with the skin play additional roles in the whole complex process.

In many skin disorders, the barrier function is compromised. This is particularly important to consider in babies who have an unfavorable ratio between the potential skin area of resorption and the body volume. Higher body concentrations of toxic xenobiotics can accumulate in infants. Another example of higher risk is encountered in some occupational settings where mild abrasions of the skin are common and occupational dermatoses are prevalent. Manipulation of toxic compounds is more risky in these conditions if adequate protection is not maintained.

Conclusion

In many circumstances, environmental xenobiotics pose a threat to the skin and thus to the individual. While the stratum corneum barrier function usually offers a high degree of protection, it can be breached by both physical and chemical damage. The consequences for workers and consumers can be considerable, so that both continuing research and a refined regulatory approach are needed to minimize the social and economic effects of a disturbed interaction between the skin and the environment.