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# WHITEPAPER:

## The human skin – more than just a shell

It is the largest, heaviest and also one of the most versatile human organs[1] .
The skin works at all times, breathes, regulates body heat and is a constant protective shield. Our skin reacts sensitively to psychological stimuli and emotions; it feels and senses extremely efficiently. With the help of UVB rays, it forms vitamin D3, stores fat and water.
In fact, our skin is much more than a simple barrier against the outside world; it is nowadays considered one of the most important immunological organs, interacting with the individual components of the skin and its microorganisms, which form a protective symbiosis with us.

### As a holobiont you are never alone

Without microorganisms on and in us, we would be quite lost; indeed, we would not be viable.
Our largest organ is colonized by a diverse milieu of microbes, most of which are harmless and even beneficial to their host[2] . Together with the skin, these microorganisms form a congenial defence system to protect our body. Unfortunately, nowadays we still have a hostile or often just an ignorant attitude towards bacteria, yeasts, mites, viruses or archaea on our skin.
The fact is, however, that skin diseases such as neurodermatitis, psoriasis, rosacea or acne are associated with a disturbed balance, i.e. an imbalance of populations or an altered diversity of microbial communities and consequently also with a higher proportion of pathogenic microorganisms.

The innate and adaptive immune responses of the skin modulate the skin ecosystem. Conversely, the microbiota also has an enormous influence on the immune system[3] .
Thus, the more cosmetic products we use, the greater the likelihood that it will react irritably with redness, dermatoses or allergies. An average woman who uses skincare products and make-up every day quickly comes up with several hundred different ingredients.
Extensive over-hygiene in modern times also damages symbiotic microorganisms of the skin in the long term and deprives them of nutrients they actually need to survive by continuously removing oils, sebum and sweat. Inflammation or itchy, dry, scaly skin are usually the result of the damaged microbiome and skin barrier with accompanying transdermal water loss.

### Human skin in numbers

Average body surface area for men 1.9 $m^2$ and for women 1.6 $m^2$
(Formula according to Dubois for calculation for cytostatics, or for burns)

Body surface with all skin appendages such as hair, nails and sweat or sebaceous glands:
20 $m^2$

Weight: 3 - 5 kg, with subcutaneous fat up to 20 kg
Skin cells: 60 billion cells per $m^2$ , i.e. a total of approx. 110 billion cells
Thickness: 0.3 - 4.0 mm, depending on the body region such as eyes or soles of feet

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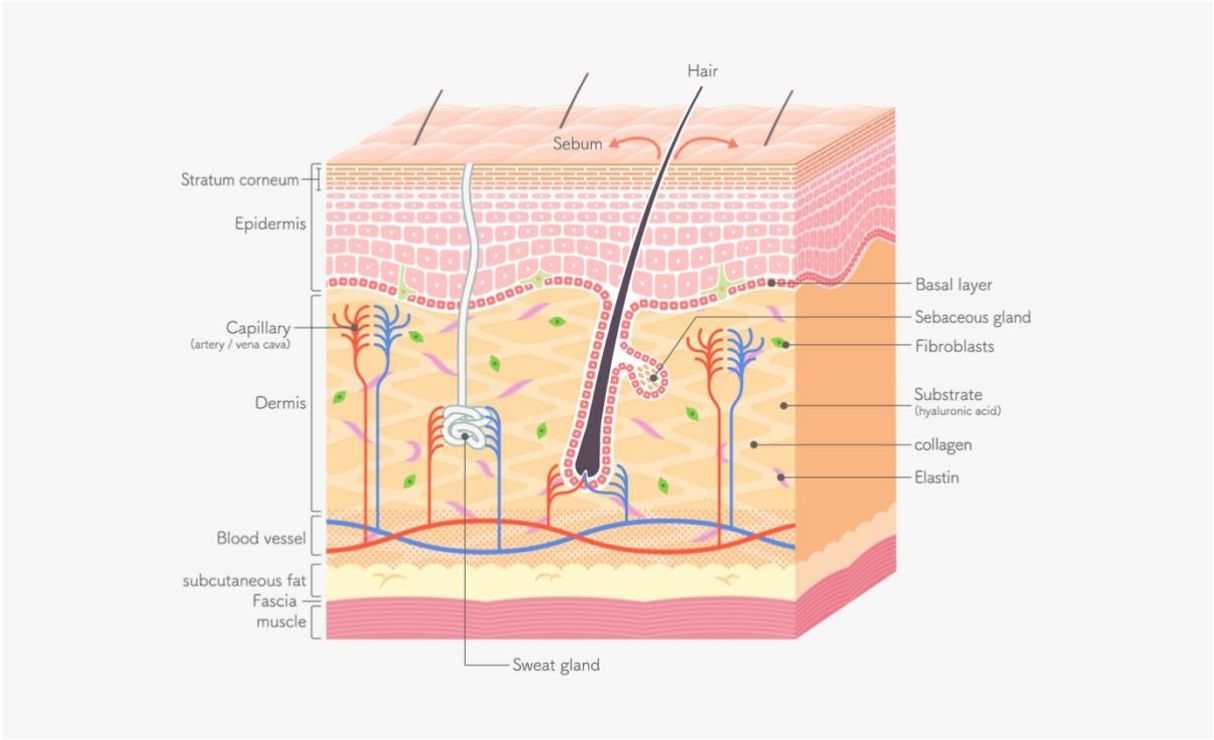
The skin consists of three layers: **Epidermis, dermis** and **subcutis**.

On the very outside is the epidermis, which consists of a total of five layers, such as the horny layer, the prickle cell layer and the basal cell layer with the pigment-forming cells. New cells are constantly formed and old ones are shed, so that the epidermis regenerates itself approximately every 28 days.

The somewhat thicker dermis or corium (dermis) adjoins the epidermis. Blood and lymph vessels, hair follicles, nerve endings and sweat, scent and sebaceous glands are located here. It consists of a fibrous network containing mainly collagen and elastin. The subcutis (lower skin) with fat layer, blood vessels and nerves is the link between muscles and skin.

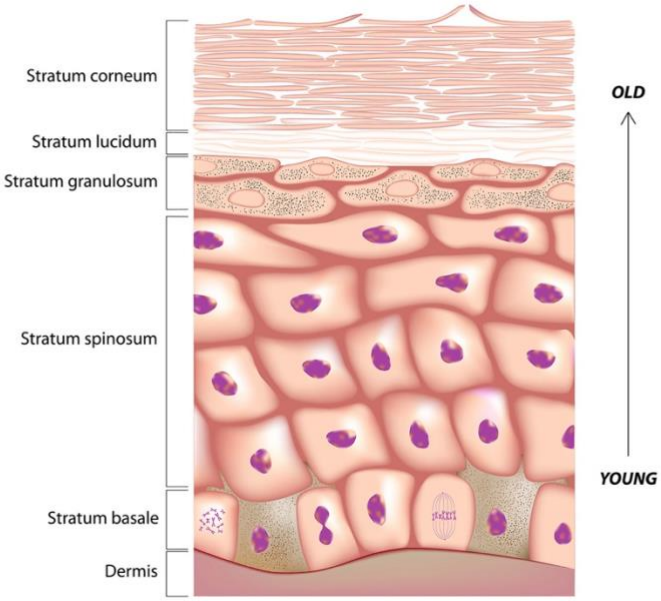



Picture: © stock.adobe.com

**Epidermis** as the outermost layer of skin – Physical barrier with multiple tasks

- constant renewal of the outermost cells-
prevents the penetration of foreign microorganisms
- prevents the penetration of toxins-
regulates the water balance-
prevents loss of nutrients- prevents
UV damage

## Five layers of the epidermis

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**Stratum corneum** (horny cell layer): Its uppermost layer is the **stratum disjunctum**. Cell clusters dissolve here and horny scales, the so-called squamae, fall off.

**Stratum lucidum** (shiny layer): This thin layer houses transitional stages of corneocytes and keratinocytes whose keratinization is not yet completely finished. The cells are filled with eleidin, a transitional product of keratohyalin and keratin. This layer exists mainly on highly keratinized areas of the skin.

**Stratum granulosum** (granule cell layer): During the transformation of keratinocytes into corneocytes, there is an increased accumulation of granules of keratohyalin on the one hand and the loss of other cell organelles on the other.

**Stratum spinosum** (prickle cell layer): This is where the keratinization process of the keratinocytes begins. In addition, **Langerhans cells,** i.e. cells of our lymphatic defense system, are located in this area.

**Stratum basale** (basal cell layer): The lowest layer of the epidermis consists of only one layer of adult stem cells and is connected to the basement membrane. Mature keratinocytes form from these cells and migrate to the skin surface within a few weeks. Melanocytes also produce the pigment melanin here, which is stored in horny cells of the skin and hair.

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The **stratum corneum**, also called the horny layer or horny cell layer, is the uppermost layer of the **epidermis** and, depending on the area of the body, it consists of 15 to 200 cell layers.
Completely keratinized corneocytes (horny cells) are dead keratinocytes. Filled with the supporting protein keratin, they no longer have any cell organelles and form a water-repellent, wafer-thin protective film with intercellular lipids. These hydrophobic lipids consist of three main fractions, namely ceramides (30%), with a unique and very complex sphingolipid group, free fatty acids (30%), as well as cholesterol and its derivatives (30%).

## Hydrolipid mantle

Further components of the **Natural Moisturizing Factor (NMF)** combine with the epidermal protective layer of corneocytes with lamellar lipids to form an acid protection or hydrolipid mantle[4] .
These are hydrophilic amino acids and peptides, among others from the degradation of the structure-forming epidermis protein **filaggrin.** Furthermore, pyrrolidone carboxylic acids (PCA), lactate, urea and the neutral carbohydrate fraction such as glucose, fructose or lactose also belong to the NMF.

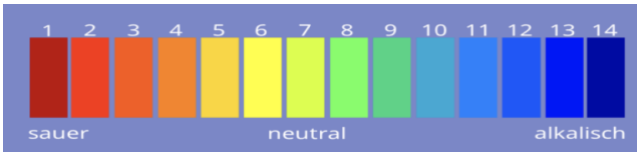
Until now, the **structure of the stratum corneum** was often illustrated with the **brick-and-mortar model**, i.e. regularly arranged layers of dead corneocytes with lipids in between.
However, it is now known that its stability and protective function is actually based on the following factors:

- Corneocytes and their hook-like structures
- Transmembrane proteins, the so-called corneodesmosomes
- Bilayers, i.e. bilayer structures of long-chain lipids
- Tight junctions, i.e. inter-cell contacts

For years, the **transport and penetration pathways of** active substances through the stratum corneum have been the subject of research. Currently, three penetration pathways are postulated: It is assumed that a hydrophilic and an intercellular, lipophilic pathway are very possible. However, a pathway through the cells, i.e. transcellular, is considered unlikely, as the substances would have to penetrate or diffuse alternately through lipophilic and hydrophilic layers[5,6] .

### pH (lat. potentia hydrogenii)

The pH value is the negative decadic logarithm of the hydrogen ion concentration of an **aqueous solution** and is considered a measure of its acidic or alkaline character.
The pH value is on a scale between 0 and 14, with a value < 7 being acidic, 7 being neutral and > 7 being alkaline.



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## pH value of the skin

The skin with the uppermost epidermal layers generally has a slightly acidic pH value. On average, depending on the skin area, it is between 4.1 and 5.8[7] , whereby the armpit, as well as the outer genital and anal areas, represent a physiological gap in the acid mantle due to an increased number of apocrine sweat glands and have a somewhat higher pH value of approximately 6.5. The mucous membranes of the vagina, on the other hand, have an acid pH of 3.5 to 4.5 in a healthy state due to the acid production of commensal lactobacilli.
Slight changes in the pH value of the skin are actually tolerated by our skin inhabitants without any major impairment of their growth[8] , however, they often require a pH optimum of 5[9] for the enzymatic production of antimicrobial fatty acids or small molecules, i.e. certain low-molecular compounds.

# Skin microbiome

The main tasks of the skin microbiome are thus to protect and strengthen the skin barrier against pathogenic microorganisms and to maintain the appropriate pH value of the skin surface.
**Resident** microorganisms are part of the physiology of our skin. They exist in the stratum corneum of the epidermis and the corresponding ducts and openings of hair follicles or sebaceous and sweat glands. **Transient** bacteria, on the other hand, are only found temporarily on the skin. Due to their so-called **colonization resistance,** resident microbes already initially prevent the colonization of potentially harmful or foreign microbes. With their metabolic products, they ensure the balance of the populations and prevent the growth of pathogenic invaders.
Our skin with all its appendages is the habitat for about 1000 different species of bacteria and about 80 genera of fungi. In total, it is estimated that there are about 10 billion ($10^{10}$ ) microorganisms on our skin.

Per $cm^2$ of skin, there are up to 2 x $10^6$ in the armpit or on the scalp, $10^3$ on the hand, $10^5$ on the forehead, $10^2$ on the back and up to $10^3$ on the soles of the feet.

### Individuality of the skin microbiome

Nevertheless, the composition of the skin microbiome is so unique for each person that one speaks of the "microbial fingerprint". It is shaped inter-individually by the type of birth, genetics, lifestyle, gender and also by age or ethnicity.

Ideally, however, microbial communities of the skin of a healthy adult are relatively stable over certain periods of time[10]. However, in post-pubertal adolescents, the relative abundance of certain bacterial genera restructures in favor of lipophilic representatives such as *Cuti* (formerly *Propioni*) and *Corynebacteria* or yeasts of the genus *Malassezia* due to hormonal changes[11].

Babies, whose microbiome only stabilizes in the first three years of life, and ageing or senescent people with an altered skin condition and the associated change in microbiota are particularly vulnerable in this context.

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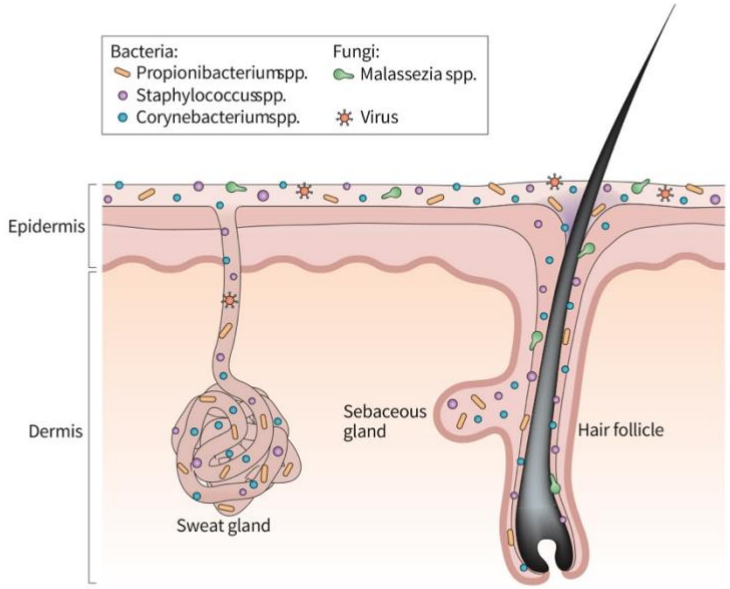
Despite these enormous differences, however, our skin microbiome is largely dominated only by the four bacterial phyla *Actinobacteria*, *Proteobacteria*, *Bacteriodetes* and *Firmicutes.* And of these, mainly the three genera - *Staphylococcus ssp*. , *Corynebacterium ssp*. and *Cutibacterium* (formerly *Propionibacterium*) *ssp*. - account for over 60 % of existing bacteria[12] .




Picture: © Byrd

## Different microclimates of the skin

The arrangement of the microbiota of the different body regions of an individual person also shows such a high variability that this can actually be compared to different climate zones of the earth. Bacteria are extremely flexible, however, and so they adapt to these topographical features of the skin, such as hair follicles, sweat or fat glands in the depths of the dermis, but also on its surface in folds and crevices, in a very specialized way.
These regional differences, divided into **seborrheic**, **moist** or **dry** zones, are determined, as already mentioned, by the physical or chemical characteristics of the skin surface.
Intertriginous areas such as the armpits, intimate area, interdigital spaces between fingers and toes, but also the crook of the arm or groin provide a moist, somewhat nutrient-rich environment, ideal for the growth of staphylococci; the forehead and scalp, nose or nasolabial fold provide a seborrheic microclimate for lipophilic microorganisms, such as *Cuti* - and *Corynebacteria* or *Malassezia yeasts.* Dry areas such as the inner forearm or thigh are usually the habitat of *Streptococci* and *Staphylococci*.

## Survival artists

Our microorganisms therefore inhabit the most diverse areas of our skin, but in contrast to the intestine, it actually offers only extremely inhospitable living conditions. It is acidic, dehydrated, covered with salty sweat and rich in antibacterial molecules such as free fatty acids, sphingosine, $NO_2$, immunoglobulins and antimicrobial peptides (AMPs), and it is not particularly warm[13].

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Nevertheless, they use all the resources available to survive and even thrive. They metabolize amino acids and lipids from the sebum or stratum corneum, as well as urea and ammonia from sweat as nitrogen sources, and glucose or vitamins. Many genera are also halotolerant, which means that the high salt content of the sweat does not bother them much.

## Battle of the "giants"

***Staphylococcus epidermidis*** is the most widespread opportunistic skin strain and a potent contender against the naturally occurring pathogenic ***Staphylococcus aureus***, which is involved in many diseases, such as **atopic dermatitis,** where it colonizes the skin in unnaturally high bacterial numbers and damages it.
With other representatives of coagulase-negative *Staphylococci*, *S. epidermidis* produces proteins that interact with human immune cells, thus selectively killing infectious germs, or can also relieve inflammation after injuries. A special strain of *S. epidermidis* also has the ability to produce 6-N-hydroxyaminopurine (6-HAP), a metabolic product that has the ability to prevent skin cancer tumor cells from growing - without affecting healthy cells[14] .

***Cutibacterium acnes*** is the best known member of the genus of gram-positive anaerobic *Propionibacteria*, which usually tend to colonize hair follicles where oxygen levels are low. *C. acnes* is also actually able to keep *S. aureus in* check[15] , but at the same time some strains of this genus (phylotype IA1)[16] are involved in the development of acne lesions. They produce large amounts of virulence factors such as light-sensitive porphyrins[17] or hyaluronate lyases, which are mediators of inflammatory reactions of the skin. The fact is, however, that these are not just bad guys: the homeostasis that is important for skin health depends on a distinct diversity of *C. acnes* strains, whose possible predominance is regulated at any time by other competitors, such as *S. epidermidis.*

The *Lactobacilli* of the vagina also use a variety of weapons against unwelcome invaders. ***Lactobacillus crispatus*** and other champions of this genus produce antimicrobial substances such as $H_2O_2$ and bacteriocins in the vagina on the one hand, and on the other hand they keep harmful germs such as ***Gardnerella vaginalis***, ***Neisseria gonorrhoeae*** or ***Candida albicans*** in check by regulating the pH value through the production of lactate[18] .

## Conclusion

The interaction of our immune system with the microorganisms residing in the skin is extremely close and finely balanced. There is sophisticated, effective communication between the skin's microbiota, epithelial cells and our innate and acquired immune system to eliminate potential pathogens and protect us from harmful, chemical and physical environmental signals.

Increasingly advanced findings in microbiome research in recent years have consequently also led to a paradigm shift among manufacturers and consumers of body care products and cosmetics, as an **intact, balanced, diverse microbiome of** the skin is immensely important for the health and thus ultimately also for the beauty of our largest organ.

[1] https://www.krebsgesellschaft.de/onko-internetportal/basis-informationen-krebs/krebsarten/hautkrebs/der-aufbau-der-haut.html
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