

Chapter 5

The Evolution of Human Skin and the Thousands of Species It Sustains, with Ten Hypothesis of Relevance to Doctors

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Abstract The entire skin is covered in microscopic life. The composition of this life—which species are present—has great importance for many aspects of dermatology. Little about this composition makes sense, except in light of evolution.

Keywords Armpits • Bacteria • Belly buttons • Genitals • Wafting

Our skin is what we most immediately perceive of each other. It is the largest human organ [1, 2] and the one through which our bodies meet the world and all of its delights and assaults. It is also, to an extraordinary extent, misunderstood. Here I discuss the key moments in our evolutionary history that are likely to have shaped our skin relative to that of other primates and mammals. I then offer a half dozen hypothesis as to the adaptive role of our skin and the species that live on. In each case, considering our skin in light of evolution and ecology fundamentally alters (or, in the more speculative cases, has the potential to alter) our understanding of its problems and their treatment.

The Ancient History of the Skin

The surface of the body is an ancient feature of all animals. In all animals it serves to protect the body. In a small subset of animals this protection is due primarily to the physical and chemical features of the surface itself. In termites, for example, the

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termite integument has evolved a smooth, surface that makes it easy for the termites to groom off pathogens. If one puts an individual fungal spore on the body of a termite, that termite's brothers and sisters will groom the spore off, ingesting it and, in doing so, preventing it from making its way into the bodies of its kin. The termite's integument evolved in such a way as to make it easy for termites to keep their outer surfaces sterile (their inner surfaces, on the other hand, abound with microbes on which they depend. Most medicine has proceeded, across the last hundred years, as though something similar is true for humans and other vertebrates, as though the skins of vertebrates, like the exoskeletons of termites, were sterile but for the occasional arrival of a pathogen. This is not the case.

In many, perhaps most, animals, including all mammal and bird species studied to date, the outer layer of the body is more complex. In such species, it is impossible to prevent organisms from colonizing the body and so animals have instead evolved outer coverings and glands that help to favor beneficial organisms by producing the habitats and food they prefer and disfavor problematic organisms through the production of selective antimicrobial compounds [3]. In such species (including humans) the outer surface is not smooth and sterile but instead colonized by a dense layer of microbes, microbes actively fed and specifically housed by the body. The microbes on the human body are a great extent predictable as a function of the biology of the skin and its glands [4–6], and hence best viewed as an ecosystem engineered by the skin (and genes) and, hence, an ecosystem under the influence of natural selection.¹ In healthy individuals this ecosystem includes hundreds, if not thousands, of kinds of bacteria,² viruses that attack those bacteria, archaea, protists and even animals such as mites.

The beneficial microbes living on the skin have can play multiple roles.³ They are the first line of defense against pathogens [7, 8]. Most pathogens never encounter

¹We tend to think of beavers as ecosystem engineers in as much as their behaviors, which are encoded by their genes, lead them to build dams and lodges. These behaviors and the genes that underlie them are under natural selection such that natural selection can favor one lodge type over another via its effects on genes that influence behavior. In the same way, our bodies engineer the ecosystem that lives on them and natural selection can influence this ecosystem through its effects on our skin, its glands and the compounds produces in those glands. Our engineered skin ecosystem, in short, evolves.

²Although this diversity is great, it is in some ways deceptive. Many species of bacteria, for example, are found on the skin, but these species derive disproportionately from just a handful of the bacterial phyla found in any pinch of soil. Best represented are the phyla Actinobacteria, Firmicutes, Proteobacteria and Bacteroidetes. Then within these phyla a few genera are disproportionately important, particularly *Corynebacterium*, *Staphylococcus*, *Propionibacterium*, and *Streptococcus*.

³Of note, beneficial is a term with some baggage. Mutualisms such as those described here are relationships in which organisms of two different species both benefit from each other's presence. However, mutualism is always a term reflecting the net condition. A beneficial microbe might have some costs, so long as its net effect is benefit. Similarly, the costs and benefits of any particular microbial species to human or other hosts are conditional. They depend on circumstances. A species that was beneficial 12,000 years ago to humans, might not be today. By the same token, a species that was not historically beneficial might be beneficial in light of our modern diets and lifestyles. In as much as human bodies (and their underlying genes) evolve relatively slowly this has the potential to lead to mismatches between the microbes our bodies favor and those that benefit us.

mammal immune systems; they instead first encounter the microbes living on mammal fur and skin, microbes with the ability to kill pathogens, whether through the production of antimicrobials (to which they themselves are resistant) or through other means of competition. In other words, the microbes on the skin are a defensive layer. Skin microbes also aid in the development of the immune systems. Unlike, for example, the heart, the immune system does not develop in isolation, it develops in interaction with skin and gut microbes. Many immune disorders now seem to relate to problems during this development [9–11].

Beneficial skin microbes are also used by mammals in finding mates. Skin microbes produce volatile (airborne) compounds during metabolism. Many mammals use these compounds as pheromones. Pheromone signals are then altered through changes in what the body feeds skin and gland microbes (In humans, the microbe food is altered in response to stress, and sexual activity, for instance). What do skin microbe volatiles signal? We are only beginning to learn. Based on insights from ecology and evolution, however, it seems likely that these volatiles provide signals of the genetic background of the host (which immune genes the host has, for example). In as much as it is costly for the host to feed the microbes on the skin, these volatiles might also be an honest signal of host health; it is, one might speculate, only possible to feed an abundance of skin microbes and their bouquet if well fed. Odors also provide a signal of group membership; hyenas recognize those individuals who are part of their group based on the odors of their bacteria [12]. Finally, it has long been known that individual hosts infected by pathogens produce unique odors. The absence of these pathogen odors and the presence of the odor of healthy microbes might also be a signal of health. It is interesting in this regard to note that the ability of some cats and dogs to identify humans who are sick may relate to the ability of the cats and dogs themselves to identify other cats and dogs that are sick so as to avoid mating with them.

Finally, in as much as this layer of life has been present on mammals and other vertebrates for hundreds of millions of years, those organisms that seek out mammals as food use them to find those mammals. In doing so, they are conducting a sort of ecological espionage, honing in on signals meant for potential mates, or accidental signals of the processes being carried out by beneficial microbes. Mosquitoes, for instance, find mammal hosts by flying up the rivers of CO₂ that flow out of their mouths, but appear to choose which mammal to bite based on the smell of the volatile compounds produced by skin microbes. The odor of some microbes attracts mosquitoes; the odors of others repel them [13, 14]. The presence of these repellent microbes may then be a benefit in terms of deterrence of mosquitoes.

In short, for hundreds of millions of years the skin has really been three things, the skin itself, the organisms living on the skin, and the glands of the skin, a key role of which is to feed and favor some organisms relative to others. If we think about the skin in this light, and as ecosystem that has evolved in response to natural selection, many new hypotheses emerge as to the function of strange attributes of mammal skin in general and human skin as specific case, for example, the problem of stinky feet.

Hypothesis 1: Stinky foot bacteria are beneficial I do not need to tell you that human feet can be stinky. In this, we are not unique. Dog feet have a characteristic odor, as do those of cats and pigs. In each case, this characteristic odor is produced by a particular mélange of bacteria. In humans, two dominant odor producers are *Staphylococcus epidermidis* and *Bacillus subtilis*. It is *Bacillus subtilis* (“subtilis” being a misnomer on par with, for example, Greenland) that can lead feet to smell like a mix between, say, dead squirrel and rotten fish. The standard approach to thinking about these odors, to the extent anyone wants to mention them at all, is to ponder how to get rid of them. Evolutionary thinking, however, begs a different question. It begs us to ask why feet stink in the first place.

Until very recently most humans walked barefoot. When walking barefoot humans, like most mammals, we are very susceptible to foot injuries (cuts and scrapes) that could become infected, particularly by fungi. Fungal infections are more problematic for mammals in those parts of the body where circulation is poor, which include the feet. Given that this is the case, it would be adaptive if human foot skin had evolved to favor bacteria that produce antifungal compounds.

It may be that the unique bacteria of modern feet (including the dominance *Bacillus subtilis*) are due to the use of shoes and socks (I know of no studies of the foot bacteria of individuals who do not wear shoes). But for a moment, let’s assume that this is not the case. Could the body conceivably have a way to favor specific bacteria on feet? And if so, why?

We know that the body produces large amounts of sweat through the feet (far more than is necessary for cooling, and why cool the feet anyway?). This sweat is enriched for leucine relative to other parts of the body [15] an expensive amino acid. *Bacillus subtilis* thrives on leucine. It is in metabolizing leucine that *B. subtilis* produces isoflavic acid the compound characteristic of the smell of stinky feet [16]. *Bacillus subtilis* also produces antifungals, antifungals that, for instance, are capable, at least in the lab of killing several fungi often found as pathogens on feet [17]. In other words, our feet may have evolved to produce lots of sweat, with leucine, to feed specific bacteria that kill fungi that reduce our risk of foot infection.

The idea that our bodies actively feed specific foot bacteria as a defense against fungal pathogens needs to be tested. But if right it has important implications particularly for individuals, such as those who are immune-compromised or diabetic, namely that any behaviors that make bacteria with metabolic abilities similar to *Bacillus subtilis* less abundant are likely to increase our risk of foot infections.

Hypothesis 2: The initial composition of microbes on the skin influences the likelihood and rate of wound healing This is a simple idea, so simple that one might imagine it has been very well-studied. A variety of studies have begun to link the abundance of specific microbes on the skin to diseases states. Psoriasis lesions, for example, have a relatively greater abundance of Firmicutes and relatively fewer Actinobacteria and Proteobacteria than does health skin [18]. Patients with atopic dermatitis tend to have a lower diversity of skin microbes than do individuals with healthy skin; their skin is dominated by species of *Staphylococcus* [19]. It is almost

inevitably true that the precise composition of microbes on the skin where a wound occurs is likely to influence the healing of a wound. This doesn't seem like an Earth shattering statement, but as far as I know no clinicians actively measure the composition of skin microbes before considering treatment of wounds and infections. At most individual microbe taxa (e.g., specific pathogens) are searched for. We know that wound healing varies greatly among humans, among human body parts, and between humans and other mammals. This variation must be in part due to variation in the initial composition of microbes.

Hypothesis 3 No infection of a mammal, ever, on Earth, has ever been due to just a single species of pathogen. Every infection will always involve both the pathogen or pathogens and all of the commensal species with which it is interacting. Most infections likely represent the actions and chemical compounds due to tens if not hundreds of species. Again, this seems obvious. Again, if it is true it calls for different and new approaches to surgical incisions, surgeries, wounds and infections.

More ancient history of the skin, including face mites Face mites (*Demodex spp.*) appear to have evolved with the origin of mammals [20]. They live inside hair follicles and glands. Very few species of mammals have been studied for their *Demodex* face mites; yet it is likely that all mammals possess one or probably more often more than one species found nowhere else (and given that these mites are host specific, this would mean that there might be as many as 10,000 *Demodex* species, two per mammal species, even though only a few tens are so far named). Humans are host to two named species of face mites, *Demodex folliculorum* and *Demodex brevis*, and based on our research, additional as of yet named species [21, 22]. All adult humans have these mites in the follicles on their faces but also elsewhere on the body. These mites become more abundant in conditions of mange, and also in humans with rosacea. In neither case, however, do the mites appear to cause these diseases (though they are clearly part of the story). The average human host, like the average mammal host more generally is likely to host tens of thousands, but perhaps even hundreds of thousands of individual mites on his or her body. These mites and their abundance have been a dependable presence with which mammal bodies have coevolved for more than a 100 million years. In light of the ancient biology of these mites, I offer an additional hypothesis.

Hypothesis 4 Counterintuitively, *Demodex* face mites could be used cure rosacea. Rosacea is a common immune-related problem of the skin. It seems likely that one could devise a clinical treatment with face mites that could actually help to treat rosacea. Given the abundance of face mites on humans, that we do not generate an immune response to these mites most of the time means they are producing, almost certainly, immunosuppressants. If we could harness these immunosuppressants we might use them in treating rosacea. An alternate approach would be to manipulate the composition of bacteria living in face mites. It has been suggested that while face mites themselves do not cause rosacea, that perhaps particular bacteria associated with the mites do. If this were the case, one could imagine manipulations of the

microbiomes of face mites in ways that remedy rosacea. In as much as all adults, regardless of their hygiene behavior, appear to have face mites, the idea of treating skin disorders through manipulation of mite composition is perhaps less radical than it initially seems.

Ape Skin

Primates in general, when compared to other mammals, seem to be particularly rich in glands. If we take the function of these glands to primarily be to alter microbial composition of the skin, then this diversity and abundance of glands represents a rich arena for future studies likely to alter our understanding of what it is to be a primate. Some of these glands, however, we know a little more about, among them a set that are more common in apes (gorillas, monkeys, chimpanzees, bonobos, humans) than in other primates, the apocrine glands. Apocrine glands are concentrated in the armpits, around the nipples, in the belly button and perianal and genital regions. They produce compounds that feed a subset of slow growing microbes, including species of *Corynebacterium*. As a result of the food given to *Corynebacterium* species by apocrine glands, these bacteria and their relatives are far more abundant in apes than in other primates [23]. *Corynebacterium* bacteria seems likely to be fed by ape bodies because they offer some value to the apes [24, 25].

Hypothesis 5 The increased investment in apocrine glands, their products and microbes in apes is likely to have been due to changes in the need for one of the roles of such microbes, whether as a pheromone, in pathogen defense, or in deterrence of mosquito vectors of pathogens. This possibility has gone totally unexplored. By the same token, the differences in the apocrine glands and their bacteria among ape species are likely to reflect differences in the mating biology, pathogen and vector risk of these primates.

Hypothesis 6: Apocrine bacteria help to defend us against infection Apocrine glands are larger and more dense and differently distributed in humans than in other apes and in other apes than in primates more generally [26–29], as would be expected if these glands had been evolving recently in response to selection to play a more rather than less important role.⁴ These glands are found in the armpits, but also in other regions where bacterial (rather than fungal) infections are common. These include the belly button, where infection after birth can be deadly, the perianal and vaginal regions. We also know that under stress that the microbes in the apocrine glands are fed more by our bodies, become more abundant and secrete more extracellular compounds. I hypothesize that the apocrine glands play the role, in part, of preventing infection in wounds and other openings to the body cavity. In line with this prediction I recently received a call from a doctor who noted that in his

⁴In addition, key features of the cell biology of human skin, including the sugars associated with cells, are also different from those in other apes in ways that seem likely to be of most consequence to microbes [33].

practice that he had dramatically reduced his rate of surgical infection through laparoscopic surgery. This is what would be expected if the bacteria being fed by the apocrine glands in the belly button help to prevent infection.

Early Hominid Skin

The skin is an unusual organ in many regards, not least of which because the skin of humans differs in many ways from that of our closest living relatives. In short, we are naked. They are furry. Our bodies are not, of course, totally naked (nor are all other mammals totally furry. See, for example, naked mole rats). We have diminutive hairs all over our bodies. But these hairs are too small to be of functional consequence. Too small to keep warm or protect us from the sun [30]. A relatively large literature has considered the loss of hair from human skin, our “nakedness,” in no small part because this nakedness predisposes us to many of the most common skin problems, including skin cancers. It makes wounds more likely, something I have noticed on the top of my head since losing one of those few bits of hair humans maintain (or that many humans do anyway). It is also this nakedness that required our ancestors, in moving into cold environments, to invent clothes. One might also contend that our views of nudity, body art and style all also relate in one way or another to our naked condition. If we were covered in yak-like fur, nude beaches would be less titillating (and more sweaty). A relatively large literature now considers this loss of fur. Among the most plausible explanations for it relates to the pathogens vectored by ectoparasites.

Hypothesis 7 One body of work suggests that the skin of humans is relatively naked due to the influence of ectoparasites. In being hairless humans have escaped to a great extent high densities of lice, fleas, some mites and other arthropods that live in the fur. To remove a louse from your skin you need only squish it and wash your clothes. No such luxury exists for your cat. It is hypothesized that the genes of any of our ancestors who were less hairy and louse-bitten were favored because many arthropods transmit pathogens. Those of our ancestors with less hair may have been less likely to die of the infections ectoparasites transmit.

Hypothesis 8 Conversely, *hairier individuals are almost certainly host to different organisms (be they multi- or single-celled) and, as a result, will have different risks associated with medical interventions.*

More, Early Human Skin

In addition to the risk to early humans posed by vector born pathogens, early humans also began to face many new pathogens more generally. That this is the case is beyond debate. Modern humans are now host to more than 200 pathogen species, whereas fewer than a 100 infect gorillas and chimpanzees (for example). As a result of this shift, we know many shifts in human genes, particularly those associated

with immune systems. It is likely that skin biology, and skin microbiology in particular, also changed in response to the transition to environments in which pathogens were more common. One can imagine many changes. I'll just offer one, a change related to the increase in the risk of vector-borne diseases in early human settlements.

Hypothesis 9: In malarial regions human skin is more likely to favor microbes that are less attractive to malaria mosquitoes Once vector-borne pathogens became prevalent in human societies strong selective pressures would have favored individual human lineages with skin that was less attractive to vectors. These lineages would have been favored disproportionately in those regions where malaria has been common the longest.

Our Modern Skin

Our modern skin differs from that of other apes because of our loss of fur and unique glands, but it also differs from that of humans living just a few 100 years ago. Hygiene has changed dramatically in the last 200 years. Based on historical sources (e.g., gross and detailed stories of the washing habits of kings) and studies of non-human primates, it seems as though until relatively recently that the washing of human bodies was relatively rare, that feces and fecal microbes could often be found on the body, and that slow growing microbes could have grown with little interruption so long as they could compete with other microbes [31, 32].

Even before the advent of hygiene products such as antiperspirants and body sprays modern hygiene led the slow growing microbes on the body to be disturbed with high frequency. It also washed fecal microbes from the skin and hair. These changes have been hugely beneficial to public health, but in as much as they are changes relative to the conditions in which our bodies evolved over the last 300 million years (or more), they are probably not without unintended consequences. In addition, however, to these changes we now know that antiperspirants have a large effect on skin microbes. They, quite predictably, disfavor the microbes fed by our apocrine glands, and favor fast growing species. The microbes we now think of as the medically normal inhabitants of the skin (such as *Staphylococcus*) are composed almost exclusively of those favored by the use of antiperspirants and, before that, likely by public health in general [31, 32].

Hypothesis 10: Antiperspirant use makes our skin more susceptible to infection Our armpits contain many apocrine glands that appear to have evolved to feed *Corynebacteria* species and their relatives. Antiperspirants work by closing down the function of apocrine glands. This leads *Corynebacteria* species to become less abundant. This in turn favors a high diversity of relatively unusual bacteria. Those bacteria include *Staphylococcus* bacteria, including, I will speculate, the subset of fast-growing *Staphylococcus* most likely to be pathogenic.

Conclusions

We still know relatively little about the evolution of human skin and the species associated with it. No comprehensive survey has yet considered the skin in full. We do not know, for example, how many and which animal species live on the skin. It is likely that many more animal species, in addition to *Demodex* mites, are common even on healthy humans. A second necessity is more thorough study of the skin and skin biology of non-human primates and other mammals. The literature, for example, on the evolution of skin glands of primates has scarcely been improved on in the last 50 years. A third necessity is an understanding of the genetics of these changes. Finally, and most importantly, this collective understanding must be brought to bear on modern medicine. We still do medicine as though our bodies were sterile vessels, sterile termite-like bodies on which the occasional pathogen lands. Until this perspective changes, until we recognize the richness on our skin and its consequences, we will continue to make clinical choices that leave patients unhappy, sick and, in many cases, dead.

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