The Miracle of Skin

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Surface Matters

By

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PREFACE

The Odyssey Begins

I am a dermatologist who has worked in both clinics and the laboratory for almost five decades. During this time, I came to love and admire this organ of interest, though at the same time, I also recognized how poorly the skin is understood and how much it is under-appreciated. Though I have long wanted to set matters straight, I put this project aside for many years. But that time has now arrived – let me invite you to join here in a celebration of a remarkable organ, and in particular, of its "business" end, the skin's thin, outer layer - the epidermis.

I must confess that when I started my medical training, skin held no interest for me. Both my father, Hans Elias,[1] and my maternal uncle, Fritz Buchthal,[2] were medical scientists, so becoming a doctor was preordained. That I should follow in their footsteps was an expectation, not a matter of choice. The parental debate did not center on whether Peter should become a doctor – a given - but rather whether or not he should become a nephrologist, favored by my father, because "the kidney is such a fascinating organ," or should it be pediatrics, as favored by my mother, Anneliese, because "Peter is so fond of children."

My ultimate selection of dermatology as a chosen field arose serendipitously. Needing extra money during medical school, I took a part-time job washing dishes in the laboratory of Dr. William Epstein, then Chairman of the Dermatology Department at UC San Francisco.[3] But soon after hiring me, Epstein discovered that I could

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[1] See Hildebrandt 2012.

[2] See Trojaborg 2004.

[3] See Epstein JH 2007.

operate an esoteric piece of machinery, the electron microscope. So, the job morphed into a research associate position. Even after graduating from medical school, I was still undecided about my final career path, so I accepted an internal medicine residency at UC San Francisco.

At that time, the Vietnam War, to which I had long been opposed,[4] was underway, compelling each young male physician to contribute skills to the war effort. Fortunately, Epstein intervened on my behalf by finding me a position as a research associate in the Dermatology Branch of the National Institutes of Health – an offshoot of the Public Health Service (at the time, we research fellows were referred to as "yellow berets").[5] We never learned how to clean a rifle, but we nonetheless emerged as Vietnam vets.

The National Institutes of Health occupied dozens of buildings, of which the largest was Building 37, then cited as the biggest brick structure in the U.S. Along the dark corridors of the Dermatology Branch of the NIH, a variety of oddball scientists were hidden deep within the recesses of their laboratories, most not even performing skin-related research. After my arrival, I tested the waters with each of them, until I reached the Microscopy Unit, headed by Bruce Wetzel, PhD, a well-known, iconoclastic cell biologist. Bruce took me under his wing, mentoring me not only in science, but also in the importance of using language precisely. Yet, I emerged from these two years without having identified my calling.

I still had not found my calling as I began my dermatology residency in the Harvard program. Fortunately, at some point, I was alerted to a department member, Irwin Blank, PhD, whose lab lay in

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[4] As a young physician, I participated for a time in assisting potential draftees to obtain deferments on the basis of medical disabilities. Along the way, I realized that these efforts did not impact the war effort, they merely shifted the burden from the educated middle class to the less fortunate. Consequently, I published my concerns in the medical literature and thereafter desisted in these efforts (see Elias 1973).

[5] In time of war, the Public Health Service becomes part of the U.S. Coast Guard, under command of the Navy. I was, therefore, enlisted as a Lieutenant Commander.

the distant corridors of the Massachusetts General Hospital. Upon meeting him, I instantly could see that he was both kindly and wise beyond his years. Already a Yoda of his day, Blank was well-known for his pioneering studies on drug delivery across the skin. But at that time, skin was considered much like a sheet of plastic wrap, not much better than Aristotle's long-ago comparison of skin to a rind of cheese. Searching for my own niche, I ventured the question: "Irwin, what is known about the structure of the skin barrier?" His answer came like a clarion call: "Frankly, Peter, we know very little about the structural basis for the skin barrier." Voila! I had found my research calling.

Henceforth, I was catapulted into a life-long career exploring the mysteries of skin. The following chapters describe how that path evolved; first, from an elucidation of the structural basis of the barrier; then to its biochemical basis; and later to how its critical function responds when exposed to often hostile, environmental stressors. The reader will soon accompany me on these explorations – how I "peeled the onion," always seeking a deeper understanding of the skin.

Fortunately, funding agencies, like the NIH and the Veterans Affairs Administration, recognized the potential importance of this effort. Indeed, I am eternally grateful for their years of ongoing support. With their assistance, my lab discovered not only how our skin supports life in an ever-changing, often hostile terrestrial environment, but also the dire consequences for our patients when the barrier fails. Later in this volume, I describe how some of the most common skin disorders, like atopic dermatitis and psoriasis, as well as a group of inherited disorders called "ichthyoses," stem from problems with the skin barrier. Finally, I provide an Epilogue that describes some of our attempts at "fixing the barrier."

Nonetheless, it seems safe to say that when most people think about their own skin it is usually not with admiration, but rather with consternation or concern, as for example: "What is this growth on my back?" Or perhaps we view it with irritation or dismay: "How can I get rid of this ugly vein? This unsightly blemish? These tell-tale wrinkles?" And haven't we gazed at other's skin with envy ("so youthful, so

clear!") or disgust ("what is that thing on that person's face?") or even fear ("is it contagious?").

Surely no other organ engenders such a panoply of emotions. In contrast, do we hate our lungs or our heart? Do other peoples' livers or kidneys arouse our feelings? This impassioned, albeit mostly negative attachment to skin makes it rather odd in comparison to other parts of our body. Indeed, I contend that the very fact that our skin faces the outside world and that it is the most visible organ has engendered negative attitudes that have pervaded concepts of skin, not only from the personal perspective, but even in the scientific realm. As a result, skin, let me submit, is the most overly invested, yet underrated of organs.

From the all-too-common jokes about dermatology and dermatologists,[6] it is evident that skin still has a problem with its

[6] Consider for example, this transcript from a 1997 episode ("The Slicer") of the television comedy, "Seinfeld," where Jerry forgets that there are dermatological issues (skin cancer, for one) much larger than a pimple.

Elaine: How was the doctor date?
Jerry: She spent an hour and a half making me feel, if I don't save lives, I'm worthless.
Elaine: Well, she's very focused. Dermatology is her life.
Jerry: Dermatology?
Elaine: Yes, she's a dermatologist.
Jerry: Saving lives? The whole profession is; eh, just put some aloe on it.
George: When are you going on your next date with her?
Jerry: What's the point?
George: What! You're gonna pass up a wonderful opportunity to put that "aloe pusher" in her place?
Jerry: Revenge date? That sounds like you more than me.
George: This could be so sweet, Jerry. Saving lives? She's one step away from working at the Clinique counter!
Jerry: Dermatologist? Skin doesn't need a doctor!
George: Of course not! Wash it, dry it, move on!
Jerry: You're right. I'm gonna call her right now and tell her off.
[Jerry is on the revenge date with Sara.]
Sara: Restaurant, flowers...this is so nice.

reputation among the general public. Regrettably, this attitude is pervasive, even among physicians and scientists who should know better. I am continually dismayed, for example, that the many admirable, nay even critical functions of skin are so frequently glossed over. Why else do treatises inevitably begin with the words: “Skin is the largest organ of the body”? As if size alone provides its principal merit.

Our skin is not merely vast, it is also highly purposed. It is my goal in the pages that follow to convince readers that there is one purpose of the skin that is both hierarchically primary and overarching – our skin is tasked with protecting our precious internal reservoir of water against its loss.

Whatever you have previously thought about skin, the concepts that you will encounter in the pages that follow will likely challenge your assumptions, and in the process, I hope that it will engender new-found respect for this most remarkable of organs. I guarantee that you will find information about the skin here that is not available elsewhere, as together we explore many new concepts. I have attempted to make this information accessible to any curious reader - a medical background is not a prerequisite - only a desire to understand how our skin operates at a deeper level.

I am deeply indebted to both my wife and co-worker, Mary L. Williams, MD, and to my administrative and editorial assistant, Joan Wakefield, for their generous feedback and many useful edits. Several other friends and colleagues, including Gary Thorpe, Joe Neigel and Doug Carmichael, deserve a special mention for their thoughtful suggestions. Finally, I would like to dedicate this volume to the memory of Edward O. Wilson, who consciously and unconsciously inspired many of the ideas that emerged during the writing of this book.

Jerry: Well, I'm a classy guy. How's the life-saving business?
Sara: It's fine.
Jerry: It must take a really really big zit, to kill a man!
Sara: What is with you?

PART I:

MIRACLE WRAP

CHAPTER 1

IN PRAISE OF SKIN

> "*La fixité du milieu intérieur est la condition de la vie libre…* Nothing is more crucial to the survival and independence of an organism – be they elephants or protozoa – than the maintenance of a constant internal environment."
> —Claude Bernard, as paraphrased by Oliver Sacks [7]

This is a book about the marvels of skin – its life-enabling gifts, which quietly and without fanfare or accolade, carry us from birth to death. So trustworthy is our skin that we have the luxury of taking its efforts entirely for granted. Nonetheless, skin's silent labors are not entirely a mystery. We know that it covers and envelops us, protecting our soft and vulnerable insides from injury. It shields our insides from harmful rays of sunlight, while at the same time harnessing some of these same beams to manufacture vitamin D.[8] It holds at bay hordes of deadly microbes that try to breach its fortifications and infect our deeper tissues, and it similarly excludes a host of chemicals and allergens from our surroundings. Skin, too, is tasked with maintaining the constancy of our internal temperature. Using its insulating layer of "subcutaneous" fat, skin holds in our body's warmth. When we are chilled, it can release some of the energy stored in this fat to generate heat. And when we are too warm, skin produces sweat that as it evaporates from the skin surface, cools an overheated core.

Clearly, this is an impressive list of functions. Yet, the very length and variety of this list risks obscuring the recognition that skin does indeed possess a primary purpose; one overridingly critical function; a

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[7] See Sacks 2015.
[8] See Young 2010.

task that is in fact its *raison d'être*; and one that came first, such that only later during evolution were these many other roles relegated to skin. Unquestionably, the most fundamental of the skin's essential benefactions is that it renders us water-tight (Fig. 1-1).

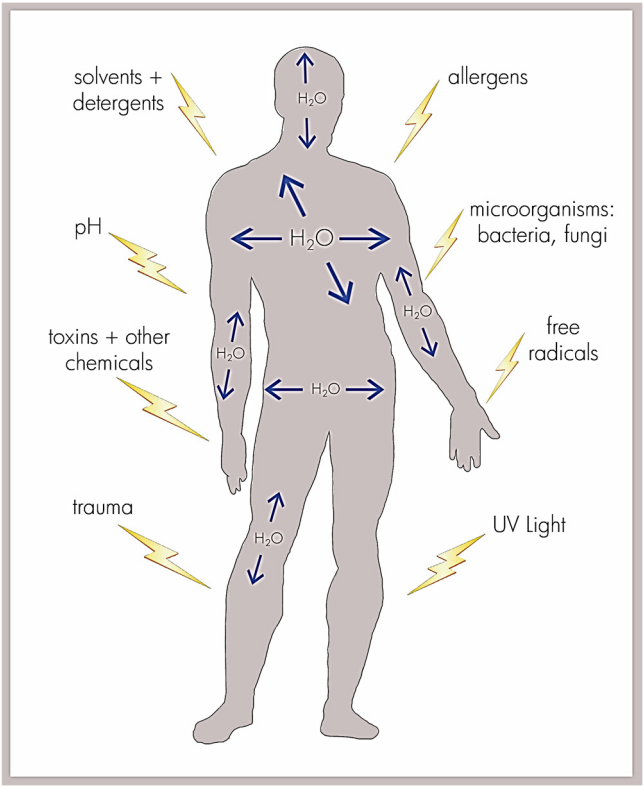

Fig. 1-1: The many defensive functions of the skin. The prevention of dehydration from water evaporation from its surface is its most critical function (drawing by Jessica Kraft).

Consider that we are made mostly of water - at least 70% of our body is nothing other than water - yet we inhabit a world surrounded by a much drier atmosphere. As watery beings, we inevitably confront an elemental law of physics: water, when exposed to dry air,

will vaporize. Just as a shallow puddle on a warm sunny day soon evaporates, leaving behind only a residue of cracked mud. Without our waterproof cloak, we, too, would simply dry out. We'd be like prunes, not plums; or raisins, not grapes. By holding in our body's precious fluid reservoir, skin permits the miracle of life in a dry world.

The Barrier Imperative

Herein lies our existential dilemma: we are a system of life based upon water, yet many eons ago, our vertebrate progenitors chose to depart from the watery comfort of the seas for a life on dry land. These primordial immigrants – both plant and animal - had to adapt their "skins" to retain their bodily fluids. It was either that or, as we will see, we would need to remain tethered, like a frog, to a water-based habitat.

Variety may be the spice of life, but not for our cells, because, above all else, they strive to maintain the *status quo*. Each of our cells can be thought of as a tiny factory housing a host of tightly orchestrated biochemical reactions. The manufacture of new proteins, the burning of fats and sugars to generate energy, the decoding of our DNA, the transport of molecules in and out of the cell - all these chemical transformations and actions together define the very essence of life itself. But they require constancy and consistency. Each reaction flourishes only within a narrow range of temperature, and each depends upon a finely tuned concentration of hydrogen ions (or pH), as a precisely composed solution of salts. It is the volume of water in which these salts, hydrogen ions and organic molecules are dissolved that determines their critical concentrations, and it is in this way that water bestows the gift of life.

The overriding mission of every living being is to maintain the constancy of its internal milieu, its cellular "homeostasis,"[9] and water holds the key. A fundamental strategy to this end is structural. By erecting barriers or walls, living organisms isolate the internal from the external, and control the passage of materials from both the

[9] Ibid.

inside-out and the outside-in. This phenomenon of fortification manifests at every level, from the microscopic interior world of the cell to the interface of the organism with its external environment. Inside the cell, fatty (or "lipid"-rich) membranes surround each tiny particle or "organelle," thereby segregating each chemical reaction to specific compartments, such as its nucleus or mitochondria. The cell itself is enclosed by a plasma membrane that sequesters the cell's interior from its surrounding milieu, a film of "interstitial" fluid, and regulates the flow of molecules and molecular information in and out. Protective sheaths encapsulate the internal organs (for example, the dura mater encloses the brain and spinal cord; the pericardium covers the heart), while the blood stream itself is corralled by vessel walls that channel its cargo of oxygen and nutrients to their proper destination. But the organism's ultimate structural barrier – that first and final defensive wall – is its "integument," or skin.

Not only is the cytoplasm of our cells a salty solution, similar to the seas from where we came, our precious human blood is also a watery soup of blood cells, salts and nutrients. Some of this salty solution coursing through our "capillaries" (the smallest branches of our vascular system) percolates outward through the walls of these tiny vessels and into the spaces that lie between the cells of every tissue, where it bathes, nourishes and replenishes them, while carrying away their wastes. This "interstitial" water, [10] siphoned from our blood, similarly bathes and feeds the layers of "epidermal" cells that line our surface which meets the dry air.

And it is there, at the skin's interface, where we confront the inviolable law of nature: water in contact with dry air will vaporize. And as the laws of physics tell us, the rate of evaporation from the surface of a body of water – which is what we in essence are - depends upon both the ambient temperature and the vapor pressure

[10] Two-thirds of the body's water is held within the cytoplasm of cells; of the remaining one third, about 75% flows in the blood or lies between cells. Interstitial fluid is similar to plasma in its composition, except that it contains much less protein.

of water in the atmosphere, its "relative humidity."[11] Without some sealant in place - without some waterproofing system interposed between our body fluids and the outside air – the water molecules trickling between the outermost layers of skin cells would inevitably escape into the atmosphere. And soon these pioneer escapees would be joined by an outpouring of more water molecules rushing outward and into the air. On and on this process would continue, relentlessly siphoning off precious water from our blood, and soon, too, from our cells, to satisfy a vast and thirsty atmosphere.[12] It is this potential for loss of water - from the fluid surrounding the outermost cells of "skin," then from "blood," and ultimately, from all cells - into the surrounding, drier atmosphere that constitutes an ever-present threat for all plants and animals that seek to inhabit dry land. Of course, we terrestrial beings solved this dilemma eons ago with the evolution of our remarkable, nearly water-tight "integuments." By constraining our body fluids from wanton dissipation, skin holds the very key to life on land. It is both the bulwark protecting our internal water and our bastion defending against assaults from the chaotic world outside.

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[11] We place our clothes lines in a sunny part of the yard to dry our laundry more quickly. Sunlight warms the water our clothes hold, setting its molecules in motion, and thereby hastening their movement out of our clothes and into the air. Wind facilitates this process, by blowing off the now humidified layer of air just above the clothes' surface, and replacing it with the drier, ambient air. On rainy days, we use a clothes dryer to tumble damp clothing about in hot air.

[12] As water evaporates from the skin's surface, it leaves behind its cargo of salts in the interstitial fluids. As these salts are returned to the circulation, the loss of "free" water upsets the delicate balance of their concentrations within the blood. Because sodium is the most abundant "cation" (positively charged ion) in blood, the dehydration caused by excessive transepidermal water loss is a "hypernatremic dehydration" – i.e., resulting in too little water containing too high a concentration of sodium. This is the form of dehydration that certain infants born with an inherited disorder of the skin barrier, like congenital ichthyosis, are most prone to develop.

Let us be clear about one important distinction: the problem of water leakage out of the skin under consideration here is fundamentally different from the water that we humans lose through the process of sweating. We sweat to prevent our core from overheating. Sweat is a salty solution, manufactured in specialized, "eccrine" sweat glands, located deep in skin and delivered to its surface when cooling of the body is required. One might ask, why deliver a salty solution, when it is only free water that is needed for the cooling effect of evaporation. Teleologically, the adaptation of a salty form of sweat may have evolved to avoid the adverse effect of water loss via the transepidermal route, which poses the risk of hypernatremic dehydration (see Page 6). While any form of dehydration is perilous, hypernatremic dehydration is by far the most dangerous, because a too rapid correction of the fluid and electrolyte imbalance can induce potentially fatal cerebral edema (brain swelling) (as perhaps might have occurred when an aboriginal hunter paused to slake overpowering thirst by gorging on water). Hence, a salty sweat likely had evolutionary merit. Sweat constitutes a type of evolutionary tradeoff: it contains water that we willingly discharge from the skin - risking dehydration in the process - in order to serve another need – the imperative to regulate our body's core temperature. Sweating is an intermittent and controlled process of secretion that is switched on and off by signals from the central nervous system as needed to maintain a constant internal temperature. [13] I will consider this remarkable human innovation, "eccrine" sweating, in greater detail when I discuss the evolution of human skin later. For now, however, I am concerned with another mechanism, the ongoing and passive leakage of water out of our skin – a never-ending process that is unresponsive to our immediate need to regulate body heat. This process of water leakage is constant and uncontrolled, its speed

[13] It is true that sweating can also be emotionally triggered. This form of sweating is part of our "fight or flight" response system. One can think of it as thermoregulation in advance - in preparation for the expenditure of metabolic energy and accumulated heat that will occur when we choose to either run away or stay in place and fight.

dictated only by the thirst of the air and the strength of the skin's fortification, its "permeability barrier."

Fundamentally then, this book on the marvels of skin is about water, or perhaps more precisely, it is about water and life on dry land, for they hold the key to understanding why we have skin. This formulation – skin, water, life on land – is not immediately self-evident, in the way that, for example, a book about the marvels of lungs could be readily understood as one that is about oxygen and life on land. But, as I will endeavor to convince readers, it is truly water, and the imperative for its conservation, that holds the key to understanding skin.

In this tribute to skin and its permeability barrier, we will see both how our own skin is constructed, and how the skin of other, unrelated terrestrial species solved this universal mandate. I will trace the steps of discovery and examine how negative attitudes towards skin impeded understanding of its life-enabling attributes. I will consider how the necessity for a competent skin barrier honed the evolution of certain novel characteristics of human skin: its relatively hairless state, its ability to cool through sweating, and its tonal shades of coloration as modern humans migrated across the globe.

I hope that in revealing these marvels of skin, it will never again be necessary to invoke its size when considering its importance. As I undertake this homage to the skin's barrier, I will largely set aside consideration of those aspects of skin that serve for many of us as its most important feature, namely, its role(s) in our interpersonal lives. These set-aside considerations include our preoccupation with the appearance of our skin - its color and texture, its beauty and its imperfections; as well as the ways in which our skin becomes a proxy for ourselves, as it serves to reflect or mask our innermost, core being. These set-aside considerations also include skin's sensual repertoire, the role that physical touch plays in our social lives - to the point that the word "skin" even became synonymous with sex - as one can easily demonstrate by typing the word into any internet search engine. We humans are a social species, and skin's social meanings dominate the current lexicon on skin. Our concerns over its color, its beauty or its blemishes [or as S. Connor (2003) phrased

it in *The Book of Skin*, “its sheer, vulnerable, embarrassing nakedness…”], and its sensuality pervade the printed pages, clutter cyberspace, permeate the airwaves and line the pockets of myriad professionals and entrepreneurs. These abundantly considered aspects of skin, its social roles – whose importance I fully acknowledge - are not my focus here. [14] In fact, skin is not the largest organ in the body – minus its highly variable layer of subcutaneous fat, the muscular and skeletal systems possess far greater heft. The skin certainly doesn’t need to rely on some permutation of “bigger is better” to claim its status. Skin is eminently worthy of our respect, because without it we would shrivel and die. Period. Yet, as obvious as that may now seem, this understanding certainly has not always been the case. It took many centuries for skin to achieve any recognition for its vital work. And only in recent decades have we learned how it is able to thwart the laws of physics and hold back the outflow of water. My story of skin begins with a consideration of its inconsistent past.

[14] See Ackerman 1990, Benthien 2004, Connor 2003 and Montagu 1986.

CHAPTER 2

WHY HAVE SKIN:
THE HISTORICAL PERSPECTIVE

> "And the Lord said to Satan, 'Have you considered my servant Job, that there is none like him on the earth, a blameless and upright man, who fears God and turns away from evil? He still holds fast his integrity, although you incited me against him to destroy him without reason.' Then Satan answered the Lord and said, 'Skin for skin! All that a man has he will give for his life. But stretch out your hand and touch his bone and his flesh, and he will curse you to your face.' And the Lord said to Satan, 'Behold, he is in your hand; only spare his life.' So Satan went out from the presence of the Lord and struck Job with loathsome sores from the sole of his foot to the crown of his head. And he took a piece of broken pottery with which to scrape himself while he sat in the ashes. Then his wife said to him, 'Do you still hold fast your integrity? Curse God and die.' "
> —Job 2:3-9 [15]

First Steps

When looking back on the place skin has traditionally occupied in the Western scientific tradition, I can only conclude that it was both unusual and lesser. And, in an implicit manner, this tradition continues today. Consider, for example, that one of the most powerful and important medical disciplines, *Internal Medicine*, still defines itself by the one organ it doesn't treat (the skin as an internal organ is not considered "internal" by this journal). As a devotee of the skin, I

[15] King James version of the Bible. See "The Curse of Job" later in this chapter.

blame the 4th century B.C. Greek philosopher, Aristotle, for starting matters off on this wrong footing.

Aristotle paid little attention to the skins on his specimens, as he searched among the lowliest of land and sea creatures in his quest to divine the universal laws of nature. [16] He considered their "integuments" (the more general scientific term for skin) to be little more than a hardened, dry crust, which he likened to the rind on a round of cheese. By his words, which were considered inviolate until the Enlightenment, skin is "formed by the drying of the flesh like scum upon boiled substances…not only because it is on the outside, but because what is glutinous, being unable to evaporate, remains on the surface."[17] It is evident that Aristotle recognized the propensity of water to escape through our body surface, and he even seemed to propose some sort of role for "skin" – as the dried-up residue of what is left behind as water departs – in forming an impediment to its movement. But if one stretches his words to embrace this concept, the skin barrier that he (almost) proposes would still be a structure formed passively - a mere happenstance - rather than a biological structure designed through the forces of evolution to execute specific and critical functions. In the higher animals that Aristotle studied - mammals, birds and reptiles – he did acknowledge functions for hair, feathers, and nails, all of which are indeed derivatives (or "appendages") of skin, yet the skin itself received no comparable recognition of its usefulness or purpose.

The Romans followed the Greeks in many endeavors, including in their continuing embrace of dismissive attitudes towards skin. For the father of vivisection, Galen of Pergamon (129-c.200 AD), skin was simply an annoying wrapper, an impediment to his early explorations of the internal organs.[18] One could argue that in the

[16] See Stott 2012.

[17] See Connor 2003.

[18] Galen was a philosopher as well as a physician and surgeon whose observations dominated Western medicine for over 1300 years. Based upon his dissections of monkeys and pigs, he discovered that nerves control locomotion, and described the circulatory system for the first time. Andreas

absence of microscopes to reveal the details of its organization, these early scientists had no means to explore skin secrets. Yet, their failure to ascribe any functional importance to skin remains curious. It is as if its very familiarity, that which always lay before their eyes, bred indifference.

I don't expect much from the Middle Ages, and not with respect to scientific revelations. Still, one might wonder if indeed the people of these allegedly dark times had not come close to figuring out what skin is about. This rather surprising possibility is suggested by their adoption of an extreme punishment, flaying - the stripping off of a person's entire suit of skin - until it hung off "from the body like the drooping clocks of Salvador Dali." [19] They flayed prisoners alive as recourse for the most heinous of crimes.[20] While there is no record to suggest that its advocates and practitioners understood the cause of the death that would ensue – i.e., that the extreme dehydration caused by loss of the skin's barrier to water movement would result in cardiovascular collapse – they clearly understood that flaying provided a reliable means of death. And perhaps best of all from a punitive perspective, it promised both a relatively prolonged and exquisitely painful demise.

I do have higher expectations for scientific advancements during the Renaissance, when, after the long medieval winter, the explorations of human anatomy resumed once again. But alas for skin, little changed. When scientists of the Renaissance - the famed Leonardo da Vinci and others - undertook their explorations of the human body, they too considered skin to be an impediment, a minor obstacle to their vivisections. Without pause to ponder the significance of skin or its possible functions, they carefully placed their incisions and peeled the cadaver's hide aside, like a sheet, stripped off and consigned to the trash bin. As Aldersey-Williams notes, the 17th century artist, Rembrandt, in his famous painting, The Anatomy Lesson, captured

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Vesalius extended Galen's observations to humans, culminating in the publication of his famous atlas, *De humanis corporis fabrica*.

[19] See Aldersey-Williams 2013.

[20] For the reader interested in the history of flaying, see Benthien 2004.

the "perception of the body as a storeroom or treasure chest, an assemblage…of mysterious and intriguing parts…,"[21] but skin, of course, was to be left behind in all this excitement. Alessandro Benedetti (?1450-1512), an anatomist from Padua, continued to view the skin merely as a dried-out crust, just like the one that forms on one of Italian staples, polenta.[22] Another more famous and somewhat later Italian anatomist, Vesalius (1514-1564) also largely considered skin something to be incised and pulled aside in order to reveal the interesting internal structures below. His texts are replete with references on where on the body to place one's incisions. Nonetheless, he did pause long enough to recognize that skin too had structure.[23] He was the first to describe its several layers, a cuticle (or "epidermis"), the dermis, the subcutaneous fat, and an underlying "fleshy membrane" (or in modern terms, "fascia"). Observing that vessels and nerves were found in the dermis, but not the epidermis, he concluded that the dermis was the "true" skin, while the thinner, overlying epidermis was but an efflorescence of the dermis - once again, a mere residue, passively deposited on its surface. Nonetheless, Vesalius and his predecessor, Benedetti, must be credited with recognizing that skin now had at least one function: the sensation of touch and temperature.

Besieged by Many Problems

Skin finally began to receive more focused attention during the Age of Enlightenment. Yet even so, it still was not considered to be an organ, that is, a part of the body charged with specific duties, or performing specific, essential functions, as, for example, the heart or lungs. Instead, skin increasingly became of interest as a region of the body prone to vexations, and its disturbances and diseases began to

[21] Aldersey-Williams 2013.

[22] See Lind 1975. While today's polenta is made from corn meal, corn (being an import from the New World) would not have been available in Italy in Benedetti's time. However, the translator notes that by polenta he refers to pearl barley. In any case, the image of skin as a hardened crust is still apt.

[23] Vesalius 1555.

be systematically described and categorized. The Austrian, Joseph von Plenck (1735-1807) was an early pioneer in this endeavor.[24] Because he was a botanist, as well as a physician, von Plenck coined descriptive terms for skin conditions using analogies to the plants he also studied. If a skin lesion was round or oval and a little scaly, then it brought to his mind lichens, those flat, round, and moss-like plants often found growing on the surface of rocks. Even today, thanks to von Plenck, names of a number of dermatologic disorders contain the word "lichen."[25] And still in current dermatologic parlance, when other skin lesions bear a resemblance to one of these disorders, they are said to be "lichenoid" (or like lichen).

Once the notion that skin disorders mimic phenomena of the natural world became established, there was no stopping it.[26] Dermatologic terminology soon spread beyond the world of plants into the animal kingdom. Destructive skin conditions that result in deep. disfiguring ulcers and scars were thought to resemble the bite of a wolf (c*anis lupus*). Although wolves are no longer a common scourge, this terminology remains in use. One of these, *lupus vulgaris* (or "common" lupus), is now recognized to be a manifestation of tuberculosis in the skin, and fortunately is no longer a common condition, while another, lupus erythematosus (or "red" lupus), is an immunologic disorder, which variably affects the skin and internal organs.[27] Another zoological term still employed in clinics is

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[24] Joseph Jacob Ritter von Plenck (1735-1807) is considered the forerunner of modern European dermatology (see also Holubar 1984)

[25] There's lichen planus ("flat" lichen), lichen aureus ("golden" lichen), lichen simplex chronicus ("common, chronic" lichen), or my personal favorite, pityriasis lichenoides et varioliformis acuta ("acute, flakey lichen-like and smallpox-like").

[26] This phenomenon of naming diseases by their resemblance to something in nature probably did not start with von Plenck. The thickening and swelling of the skin as a result of chronic lymphatic obstruction was referred to as "elephantiasis" (a term still in use) by Vesalius, and this terminology may well have preceded him.

[27] In profane usage, the term "wolf" also came to apply to erosions and ulcerations arising from protracted friction, especially in body folds, after

"ichthyosis," which denotes a family of genetic skin conditions where a rough, dry skin surface was thought to resemble the scales of fish (*ikhthýs* in Greek) skin. (I will return to this family of genetic disorders in a later section when I consider conditions in which the skin barrier fails.)

For better or worse, this penchant to name dermatologic lesions and disorders after some fanciful resemblance continues even today. Not so long ago, a rare inherited disorder, characterized by numerous skin folds and rolls of fat in affected infants, was termed the "Michelin Tire Baby." Dermatologists are not alone in this sort of descriptive terminology. The accumulation of fat on the upper back which can be induced by an excess of corticosteroids is referred to as a "buffalo hump," for example. Trisomy 21 or Down's syndrome was initially called "mongolism" in reference to the physiognomy of the Mongol population. It is no longer considered appropriate to use medical terminology that can be misinterpreted as pejorative. However, some entrenched terms, like "ichthyosis" persist. [28] Taxonomy can be useful in providing a structure for further scientific explorations of cause and effect, but in dermatology it has too often become an end in itself, something akin to stamp collecting. Just providing a name can impart a false sense of knowledge, because it represents only a first and very limited step towards understanding a disease or condition. Considered in this light, these fanciful names for skin disorders may not have retarded the quest to understand their causes or to discover new treatments, but I don't believe they helped, either.

A Scottish physician, Robert Willan (1757-1812), wrote the first textbook of skin disorders, and in so doing, he became the father of dermatology.[29] Yet, even Willan did not consider skin to be a true

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prolonged running or horseback riding. Professor Peter Fritsch, Innsbruck Austria (personal communication).

[28] See Ross 1969.

[29] Between 1788 and 1808, Willan published a four-volume treatise called *Cutaneous Diseases*, followed by the first color atlas of dermatologic disease entities. He was the first to realize the importance of illustrations in disease descriptions (see Grzybowski 2011).

organ, charged with specific functions. In other words, skin's problems were well along the road to recognition long before there was any real appreciation of its critical, life-enabling tasks. Still, some recognition did arise during this era of rational thought and classification. Giovani Battista Morgagni (1682-1771), [30] the father of modern anatomical pathology, proposed that the skin must mediate the outward movement of water, comparing it to the cuticles on the leaves of plants, which already were known to impede the loss of water.[31]

The Purpose of Skin

Nonetheless, almost another century would pass before Sir Thomas Chevalier (1767–1824), who held the distinguished office of Surgeon Extraordinaire to the King of England, finally elevated the status of human skin to that of an organ. Bearing in mind that by the first century, Galen (129 AD - 216 AD), a Greek physician, had proposed roles for the heart, liver and lungs in the distribution of blood and "vital humors" to the tissues, and that in 1628, Sir William Harvey, through experimentation and deductive logic, demonstrated the functional interconnections of arteries and veins in the circulation of blood[32], it is remarkable that it wasn't until centuries later that skin would finally be recognized as an organ invested with its own critical functions. Indeed, despite being the most visible and most accessible of all, skin holds the distinction of being the very last organ to be recognized as such.

In 1823, Chevalier gave a series of lectures to the Royal College of Surgeons, in which he chastised his colleagues for failing to obtain a "requisite analysis of skin structure, as if this were.... the only organ of sensation of which anatomical knowledge is needless

[30] See Morgagni 1769. Morgagni began as an anatomist, but became the father of anatomical pathology, linking observations under the microscope to clinical diseases for the first time, which he published at the age of 79.
[31] See Samuels 2008.
[32] See Schultz 2002.

or....subordinate."[33] "Surely a surface by which so much is absorbed, so much is transpired, so much is felt, so much is regulated, and by which all other parts are enclosed, should have a more powerful claim on our investigation. It guards against dangers from within the body, and from without. No... (tissue)… is more uniform in its composition, or more diversified in the arrangement of its parts in performing its appointed tasks of protecting and covering." [34] With considerable prescience, Chevalier also observed that "late in fetal life, the skin rapidly bursts into full maturation," speculating that this development prepares the neonate for life outside the womb. Indeed, improvements in the ability to nurse premature newborns through their perilous adaptation to life outside the womb have pushed back the age of viability from the 28 weeks of gestational age, during the era that I was a medical student in the 1960s, to the 25, or even 24 or 23 weeks of today. Presently, the age of extra-uterine viability directly abuts the timetable for development of the skin's permeability barrier. Consequently, immaturity of the skin has now emerged as one of the paramount obstacles to the survival of the extremely premature infant. At long last, skin was now declared to be worthy of study. Yet, while Chevalier sparked a dawning recognition of the critical functions of skin, more than one hundred and fifty years would pass before the structural basis for the most important of these functions, its provision of a barrier against the loss of water, would be uncovered.[35]

What stood in skin's way? For the ancients, like Aristotle, Galen and Vesalius, it would seem that skin lacked intrigue. There was no mystery to uncover, because there it lay, right before one's eyes.[36] Even after tools such as the microscope became available to explore

[33] See Chevalier 2010.

[34] See Visscher 2014.

[35] My publication (see Elias 1975) provided an initial description for the structural basis for the mammalian skin's permeability barrier.

[36] Some surgeons today could be accused of a similar cavalier attitude towards skin, in view of their propensity to execute quick closures of their wounds with stapling devices, rather than taking the time to produce a respectful and attractively hand-sutured approximation of wound edges.

its structure in finer detail, skin was still slow to receive scientific attention. Now, with the benefit and bias of hindsight, looking back upon these long centuries of neglect, I suspect that yet another set of peculiarities of skin conspired to impede the exploration into its most critical functions.

The Curse of Job

It has been the skin's misfortune that many diseases bearing the greatest social dishonor and stigma leave their all too visible marks upon it.[37] Consider, for example, the deep-seated dread provoked by leprosy across cultures and millennia. Even in our own country, its victims have been publicly ostracized. As recently as the 1960s, Hawaiians afflicted by leprosy were forcibly removed from their homes and exiled to an isolated colony on the island of Molokai. It did not pass unnoticed by the populace that this infection first manifests its presence by producing faint patches of more lightly colored skin, years before it maims the body and further disfigures the skin. Still today, in some countries where Hansen's disease (the current euphemism for leprosy) remains endemic, any skin disorder, such as vitiligo, that produces patches of lighter pigmentation, can induce a disproportionate degree of anxiety.[38]

Similarly, the predilection of sexually transmitted diseases, like syphilis and gonorrhea, to produce lesions on the skin has cast suspicion more generally upon anyone afflicted with rashes or sores.

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[37] It is difficult to sort out cause and effect here. The derivation of the word "stigma" is relevant to this point. In Greek, it was the mark left on the skin by a pointed instrument. In the 16th century it came to mean a mark on the skin made by branding - from a mark on the skin to the concept of *social stigma*, defined as the disapproval of, or discontent with, a person on the grounds of characteristics that distinguish them from other members of society. *Stigma* can be attached to a person who differs from *social* or cultural norms. The concepts of social disapproval and skin disorders are thus intertwined in our language (and, as a consequence, in our minds).

[38] For historical images of the disfigurement from untreated leprosy, see Barnett 2014.