LOOKING AT THE MEMBRANES AND BOUNDARIES OF PATIENTS

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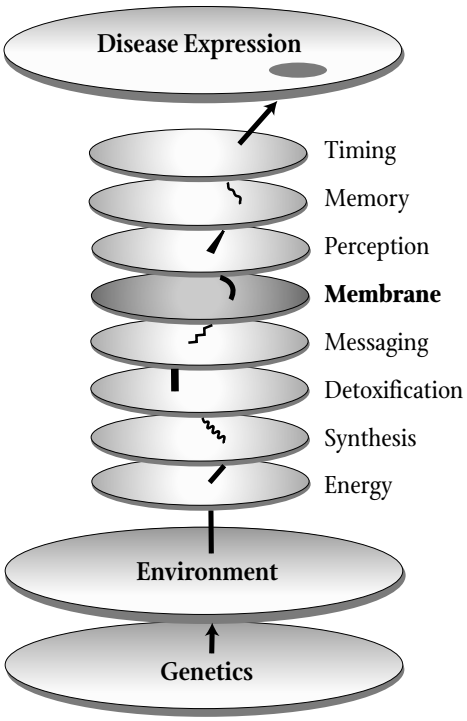
Can one think of any pathology that does not involve a loss of integrity of a surface or boundary? In 1978, I accepted the job of Director of the Gesell Institute and failed in my first attempt to get funding from a local New Haven Foundation. I found myself, after hanging up the phone, in an endless black void in which the very architecture of my perceptual world lost its limits in time and space. Just as that brush with dark depression taught me something about the structure of consciousness, my first view of electron micrographs as a first-year medical student in 1960 revealed that the inner workings of the cell were not mush, but membranes—surfaces, boundaries, limits, membranes, compartments. Now, when confronted with the puzzle of my patients' difficulties, I try to take stock of their surfaces by simply imagining each, in a kind of review of membranes, as a companion to my review of systems. After all, our notion of systems is very much a product of renaissance anatomy, and does not account for modern understanding of histology and the three-dimensional construct we can create from its tiny slices.



Let's start our inventory with the cell membrane. If we were to include, with the external cell membrane, the inner membranous structures of the endoplasmic reticulum, the Golgi apparatus, nuclear membrane, mitochondria, vacuoles, and liposomes, the total acreage amounts to the dimensions of several football fields—a vast enterprise of diaphanous oily structures that are as slippery and mobile as quicksilver. My patients' health depends on the integrity and flexibility of all of these membranes, which in turn depend on their constituent lipids for that integrity and flexibility. I find it odd that of all the kinds of fatty molecules we animate creatures are able to synthesize from carbohydrate or other lipids, we cannot make—but must eat—the linoleic and alpha linolenic acids of which the constituent fatty acids of our lipid membranes consist or are made.

Imagine, for a moment, the fictional committee meeting of the earliest ancestors of our cells, when they were but isolated, single-cellular organisms bent on achieving a multicellular status. Knowing what we now know about intercellular communication, how do we imagine that communication in that committee could have taken place? At first, the only option would have been direct contact, cell membrane to cell membrane. That must have been tiresome and rendered obsolete by the dispatch of membrane molecules, whose travel would substitute for the displacement of whole cells about the gathering. Thus was born the system of molecules we now understand as cytokines: messengers derived from the structural components of the cell membrane, like stones cast by masonry walls except for the opposite sense of rigidity conveyed by that analogy. Mobility in place, and motility of its component molecules transformed into messengers as prostanoid cytokines, are the features that capture our attention as we consider the difficulties of patients with an insufficiency of the component flexible molecules of cell membranes, and a resultant substitution by stiffer molecules. As discussed in my

previous *Lenses* article describing features of the dopamine D4 receptor site and its pathology (*IMCJ*. 2004;3:6:10-13), the consequences of stiffness (either from poor methylation or from abnormal saturated constituents) are diminished function in terms of cellular capacity for receiving messages, as well as for providing the materials needed for cytokine production. In that article, I described a young man with a kind of rigidity—or poor modulation—of behavior, accompanied by dry, stiff, or brittle qualities in his hair, skin, and nails. Supplementation with tablespoon quantities of flaxseed oil brought about dramatic improvement in his tantrums, as it also did in his integument. Of all our efforts to see the biochemistry of our patients in their physical appearance, none is as straightforward as the implication of membrane pathology from lackluster skin and associated signs.

Our notion of integrity of our lipid membranous acreage extends from its constituent molecules to its electrical properties, not so much in the sense of the ion flux associated with neuromuscular impulses as in the sense of the potential loss of electrons. The tight packing of the component-stacked unsaturated fatty acids of cellular membranes provides a milieu in which oxidative stress may spread like falling dominoes in ways that are more extensive than, say, oxidative damage to a protein. When I take inventory of of an individual patient's membranes, I include the question of oxidative stress along with that of his or her fatty-acid nutrition and methylation. Such a question about oxidative stress regards the total collective surface of *all* the molecules of the organism—not just the lipid membranes—as a kind of infinitely complex boundary whose integrity is subject to oxidative wear and tear.

As I consider how the functioning of surfaces may affect the expression of his or her genetic inclination to disease, a third, less subtle surface I visualize is the mucous membrane of my patient's digestive tract. Here we can see a "double-velvet," the nap of which constitutes a topology which, if flattened, would be the size of a tennis court. So, size alone would qualify the digestive-tract surface as a big budget item in any assessment of a human's health. If we all walked about with our digestive surfaces exposed like the sails of a yacht, there would be no question concerning the significance of the integrity of this inner skin. How much better off would we be, exposed to the world so that the mystification of our innards would be undone by simple visualization and escape from endoscopy? Still, I suppose, our digestive sails would be subject to the same hair-splitting as in dermatology, and in most conditions, however eponymically distinctive, would still be treated with anti-inflammatory drugs without any thought as to what food or flora might be causing that "rash." Food and flora are the two agenda of the digestive membrane and its pathologies, including its permeability or lack thereof. The "leaky gut" notion has captured the imagination of laypersons and professionals alike and has taken on a mystique as the cause of trouble, comparable to the notion that depression is the cause of sadness. One would think that if increased intestinal permeability caused diverse absorptive anomalies, then patients with a high urinary lactulose/mannitol ratio, after loading, would show correlated changes in the several consequences we would attribute to leakiness: higher urinary excretion of peptides (including dipeptides as well as polypeptides), a greater tendency toward formation of antibodies to foods, increased urinary levels of gut-derived microbial metabolites, and other markers consistent with yeast problems. An analysis of a group of my autistic children's data showed no such correlation, making me reject the idea of leaky gut as an underlying phenomenon—a kind of tide upon which these various boats all rise and fall—and suggesting to me that leaky gut may be much more selective as both cause and effect in relation to food allergy, peptiduria, yeast problems, and other forms of dysbiosis.

The lungs are another hidden tennis court-sized surface, but with a much less complex ecology than the gut. The place where I notice some implication of the systemic effects of subtle pulmonary variation in individuals without lung disease is on the exam table when I ask for a deep breath and see the patient's shoulders rise with chest expansion and abdominal contraction. Only the occasional yoga teacher, singer, or wind instrumentalist displays a stationary chest and expanding gut with the efficient descent of his or her diaphragm. Here we have an example of a perfectly good membrane being abused during its proper function of ridding blood of carbon dioxide and gathering oxygen. There are rhythmic aspects of this physiology that I will take up in a later *Lenses* article, when I will raise the question—How many of our patients have inefficient breathing and a mild chronic respiratory acidosis because they go around sucking in their guts and sticking out their chests, and do so even more so when under stress (which is most of the time)? Thus, via self-consciousness, we return to consciousness and its boundaries, also a topic to be explored toward the end of this series of essays.

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