THE JOURNAL OF INVESTIGATIVE DERMATOLOGY, 67:672–676, 1976

Vol. 67, No. 5, Part 2 of 2 parts
Printed in U.S.A.

PERMEABILITY OF THE SKIN: A REVIEW OF MAJOR CONCEPTS AND SOME NEW DEVELOPMENTS

ROBERT J. SCHEUPLEIN, PH.D.

Department of Dermatology, Harvard Medical School, Boston, Massachusetts, U. S. A.

Before any topically applied drug can act either locally or systemically, it must penetrate the "barrier layer" of the skin, the stratum corneum. The penetration of the stratum corneum is the necessary first step, not only for the therapeutic action of applied drugs, but also for any injury produced by externally applied chemical agents or antigenic substances. Since literally thousands of different substances produce delayed hypersensitivity reactions in apparently normal skin, it is evident that the protective permeability barrier of the skin is not perfect.

What is the nature of the barrier layer? How do molecules get through it? Is the stratum corneum uniformly impermeable or is one part more permeable than another? How fast does penetration occur; and how is this affected by the chemical nature of the penetrating molecules? Can the permeation rates of substances be modified by using different vehicles or by hydration? What concentration levels are produced in the viable layers of the skin by the topical application of a drug? Is the blood perfusion rate a controlling factor in percutaneous absorption? Answers to these and related questions are of obvious importance to dermatologic practice, to the formulating of topical preparations, and to skin physiology in general. These issues have been the major concern of investigators of skin permeability.

STRUCTURE OF THE STRATUM CORNEUM

Through most of the 1950s, attention was focused on the question of the precise location of the barrier layer within the stratum corneum. To the skin biologists of that era, the stratum corneum appeared to be a highly porous tissue composed of a coarse network of loosely connected cells; clearly not, so it seemed, a plausible candidate for the major permeability barrier of the skin. A variety of skin conditions involving chapped, dried, or desquamating horny layers and the appearance of the tissue in histologic cross sections (Fig. 1, *top*) lent support to this view. The damage inflicted on the stratum corneum by the usual histologic techniques was not fully appreciated until relatively recently. Attention was drawn to the junction of the viable epidermis and the stratum corneum, where there exists a transitional zone which appeared more compact. Rein [1] had theorized that this region was the site of a permanent electrical double layer, impermeable to anions. This layer, identified by some as the stratum lucidum, became the site of the skin's major diffusional resistance in the minds of most authoritative investigators. This mistaken conception persists to this day in some textbooks, although we now know it is not true.

The stratum corneum is now widely acknowledged to be essentially uniformly impermeable. The best direct evidence comes from studies that reveal the location of substances within the stratum corneum some time after application. These studies show that the outer layers, in fact, greatly impede penetration and are not significantly different from the inner layers. Careful morphologic studies using less destructive techniques give no reason to doubt this conclusion. This change in our conception of the stratum corneum from a friable, porous tissue to a coherent, compact membrane has accompanied the increasing sophistication and fidelity of our techniques of visualization using electron microscopy and scanning electron microscopy (Figs. 1, 2).

BIOPHYSICS OF TRANSPORT

Penetration experiments on hundreds of substances have demonstrated that the stratum corneum behaves like a passive diffusion barrier [2]. Differences between "live" and "dead" skin have been observed but these cannot be ascribed to active transport processes.

Data on the penetration of water and low-molecular-weight nonelectrolytes have given clear evidence that permeability through epidermis (stratum corneum included) is proportional to concentration [3]. Tissue:vehicle partition coefficients were obtained and these correlated well with measured permeabilities and explained the observed increase in permeability in ascending homologous series of nonelectrolytes [4]. Further work led to an expanded form of Fick's law for steady-state transport through skin:

$$J = (DK/\delta)\,\Delta C_v = k_p\,\Delta C_v \qquad (1)$$

where:

J = solute flux;

D = solute diffusion constant in the stratum

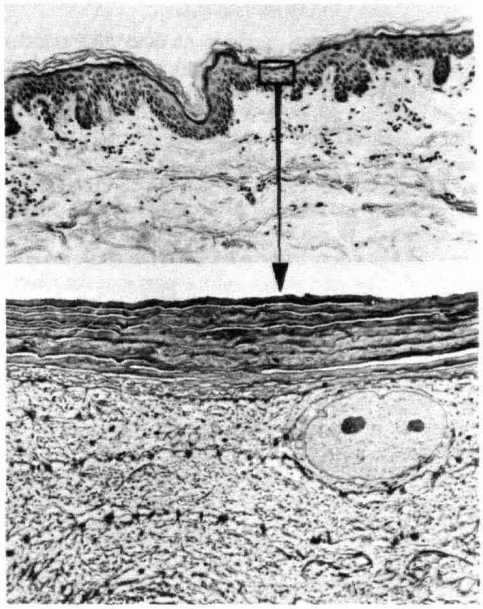


FIG. 1. *Top*: Stained cross section of human skin. Stratum corneum has porous appearance typical of histologic preparations (× 57). *Bottom:* Electron photomicrograph of uppermost layer of epidermis. Stratum corneum appears more compact than above, but spaces are evident between cells; these are not present in well-prepared specimens (× 2,200).

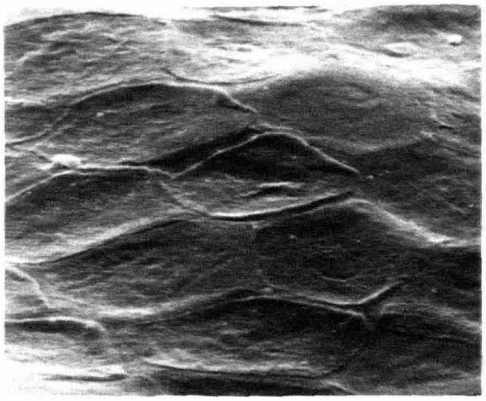


FIG. 2. Scanning electron photomicrograph of uppermost layer of stratum corneum. The overlap and close packing of adjacent cells is evident (× 540).

ΔC_v = external concentration difference of solute in the vehicle on opposite sides of the tissue.

This relation succinctly summarized hundreds of observations and became the fundamental basis of more sophisticated studies. By measuring the apportioned [5]. Dermal resistance was found to be negligible except possibly in the case of extremely lipid-soluble, highly diffusable penetrants (Fig. 3). The diffusion constants for low-molecular-weight nonelectrolytes are approximately $10^{-9} \cdot cm^2 \cdot sec^{-1}$ and $6 \times 10^{-6} \cdot cm^2 \cdot sec^{-1}$ for stratum corneum and dermis, respectively.

CHEMICAL NATURE OF THE PENETRANT

It became clear that hydrated stratum corneum had an affinity for both water-soluble and lipid-soluble nonelectrolytes. As a result, the stratum corneum, while not very permeable to any substance, is slightly permeable to both water-soluble and lipid-soluble substances. Both the mechanism of diffusion and the diffusion pathway through the tissue taken by penetrating molecules appears to depend upon whether they are water-soluble or water-insoluble, lipid-soluble molecules. Activation energies for the permeation of water and water-soluble alkanols were found to be = 15 kcal. $mole^{-1}$; the activation energies for the corresponding lipid-soluble alkanols are = 10 kcal $\cdot mol^{-1}$. Increasing the polar character of the penetrant molecule by increasing the number of polar groups resulted in higher activation energies and still lower permeabilities (Fig. 4). From these and other data it was determined that the major pathway for water-soluble molecules was primarily transcellular, i.e., through cells and cell walls alike without discrimination. The lipid-protein-water keratin structure within the cells (Fig. 5) was pinpointed

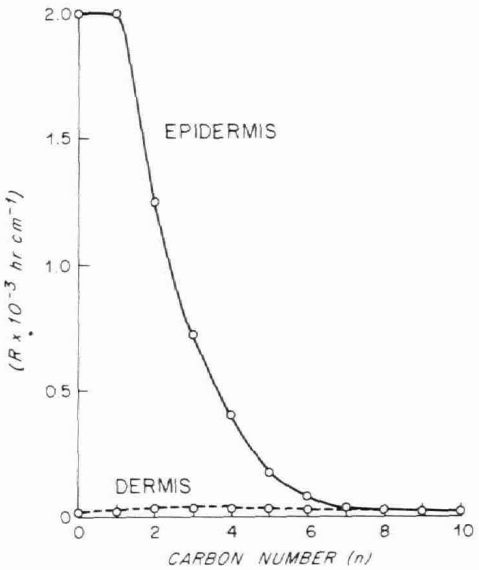


FIG. 3. Relative effectiveness of epidermis (including

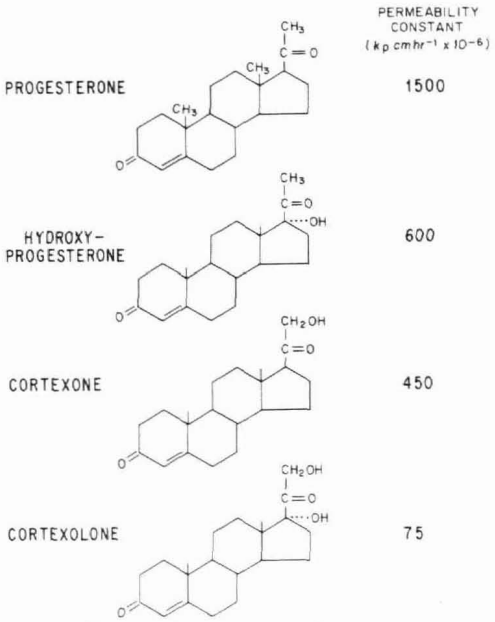


FIG. 4. Decrease in the permeability constant of steroid molecules as more hydroxyl groups are introduced [4].

as the site of the tissues' major diffusional resistance for water-soluble molecules. A great deal of evidence supports the hypothesis that the water within this structure is "bound" in the sense that the diffusion of this water and the solutes dissolved within it occurs very slowly.

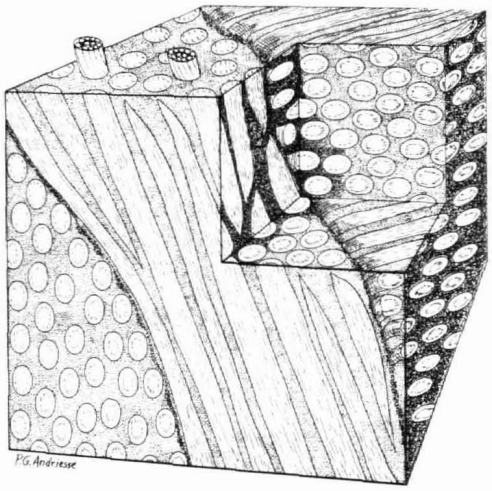
The pathway for lipid-soluble molecules is not known; it presumably follows the endogenous lipid within the stratum corneum. Present evidence suggests that the bulk of these lipids are intercellular. But earlier work suggested that lipids were also located between the keratin filaments within the cells [6].

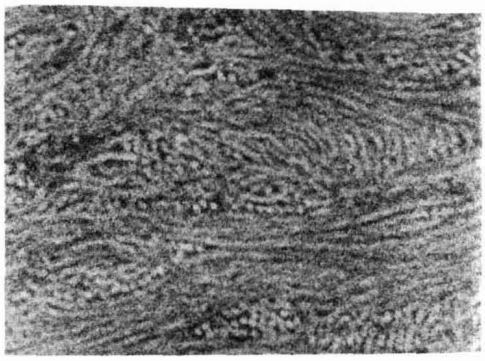
SKIN APPENDAGES [5]

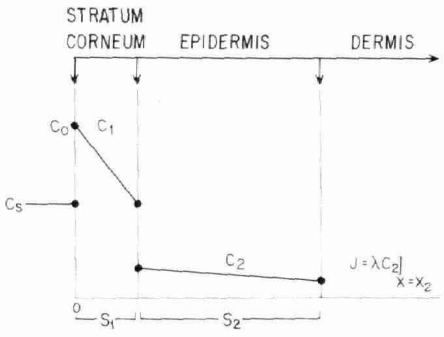
Sweat ducts and hair follicles can act as diffusion shunts, i.e., relatively easy pathways through the stratum corneum. For the most part, the effect of these appendageal shunts is minimized owing to their relatively small total fractional area $\sim 10^{-3}$ (on abdominal skin). But for ions, polyfunctional polar compounds, e.g., cortisol, and extremely large molecules that can penetrate the bulk stratum corneum only very slowly, diffusion through shunt pathways can be very significant and must be taken into account. Since the lag times for a shunt pathway can be quite small, this route of entry is the likely one when a chemically complex drug is observed to produce a pharmacologic re-

VEHICLES [7,8]

Most liquids can damage or alter the stratum corneum; organic solvents and particularly mixtures of organic solvents, e.g., chloroform:methanol, ethanol:ether, are efficient delipidizing solvents and rapidly damage the barrier. Vehicles are normally chosen from mild or innocous liquids and the influence of the vehicle on the release and penetration of the solute is still not completely understood. Some progress has been made, however, and in contrast to past doctrine it is now clear that vehicles can affect solute permeation even if the stratum corneum per se is not affected. As shown by equation (1) the flux depends on the product of external concentration (if $\Delta C_v = C_v$ and the partition coefficient $K = (C_m/C_v)$ where C_m is the solute concentration in the tissue). As the vehicle is changed so that the solute becomes less soluble in it, C_m and K increase and so does permeability. For example, the polar alkanols







$$\frac{\partial}{\partial x}\left(D\frac{\partial}{\partial x}\right) = 0 = \frac{\partial c}{\partial t} \quad \text{Steady State}$$

$$J = \frac{C_S}{\frac{\delta_1}{D_1 K} + \frac{\delta_2}{D_2} + \frac{1}{\lambda}} = k_p C_S$$

$$\frac{1}{kp} = \sum_1^3 R_i = R_{SC} + R_{Expid} + R_{Perf}$$
$$= 10^7 + 4 \times 10^3 + 3\text{-}30 \times 10^3 \ (\text{sec cm}^{-1})$$

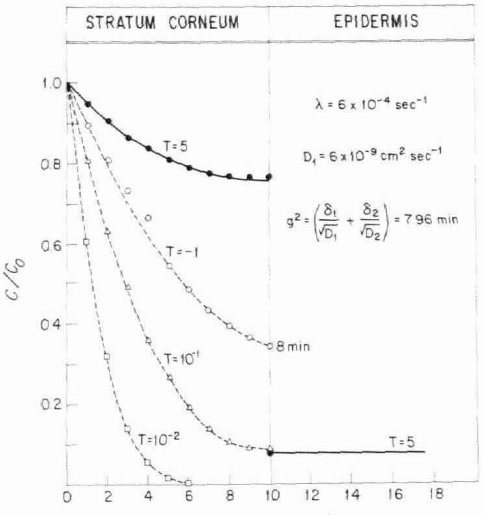
FIG. 6. Steady-state concentration levels in the skin. *Boxed equation* shows the limiting form of the permeability constant to be an additive function of three separate diffusional resistances.
D_1 (stratum corneum) $= 6 \times 10^{-9} \cdot \text{cm}^2 \cdot \text{sec}^{-1}$
D_2 (viable epidermis) $= 5 \times 10^{-6} \cdot \text{cm}^2 \cdot \text{sec}^{-1}$
$K = 10$
$\lambda = 6 \times 10^{-4} \cdot \text{cm} \cdot \text{sec}^{-1}$

penetrate better from organic vehicles than they do from water.

It has been suggested that for saturated solutions, C_m should, ideally, be constant and that the penetration of a solute from its saturated solution should be maximal and independent of the vehicle used. Behavior of this type has been observed in isolated instances but it is by no means generally true [8]. Apparently, most vehicles are absorbed to some extent by the stratum corneum and produce direct effects on it. These lead to changes in the solubility and diffusivity of substances in the tissue and, accordingly, in their permeation rates. Water and aprotic solvents like dimethylsulfoxide are capable of increasing permeation rates markedly. Neither vehicle acts as a "carrier" nor is the increased permeation due simply to a more favorable partition coefficient for the particular solute or to irreversible tissue damage [9].

action in the skin. It is not usually appreciated that not only penetration must occur, but adequate penetration must occur to give effective concentration levels at the site or sites desired. At the present time it is not feasible to measure experimentally the time-dependent concentration levels in the skin after a substance is applied topically. However, this kind of information is now well within our capacity to calculate using a realistic model for the skin. The skin can be considered to be a composite diffusion media corresponding to stratum corneum, epidermis, and a thin layer of dermis, each with its corresponding diffusion constant, thickness, and partition coefficient. This overlays a reservoir (the blood stream) which offers a diffusional resistance inversely proportional to blood flow and which is saturable by the solute.

The problem is mathematically complex and has to be solved by approximate methods. Some initial results are given in Figures 6 and 7 which are steady-state and time-dependent concentration levels, respectively. The expression for the flux in Figure 6 shows that the rate of blood perfusion can be treated as an additive resistance after steady state is achieved. The numerical values suggest that it is negligible even under basal conditions. Because the diffusivity of the viable epidermis and dermis is so much greater than the stratum corneum, the concentration levels in the epidermis are, for all practical purposes, always flat. Both Figures illustrate the role of the partition coefficient in markedly lowering the concentration of lipid-soluble nonelectrolytes in the viable tissue as compared to their concentrations in the stratum corneum.



REFERENCES

1. Rein H: Z Biol 81:125, 1924
2. Tregear RT: *In* Monographs in Theoretical and Experimental Biology, vol 5. New York, Academic, 1966
3. Scheuplein RJ, Blank IH: J Invest Dermatol 60:286, 1973
4. Scheuplein RJ, Blank IH: *Physiol Rev* 51:702, 1971
5. Scheuplein RJ: J Invest Dermatol 48:79, 1967
6. Brody I: J Ultrastruct Res 4:267, 1960
7. Higuchi T: J Soc Cosmet Chem 11:85, 1960
8. Poulsen BJ: *In* Advances in Biology of Skin, vol XII. Edited by W Montagna, R Stoughton, EJ Van Scott. New York, Appleton–Century–Crofts, 1972, p 495
9. Elfbaum SG, Laden K: J Soc Cosmet Chem 19:841, 1968