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A Domain Mosaic Model of the Skin Barrier

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The skin barrier primarily protects the body against uncontrolled loss of water and in addition prevents water and matter of the environment from indiscriminately entering the living system. The current concept of the skin barrier suggests that permeability is governed by a hydrophilic and a hydrophobic "channel". To account both for the barrier function and the hydrophilic and hydrophobic pathways through this barrier, we propose a new model, "the domain mosaic model of the skin barrier", which depicts the bulk of the lipids as segregated into crystalline/gel domains bordered by "grain borders" where lipids are in the fluid crystalline state. Such an arrangement provides for an effective "water-tight" barrier that allows a minute and controlled loss of water to keep the corneocytes moistened. In addition the model provides for the necessary mechanical properties permitting bending and stress imposed on the skin surface. Furthermore, the fluid character of the "grain borders" represents areas where lipid and hydrophobic molecules may diffuse through the system on down-hill gradients. It is suggested that in the border areas between the crystalline domains, structural transformations of the lipid organization due to permeation promoters may take place without structural changes in the bulk organization of lipids in the crystalline or gel phase. ***Key word: Epidermal lipids.***

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INTRODUCTION – THE FUNCTION OF THE INTEGUMENT

The integument is a highly specialized structure that provides a number of functions, the main one being formation of an essentially water-tight barrier which allows complete control of the internal aqueous balance of the body and hence control of the body physiology. Such a barrier function also provides protection from environmental chemical hazards. In addition to this all-important function, the integument must provide a mechanically strong and resilient structure that can take physical strain and stress.

Relating these functions to the anatomical structures of the integument, we find that the water barrier is almost exclusively located to the stratum corneum of the epidermis whereas the mechanical properties are mainly provided by the connective tissue of the supporting dermis. However, to be functionally intact even under (and immediately after) mechanical stress, the integrity of the stratum corneum and its barrier (physical and chemical) must remain unimpaired. The stratum corneum cells, the corneocytes, which essentially contain only the fibrillar protein keratin in a structureless protein matrix, therefore must have plastic properties. This is achieved by hydration of the keratin (1), i.e. water is a plasticizer of keratin. When the corneocytes lose their water, the keratin becomes non-elastic and even brittle. In such a condition the integrity of the stratum corneum is threatened.

The entire horny layer is to be regarded as a barrier towards the environment. However, the horny layer and its components are continuously exposed to physical and chemical degradation forces of the environment, and it is therefore a requirement that the barrier is continuously renewed to maintain the water homeostasis of the body.

It has been established beyond doubt that the barrier to water resides in the intercellular lipid structures of the stratum corneum (2–5). A closer look at the skin barrier reveals that it can be described as composed of two major components: a hydrophilic component, the keratin, and a hydrophobic one, the intercellular lipid material which represents a lipophilic/hydrophobic constituent. Elias (6) has depicted the stratum corneum skin barrier as a "brick and mortar" structure. Thus corneocytes (keratin) represent the hydrophilic brick part, whereas the intercellular lipids represent the mortar, the hydrophobic part. Seen in more dynamic terms the keratin constitutes the main hydrophilic pathway and the lipids the hydrophobic pathway in the Elias model (6) as initially presented.

Thus, the main role of the lipid phase is to act as a barrier against water loss from the body but also to prevent free access of water and foreign substances into the body.

A model of the skin barrier must account not only for the consequences of the special physiological requirements on the skin, i.e. to provide a completely water-tight barrier and at the same time allowing a minute loss of water that plasticizes the keratin, but also for the mechanical demands on the integument. How can these seemingly conflicting requirements be met?

In this article we propose a model of the skin barrier which on a theoretical basis meets essentially all the requirements given above but which also provides an understanding of the old concepts of a hydrophilic and a hydrophobic pathway through the skin. The model is based on modern lipid research (c.f. 7) and its biological counterpart is the Singer-Nicholson model of the cell membrane (8) and Elias model of the skin barrier (6). In the following we will refer to this as "the domain mosaic model of the human skin barrier".

FUNCTIONAL ANATOMY OF THE STRATUM CORNEUM

The area of the skin surface of a male person of 70 kg is approximately 1.80 m^2. At rest, a total of about 350 ml of water is lost per day through this skin surface by perspiratio insensibilis, the unnoticed perspiration, which does not include secretion from the sweat glands (9). The perspiratio insensibilis amounts to 2.25 $\mu l.m^{-2}.s^{-1}$, i.e. we can regard the stratum corneum as a water-impermeable structure.

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Physical and chemical agents that continuously act on the skin will abrade the epidermal surface mechanically but will also extract more or less selectively and in other ways change the composition of the intercellular lipids. A continuous renewal of the lipid structures that constitute the water barrier is therefore necessary. Such a continuous renewal requires that the surface layer of the horny layer is shed at a pace largely synchronous with the addition of new corneocytes and intercellular material at the bottom of the stratum corneum (10). This process ensures that the thickness of the stratum corneum remains approximately constant.

The corneocytes

Over a distance of approximately 100 μm the columnar or rounded cell progenies of the germinative, basal cells of the epidermis are transformed into flat corneocytes filled with keratin, i.e. a fibrous protein in an unstructured protein matrix. During this differentiation the lipid membranes of the basal cells are replaced by a layered proteinaceous structure completely enclosing the keratin in the corneocyte (c.f. 11).

The stratum corneum cells are joined through desmosome-like structures and through the cohesive effects of the intercellular lipids. The desquamation of the outermost layer of the stratum corneum, the stratum disjunctum, is a result of enzymatic processes involving proteases and lipases acting on the desmosomes and intercellular lipids, respectively (6).

Keratin is characterized by its insolubility, its high content of sulphur (cystein and cystin residues) and its conspicuous affinity for water (1). If the corneocyte keratin is deprived of its water the material becomes brittle and breaks easily.[1] Hence, for a supple skin a constant flow of water to the corneocytes is a necessity.

The intercellular space

The intercellular space between the corneocytes has been estimated to occupy approximately 20% of the total stratum corneum volume (12). In contrast to the open spaces of the Malpighian layers of the epidermis, the intercellular space of the intact stratum corneum is filled with lipids which form a continuous lipid compartment (3,6,13). These lipids are derived from ovoid and rounded structures filled with lipids organized in stacks of bilayers, the lamellar bodies[2]. The lamellar bodies can be observed by transmission electron microscopy (TEM) in the upper part of the stratum spinosum and finally accumulate at the upper border of the stratum granulosum cells facing the lowermost corneocytes. Here the envelope of the lamellar bodies fuses with the cell membrane of the granulosum cell and the lipid material is extruded into the previously void intercellular space. The lipid phase is subsequently organized into stacked bilamellar structures, presumably sandwiched with a continuous water phase.

[1] You can test this by cutting a piece of callus from your heal, bend it and notice how flexible it is. Let it dry over night and try again to bend it. When completely dry it will break with a snap!

[2] Also known under the synonyms Odland bodies, membrane coating granules – MCG.

LIPIDS OF THE EPIDERMIS

Content of lipid classes

The phospholipid part of the total lipid content of the epidermis is approximately 60% in the stratum germinativum and drops to about 20% in the stratum spinosum to approach nearly nil, approximately 0.1% in the stratum corneum (14,15).

It is conceivable that the overall organization of the integument, for example if it carries a furry coat, will influence the specific details of the barrier such as the total lipid composition. Hence, when the aim is to understand how organic and inorganic allergens and irritants may penetrate the epidermal barrier the choice of experimental animal must be made with utmost care if the results are to be relevant for corresponding situations for human skin. Gray & Yardley (14) who were among the pioneers in skin lipid analysis, showed that pig skin and human skin display a remarkable resemblance in their lipid composition (which incidentally is also true for the architecture). Rat skin, on the other hand, is dominated by wax esters which are absent in human (or pig) skin. In the horny layer of human skin the content of lipids was found to be 8% of the total dry weight. Neutral lipids were estimated to comprise >95% of the lipids and the ceramide part was approximately 17%. In fractions of the total stratum corneum lipids cholesterol has been reported to comprise almost 20% , cholesteryl esters 0.7%, fatty acids 26%, triacylglycerol 2.6% and ceramides ~49% (16).

It should be noted that there is a regional variation in the lipid content of the stratum corneum which approximately corresponds to the regional permeability properties of the barrier (17).

Lipids of the barrier

The unusually high ceramide content for a human (or for that matter mammalian) tissue has been confirmed by several authors. Gray & White (18,19) isolated 4 ceramide factions that were all characterized by a high proportion (50% – 80%) of fatty acid chains with 24 to 30 carbons (C_{24} – C_{30}). The conclusion was that these long chains of the glycosphingolipids and ceramides in addition to the 2-hydroxy fatty acids with melting point >75°C are likely to provide resistance to temperature variations, UV-exposure and air oxidation and still be amphiphilic enough to form stable lipid phases.

From the basal cell layer to the stratum corneum the chain lengths of the lipids increase conspicuously. Recently Long et al. have demonstrated the presence of six different ceramides in the horny layer of man (20). Their results show that a conspicuous feature of many of these ceramides are chain lengths> C_{24}. The authors also isolated cholesteryl sulphate. Schwartzendruber et al. (21) have shown that corneocytes have a chemically bound lipid envelope. Using mild alkali hydrolysis Wertz et al. (22) have shown covalent bonding of proteins of the corneocyte envelope by C_{30} – C_{34} omega-hydroxyacids and hydroxyacylsphingosines as well as saturated fatty acids with chain lengths C_{14} – C_{22}. Such covalently bound lipids are thought to represent anchoring units which allow the intercellular lipids to be organized into a lipid envelope around the corneocyte by binding to the hydrophobic phase of the bilamellar systems. A technically interesting point raised by the authors suggests that 95% ethanol

is a solvent which can extract all ceramides from the intact epidermis. Finally, by isolating ceramides by preparative TLC (thin layer chromatography) Wertz et al. (23) have shown that these lipids can form bilayers at physiological pH. We must conclude that a system containing aliphatic chain lengths in the range $C_{18} - C_{34}$ is likely to be in a crystalline or a gel phase at normal skin surface temperature (approx. 28°C – 32°C).

Pathways of synthesis

Using radioactive 1–^{14}C-acetate injected intradermally into pigs Hedberg et al. (24) recorded the pathway of lipid synthesis. As a general trend all activity was first recorded in the aliphatic carbon chains of the phospholipids. Later the activity was transferred via glycosylceramides to ceramides 1–7 days after labelling. The free fatty acids show the same pattern of labelling. Significant uptake only a few hours after the injection was demonstrated for the triglycerides and the interpretation is that these moieties represent intermediate stages in the lipid metabolism.

It is notable that phospholipid synthesis occurs also in the stratum granulosum where ceramides and free fatty acids are produced as well. If synthesis of phospholipids was confined only to the basal cell layer a delay of approximately 14 days should have been recorded, corresponding to the cellular turnover rate for keratinocytes of the epidermis. On the basis of the same sort of argument it is suggested that the glycosylceramides are likely to be intermediates to the ceramides. The results suggest that the aliphatic carbon chains of the fatty acids of the stratum corneum have been synthesized de novo via phospholipids in the epidermis. The impressive chain lengths found in the stratum corneum lipids support this notion.

Cholesterol is synthesized within hours after the labelling and the esters are labelled 3–7 days later.

As stated above, the lipids destined to form the lipid barrier of the skin are organized into lamellar structures which form more or less spherical bodies surrounded by a membrane apparently identical to that of the cell membrane. At the stratum granulosum border towards the first layer of the stratum corneum the membrane of the lamellar bodies fuses with the cell membrane and the lamellar body content is deposited in the intercellular space. Subsequently the lamellae are oriented along the cell envelope of the corneocyte and fuse into sheets of lipids which in the TEM can be demonstrated as stacks of lipid lamellae (2,25).

PHASE BEHAVIOUR OF LIPIDS

Lipids that can form biological membranes are characterized by a hydrophobic part, generally fatty acid hydrocarbon chains, and a more or less hydrophilic head. For thermodynamic reasons the hydrophobic parts of the lipid molecules are segregated to form a separate region, while the hydrophilic head group faces the surrounding aqueous phase (7). The cohesion of such aggregates, e.g. liposomes and bilamellar structures, depends on a number of factors such as the charge of the head group and its hydration sphere, the hydrocarbon chain length, degree of unsaturation of the aliphatic chains and temperature. The major forces involved in a bilamellar organization are hydrophobic interactions between the hydrocarbon tails which cause the molecules to associate, and also to the hydrophilic character of the head group which requires that this stays in contact with the water phase. We can see this as two opposing forces acting in the interface region, the first tending to decrease, the second tending to increase the interfacial area per head group, i.e. both having effects on the packing density of the lipid units in the bilayer. Lipids in lamellar bilayers of liposomes and membranes can be found to exist in either of two main states depending on the temperature of the system, a fluid crystalline state and a crystalline or a gel state. If the temperature is lowered the lipids are forced into a crystalline state. When such crystalline bilayers have water on both sides they are termed gel phase.

From a biologist's point of view the Singer-Nicholson fluid mosaic model of the cell membrane (8) brought to attention the fact that lipids of mammalian tissues aggregate into a more or less fluid state at ambient temperature. In this state the lipid units freely diffuse in random paths in the plane of the lipid bilayer ($D = \sim 10^{-11}$ m^2 s^{-1}). A transfer of a lipid molecule from one side to the opposed layer of the membrane bilamellar structure through a "flip-flop" process is a possible, but relatively rare event occurring on time scales of seconds and can therefore be neglected in the present context (7). This fluid crystalline phase, which represents a relatively open structure, allows a nearly free and undirected passage of water which is more than eight orders of magnitude faster than the passage of monovalent ions such as K^+, for which the membrane is more or less impermeable as it is to most other ions (26). The fluid crystalline state, which is characteristic of membranes of living cells, allows the cell membrane to have plastic properties which, in addition to the said physiological properties, permits stress without undue strain under normal conditions.

If the temperature is lowered a phase transition may occur which forces the lipid units into a crystalline or a gel phase. Thus in the gel phase the lipid units are densely packed and this phase is virtually impermeable to water compared to the fluid crystalline phase. For a single type of lipid forming a bilayer phase there is a defined temperature at which this transition between the crystalline and the fluid crystalline phase takes place, the transition temperature (7). This temperature will be influenced by the chain length and the degree of unsaturation in the aliphatic chain(s), to the effect that greater chain lengths require higher temperature for the transition to occur whereas a higher degree of unsaturation moves the transition temperature to lower values. In mixtures of lipids the transition temperature will depend on the proportions of lipids included in the bilayers and will hence be different from that of a pure single moiety type of bilayer. At least in part this may be due to a segregation of the different lipid species into separate domains (7,27). Consequently, depending on the tissue and the climatic environment, the transition temperatures for mammalian membrane lipids are normally within the range of 0°C – 40°C.

PHASE BEHAVIOUR OF SKIN BARRIER LIPIDS

The Singer-Nicholson model of the cell membrane (8) allows a free, bi-directional diffusion of water over the membrane bilayer. The osmotic control of the intracellular water content is related to an active and a passive transport of ions over the

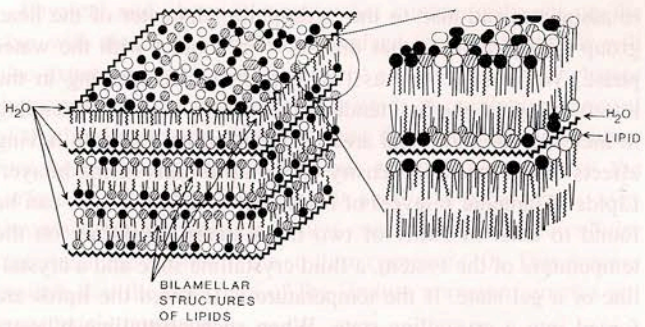

Fig 1. Traditional model of "stochastic" lipid arrangement in bilamellar structures. There is a completely random distribution of the lipid units in the plane of the lipid bilayers.

membrane of a living cell (26). This is fundamentally different from the function of the stratum corneum barrier, which is designed to enclose the entire body system in a water-tight envelope. Consequently, if the barrier properties of the skin are such as to effectively prevent water from leaving the organism, we expect the bulk of the lipids to be in a crystalline or gel phase. It has been shown that lipid extracts from human skin have several transition temperatures (28–32), a lower one around 37°C to 40°C, i.e. above the normal temperature range of the skin, but still at a physiologically acceptable temperature. In addition there are further indications of hydrocarbon chain melting at higher (unphysiological) temperatures. The transition in the physiological temperature range is ascribed to a gel-liquid transition of the lipid bilayers, an interpretation supported by the reversible character of this phase change and additional data from wide-angle diffraction studies (29,33). Studies by Thewalt et al. suggest that the phase behaviour of the intercellular lipids of the stratum corneum is even more complex and that some lipid components have lipid motions even more inhibited than is found in the gel phase (34). Tanaka and co-workers (31) have shown that membrane lipids of the epidermis show increased fluidity in the basal layers as compared to the granular layer and the horny layer. This corresponds to a dominance of lecithin and sphingomyelin in the basal cell layer ($<C_{20}$) in contrast to the much longer aliphatic chains ($C_{22} - >C_{30}$) of ceramides etc in stratum corneum.

According to Lampe et al. (17) there is a relation between the permeability of a certain skin region and its lipid composition. The ratio of neutral lipids to sphingolipids is in general proportional to the known permeability of the said area, i.e. a higher content of neutral lipids and a lower content of sphingolipids provide a better barrier function.

In recent years evidence for segregation of lipids in the barrier has accumulated (29,35). Iraelachvili et al. (7) discuss experimental evidence for a corresponding segregation of the lipids in cell membranes in their review of the physical principles of membrane organization. Such a segregation may occur if there is a significant difference in the chain length of different lipids in bilamellar structures consisting of several lipid types. Also, the head group influences the total organization of the lipid in a bilayer, e.g. the relatively large head group of lecithin with a large hydration sphere induces a significant tilt in the hydrocarbon chains, whereas in bilayers of phosphatidylethanolamine, which has a smaller head group and hydration sphere, the hydrocarbon chains remain in a perpendicular orientation. Segregation between anionic and neutral lipids can be induced by cation binding, e.g. Ca^{2+} which is often stoichiometric. When phase separation between frozen and fluid lipids occurs, it has been observed that they usually separate into domains containing different mixtures of each species. It is of interest to note that cholesterol partitions into the fluid phase because of the rigidity of the molecule (7).

In cell membranes phase separation can be seen as a functional advantage because it can help to maintain a constant lateral pressure when the membrane area is changed. This may occur on incorporation or removal of membrane material or at thermal and osmotic shock. Heterogeneity of the lipid composition is thus one factor that provides for stable bilayers (7). Conceivably this line of reasoning can used in connection with the organization of the barrier lipids.

Atomic force microscopy has demonstrated that short-range orders exist in lipid systems brought into gel phase by a Langmuir-Blodgett technique and deposited on a mica substrate (36). Such a short-range order is likely to be established with time through diffusion processes and will disappear on melting. Preliminary experiments on skin lipid extract using scanning microcalorimetry yielded different transition temperatures for the first and subsequent runs, indicating that melting at temperatures >70°C randomizes the initial ordering (P. Sellers, unpublished observations). Short-range orders are also a characteristic feature of x-ray diffraction studies on stratum corneum lipids (29,33).

PHYSIOLOGICALLY IMPORTANT ELEMENTS AND THEIR RELATION TO THE SKIN BARRIER

Although substantial efforts have been made to identify the true composition of the stratum corneum lipids, no true consensus has yet been reached. This is understandable both from a technical, methodological point of view and from a biological one. The latter aspect was recently demonstrated by Bowstra et al. (33), who recorded conspicuous differences in ceramide and cholesterol content from a set of nine normal individual skin donors. Further investigations into individual variations in lipid composition of the barrier as related to age, sex etc may provide interesting data relevant to the skin in disease.

Experimental studies on skin barrier analogues mainly consisting of commercially available sphingolipids, ceramides and cholesterol (and derivatives of these) have tried to take into account physiological factors such as represented by salt buffer systems (35). It is interesting that elemental analyses of skin cross-sections using particle probes that have detection limits at 200 ppm (electron microprobe) (37) to 1 ppm (proton microprobe) (38) have shown that stratum granulosum and stratum corneum have non-physiological contents of elements such as Na, K, Cl, P, Mg and Ca.

THE THREE-DIMENSIONAL ARRANGEMENT OF LIPIDS IN THE SKIN BARRIER

A domain mosaic model

Transmission electron microscopy has revealed that the lipids of

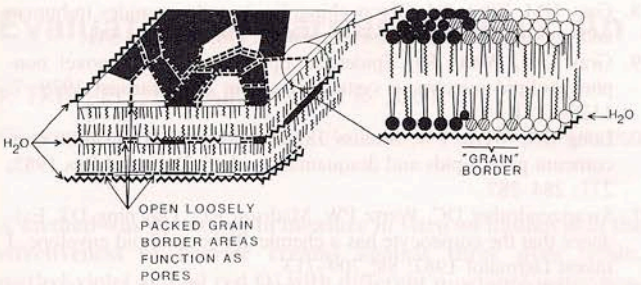

Fig 2. "The domain mosaic model" including grain borders. Lipids with very long chain lengths are segregated into domains in the crystalline/gel phase separated by grain borders populated by lipids with relatively short chain lengths in the liquid crystalline state.

the intercellular spaces of the stratum corneum are organized in stacks of bilayers. In relation both to structure and function the current concept of the epidermal (stratum corneum) barrier can be generalized to the "brick-and-mortar" model of Elias (6), although this simplified model does not do justice to the complexity of the physical constraints on the lipid barrier (5). The actual molecular arrangement of lipids (and proteins) of the barrier is still under debate and no single model has won general acceptance. A review of the topic and relationships to a possible lipid-protein partitioning model for skin penetration enhancement was recently published by Barry (28).

Undoubtedly influenced by the Singer-Nicholson model (8), dermatologists and scientists perceive the arrangement of the lipid units in the barrier as completely randomized (Fig. 1). However, if this was the correct model it would mean that diffusion in the plane of the lipid bilayers would be at hand, i.e. the bilayers would be in the liquid crystalline state. This is not compatible with the fact that there are very long fatty acid chains in the barrier lipids; i.e. a crystalline or a gel phase would dominate the barrier. This sort of arrangement of lipids can be conceived as a quasi-two-dimensional system (Fig. 2).

One of the major problems encountered, should the barrier lipids all be in the crystalline/gel state, is that the mechanical properties of the lipid barrier would be endangered. This has led us to suggest that the bilamellar structure of the barrier can be envisaged as "domains" of segregated lipid moieties in the crystalline/gel state using a two-dimensional analogy from material science where individual metal microcrystals in an alloy form a three-dimensional array. A highly polished surface of such an alloy grain mixture would appear as a pattern of mosaic domains of metal crystals separated by grain borders. In the crystalline state lipid aggregates corresponding to such mosaic domains are connected to their neighbours by "grain borders" within which the lipid units are actually in the fluid crystalline state (Fig. 2). If, for energetic reasons, it is necessary to close the border zone towards the fluid phase we envisage this to occur through incorporation of relatively short-length hydrocarbon lipids that allow a short radius of closure. Corresponding aggregations could appear at the border of the fluid phase. It is conceivable that such fluid areas are dominated by lipids with relatively short hydrocarbon chains, free fatty acids etc with chain lengths $< C_{20}$.

This "domain mosaic model" thus envisages the bulk part of the barrier mainly to be in the crystalline/gel state, effectively hindering water to be lost from the organism. In contrast, the fluid state grain borders will indeed allow some water to permeate the barrier towards the corneocytes, providing for the necessary water to keep the keratin pliable and in mechanically optimal condition. In addition, the fluidity of the grain borders will provide for areas where bending of the bilamellar structures can occur without structural disrupture of the barrier as would be the case if bending took place in a crystalline region.

This tentative model can also explain some features of calorimetric data. The width of the transition peaks recorded by several authors (29,30) can be related to the fact that the domains have a slightly different composition which means that the calorimetric peak is actually a composite peak of overlapping transitions from different domains. Interestingly, the broad low-angle diffraction maxima recorded from human stratum corneum have been interpreted as representing a whole range of repeat distances (29). It is expected that an inconsistency in sequential measurements by scanning microcalorimetry of stratum corneum lipids occurs, as can be explained on a corresponding basis. When reaching temperatures above 340 K (67°C), melting of the lipid bilayers is expected to occur. Within the time span of an experiment the lipid units are not allowed to regain the segregated domain structure instantly after the melting process and a stochastic mixture of the lipids will be at hand when the temperature is lowered on reversing an analysis. Any additional more or less immediate calorimetric run will thus not yield exactly the initial data.

The domain mosaic model provides a generalized concept for the barrier function as well as a concept for the two pathways of permeability, the hydrophobic and the hydrophilic pathway, and is consequently not in conflict with current views on skin permeability. It is conceivable to see the fluid crystalline state of the grain borders as a region where lipids and corresponding hydrophobic molecules will permeate the barrier by diffusion forces. At the same time the fluid phase allows a down-gradient penetration of water from the lower epidermal strata towards the stratum corneum.

When the skin surface is subject to stress more or less parallel to the skin surface it is conceivable that the grain borders due to their fluidity will take upp the strain in parallel, allowing the domains in the gel phase to be virtually uninfluenced by the mechanical force. A corresponding argument can be used for any occurring bending of the barrier which under mechanical stress and strain will remain functional also from a permeability point of view.

The conspicuous increase in permeability occurring when the barrier is infiltrated with detergent can be understood as follows. The detergents, which generally have chain lengths $< C_{18}$, will

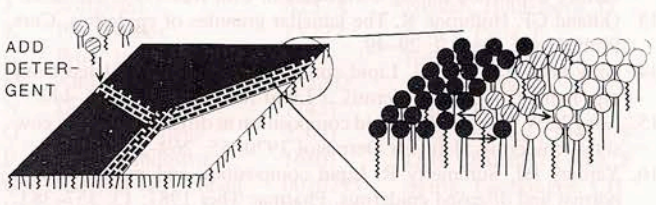

Fig 3. Effect of detergents on the " domain mosaic model". Only one sheet of the bilamellar membrane structure is shown. The detergents infiltrate primarily the fluid regions represented by the grain borders.

preferentially reside in the fluid crystalline phase and to a certain extent fluidize lipid units of the border of domains whereby the width of the grain border will increase and hence, permeability will increase perceivably (Fig. 3). Within the grain borders structural changes of phase properties may occur in the constituent lipids (e.g. transition to a cubic phase), whereby channels for water will be formed, additionally increasing the water permeability of the skin barrier. Such transitions may take place at very low energy costs (7,39,40).

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