Skin Barrier Structure and Function: The Single Gel Phase Model

Lars Norlén

Department of Physics, University of Geneva, Geneva, Switzerland

A new model for the structure and function of the mammalian skin barrier is postulated. It is proposed that the skin barrier, i.e., the intercellular lipid within the stratum corneum, exists as a single and coherent lamellar gel phase. This membrane structure is stabilized by the very particular lipid composition and lipid chain length distributions of the stratum corneum intercellular space and has virtually no phase boundaries. The intact, i.e., unperturbed, single and coherent lamellar gel phase is proposed to be mainly located at the lower half of stratum corneum. Further up, crystalline segregation and phase separation may occur as a result of the desquamation process. The single gel phase model differs significantly from earlier models in that it predicts that no phase separation, neither between liquid crystalline and gel phases nor between different crystalline phases with hexagonal and orthorhombic chain packing, respectively, is present in the unperturbed barrier structure. The new skin barrier model may explain: (i) the measured water permeability of stratum corneum; (ii) the particular lipid composition of the stratum corneum intercellular space; (iii) the absence of swelling of the stratum corneum intercellular lipid matrix upon hydration; and (iv) the simultaneous presence of hexagonal and orthorhombic hydrocarbon chain packing of the stratum corneum intercellular lipid matrix at physiologic temperatures. Further, the new model is consistent with skin barrier formation according to the membrane folding model of Norlén (2001). This new theoretical model could fully account for the extraordinary barrier capacity of mammalian skin and is hereafter referred to as the single gel phase model. ***Keywords: stratum corneum/lipids/ceramides. J Invest Dermatol 117:830–836, 2001***

The objective of this study was to present a new model for the structure and function of the mammalian skin barrier.

From the 50s to the 70s it has been shown that the human skin barrier primarily is located at the intercellular lipid matrix of the stratum corneum (Blank, 1952; Breathnach *et al*, 1973; Elias and Friend, 1975). Since then several models for the structure and function of the mammalian skin barrier have been proposed, including the "brick and mortar model" of Michaels *et al* and the "domain mosaic model" of Forslind (Michaels *et al*, 1975; Swartzendruber *et al*, 1989; Fenske *et al*, 1994; Kitson *et al*, 1994; Forslind, 1994; Engström *et al*, 1995; Menon and Elias, 1997; Bouwstra *et al*, 1998; Menon *et al*, 1998; Norlén, 1999). There still lacks a comprehensive model, however, that is capable of explaining the structure and function of the mammalian skin barrier, when newer findings regarding stratum corneum lipid composition and lipid distributions have been taken into account (Wertz *et al*, 1987; Norlén *et al*, 1998). Such a theoretical model may provide for a rational design of experimental studies on skin diseases, skin permeability, topical drug administration, skin protection, cosmetic formulations, etc.

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Reprint requests to: Dr. Lars Norlén, University of Geneva, Department of Physics, GAP-Biomedical, 20, Rue de l'École de Médecine, CH-1211 Genève 4, Switzerland. Email: lars.norlen@physics.unige.ch

THE SINGLE GEL PHASE MODEL

Basic idea The principal objective of the skin barrier is to be as tight as possible, except for a minute "leakage" of water needed for the hydration of the keratin of the corneocytes (Blank, 1952; Guyton and Hall, 1996). The skin must also ensure that the barrier capacity is optimal even under widely and abruptly changing environmental conditions (e.g., temperature, pH, salt concentrations, relative humidity, etc.). Consequently, (i) sudden transitions of the physical state of the intercellular lipid matrix of stratum corneum, with possible different permeabilities between the two phases on either side of the transition temperature, and (ii) phase separation between lipids, where permeabilities could be locally enhanced at the interface between different domains (Clerc and Thompson, 1995), will therefore be avoided as much as possible by the mammalian skin. (Note that the current use of the word "phase" in a biologic context is not necessarily reflecting thermodynamically stable phase states as the composition of biologic systems cannot be regarded as constant.) Thus, from a functional point of view the stratum corneum intercellular lipid matrix should be as homogeneous as possible (i.e., ideal physical state, no abrupt phase transitions, as little phase separation as possible). This can, however, only be achieved by heterogeneity in the lipid composition, which (i) broadens phase transition zones, (ii) stabilizes gel phases, and (iii) ensures that the lamellar morphology remains intact so that no "pores" or nonlamellar structures are induced. [A gel phase is a crystalline lamellar lipid structure that usually has a hexagonal hydrocarbon chain packing with rotational disorder along the lipid chain axes

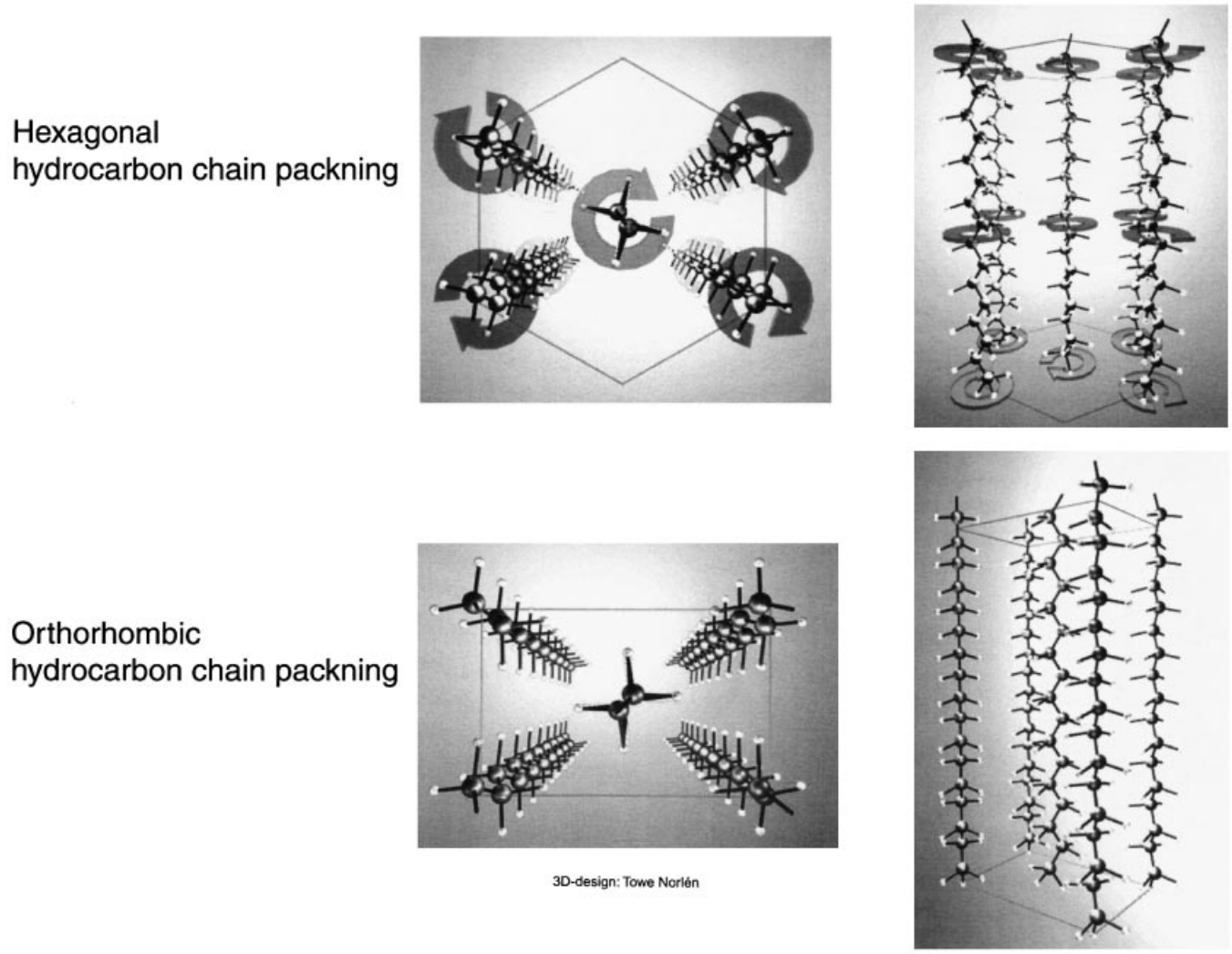

Figure 1. Hexagonal and orthorhombic hydrocarbon chain packing. Note (i) that the lipid alkyl chains are rotating along their axis in the hexagonal chain packing, and (ii) that in the orthorhombic chain packing the plane through every lipid chain is fixed and perpendicular to those of its nearest neighbors. View from above (left) and vertical (right) to the plane of the lipid membrane.

and usually contains some water between the lamellae (**Fig 1**) (cf. Hernquist, 1984, pp16–18, 24–31; Small, 1986, pp98–101; Larsson, 1994, pp13–14, 27.]

The most characteristic features of stratum corneum lipid composition (Wertz *et al*, 1987; Norlén *et al*, 1998; Norlén *et al*, 1999a) are: (i) extensive compositional heterogeneity; (ii) almost complete dominance of saturated, very long hydrocarbon chains (20–36C); and (iii) large relative amounts of cholesterol (**Table I**). These are likewise the main factors stabilizing gel phases (Evans and Wennerström, 1994, p412; Larsson, 1994, pp27, 43; Takahashi *et al*, 1996). [NB: the stability of gel phases increases with chain length and with compositional impurities (e.g., heterogeneity in chain length distributions) (Evans and Wennerström, 1994, p412; Larsson, 1994, pp27, 43; personal communication with Professor Kåre Larsson.] Further, intermixing of different lipid species may be facilitated by the quite stable alkyl chain length distributions of stratum corneum ceramides and free fatty acids (mainly C24:0–C26:0, **Table I**) and by the large relative amounts of cholesterol (approximately 30 mol%, **Table I**) (Sparr *et al*, 1999). In addition, the fact that the sphingosine bases (sphingosine plus dihydrosphingosine) of the ceramides generally are monounsaturated (on average 0.8 double bonds per molecule, **Table I**) and with medium hydrocarbon chain length (approximately 18C per molecule, **Table I**) may contribute to increase the lipid chain mobility of the lamellar gel phase and promote intermixing between ceramides of considerable difference in acyl-chain length (C20:0–C36:0).

It is therefore proposed here that the skin barrier, i.e., the intercellular lipid within the stratum corneum, exists as a single and coherent lamellar gel phase. This membrane structure could be stabilized by cholesterol and by heterogeneities in lipid composition and may possess virtually no phase boundaries.

A single and coherent gel phase may be ideal in a biologic context as a barrier towards the environment. This is because it is a continuous lipid structure with pronounced compositional heterogeneity that may, irrespective of the environmental (physiologically relevant) conditions, possess (i) low permeability (due to the close-packing of the saturated long hydrocarbon chains), at the same time as being (ii) mechanically resistant (due to its ''plasticity'' or ''pliability'' rendered by the retained rotational disorder of the hydrocarbon chains in the hexagonal arrangement, cf. **Fig 1**), and expressing (iii) little or no tendency for phase transitions, phase separation, or induction of ''pores'' or nonlamellar structures.

Role of cholesterol Cholesterol could be a key component for stratum corneum barrier capacity, as *in vitro* it: (i) promotes lamellar structures at high concentrations (> 30 mol%) (Takahashi *et al*,

Table I. Mean number of carbons and double bonds per alkyl chain of stratum corneum lipids from epidermal cysts (calculated from Wertz *et al*, 1987)

Lipid species		Mean carbons per alkyl chain	Mean double bonds per alkyl chain	> 95 mol%	Notes
Ceramide 1 (3wt% of total)	long chain base (sphingosine)	18.7	0.8	C17–22	33 mol% C18:1
	amide linked fatty acid (ω-OH)	29.9	**0.0**	C26–32	59 mol% **C30:0**
	ester linked fatty acid (non-OH)	18.4	0.8	C14–24	24 mol% C18:2
Ceramide 2 (9wt% of total)	long chain base (sphingosine)	18.7	0.8	C17–22	37 mol% C18:1
	amide linked fatty acid (non-OH)	23.5	**0.0**	C16–30	54 mol% **C24–26**
Ceramide 3 (5wt% of total)	long chain base (phytosphingosine)	20.2	0.0	C16–25	61 mol% C19–22
	amide linked fatty acid (non-OH)	23.4	**0.0**	C16–28	51 mol% **C24–26**
Ceramide 4/5 (12wt% of total)	long chain base (sphingosine)	18.4	0.7	C16–22	32 mol% C18:1
	amide linked fatty acid (α-OH)	23.3	**0.0**	C16–26	70 mol% **C24–26**
Ceramide 6I (2wt% of total)	long chain base (phytosphingosine)	19.5	0.0	C16–25	61 mol% C18–20
	amide linked fatty acid (α-OH)	23.1	**0.0**	C18–28	69 mol% **C24–26**
	ester linked fatty acid (α-OH)	20.4	0.0	C16–26	70 mol% C16,24,26
Ceramide 6II (11wt% of total)	long chain base (phytosphingosine)	20.2	0.0	C16–24	48 mol% C20–22
	amide linked fatty acid (α-OH)	23.9	**0.0**	C16–26	81 mol% **C24–26**
Free fatty acids (9wt% of total)		21.3	**0.1**	C16–26	45 mol% **C22–24**
Cholesteryl esters (10wt% of total)		17.9	0.7	C16–18	69 mol% C18:1
Cholesterol (27wt% of total)					

1996) (i.e., decreases the risk for inducing ''pores'' or nonlamellar phases with possible harmful effects on barrier function); (ii) increases the chain mobility of lipids in the gel state (de Kruyff *et al*, 1974) (i.e., render gel phases less viscous or more ''plastic'', i.e., ''pliable'' and therefore more mechanically resistant); (iii) broadens phase transition regions (Takahashi *et al*, 1996), or in some cases may entirely abolish subtransitions between gel phases (i.e., stabilizes gel phases) (McMullen and McElhaney, 1995); and (iv) probably has line-active properties (cf. two-dimensional surfactant – ''lineactant'') in biologic membranes (i.e., promotes intermixing of different lipid species) (Sparr *et al*, 1999). Consequently, the *in vitro* behavior of cholesterol speaks in favor of the single gel phase model.

Too much cholesterol (above its solubility) would lead to the formation of pure domains of crystalline cholesterol and hence increase the risk for discontinuities in the lamellar structure. Consequently, for optimum barrier capacity, the relative amount of cholesterol should be as large as possible but not above the solubility of cholesterol in the lamellar structure, i.e., about 30 mol% (Subramaniam and McConnell, 1987; Lieckfeldt *et al*, 1993; Engblom *et al*, 1998; Norlén and Engblom, 2000). In fact, a depressant effect on water permeability has been observed on addition of cholesterol to ceramide containing, sphingomyelin and phosphatidylcholine membranes (Finkelstein and Cass, 1967; Fettiplace, 1978; Lieckfeldt *et al*, 1993; Schaefer and Redelmeier, 1996, p93). Further, a high cholesterol/ceramide ratio has been shown to render the lamellar lipid organization of mixtures of stratum corneum lipids less sensitive to variations in skin ceramide composition (Bouwstra *et al*, 1999). Cholesterol thus seems to stabilize the preferred morphology of the stratum corneum intercellular lipid, which is in accordance with the single gel phase model.

Proposed molecular arrangement The detailed lamellar arrangement of the stratum corneum intercellular lipid matrix is difficult to predict. In general, a bilayer conformation with alternating layers of water and lipid is probable. This is because, during the preliminary stages of skin barrier morphogenesis the ceramides (or their precursors, the glycosyl ceramides) should be in a hairpin conformation (i.e., with the two alkyl chains pointing in the same direction (cf. **Fig 2*a***) (Corkery and Hyde, 1996), as this is a prerequisite for them to be solved in a liquid crystalline membrane (cf. the membrane folding model of Norlén, 2001). [Note: The crystal form of a plasma membrane galactosyl ceramide has been shown to form a bilayer structure with tilted chains (Pascher and Sundell, 1977).] During the formation of the crystalline stratum corneum intercellular lipid matrix, however, a morphologic transition of the ceramides from hairpin to splayed chain conformation (i.e., with the two alkyl-chains pointing in opposite directions (cf. **Fig 2*b***) (Corkery and Hyde, 1996) is possible. This is because the length difference between the hydrocarbon chain of the amino-alcohol (usually a 18C sphingosine or phytosphingosine base, **Table I**) and the saturated, very long (usually 24–26C, **Table I**) amide-linked fatty acid of the skin ceramides implies that their crystal forms pack in a splayed chain conformation where the sphingosine and fatty acid chains form separate matrices. This has been shown experimentally by Dahlén and Pascher (1979). In a compositionally heterogeneous system, however, such as the stratum corneum intercellular lipid matrix, which in addition may contain water, it is not unlikely that the amino-alcohols of the ceramides may be

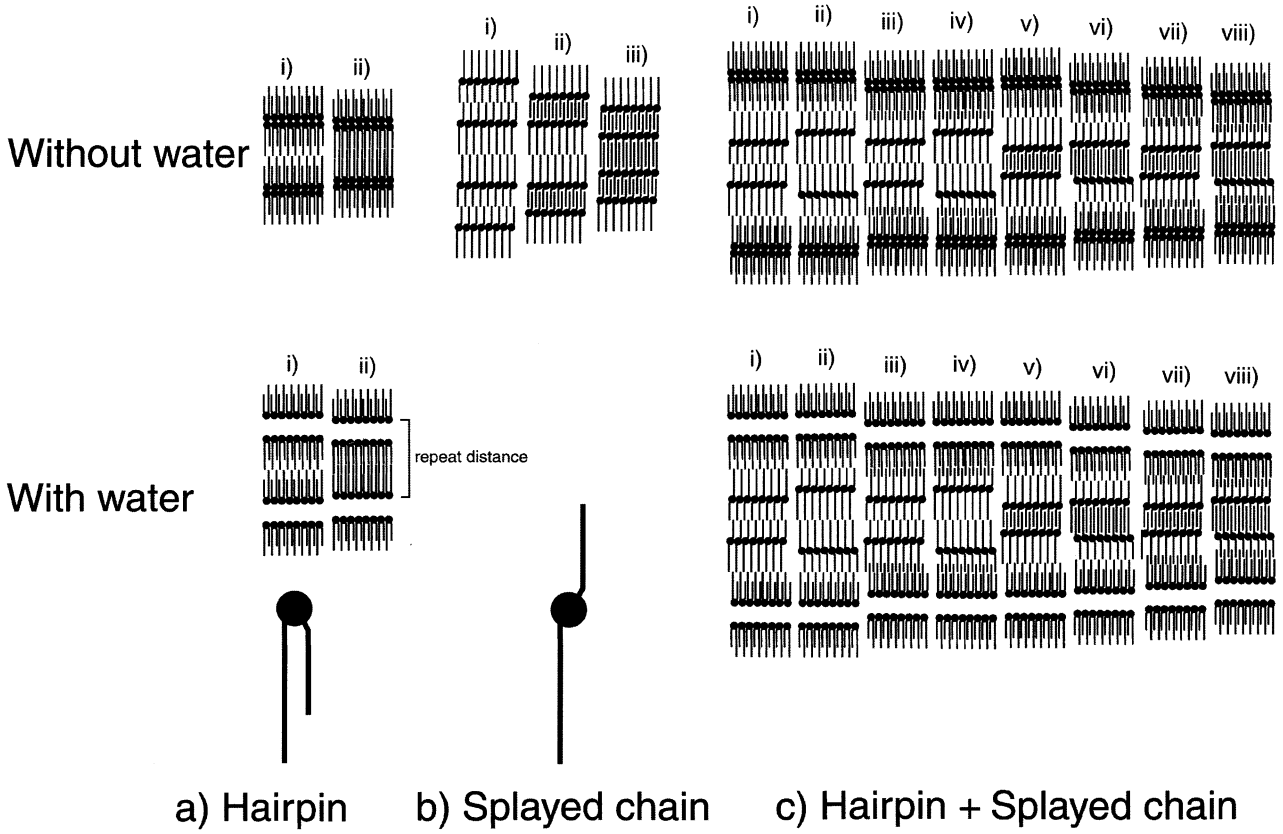

Figure 2. Different possible ceramide conformations of the proposed single and coherent lamellar gel structure representing the skin barrier. The presence of water will necessitate a hairpin ceramide conformation (*a*) or mixed splayed chain (*b*) and hairpin ceramides (*c*). Note (1) that the presence of water swells the lamellar phase, and (2) that both interdigitated and noninterdigitated hydrocarbon chain conformations are possible. In addition, different tilts of the hydrocarbon chains with reference to the lamellar plane may be present in separate matrices of the stacked lamellar structure (not shown). (i)–(viii) signify different lamellar ceramide chain packing alternatives.

incorporated in the same layers as the amide linked saturated long chain fatty acids (i.e., that the ceramides pack in a hairpin conformation) as both alkyl-chains are part of the same molecule. Also, the effect on ceramide chain packing of the double bond of the sphingosine bases may be relatively small as it is located close to the hydrophilic end, i.e., the head group, of the molecule (C4=C5; Gurr and Harwood, 1991, p256).

Further, it has not yet been established whether water is present, or not, between the lamellae of the stratum corneum intercellular lipid matrix. The possible presence of water, like the two possible crystalline ceramide conformations (i.e., hairpin *vs* splayed chain), complicates the interpretation of long spacings reported from small angle x-ray diffraction (SAXD) experiments (64 and 134 Å, respectively) (Bouwstra *et al*, 1991) and broad and narrow electron density regions observed in transmission electron microscopy experiments (Swartzendruber *et al*, 1989), respectively. If the proposed single and coherent lamellar gel structure of the stratum corneum intercellular space contains water between the lamellae, which is supported by the finding that hydration of the stratum corneum decreases lipid transition temperatures (Golden *et al*, 1986) and increases lipid disordering (Alonso *et al*, 1995), it would in turn necessitate the presence of ceramides with a hairpin conformation (**Fig 2*a***). On the other hand, if the proposed single and coherent lamellar gel structure does not contain any water, which is supported by the absence of swelling of the intercellular lipid matrix upon hydration of the stratum corneum (Bouwstra *et al*, 1991, 1992), the unique presence of ceramides with a splayed chain conformation remains an alternative (**Fig 2*b***). In both cases (with or without water), however, the presence of a combination of hairpin and splayed chain ceramides is possible (**Fig 2*c***).

To complicate the interpretation of stratum corneum SAXD long spacings and stratum corneum transmission electron microscopy electron density distributions even further, the ceramides of the intercellular lipid matrix may express interdigitation of the hydrocarbon chains (**Fig 2**). In addition, different chain packing, with possible different tilts with reference to the lamellar plane, may be present in separate matrices of the stacked lamellar structure. It should be noted, however, that all the different possibilities for the detailed molecular organization of the stratum corneum intercellular lipid matrix mentioned above are compatible with the single gel phase model.

Hexagonal *vs* orthorhombic chain packing The notion of a single and coherent lamellar gel phase in the lower stratum corneum is not inconsistent with the wide angle x-ray diffraction (WAXD) findings of Bouwstra *et al* (1992), who could not exclude phase coexistence (e.g., of lipids with orthorhombic and hexagonal hydrocarbon chain packing, respectively; cf. **Fig 1**) in isolated stratum corneum at physiologic temperatures (Bouwstra *et al*, 1992), as the isolated stratum corneum was studied as a whole (cf. below). Also Bouwstra *et al* (1991) observed that the 134 Å repeat distance disappeared at full hydration (60wt% water) (only the 64 Å repeat distance remained) indicating that the ordering of the structure is more homogeneous at high water concentrations, i.e., in the lower part of stratum corneum facing the viable epidermis.

Using electron diffraction, Pilgram *et al* (1999) reported coexistence of orthorhombic (dominating) and hexagonal chain packing lattices (cf. **Fig 1**) in the lower part of the stratum corneum. This could be explained by the fact that, for pure ceramides (tetracosanoylphytosphingosine) in the crystalline state, the phase

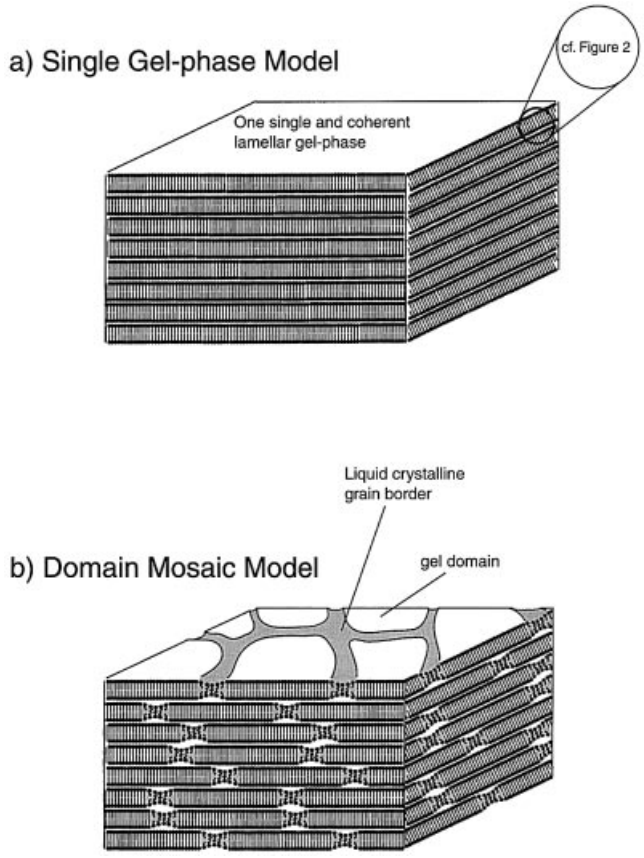

Figure 3. The single gel phase model *vs* the domain mosaic model. (*a*) Single gel phase model; (*b*) domain mosaic model. Note the presence of phase separation between liquid crystalline and gel domains in (*b*) and the absence of phase separation in (*a*). The single gel phase model proposes that the skin barrier is composed of a single and coherent lamellar gel structure in the intercellular space of stratum corneum.

transition from hexagonal to a more orthorhombic chain packing is reversible and continuous (from 106 down to 21°C) (Dahlén and Pascher, 1979). This implies that the amide linked fatty acid chains may express an orthorhombic packing in the upper part (i.e., closest to the polar head group) and a looser, more hexagonal packing in the lower part (i.e., the end of the hydrocarbon chain) simultaneously (personal communication with Professor Kåre Larsson). Thus, in a multicomponent biologic system, such as the stratum corneum intercellular lipid matrix, the ''impurity'', or compositional heterogeneity (i.e., mixture of many different chain lengths) of the single and coherent gel structure may remain unperturbed (i.e., no or little lateral diffusion may take place) during the continuous transition from hexagonal to orthorhombic chain packing. This in turn implies that the proposed single and coherent gel phase may remain intact, i.e., no phase separation occurs. However, if lateral diffusion accompanies an orthorhombic close-packing of the hydrocarbon chains (e.g., due to dehydration during sample preparation) the transition may not be reversible and phase-separation may ensue.

The desquamation process The intact, i.e., ideal or nonperturbed, gel phase is probably mainly located to the lower stratum corneum where the water concentration is high (approximately 40% w/w) (Warner *et al*, 1988; von Zglinicki *et al*, 1993) promoting a higher degree of lipid chain disorder (Alonso *et al*, 1995). Phase separation, e.g., between different crystalline or even liquid crystalline structures (cf. domain mosaic model of Forslind, 1994), however, is likely to occur in the stratum corneum as a whole, but may predominantly be confined to the upper layers. This is because in the upper part of stratum corneum (i) the water content is lower (promoting lipid phase transitions and phase separation (Guldbrand *et al*, 1982; Evans and Wennerström, 1994, pp440–443), and (ii) the heterogeneity of the lipid ''fauna'' is larger than in the lower stratum corneum. [For example, suboptimal cholesterol concentrations and introduction of medium chain and unsaturated free fatty acids, due to breakdown processes and recycling and intermixing with sebaceous gland lipids during the desquamation process (Bonté *et al*, 1997; Norlén *et al*, 1998; Norlén *et al*, 1999a).]

As the water content in the stratum corneum decreases closer to the skin surface, the first lipids to segregate into separate crystals should be those with the longest, saturated alkyl chains. High cholesterol levels, however, may partly inhibit crystalline segregation (cf. line-active properties (Sparr *et al*, 1999). In addition, compositional impurities (e.g., broad alkyl chain length distributions) stabilize gel phases of, for example, alcohols and monoglycerides (Larsson, 1994, p27; personal communication with Professor Kåre Larsson), which also may be true for the intercellular lipid matrix of the stratum corneum.

Mechanical properties The postulated single and coherent lamellar gel phase may very well be ''plastic'' enough to resist mechanical stress imposed on the skin. This is especially true as the lateral expansion of the skin is limited due to (i) the form stability of corneocytes internally reinforced by the organization of anchoring keratin filaments in the plane of the cell (Swanbeck, 1959; Norlén *et al*, 1997), and (ii) that the desmosomes on the corneocyte cell edges persist into the final desquamation (Mils *et al*, 1992). In addition, the macro scale bending of the skin will have a limited effect on the single lipid molecules on a molecular scale (in the order of 10^{-5} degrees angle per molecule).

Proteins in the stratum corneum intercellular space? A consequence of the proposed single and coherent lamellar gel phase of the stratum corneum intercellular space is that proteins will have a very limited solubility in the stacked lipid layers (Evans and Wennerström, 1994, p270); however, this does not exclude that proteins may be associated to the lipid lamellae of the proposed gel structure.

Comparison with earlier models The first model of the mammalian skin barrier, the brick and mortar model, presented by Michaels *et al* (1975), treats the skin barrier as a simplified two-compartment system with a discontinuous protein compartment embedded in a continuous, homogeneous lipid matrix. The authors, however, pointed out that both compartments had to be largely heterogeneous in nature. Therefore, the single gel phase model contains no contradictions of with respect to the brick and mortar model.

The basic idea of the present model for the detailed structure of the skin barrier, the domain-mosaic model, presented by Forslind (1994) in the mid-90s, is the presence of coexisting crystalline and liquid crystalline lipid phases (cf. Friedel, 1922; Small, 1986, p49; Larsson, 1994, p47) (**Fig 3*a***). The following, however, make the presence of a liquid crystalline lipid structure in the stratum corneum unlikely.

1 Water permeabilities of biologic membranes in the gel state and the intercellular lipid matrix of isolated stratum corneum are in the same order of magnitude, i.e., approximately 2–3 orders of magnitude lower than for liquid crystalline membranes (Carruthers and Melchior, 1983; personal communication, Professor Håkan Wennerström). [The water permeability of the intercellular lipid matrix of isolated stratum corneum is of the same order of magnitude as the water permeability of model membranes in the gel state ($0.5–2.0 \times 10^{-5}$ cm per s) (Carruthers and Melchior, 1983). This is evident from the measured permeability of human and pig stratum corneum of $0.4–2.0 \times 10^{-7}$ cm per s (1.4×10^{-7} cm per s, Scheuplein and Ross, 1970; $0.4–2.0 \times 10^{-7}$ cm per s, Blank *et al*, 1984; 1.1×10^{-7} cm per s, Potts and

Francoeur, 1991; 0.7×10^{-7} cm per s, Norlén *et al*, 1999b) when it is taken into account that the intercellular lamellar lipid matrix corresponds approximately to 1–10% (Edwards and Langer, 1994) of the total stratum corneum thickness and that these lipid lamellae essentially are the rate-limiting step for water diffusion in a direction vertical to the plane of the skin. In addition, water may be present between the lamellae of the intercellular lipid matrix and further reduce the effective diffusional path length for water.]

2 No endogenous lipids with medium chain (C12–C18) or unsaturated alkyl-chains have been detected in the inner/lower stratum corneum (Norlén *et al*, 1998) (the hydrocarbon chain length distributions of ceramides and free fatty acids being quite stable around C24:0–26:0, **Table I**; Wertz *et al*, 1987; Norlén *et al*, 1998).

3 The high relative amount of cholesterol (approximately 30 mol%), which would prefer to be associated with medium chain lipids when these are present (Engblom *et al*, 1998; Sparr *et al*, 1999) and also has the effect of decreasing molecular chain mobility and mean head group area of lamellar liquid crystalline structures, i.e., cholesterol makes these more gel-like (de Kruyff *et al*, 1974).

4 The absence of any signs of swelling of the intercellular lipid matrix on hydration of the stratum corneum (Bouwstra *et al*, 1991) (as liquid crystalline phases swells more readily than crystalline gel phases).

Swartzendruber *et al* (1989) and Bouwstra *et al* (1998) have presented models for the detailed molecular organization of the skin barrier based on the long spacings of SAXD (64 and 134 Å, respectively) and the broad and narrow electron density regions observed in transmission electron microscopy experiments, respectively. For the time being, however, it is difficult to interpret these results as (i) the ceramides may be in splayed chain and/or hairpin conformation, (ii) water may be present between the lamellae, (iii) hydrocarbon chain interdigitation may occur, and (iv) different chain packing, with possible different tilts with reference to the lamellar plane, may be present in different matrices of the stacked lamellar structure (cf. **Fig 2**).

The single gel phase model differs significantly from earlier models in that it clearly states that no phase separation, neither between liquid crystalline and gel phases (cf. the domain-mosaic model of Forslind) nor between different crystalline phases with hexagonal and orthorhombic chain packing, respectively (cf. Bouwstra *et al*, 1992; Pilgram *et al*, 1999), is present in the unperturbed barrier structure.

Future experiments One possible way to test the phase homogeneity of the proposed single and coherent lamellar gel structure *vs* the coexistence of liquid crystalline phases and gel phases (cf. the domain mosaic model of Forslind, 1994) as well as the coexistence of hexagonal and orthorhombic crystalline phases (cf. Bouwstra *et al*, 1992; Pilgram *et al*, 1999) could be by time-resolved synchrotron x-ray diffraction on lower stratum corneum collected immediately after stripping *in vivo*.

CONCLUSIONS

It is proposed that the skin barrier, i.e., the intercellular lipid within the stratum corneum exists as a single and coherent lamellar gel phase that: (i) does not necessarily have to contain water; (ii) does not necessarily have to be in a bilayer conformation; and (iii) may at times simultaneously express both hexagonal (closer to the hydrophobic end) and orthorhombic (closer to the hydrophilic head group) packing of the same hydrocarbon chains.

The main advantages of the single gel phase model over previous models are that it predicts a (i) continuous barrier structure, which is (ii) highly impermeable as well as mechanically resistant (due to its very particular and heterogeneous lipid composition), and (iii) will remain so, as it does not allow sudden phase transitions, phase separation, or induction of ''pores'', or nonlamellar structures no matter what the (physiologically relevant) environmental conditions are.

The single gel phase model is in accordance with stratum corneum: (i) water permeability data; (ii) lipid compositional data; (iii) SAXD (absence of swelling of the intercellular lipid matrix upon hydration) as well as WAXD (simultaneous presence of hexagonal and orthorhombic chain packing) data. Also, it contains no contradictions with respect to skin barrier formation according to the membrane folding model of Norlén (2001).

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