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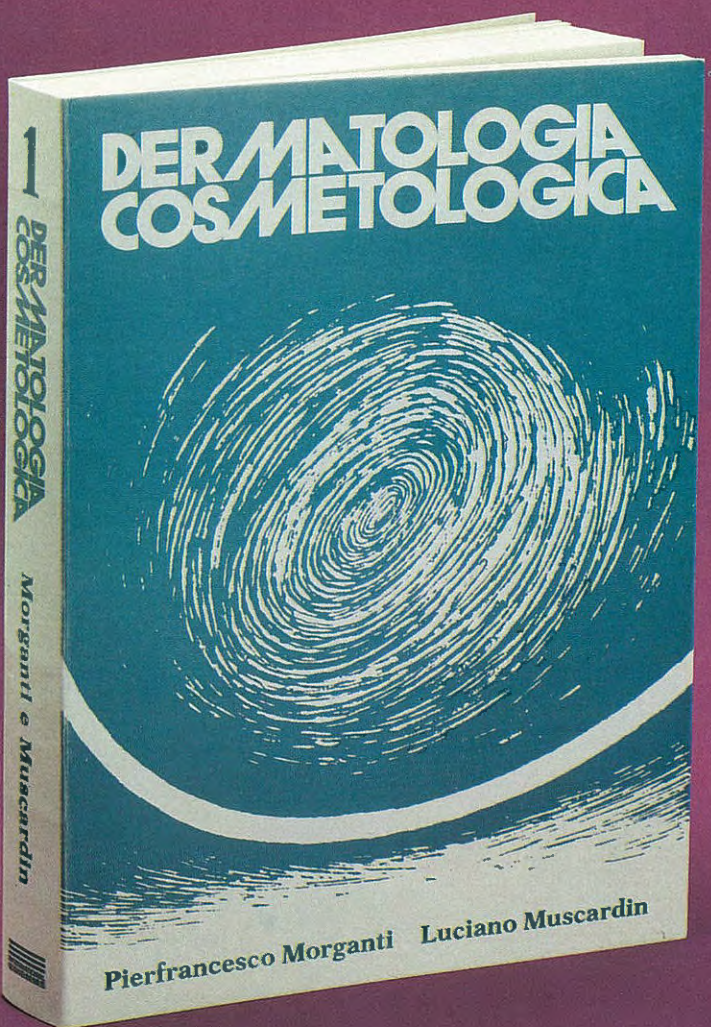

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J. Appl. Cosmetol. 11, 71-76 (July-September 1993)

SKIN TREATMENT WITH TWO DIFFERENT GALENICAL FORMULATIONS OF RETINYL PALMITATE IN HUMANS

Thom Erling, Ph. D.
Medstat Research Ltd. P.O. Box 210 - 2001 Lillestrøm, Norway

Receveid: *May 21,1993*

Key Words: *Retinyl palmitate; Skin penetration; Galenical formulations; Skin thickness; Skin elasticity.*

Synopsis

A randomized comparative double-blind within subject study of topical administration of two different galenical formulations of retinyl palmitate (RP) α 2% W/W for 3 months in 20 females, caused significant changes in skin thickness and elasticity as well as in the persons self-evaluations of skin improvements following administration of a polysaccharide conjugated RP formulation. No significant changes were observed after administration of the conventional formulation. The results indicate that the topical application of RP can bring about biochemical changes in skin quality if the neccessary hanrips are made to enhance the topical bioavailability of RP by making the substance artificially water soluble by using a suitable "tween". Conventional RP formulations do not have a similar biological effect, probably due to lack of sufficient skin penetration. Such formulations can therefore not be expected to have clinical efficacy in the treatment of wrinkles and other aging symptoms of the skin in spite of the claims made in advertisements.

Riassunto

Su venti donne è stato condotto uno studio comparato in dopppio ceco per tre mesi utilizzando due diverse formulazioni galeniche di retinil palmitato al 2% (W/W). In una delle due formulazioni il retinil-palmitato (RP) era legato ad un polisaccaride. RP coniugato ha provocato cambiamenti significativi sia nello spessore che nell'elasticità della cute rispetto al RP semplice. Questi cambiamenti sono probabilmente legati alla maggiore biodisponibilità della RP che, legata ai polisaccaridi, diventa idrosolubile e, quindi più attiva. RP tal quale non esplica, al contrario, questa attività perchè probabilmente non penetra sufficientemente attraverso l'organo pelle. Queste formulazioni nuove che esplicano una attività chimica controllata sulle rughe possono essere utilizzate come cosmetici attivi in tutte le forme di precoce invecchiamento cutaneo.

INTRODUCTION

The antiaging effect on human skin after treatment with retinoic acid is convincingly documented in a number of open and controlled studies (1-4), From a tolerability point of view, however, some patients (4-10%) report side-effects of a dermatitis type after using retinoic acid (2). The drug may therefore be unsuitable for a number of patients for antiaging treatment. Other vitamin A derivatives, however, seem to have a better local tolerability than retinoic acid and may be preferable from a cosmetic point of view. A number of cosmetic preparations with different derivatives have been developed and launched for the treatment of the aging symptoms. The efficacy documentation for these preparations is normally limited or lacking. The adds, however, claim superb efficacy.

Satisfactory skin penetration is a prerequisite for the clinical effect of the actual substance. Different ester derivatives, mainly retinyl palmitate (RP) and acetate (RA), gave been utilized in cosmetic preparations (5). In order to make the RP biologically active, modifications of the solubility have to be carried out by using "tweens". In this way the substance is made artifically water soluble and can penetrate the skin. Similar techniques are aldo used for enhancing the biovailability of drugs after topical and peroral administration (6). RP, in an active form, has been shown in animal studies to bring about biochemical changes with both epidermis and dermis (7). Parts of the action of RP in the skin may depend on its conversion to retinoic acid (8). This coversion depends on the enzymatic cleavage of the ester bonds in the retinyl to retinoic acid (9). It has been demonstrated that skin preparations can indeed convert retinyl to retinoic acid (10). Although it has been known that RP has the potential to effect a change of skin composition this potential has only to a limited extension been investigated in persons using RP preparations for cosmetic treatment of aging symptoms. In order to investigate the importance of the galenical formulation for clinical effect, we decided to carry out a comparative clinical study of two different galenical formulations.

MATERIAL AND METHODS

The study was carried out as double-blind within subject study in 20 female persons. Each of the participants used each of the two formulations either, on the right or the left volar (protected) part of the forearm, respectively. The administration of the formulations was randomized, meaning that half of the persons used formulation A on the right arm and formulation B on the left arm and vice and versa for the other persons. The total treatment period was 3 months and the cosmetic formulations were applied b.i.d. (in the morning and the evening) during the study period.

Cosmetic formulations

The two cosmetic formulations used in the study were manufactured by Pedersens laboratorier, Vejle, Denmark, and had identical cosmetic properties and appearances. The retinyl palmitate (Roche) concentrations in both formulations were 0.2%. The stability of the two formulations has been extensively tested. In formulation A* the retinyl palmitate is stabilized and conjugated with a "tween" in form of a complex polysaccharide, while formulation B contains unconjugated retinyl palmitate. The vehicles used in the two formulations were identical.

Measurements of skin thickness and skin elasticity

The measurements of skin thickness and skin elasticity were performed by Dermascan R A using ultrasound technique and DermaflexR A instruments, respectively (Cortex Inc., Aarhus,

Denmark). Measurements were carried out initially, after 1 month and after 3 months. Measurements of skin thickness and elasticity were performed by the same person (ET) on all three occasions and measurements were performed at the mid-region of the volar part of the forearm. All measurements were done in triplicate and average value were used for statistical evaluation.

*) Formulation A is identical to the marketed preparations SinceraR (S,N) and Gloria Mundi® (DK).

Self-evaluation by the participant

Self-evaluation of skin quality by the participant was performed by using visual analog scales of 10 cms with defined endpoints "no change" snf "very pronounced change". The subject was asked to score the global change in skin quality by placing a mark on the line between the endpoints. The distance from the zero point ("no change") to the mark was used as the score for the actual patient (11).

Statistical methods

A significance level of 5% was used in the tests and two-tailed tests were applied. Mean was used for estimation of continuous and near-continuous variables, and the Student procedure was used for coustruction of confidence interval of mean. The one-sample t-test was used analysing change over time within groups. Analysis of covariance and two-sample t-test were used to compare between arms with regard to continuous variables.

RESULTS

Study population

20 female persons aged between 40 and 60 years (mean (SD) of 50,3 yrs (6,2)) were included in the study and all participants concluded according to the protocol. All participants gave their informed consent to take part in the trial after having received written and verbal information about the objectives of the study.

Efficacy parameter, skin thickness and elasticity

The results from the skin thickness measurements are shown in table 1.

Table I.

Changes in skin thickness (mm) after administration of RP for 3 months (n=20).

FORMULATION		INITIALLY	AFTER 1 MONTH	AFTER 3 MONTHS
A	Mean (SD)	0,91 (0,10)	0,98 (0,10)	1,19 (0,10)
	Range	0,69-1,23	0,68-1,26	0,87-1,32
B	Mean (SD)	0,91 (0,09)	0,93 (0,10)	0,93 (0,10)
	Range	0,70-1,10	0,7,-1,12	0,74-1,10

Following the administration of the conjugated RP formulation A an average increase in skin thickness of 31% is observed, while the change in skin thickness after treatment with the unconjugated RF (formulation B) is the negligible. The increase in skin thickness following treatment with formulation A is statistically significant ($p<0.01$) while formulation B gives no significant changes.

In table II the viscoelastic properties of the skin following administrtion of formulation A and B respectively, are presented. The results show that formulation A improve the elasticity with about 18% on average ($p<0.01$) while no significant changes can be observed after treatment with formulation B.

Efficacy parameter, self-evaluation by use of VAS

The participants were also asked to make a self-evaluation of the global effect of the two formulations on the quality of the skin (including smoothness and colour). These assessments were performed using VAS, the results from the self-evaluation il shown in table III.

A significant improvement ($p<0.01$) in skin quality is reported on the forearm treated with formulation A, while no significant effect is reported on the arm treated with formulation B. Formulation A seems to improve the smoothness and the glow of the skin, which were the two most frequent changes observed by the par-

Table II.

Changes in skin elasticity (%) after administration of RP for 3 months (N=20).

FORMULATION		INITIALLY	AFTER 1 MONTH	AFTER 3 MONTHS
A	Mean (SD)	60,4 (7,4)	67,2 (7,8)	71,5 (7,9)
	Range	45,1-80,1	49,1-80,4	50,9-84,2
B	Mean (SD)	59,9 (7,1)	60,1 (6,9)	60,2 (6,5)
	Range	44,3-70,1	45,2-71,4	44,7-70,4

Table III.

Changes in VAS scores (cms) after administration of RP for 3 months (N=20).

FORMULATION		AFTER 1 MONTH	AFTER 3 MONTHS
A	Mean (SD)	1.6 (1.0)	5.9 (0.9)
	Range	0.0 - 3.1	0.8 - 8.4
B	Mean (SD)	0.7 (1.2)	0.9 (1.3)
	Range	0.0 - 1.2	0.0 - 1.6

ticipants, after chronic treatment for 3 months. The correlation between the changes in the objective measures (skin thickness and elasticity) and the observed improvement in skin quality following treatment with formulation A is striking.

Tolerability

No of the subjects participating in the study reported any side-effects following chronic administrations of the two formulations b.i.d. for 3 months.

DISCUSSION

The results from this study are in agreement with previously reported results from animal and human studies, showing that RP in active form brings about biochemical changes with dermis and epidermis (7,12). Cosmetic preparations are generally accepted to have a minimal effect on skin biology. The proven benefits of the application of cosmetic skin preparations have usually been attributed to a moisturization effect. One particular material used in cosmetic formulations, vitamin A, is known to have systemic physiological and biochemical effects (6). The role of retinoids in the regualation of skin development has, until now, mainly been focused upon the use of retinoic acid. Retinoic acid appears to be more soluble in water and is effective without a water solubilizing vehicle (6). This probably accounts for its popularity as a local therapeutical agent. Using RP in cosmetic preparations is actually a prodrug principle as the ester has to be transformed to the acid in order to exert its clinical effect. Previous studies have pointed out that suitable "tweens" have to be used to increase the skin penetration of highly lipophilic substances. The relative oil/water solubility of the different forms of vitamin A have not been compared, but differences in this respect will affect epidermal penetration. The penetration of the palmitate can readily be made equal to that of the acid by the use of special solvents. Conjugation with a complzx polysaccaride or another suitable substance will enhance the skin penetration of the lipophilic molecule and at the same time protect the substance against oxydation (degradation).

The objective parameters measured in this study, skin thickness and elasticity, indirectly verify that formulation A, which is the conjugated RP, penetrates the skin and brings about changes in the biological systems responsible for the skin's thickness and elasticity. The unconjuated retinyl palmitate, however, does not have the same effect on these objective skin parameters, probably due to lack of on a very limited skin penetration.Our results on increase in skin thickness (31%) and elasticity (18%) are in good agreement with the results reported by Fthenakis et al (12%). In this study an improvement of skin elasticity of 23% was registered after a treatment period of 6 weeks with a 0.10% RP formulation, while skin thickness was improved by 16% after 4 weeks of treatment. No significant effects in these two parameters were registered after treatment with a simple moisturizer. The slight differences might be due to a longer treatment period (12 weeks) and a higher concentration of RP (0,2%) in our study.

Beyond doubt, active RP formulations are able to bring about changes in skin composition and morphometry with good clinical tolerability. As reported by others, the concentration of RP should probably be less than 0,5% in cosmetic preparations if erythematous reactions are to be avoided.

It can be questioned if cosmetic preparations containing plain RP should be recommended for the antiaging treatment of the skin due to lack of (or at least a vety modest) biological effect, probably due to its restricted skin penetration ability. Misleading consumers to anticapte antiaging effects after continuous use of these preparations are unetichal.

More sophisticated studies dealing directly with the skin penetration of RP and studing the vitamin A concentrations in the skin and systemic circulation, should be carried out.

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USE AND STABILITY OF LIPOSOMES IN DERMATOLOGICAL PREPARATIONS

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Synopsis

In recent years liposomes have gained an increased interest as ingredients for topic formulations, both for their hydratating-humectant properties and as carriers for (trans)dermal delivery of active ingredients that exert their function at cutaneous and/or subcutaneous level.
In this paper we describe (a) some aspects of liposome use with special regard their to stability in topical formulations and (b) the modalities of skin-liposomes interactions after topical application.
A crucial aspect of the cosmetic utilisation of liposomes concerns indeed the intrinsic stability of the macromolecular structure of this vehicle, especially when liposomes are incorporated in surfactant containing forms as in the case of creams. In these conditions liposomes can be rapidly solubilized by a large variety of surfactants through a multi step process. With the aim to overcome this problem, the use of structured vehicles constituted of hydrophilic polymers has been recently proposed. With respect to this latest point, a number of mild formulations that could represent optimal vehicles for liposome incorporation is presented. Moreover we discuss the effect of the polymer used on the properties of structured vehicles (i.e. viscosity) and on the release of liposome entrapped model drugs.

Riassunto

I liposomi stanno ottenendo un sempre maggiore interesse quali componenti di formulazioni ad uso topico sia per le loro proprietà idratanti che per la loro capacità di aumentare l'assorbimento di principi attivi che esplicano la loro attività a livello cutaneo e/o sottocutaneo. In questo lavoro verranno discussi alcuni aspetti dell' utilizzazione dei liposomi, con particolare riguardo alla loro stabilità, ed i loro possibili impieghi in cosmetologia e dermatologia.
L'attività biologica dei soli liposomi "vuoti" è stata recentemente attribuita a diversi meccanismi d'azione tra cui l'interazione dei liposomi con la cheratina superficiale o con le strutture lamellari presenti a livello dello strato corneo. Per la comprensione dell'attività esplicata dai liposomi, oltre a questi aspetti sono da considerare gli effetti di composti intrappolati all'interno dei liposomi ed eventualmente quelli di metaboliti attivi prodotti a livello cutaneo. Un aspetto cruciale dell'utilizzo

dei liposomi riguarda la stabilità della loro peculiare struttura macromolecolare in relazione a possibili interazioni con altri componenti della formulazione. Quando i liposomi si trovano in presenza di tensioattivi possono infatti essere rapidamente solubilizzati attraverso un processo "multi-step". Al fine di superare questo problema, sono state recentemente proposte formulazioni basate su polimeri idrofili in grado di formare veicoli strutturati che rappresentano mezzi ottimali per un uso dermocosmetico dei liposomi. Rispetto a quest'ultimo punto saranno discussi gli effetti del polimero utilizzato rispetto alle proprietà dei veicoli ottenuti (ad esempio la loro viscosità) ed al rilascio di farmaci modello incapsulati in liposomi.

Introduction

Recently, together with a development of a number of applications for the systemic delivery of drugs, liposomes (lipid vesicles) (1) have gained interest and relevance for topical administrations of cosmetic as well as dermatological active compounds (2-6). In this respect, local administration of liposome preparations could overcome the scarce absorption through the skin often associated with the topical application of many drugs.

Many substances, in fact, are both topically and systemically ineffective when applied onto the skin. This is mainly due to their almost complete failure to penetrate the horny layer, resulting in low concentration of the active compound in the skin *strata* below *stratum corneum* (7).

The utilization of liposomes as vehicle for dermatological and cosmetic active agents could promote drug transport through the skin reducing at the same time systemic side effects by slowering the drug release. Liposomes, indeed, can incapsulate and deliver a large number of different cosmetic agents improving in this way skin absorption, adhesion and persistence of active compounds present in cosmetic formulations.

In spite of the mentioned advantages in using liposomes (with respect to other vehicles commonly employed for topical treatment), many precautions should be considered. In particular the chemical and physical stability of liposomal preparations can be a considerable problem, especially in the presence of formulation additives. In the following, we will focus on lecithin liposomes and first review a couple of their properties. Lateron, we will discuss current views on the interaction of liposomes with the skin and on the interaction of liposomes with surfactants. Finally, we will comment on the use of "mild" formulation additives which should not affect the integrity of liposomes and can therefore be recommended for cosmetic and dermatological applications.

The nomenclature in the field of liposomes is often confusing, many authors distinguish between liposomes and vesicles, but at the same time abbreviations such as MLV, LUV or SUV (multilamellar, large unilamellar or small unilamellar vesicles) are used to characterize liposomes. In the present work we use liposome synonymous to vesicle for the description of a small closed 3-dimensional structure, the boundary of which is build by one or more bimolecular layers of amphiphilic molecules.

Lecithin: the raw material for liposome production

Although liposomes can be prepared from a rather broad range of amphiphilic molecules with cationic, anionic, zwitterionic or nonionic head groups, most of the research investigations so far have focused on lecithin (= 1,2-diacyl-sn-glycerol-3-phosphorylcholine = phosphatidylcholine) or phosphatidylcholine-cholesterol mixtures. We will therefore limit ourselves in this article to lecithin liposomes. Lecithin from natural sources, such as egg yolk or soybeans, is always a mixture of different phosphatidylcholines with variations in the acyl composition. When lecithin is placed in water, different kind of liquid crystal mesophases can be formed. This phenomenon is known as lyotropic polymorphism, and it is the consequence of attractive and repulsive interactions between lecithin and water. The formation and structure of the different phases are dependent on the lecithin structure, on the concentration, on the temperature and on the pH of the medium. Different polymolecular structures can be formed: aqueous (or direct) micelles, inverted micelles, hexagonal, cubic or lamellar phases (8-11). Liposomes belong to the lamellar phase of the phase diagram. Large, polydisperse multilamellar liposomes form upon hydration of a lecithin film deposited on a glass surface, as has been shown for the first time by Bangham and Horne

(12). Smaller liposomes with defined sizes and lamellarity are generally formed by putting chemical or mechanical energy into the system (e.g. ultrasound treatment, filtration through polycarbonate filters with defined pore sizes). Although the lipid bilayer of liposomes is rather impermeable to polar, charged molecules, the liposome membrane is quite dynamic (13, 14) (see Fig.1).

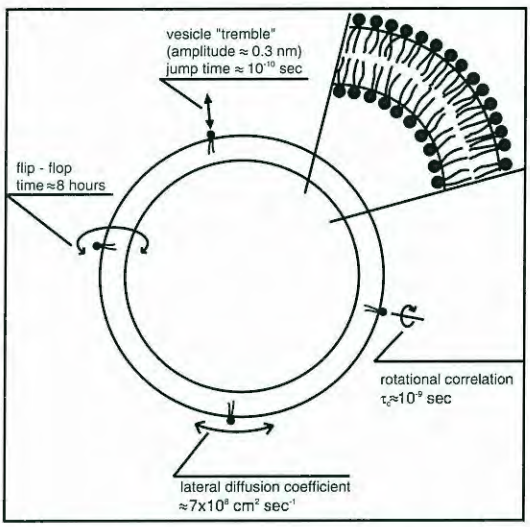

Figure 1: Dynamic properties of liposome membranes formed by dipalmitoyl phosphatidylcholine (DPPC) above the phase transition temperature (13, 14).

Apart from their aggregation form one should remember that lecithin and other glycerophospholipids are characterized by intrinsic properties (summarized in Table I) that make these compounds particularly attractive for a large variety of dermocosmetic applications.

As far as the incorporation of lecithins in cosmetic preparations is concerned, it is not possible to drawn up any simple and generally valid rule. This is mainly due to the peculiar chemico-physical properties of lecithins that require a process of individual design and preformulatory study. In addition, possible interactions of lecithins with other components of the formulation are to be considered to obtain the desired final form.

Hydrogenated lecithin

Concerning the phospholipids stability, it is to be underlined that, despite the great importance recognized to highly unsaturated vegetable oils for cosmetic application, in the case of lecithin, its sensitivity to oxidation (leading to unpleasant odours and colours) is often considered a disadvantage for its inclusion in cosmetic formulations.

In order to overcome this problem, the utiliza-

Table I.

PROPERTY PROFILE OF LECITHIN AND OTHER GLYCEROPHOSPHOLIPIDS

- Phospholipids are natural occuring row material
- Phospholipids are toxicologically safe compounds without dermatological adverse problems, even if utilized at high concentration
- Phospholipids can increase the efficacy of skin and hair care products, improving the skin moisture balance
- Phospholipids adhering to the skin surface (through extensive interactions), give a pleasant non-greasy feeling
- Phospholipids, due to their amphiphilic molecular structure and chemico-physical properties, offer the possibility for the preparation of new cosmetic forms (i.e. micelles, lamellar structures, cubic phases)

tion of more stable hydrogenated lecithin has been recently proposed (5, 15). In Table II are reported some of the possible advantages of hydrogenated lecithins, making them interesting for cosmetic applications and especially for the production of more stable liposomes with high phase transition temperatures.

tion of these lipid bilayers (mainly in a gel state), changes from the living epidermis, where phospholipids are abundant, to the *stratum corneum*, where neutral lipids predominate along with ceramides and free fatty acids. It has become apparent that many of the biological functions of the *stratum corneum*, summarized in

Table II.

POSSIBLE ADVANTAGES IN THE COSMETIC USE OF HYDROGENATED LECITHIN

- The external appearance is that of a fine powder
- Neutral colour and odour
- Stable against oxidation
- Liposomes prepared by hydrogenated lecithin are quite stable
- Toxicologically safe

Liposome composed of hydrogenated lecithin were found to be stable (in term of dimensional variations) for up to one month even when stored at 50°C. In addition hydrogenated lecithin liposomes showed a certain degree of compatibility with non ionic surfactants such as decaglyceryl mono-stearate and POE (60) hydrogenated castor oil (HCO-60) (15). Concerning the biological activity, it was recently reported that hydrogenated lecithin based liposomes showed superior properties in carrying active ingredients through the skin layers with respect to commercially available facial creams (15).

Liposome interaction with skin

Among the different functions of skin, many are directly associated with the maintenance and functioning of the protective zone with barrier properties represented by the *stratum corneum*. (16).

Human *stratum corneum* consists of corneocytes embedded in lamellar lipids. The composition

Table III, (e.g. the water-retention capacity) are clearly determined by the ceramides presence.

From these considerations, the use of cosmetics containing ceramides or their analogues can be interesting in order to restore the damaged skin barrier or the water content in very dry skins. To this aim liposomes constituted of ceramides ("sphingosomes") have been recently proposed (17). In addition, essential fatty acids could be proposed for the maintenance of epidermis integrity. Unsaturated fatty acids, such as linoleic or γ-linolenic acids, can have indeed positive effects on the *stratum corneum* barrier functions. In this view, liposome could represent an optimal vehicle for the administration of these pro-barrier compounds, in order to obtain their selective delivery at the intercellular lipid domain level.

However, the elucidation of liposome skin interactions and the principles of their dermo-cosmetic activity are still open problems. For example, the molecular events regulating the interaction of liposomes with skin, as well as their "penetration enhancer" activity are not completely elucidated phenomena (18).

Table III.

FUNCTIONAL PROPERTIES OF THE INTERCELLULAR LIPID DOMAIN OF SKIN *STRATUM CORNEUM*

- Regulation of skin water content by controlling *perspiratio insensibilis*
- Control of skin cohesion and desquamation
- Control of cutaneous and percutaneous absorption of exogenous agents, bioactive compounds and drugs
- Antimicrobial barrier
- Natural sunscreen

Some authors suggest that liposomes are able to pass the *stratum corneum* physiological barrier through the intercellular route, reaching in this way the deeper, vascularized section of the skin, possibly leading to systemic effects.

Foldvari et al. (19) for instance, have found the presence of unilamellar liposomes in the dermis after topical application of colloidal iron loaded liposomes that allowed the identification of liposomal structures in skin sections by mean of electron microscopy analysis. Other reports indicate that liposomes themselves do not penetrate intact into the skin and only the liposome forming material (e.g. fragments of lipid bilayers) associates with skin components (20, 21). According to this theory liposomes, after interaction with the lamellar phase of the intercellular lipid domain, undergo to a reassembling of the liposomal material leading to the fusion of the vesicles into lamellar sheets. In an *in vitro* study based on the interaction between liposomes prepared with a mixture of *stratum corneum* lipids (45% epidermal ceramides, 35% cholesterol, 15% free fatty acids and 5% cholesteryl sulfate) and corneocytes isolated from pig epidermis, Abraham and Downing have demonstrated that a corneocyte-induced membrane fusion process results in the transformation of liposomal material into lamellar sheets with the consequent release of the aqueous content of the vesicles (22).

More recently, a study focused on the elucidation of the interactions between liposomes and *stratum corneum* by mean of freeze fracture electron microscopy and small angle x-ray scattering techniques (23) has concluded that mainly two types of phenomena can be observed *in vitro*: (a) the interaction of vesicles at the suspension-skin interface involving absorption and fusion of the vesicles at the surface of the *stratum corneum* and (b) changes in the organization of intercellular lipid domain induced by the liposomal constituents, suggesting that efficacy of liposomes suspension mainly depends on the chemico-physical properties of the liposomes constituents. These interactions are summarized in Figure 2 where are reported the possible mechanism(s) of action of liposomes, their interactions with the skin, and finally the disruption-degradation processes of liposomal material.

It is thus likely to conclude that liposomes are unable to penetrate intact into the skin, whilst their molecularly dispersed constituents, can reach the *stratum corneum* (24, 25). Subsequently, liposome material can interfere with the molecular packing of the lipids, altering their ordered structure and possibly enhancing topical absorption of drugs. Due to these properties, liposomes should be considered both as vehicle and active agent. Empty liposomes themselves, through extensive interactions with proteins, carbohydrates and

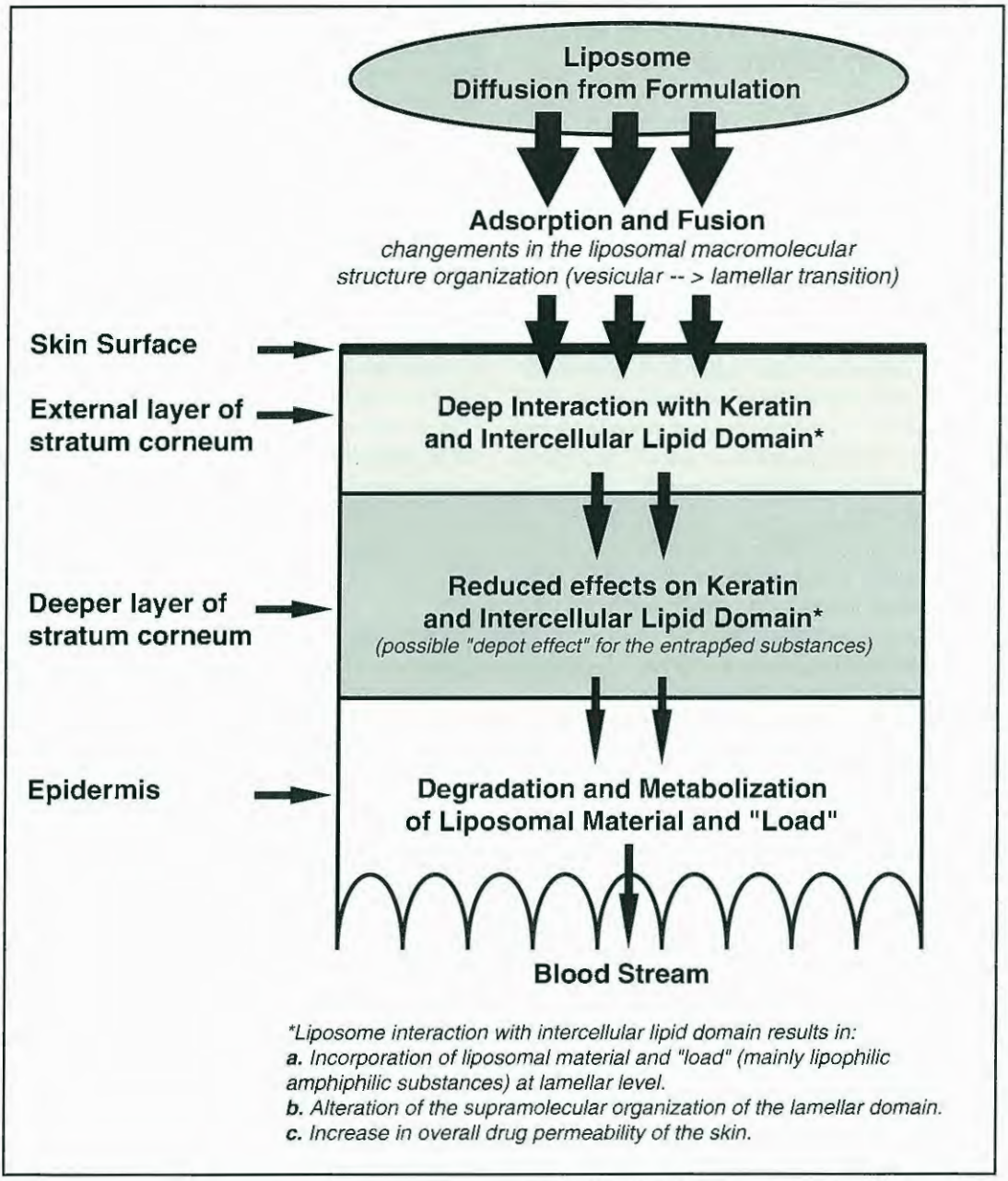

Figure 2: Schematic representation of liposome-skin interactions. Arrow number and size tentatively represent the amount of lipasomal material passing into the different skin layers.

especially skin lipids, may be useful in normalizing the damaged eczematous or dehydrated skin, restoring in this way the barrier and functional properties of the *stratum corneum* intercellular domains (26).

Liposome stability: interactions with surfactants

One of the most controversial point for the cosmetic utilization of liposomes, concerns the integrity of their vesicular structure. Drawbacks can indeed occur when liposomes are formulated in combination with detergent molecules (e.g. in cosmetic creams).

In this respect, different reports have shown that liposomes are rapidly solubilized by a large variety of surfactants with a multistep process through a lamellar-micellar transition of the macromolecular aggregates, leading to the final formation of mixed micelles composed of liposomal material and surfactants (see Figure 3) (27-31).

Analysing in detail the sequence of events leading to the solubilization of phospholipid vesicles, the following steps can be recognized (31).

Detergent binding. At low concentration, the surfactant (in the monomeric form) binds to the bilayer without deeply altering the vesicle structure. The surfactant distributes between bilayer and aqueous phase depending on its typical partition coefficient. In this first step, changes in the vesicle properties occur. An increase in membrane permeability (causing leakage of entrapped material) and in membrane fluidity can be observed, in same cases together with an augmented turbidity of the suspension.

Lamellar-micellar phase transition. Increasing the overall amount of surfactant, its concentration in the vesicle membrane reaches the saturation, after which the liposome structure will be disrupted with the formation of mixed micelles (see Figure 3), until the vesicular system is completely solubilized. During this process the turbidity of the suspension decreases due to the lower micelle light scattering compared to that of vesicles.

Size decrease of mixed micelles. In this final step, after the complete solubilization of vesicles is reached, an increase of the surfactant/phospholipid ratio in the mixed micelles is observed, with a consequent reduction of micelle size. The design of liposome-based cosmetic, the selection of lipid composition and additives must be done carefully to guarant liposome integrity in the final product. Concerning the solubilization properties of surfactants, a recent study describes the utilization of liposomes as an "in vitro" model to test the irritant properties of surfactants towards the skin (32). In this study, by measuring the leakage of the fluorescent probe carboxy fluorescein from

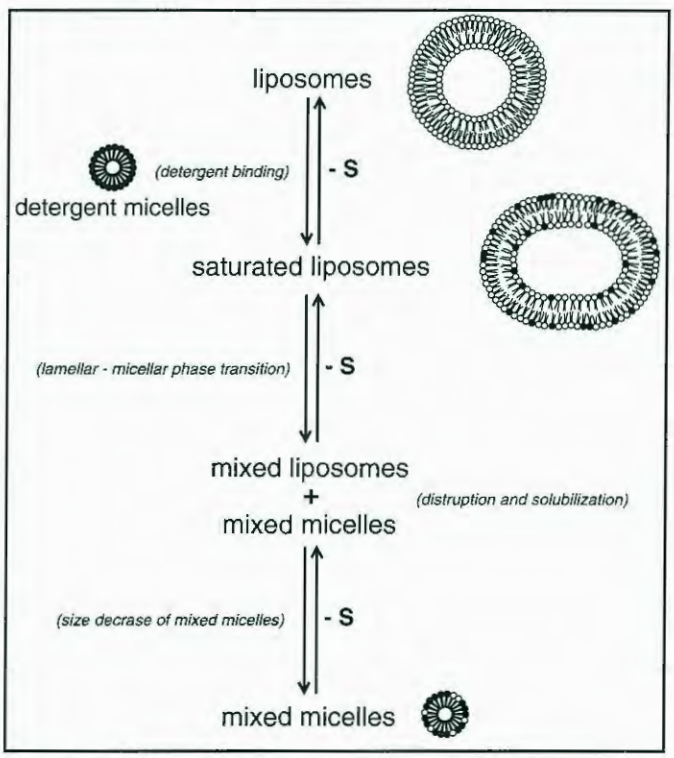

Figure 3: Liposome-surfactant interactions. The sequence of events leading to the solubilization of a suspension of liposomes after exposure to increasing amounts of surfactants is reported.

liposomes exposed to surfactant solutions, the surfactants solubilization properties are determined. From this (32) and other data reported in literature (27-31), it is clearly evident that surfactants can destroy phospholipid vesicles also when utilized at very low concentrations. These instability problems, related to common detergent use in dermo-cosmetic topic forms (e.g. skin care creams) leading to the distruption of the bilayer structure, have thus suggested different approaches for the utilization of liposomes in cosmetics.

Liposomes in cosmetic

For the design of liposome based cosmetics the analytical evaluation and standardization of raw materials are extremely important steps (not discussed here). Moreover, the choice of the lipid composition and the formulation of the final liposome containing topic forms, must be done very carefully with special regard to liposomes compatibility with surfactants additives eventually present in the finished products. Concerning the industrial processes, a variety of strategies are now available for liposome production. Without analysing in detail the different production procedures, a newly developed approach appears noteworthy. The method is based on the use of phospholipid-gel-systems recently developed by Nattermann Phospholipid GMBH (Natipide® II) (33) and Lucas Meyer (Pro-Lipo) (34), from which liposomes can be easily prepared by simple addition of water. Both systems are based on gels containing high concentrations of phospholipids in hydrophilic media. Natipide® II, for example is composed of 20% soya phospholipids (highly enriched in 3-sn-phosphatidyl-choline) mainly arranged in form of bilayers dispersed in an aqneous ethanolic base. Formation of fully hydrated liposomes is simply obtained by dilution of the gel with aqueous media containing the material to be entrapped. This new concept allows manufactnrers to produce liposomes loaded in a high yield, both with hydrophilic or lipophilic substances without specific technical equipments. Regarding the different parameters that have to be considered for admitting liposome for use in patients, it is to be underlined that it is crucial the availability of experimental techniques able to characterize the different properties of liposomes proposed for clinical use. Table IV reports a number of essential prerequisites that should be previously determined with special care by lipo-

Table IV.

FACTORS AFFECTING THE BIOLOGICAL ACTIVITY OF TOPICALLY ADMINISTERED LIPOSOMES

- Size (for cosmetic applications between 100 and 200 nm)
- Particle size distribution (as close as possible to normal distribution)
- Composition
- Incorporation (encapsulation) yield for bioactive compounds
- Intrinsic stability of liposomes
- Possible interactions with other components of the formulation (surfactants)
- Presence, concentration and stability of active agent(s)
- Release kinetic of the active agent(s)

some producers in order to correctly utilize phospholipid vesicles in dermocosmetic preparations.

Influence of liposomal vehicle on percutaneous penetration

As already described, the use of topically applied liposomes can enhance the percutaneous absorption of the encapsulated drugs. This enhancement is influenced by two main parameters: namely the type (in term of dimension and lamellarity) and composition of the used liposomes on one hand, and the formulation used to incorporate the liposomes on the other.

With regard to the first point, Michel et al. (35) have recently studied, by using *in vivo* stripping method, the effect of liposomes on the percutaneous absorption of two lipophilic model drugs. Both drugs showed an increased skin absorption when vehiculated in liposomes with respect to galenical formulations such as ointments and creams. Concerning the correlation between drug penetration through the skin and size of liposomes, only a weak dependence was observed (with SUVs a 1.5-fold greater amount of drug penetrated as compared to much larger MLVs) (35). Furthermore, Du Plessis et al. (36) have recently analyzed, by using an *in vitro* diffusion technique, the influence of lamellarity of liposome containing $_3$H-cholesterol and $_{14}$C-cholesteryl sulfate on the deposition of the radiolabeled compounds in the various *strata* of hairless mouse and pig skin. In this way the authors have demonstrated that lamellarity had little effect on the deposition of liposomal components into the different skin layers. Again, by studying the ratio between the two lipids in the strata of the skin, Du Plessis et al. have found that only in the *stratum corneum* radiolabeled cholesterol and cholesteryl sulfate maintain the same molecular ratio despite their different polarities, suggesting in this way that the diffusion of the two compounds occurs in an bilayer associated configuration (36). On the contrary in the deeper skin *strata* the two molecules are deposited at different rates since they are no longer associated as bilayer, confirming in this way the theory of the disruption of the liposomal structure at the *stratum corneum* level (23).

Liposomal formulations

Today the most often used liposomal formulations (at the moment dominating the cosmetic market) are based on colloidal agents that are able to confer the adequate viscosity to the media, without altering the vesicle stability.

In Table V are summarized some of the possible cosmetic formulations, mainly transparent or opaque gels (with different viscosity), suitable for the liposome incorporation.

Semisynthetic materials such as methylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, and carboxymethyl cellulose give, for example, low- or medium-viscosity gels (37).

More viscous gels can be prepared by using Carbopol® resins (38) (acrylic acid polymers, CTFA name: Carbomer). In addition by using polymeric emulsifiers such as Pemulen® TR-1 and TR-2 (39), either alone or in combination with other Carbopol® resins, fluid or viscous emulsion gels can be prepared. In this way, typical usage levels of traditional surfactants (3-7%) can be replaced by only 0.1-0.3% of Pemulen® emulsifiers producing stable biphasic forms without the use of surfactants.

Alternatively products of the Lubrajel rheological additive family (40) (CTFA name: polyglycerylmethacrylate and propylene glycol) can be employed for the production of viscous gels.

Finally, creams (usually oil in water) that represent innovative challenges in the liposome field, can be prepared by using mild surfactants such as alkyl-polypeptides or sorbitan mono-oleate. In this formulations more stable liposomes constituted of hydrogenated or synthetic lecithins can be incorporated without significant alterations of liposomes (15).

Concerning the influence of formulation factors on skin deposition of liposomal delivered drugs, we have recently studied the influence of the vehicle on release and activity of liposome entrapped methyl nicotinate (MN). Namely, MN

Table V.

COSMETIC FORMULATIONS FOR LIPOSOME INCORPORATION

- Aqueous dispersions
- Fluid gels based on cellulose derivatives
- Viscous hydrogels based on cellulose derivative or carboxyvinyl polymers (Carbomer®)
- Fluid or viscous emulsion gels based on polymeric emulsifiers (Pemulen®) plus 5-10% of oil phase
- O/W creams based on mild nonionic surfactants (Es. 0.5% polysorbate, 0.5% sorbitan mono-oleate) and liposomes constituted of hydrogenated or synthetic lecithins

aqueous solution, MN containing liposomes in aqueous suspension and MN containing liposomes incorporated in carboxymethylcellulose or Carbopol® 934P based gels, were analysed respect to their effect on *in vitro* drug release. The analyses were performed both *in vitro* by using a Franz cells system (41) and *in vivo* by using laser Doppler velocimetry (LDV) (42).
Our results suggest that the *in vitro* release of MN is deeply influenced by the vehicle structure; indeed, viscous media do reduce the MN permeability coefficient (see Table VI). In agreement further studies were found to confirm the influence of vehicle structure on the *in vivo* MN availability (manuscript in preparation).

Table VI.

IN VITRO PERMEABILITY COEFFICIENTS OF METHYL NICOTINATE IN AQUEOUS SOLUTIONS OR IN LIPOSOMAL FORMS

Formulation*	**permeability coefficients (cm/h)(x 10^3)‡**
Aqueous solution	29.1
Aqueous liposomal suspension	10.5
CMC-liposome	7.4
Carbopol®-liposome	7.4

*All formulations contain 5 mg/ml of methyl nicotinate
‡The permeability coefficients were determined by using a Franz cell assembled with a multi membrane Silastic®/cellulose/Silastic®) system (41).
CMC-liposome and Carbopol®-liposome were prepared by incorporating MN entrapped liposomes in 4% carboxymethyl cellulose (CMC) and 0.75% Carbopol® 934P gels.

Dermocosmetic applications of liposomes

The described properties of liposome make it a unique and powerful vehicle for local cosmetic and pharmaco-therapy applications.

Liposome treatment, in comparison to other conventional dosage forms (creams, gels, ointments) could in fact lead to a good skin partitioning of bioactive compounds, obtaining in this way a real targeting to skin. A direct consequence of these characteristics will be the challenge to improve the pharmacological activity of liposome delivered drugs towards skin, minimizing at the same time possible systemic side effects. For instance, it has been demonstrated the clinical superiority of a liposomal betamethasone dipropionate preparation respect to a conventional gel for eczema treatment. The topical liposome preparation was found able to improve the glucocorticoid antiinflammatory activity with a contemporaneous reduction of side effects (i.e. skin atrophy) (43). The same improvement of local effect was in a recent study reported by Masini et al. (44). Here the authors have compared, by using *in vitro* and *in vivo* methods, skin penetration of tretinoin incorporated in liposomes or in an alcoholic gel. This study demonstrated that by mean of liposomes, tretinoin is released in a controlled fashion, improving its local concentration in epidermis and dermis.

As direct consequence of these studies, liposome could be proposed for a large number of dermocosmetic applications. Among the most interesting at the moment investigated, some deserve to be mentioned such as skin care preparations, based on empty liposomes or moisturizing agents loaded liposomes, antiaging formulations (e.g. liposomes incorporating retinoids, sunscreens and radical scavengers), treatment of dehydrated or damaged skin (e.g. liposomes encapsulating moisturizing agents), topical mycosis treatment (e.g. liposomes incorporating amphotericin B) and finally local antiinflammatory and antiallergic therapy (e.g. liposomes incorporating corticosteroids). From these research efforts, a number of patents have been recently issued. An exhaustive list of patents in liposome field was recently published by Korting et al. (43)

Conclusions

Liposome represents an optimal candidate for topical delivery of bioactive agents. Despite the large applicability and the encouraging results obtained at experimental level for this potentially non toxic and non allergenic delivery system, further investigations are requested. Studies should be performed in order to gain more informations on different subjects such as mechanisms of horny layer penetration and deposition, longer-lasting and toxic effects, formulation influence on activity and finally liposome stability in the formulation.

Nevertheless we have to consider that there are a variety of commercialized products containing liposomes. After-shaves, sun-tan and sun-protection formulations, cleansing lotions face, body and hand care products and bath oils are just some of the liposome based cosmetics marketed now or in the next future.

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CONTACT CHEILITIS

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Synopsis

Lips are between the skin and the oral mucosa. They are covered by a pseudomucosa which, lacking the protection of a horny layer, makes them highly susceptible to damage by contact with various physical and chemical agents.
Contact cheilitis may be caused by various pathologic mechanisms: irritant contact cheilitis, allergic contact cheilitis, contact photocheilitis, immediate contact cheilitis, urticarial contact cheilitis, cold urticarial cheilitis and atopic cheilitis. The many etiological agents for cheilitis are usually substances in toiletries and cosmetics (toothpastes, mouth wash, lipsticks, lip salves), substances used in dentistry, metals (especially nickel) and food.
This work discusses our data on the etiological factors of contact cheilitis observed over a four-year period.

Riassunto

Le labbra costituiscono il punto di incontro tra la cute e la mucosa orale e sono ricoperte da una pseudomucosa, che, essendo priva della protezione dello strato corneo, le rende particolarmente esposte all'azione lesiva di varie noxae, fra cui quelle fisiche e chimiche agenti per contatto.
Le cheiliti da contatto possono insorgere per meccanismi patogenetici vari: cheilite da contatto irritante, cheilite allergica da contatto, fotocheilite da contatto, cheilite da contatto immediata, cheilite orticariosa da contatto, cheilite orticariosa da freddo e cheilite atopica. Gli agenti eziologici sono molteplici. Si tratta in genere di sostanze contenute in prodotti igienico-cosmetologici (dentifrici, collutori, rossetti, salvalabbra), sostanze d'uso odontoiatrico, metalli (in particolar modo il nichel) e gli alimenti.
Nel presente lavoro vengono riportati i dati relativi ai fattori eziologici delle cheiliti da contatto da noi osservate negli ultimi quattro anni.

Lips are between the skin and the oral mucosa. They are covered by a pseudomucosa which, lacking the protection of a horny layer, makes them highly exposed to various harmfnl agents, including physical and chemical agents that act by contact with the lips (1).
Cheilitis may be caused by various pathologic mechanisms: its various clinical and pathologic forms are listed in Table 1.

Table I.

CLINICOPATHOLOGIC CLASSIFICATION OF CONTACT CHEILITIS

Irritant contact cheilitis

Allergic contact cheilitis

Irritant contact photocheilitis

Allergic contact photocheilitis

Immediate contact cheilitis

Urticarial contact cheilitis

Urticarial cold cheilitis

Atopic cheilitis

Some forms are lip-specific, such as contact photodermatitis, immediate contact cheilitis and atopic cheilitis, whereas other forms may extend to the oral mucosa and the perioral skin (2).

Irritant contact cheilitis

This form of cheilitis affects the lips only. It is mostly associated with peeling and chapping and, less frequently, with erythema and crusts, or involving the labial commissures (perlèche).
The perioral skin area is often affected as well. Its many causes may be physical (cold, friction from toothpicks kept between the lips, tics or bad habits which include biting and pinching), or chemical in nature.
Chemical stimuli include toiletries and cosmetics for the lips and the oral cavity. They contain many substances which can cause both irritations and allergies, or only irritations, such as quaternary ammonium compounds (in toothpastes and mouth wash) and materials for cores and temporary prostheses (containing stearin, stearic acid, waxes, paraffin, boric acid, potassium fluoride, silicium) (3-5). The saliva irritates the labial and perilabial skin since it contains enzymes - e.g. amylase and maltase acting in food digestion, and other enzymes (cholinesterase, alkaline phosphatase, lipase, sulphatase, galactosidase, lysozyme, hyaluronidase, catalase, glycogenase, carbon anhydrase, mucinase) (3). Any process increasing salivation may give rise to perlèche ,as for example tobacco or gums chewing. Also spontaneous hypersalivation may cause angular cheilitis because of the saliva flowing through labial commissures.
A quite frequent habit in children and young people is the continuous moistening of the angles of the mouth, lips and perioral skin, resulting in cheilitis and irritant perioral dermatitis.
Also Down's syndrome is associated with angular cheilitis due to saliva trickling because of macroglossia. Saliva plays a key role in the onset of perlèche also with altered dentition (toothless elderlies) or rather moving dental prostheses. Under these conditions, a skin/mucosa fold forms in the labial commissures where saliva accumulates leading to irritation and soaking, and, subsequently, to perlèche.

Allergic contact cheilitis

The clinical picture often shows clear eczematous manifestations with erythema, edema, vesicles and crusts.
Lesions may be found on the lips and perioral skin or on labial commissures only. The oral mucosa is often affected as well. Possible cau-

ses include toothpastes and mouth wash, dental materials, lipsticks, lip salves, sun screens, nail enamels, cigarettes, food, topical medications (e.g. those treating mycotic perlèche or labial herpes simplex), metals (nickel), and rubber objects.

Toothpaste and mouth wash

Toothpastes and tooth powders contain flavoring agents, dyes, abrasives, detergents (alkylsulphate foaming agents or sarcosinates), propylene glycol, glycerin, thickeners (alginate, gum tragicanth, Iceland moss). Some toothpastes also contain antiseptics (mercurials, formaldehyde), preservatives, fluoride, ammonium compound, saccharin and cyclamates.

Mouth washes are medicated liquids used for mouth hygiene, for therapeutic or cosmetic purposes. They contain the same substances as toothpastes, especially flavors, antiseptics and preservatives. Among flavoring agents, cinnamaldehyde (6-8) can often be found which may also induce allergic stomatitis. A possible cause of dermatitis flare-up may be intake of cinnamon or other derivatives in food, or contact with the many food and cosmetic products containing cinnamic aldehyde. Other substances often causing allergic contact cheilitis are mainly essential oils (clove oil, cinnamon oil), geraniol, menthol and balsam of Peru (9).

Dental materials

Almost all chemical and medical substances used in dentistry may be allergenic (3, 4, 10).

Dental liquids and cements, for example, contain balsam of Peru and colophony. Both are known to be allergenic and are ubiquitous in dentistry. Balsam of Peru is also contained in food, cosmetics and topical medications.

Some essential oils, such as clove oil and cinnamon, are widely used in dental practice. They cross-react with, balsam of Peru, benzoin, vanillin and the essential oils found in orange skin. Besides dental compounds, cinnamon oil can also be found in lipsticks, chewing gums and dry vermouth; intake of these products requires contact which can obviously trigger a relapse of dermatitis.

Menthol is a component of zinc-oxide cements, and is also found in toothpastes, mouth wash, sweets, chewing gums, food, cigarettes and liquors.

Eugenol is the basic component of clove oil and other essential oils. It is used in periodontal medications, in cements and in core pastes. It causes allergic cheilitis and stomatitis (11) and cross-reacts with balsam of Peru, diethylstilbestrol and benzoin.

Resins for dental fillings are made of different kinds of monomers: methacrylate and dimethacrylate-urethanes monomers, bysphenol-epoxy resins and ethylenediamine (12). Their polymerization is induced by visible and ultraviolet light sources or by chemical agents (benzoyl peroxide, hydroquinone, camphorquinone, phthalates, tertiary aromatic and aliphatic amines, benzoin esters, ultraviolet stabilizers and antioxidants). These substances may induce contact allergy and urticaria since saliva, water, iodized water and alcoholic solutions can release non-polimerized (allergenic) monomers from dental resins.

In oral medications various potentially allergenic preservatives are used. The most common are parabens, dichlorophen, formaldehyde, perborate sodium, quaternary ammonium compounds, merthiolate, phenylmercury nitrate and ethylenediamine. In this respect, it is worthwhile recalling that ethylenediamine is present also in topical and systemic medications, and cross-reacts with aminophylline (containing ethylenediamine and theophylline) and with its antihistaminic derivatives (pyribenzamine, antazolin and hydroxyzine) (13).

Perlèche may occasionally be only a sign of denture stomatitis. Contact allergy may be induced by the materials of wbich the denture is made, the liquids for cleaning or the products for fixing it. Most dentures are today made of hot-processed acrylic resins, and allergic reactions do not occur frequently. For denture repai-

ring and coating, instead, heatless self-hardening acrylic resins are used. In the hot process, the polymerization reaction between the acrylic monomer and the different additives (hydroquinone, dymethil-p-toluidine) fully occurs, whereas in cold processes small amounts of monomers may not polimerize, thus resulting in allergic stomatitis and cheilitis.
Also, some additives to the acrylic materials turn out to be sensitizing, such as stabilizers (hydroquinone and benzoyl peroxide), plasticizers (dibutyl and dimethyl phthalates), pigments (mercury solphate, iron oxide, selenium compounds) and hardeners (dimethyl acrilates) to prevent cracking.

Cosmetics
The commonest causes of allergic disorders are found in lipsticks wich can contain eosine dyes (also potential photosensitizers), lanolin, antioxidants, cinnamon, perfume essences. Lesions affect mainly the lips while mouth corners are usually spared. The clinical picture may vary from mild erythema, to flaking, chapping, edema and crusts (14).
Lip salves contain antioxidants, lanolin, balsam of Peru and sometimes dyes (carmine) (15). An example of "ectopic contact dermatitis" is nail-enamel cheilitis or perlèche, whose common sensitizing agent is a sulphonamide-formaldehyde resin. This may occur when the freshly painted nail comes into contact with the lips, but dermatitis does not appear if the nail-enamel is dry. Formaldehyde contained in nail liquids as hardener may cause punctiform emorrhages on the lower lip rim (16).

Food
Raw or cooked carrots have caused allergic perioral dermatitis (17). Catechol in mango may have sensitizing effects, and cross-reacts with poison-ivy oleoresins. Individuals peeling oranges with their teeth may develop allergic cheilitis due to limonene, an essential oil contained in the orange skin (18). This may also cause perioral dermatitis. The orange skin cross-reacts with balsam of Peru, bergamot oil, turpentine, celery, cumin and dill. Coffee-induced persistent cheilitis with positive patch-test has been reported (19). We also observed banana allergic cheilitis with positive patch test to the fruit it self.

Nickel and rubber
In nickel-allergic individuals, the habit of keeping nickel-plated objects (pens, pins, hair-curlers, hairpins) between the lips may cause angular cheilitis. This disorder may also be caused by contact with metal containers for lipstick. In these cases, a sufficient amount of nickel was found so as to be positive to the dimethylglyoxyme test.
Rubber-sensitized individuals who bite the rubber of pencils may develop allergic cheilitis, usually due to mercaptobenzothiazole .

Case studies
In the last four years we investigated and tested 273 patients with contact cheilitis. Cheilitis was associated with perioral dermatitis in 22 patients (8%), while 91 patients (33.3%) also had stomatitis with objective and/or subjective symptoms. Sixty-three patients (23%) had a positive history of personal and/or familial atopy.
In all patients, skin tests were performed using a wide range of materials including the European standard series as well as the dental one (dental materials) and the substances previously mentioned as possible allergens. Many other food products, cosmetics and drugs (sometimes as such) which played an important role in developing cheilitis symptoms, according to patients' histories and statements, were tested. Cheilitis, whether or not associated with stomatitis and/or perioral dermatitis, was shown to be allergic in 123 patients (45%), while no allergy was detected in 150 patients (55%).
The results of patch tests are shown in Table 2. Most patients showed two or more positive reactions, sometimes to completely different materials. However, all reactions are relevant by

Table II.

ALLERGIC CONTACT CHEILITIS. RESULTS OF PATCH TESTS IN 273 PATIENTS

Substance	No. positive reactions	%
Nickel	47	17.2
Fragrance mix	20	7.3
Balsam of Peru	14	5.1
Ammoniated mercury	5	1.8
Neomycin	5	1.8
Lanolin	4	1.4
Benzocaine	4	1.4
Colophony	3	1.1
Tetramethylhiuramdisulfide	3	1.1
Parabens	2	0.7
Thiurams	2	0.7
Propolis	2	0.7
Quinoline	1	0.3
Penicillin	1	0.3
Ethylenediamine	1	0.3
Toluene sulfonformaldehyde resin	1	0.3
Copper	1	0.3
Thymerosal	1	0.3
Garlic	1	0.3
Onion	1	0.3
Toothpastes and muth wash	24	8.8

being related to substances that come into contact with the lips.

Nickel ranks first with 17.5% of positive reactions. This high rate has due to the many ways for nickel to come into contact with the lips and the oral mucosa (see above). It has also extrinsic

sults in an increased reactivity (whether immunologically mediated or not) to various chemical substances, especially irritating ones. In addition, the various haptenes easily penetrate inflammed skin in atopic patients. On these grounds, chemical stimuli of various kind (above all foods) may not only worsen cheilitis associated with atopic perioral dermatitis, but can also cause other forms of cheilitis, such as urticarial contact cheilits, immediate contact cheilitis and allergic contact cheilitis in atopic patients. Several clinicopathogenetic disorders may coexist in the same patient.

Case studies

In 9 atopic patients with perioral cheilitis and dermatitis, skin tests (open, prick and scratch) enabled us to detect urticarial contact cheilitis in 6 cases and immediate contact cheilitis in 2 cases. The food products concerned are shown in Table 5; sometimes, more than one food product was involved for the same patient.

Laboratory diagnosis

The useful skin tests for cheilitis diagnosis are shown in Table 6. Tests must be performed with fresh, raw and non-frozen food, since below a temperature of -16° C some food proteins lose their allergenic power. The same applies to centrifuged, watered-down or preserved food; many substances lose their antigenicity within 48 hours.

With the exception of the patch test for contact allergy, all other tests are performed on the volar surface of the forearm. The patch test being positive, a further control is advisable by repeating the same test and also performing the use test, which helps to support the clinical significance of positive tests. Tests may be performed on the lesion as well. As regards cheilitis, this applies to open and rub tests only. Tests being negative and the relevant history being very supportive, the prick and scratch tests can be performed on the lesion.

In patients with allergic contact photocheilits, traditional photopatch tests are usually done.

Table V.

CUTANEOUS TEST RESULTS IN 9 PATIENTS WITH ATOPIC CHEILITIS AND PERIORAL DERMATITIS

Substance	Contact urticaria (6 cases) No. positive reactions	Protein contact dermatitis (2 cases) No. positive reactions
Apple	6	-
Kiwi	3	1
Garlic	3	-
Carrot	2	-
Fennel	2	1
Tomato	2	-
Banana	1	-
Celery	1	1

Table VI.

DIAGNOSTIC TESTS IN CONTACT CHEILITIS

Clinical form	**Diagnostic Tests**
Allergic contact cheilitis	Patch test
Allergic contact photocheilitis	Photopatch test
Urticarial contact cheilitis	Open test Rub test Prick test Scratch test
Urticarial cold cheilitis	Ice cube test
Immediate contact cheilitis	Open test Rub test Prick test Scratch test Patch test Immediate and delayed reading

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BLAUE LISTE
Cosmetic Ingredients
Second, revised and enlarged edition

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Recognizing and avoiding undesired side-effects of substances with which people come in contact is a task that has aquired increasing importance.
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The "Blaue Liste" considers cosmetic ingredients, which can be significant causing allergic reactions.
It offers the producers a proposed format for ingredient declaration, and likewise addresses the physician providing him with the information on cosmetic ingredients necessary to investigate allergic reactions. Simultaneously, however, a binding concept is submitted how allergy-prone users can be protected from the particular materials. In order to make an EC-wide usability possible the text is bilingually written in German/English.
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1. Ingredient classification according to four classes of active substances: preservatives (Code P), colourants (Code C),Ultraviolet filters (Code UV), and other ingredients (Code O).

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Pharmacology/Pharmaceutics, Medicine (all fields)

LIPOSOMES: FROM PHYSICS TO APPLICATIONS

By D.D. Lasic, Liposome Technology Inc., CA, USA

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After their discovery, liposomes rapidly spread into various sciences and applications. This volume critically reviews the applications of liposomes (some for the first time), including theoretical physics, chemistry, energy conversion, ecology, genetic engineering, food industry, cosmetics and medicine, as well as their characteristics and properties. It presents the most recent developments, such as Stealth liposomes (which are invisible to the immune system and have shown encouraging results in cancer therapy). Rather than being presented in a "catalogue" style, the data is logically explained, and fundamental models and mechanism are reviewed and proposed. All of the seemingly unrelated phenomena in various methods and applications are defined using simple laws of physics, chemistry and biology. The volume will be invaluable to pharmacists and pharmacologists as to all those involved in liposome research.

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Fourth International Course on
Occupational Dermatoses

7-11 June 1994, Hotel Naantali Spa, Naantali, Finland

Background

Three international courses on Occupational Dermatoses have so far been arranged by NIVA, in 1982, 1986 and in 1991. Each course was attended by about 100 participants. Occupational dermatoses cause a significant percentage of industrial disabilities and a great number of lost work days. It has proven difficult even for an experienced dermatologist to determine the agents causing an occupational skin disease.

Objectives

The aim of the course is to provide the participants with detailed up-to-date knowledge on occupational dermatoses.

The course will comprise the latest knowledge on the progress of occupational dermatology of practical importance.

Each lecture is followed by in-depth-discussion. Group-work teaching will take place daily tutored by a faculty member. The groups will discuss problems brought in by the participants, and will review and solve questions that have come up during the lectures. Active participation of the participants is highly encouraged. Report related to occupational dermatology can also be presented as posters.

Target group

Occupational dermatologists, dermatologists and clinicians in industrial medicine with a good basic knowledge of occupational dermatology.

Main topics

- Allergic contact dermatitis
- Irritant contact dermatitis
- Immunology of contact dermatitis
- Epidermiology of occupational dermatoses
- Contact urticaria
- Immediate allergy skin testing
- Patch testing problems
- New allergens

Faculty members

D. Belsito, USA; M. Bruze, Sweden; T. Diepgen, Germany; A. Dooms-Goossen; Belgium, P. Elsner, Switzerland; T. Estlander, Finland; T.Fischer, Sweden; A. Fransway, USA; P. Frosch, Germany; K. Kalimo, Finland; A. Lauerma, Finland; H. Maibach, USA; T. Menne, Denmark; R. Rycroft, UK; J. Taylor, USA; K. Turjanmaa, Finland; J. Wahlberg, Sweden.

Location
The town of Naantali is located about 15 Km north-west of the city of Turku.

Second announcement & application form available:
from December 1993.
Application deadline:
31 March 1994
Maximum number of participants: 80
Course fee: FIM 2,000

Course secretary:
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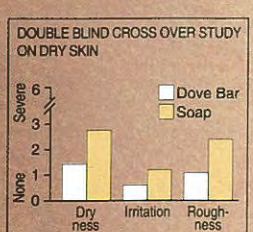

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