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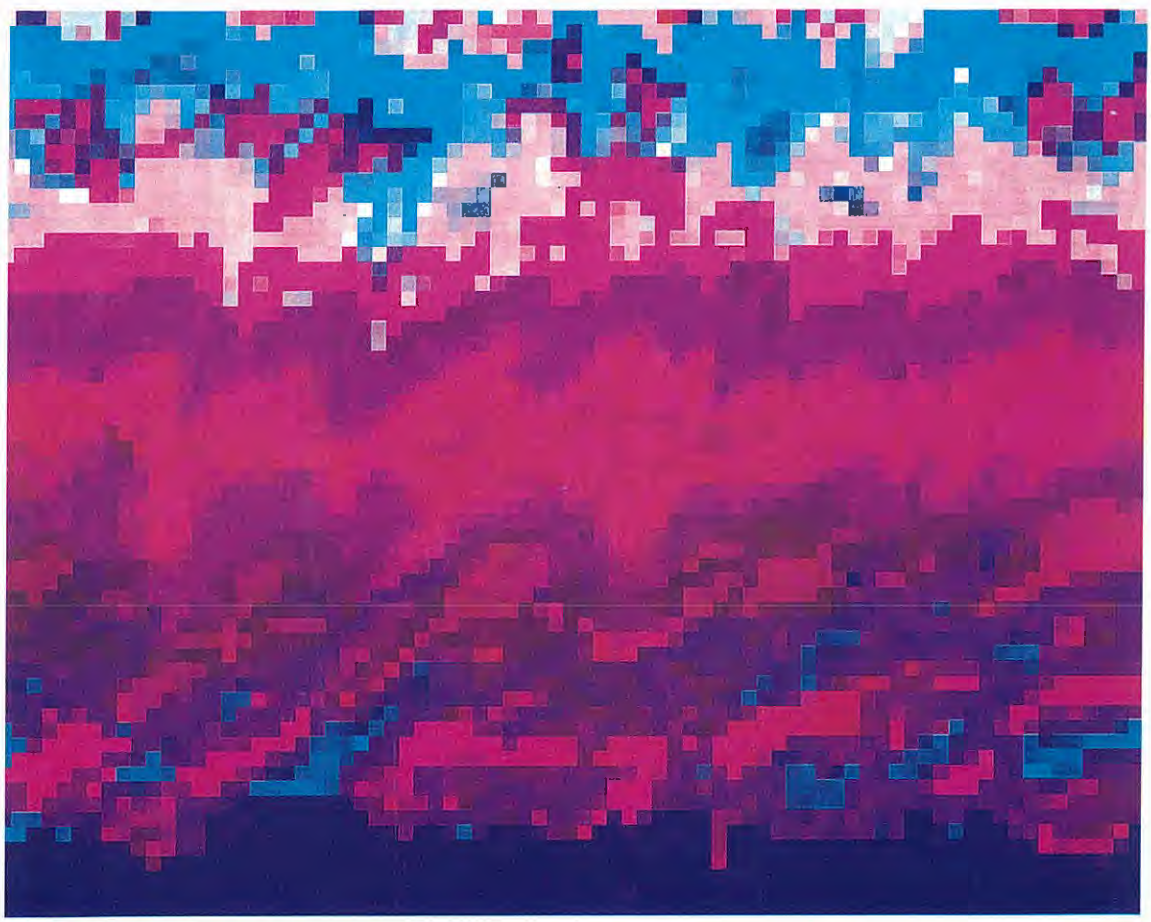

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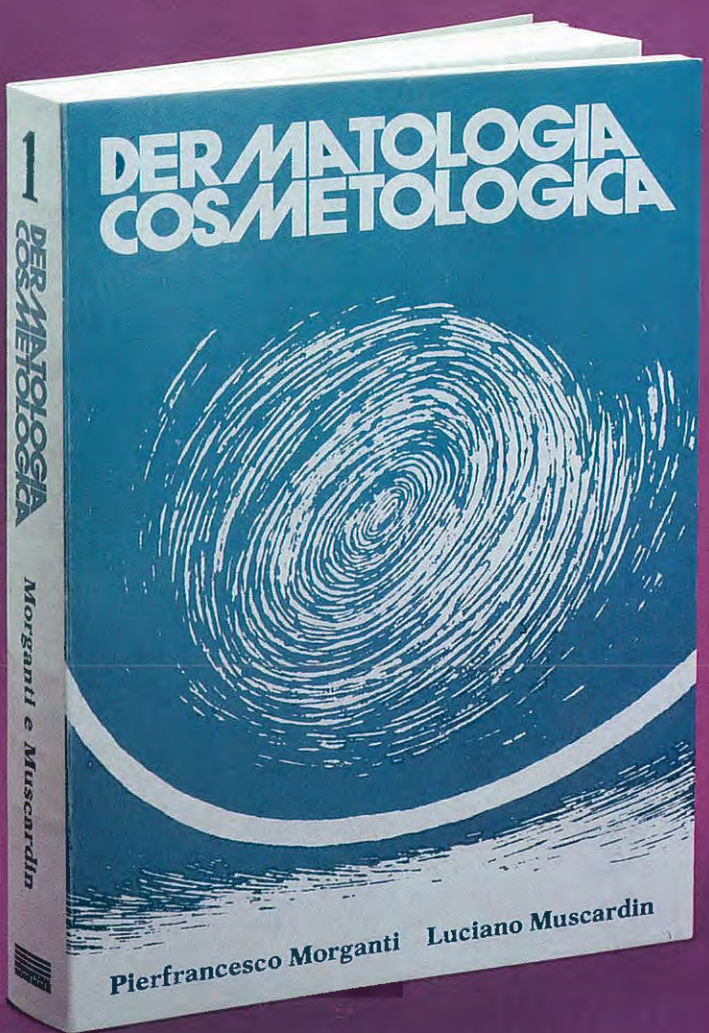

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A cura di P. Morganti e L. Muscardin
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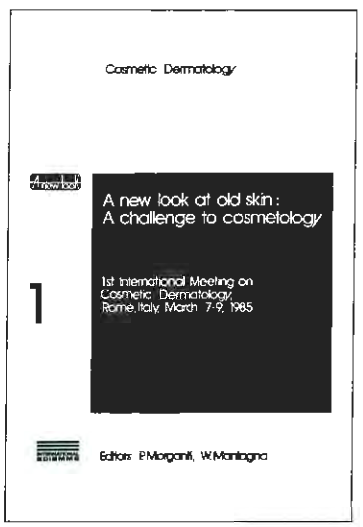
A new look at old skin: A challenge to cosmetology

1st International Meeting on Cosmetic Dermatology, Rome, Italy, March 7-9, 1985

Editors: P. Morganti, W. Montagna



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Third year undergraduates, research workers in the field of Cosmetic Chemistry, Biochemistry, Medicine, Pharmacy and Pharmacology, researchers and managers working in the cosmetic and pharmaceutical industries.

The proceedings contained in this volume provide comprehensive view of the different aspects of the skin aging with its cosmetological implications.

Contents (main chapters)

A NEW LOOK AT OLD SKIN: A CHALLANGE TO COSMETOLOGY
Editors: P. Morganti, W. Montagna

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Trimestrale di Dermatologia Cosmetologica
Quarterly Review of Cosmetic Dermatology

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LIPOSOMES IN DERMATOLOGICAL PREPARATIONS

H. Lautenschläger
Neusser Gasse 50, D-5024 Pulheim - Stommeln, Federal Republic of Germany

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KEYWORDS: *Liposomes, Polyunsaturated Phospholipids, Phosphatidylcholine, Essential Fatty Acids, Horny Layer, Liposomal Formulations, Penetration, Lipid rich Liposomal Systems.*

Synopsis

It was attempted to provide a simplified overview of a very rapidly growing field in cosmetic dermatology and to put it into some sort of context, summarizing some of the most important results concerning the field of liposomal dermatologicals and cosmetics.
1. Liposomes are a very many–sided topic, which cannot be treated with a routine formulation.
2. Liposomes are formulation and active ingredient in one.
3. The quality of the effect depends on the dose.
4. The liposomal potential is dependent on other ingredients in the formulation.
5. Liposomes have both a dermatological and a cosmetic justification.
6. The primary topic in the dialogue between the raw material manufacturers and the manufacturers of the preparations must be the working out of criteria for the evaluation of liposome-containing dermatologicals and the setting of technological standards

Riassunto

Si é cercato di dare un panorama aggiornato dei problemi riguardanti la Dermatologia Cosmetologica riassumendo i risultati più importanti ottenuti nel settore dei liposomi quali vettori di utilizzo sia dermatologico che cosmetico.
1. I liposomi rappresentano un mezzo topico particolare che non può essere utilizzato per tutte le formulazioni usuali.
2. I liposomi sono nello stesso tempo veicoli e principi attivi.
3. La qualità dell'effetto é sempre dose-dipendente.
4. L'efficacia dei liposomi é strettamente correlata con tutti gli altri ingredienti che compongono la formulazione.
5. I liposomi sono adatti sia all'uso dermatologico che cosmetico.
6. Si deve stabilire un più stretto collegamento tra produttori di materie prime ed utilizzatori per valutare attentamente le caratteristiche standard del liposoma quale prodotto finito.

Membrane-forming amphiphiles

Liposomes are defined as spherical vesicles, whose membranes consist of a bilayer of special amphiphilic molecules. (Fig. 1)

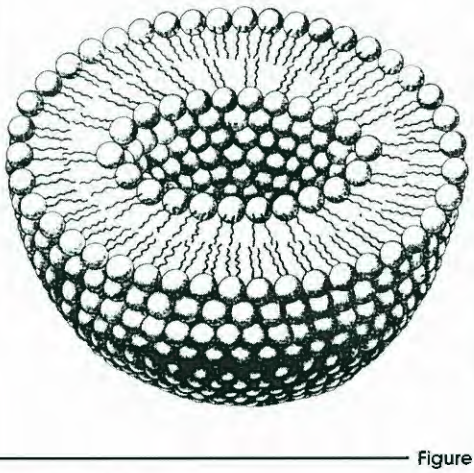

Figure 1

Liposome model

The liposomes generally referred to are composed of various phospholipids of natural, semisynthetic or synthetic origins, with the major component usually being vegetable phosphatidylcholine (Fig. 2):

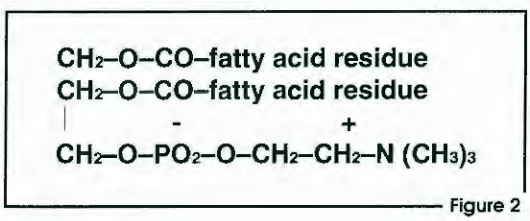

Figure 2

Phosphatidylcholine

Niosomes are, from a chemical point of view, special cases of liposomes. Besides ethoxylated fatty alcohols the main components of niosomes are synthetic polyglycerol ethers (Fig. 3).

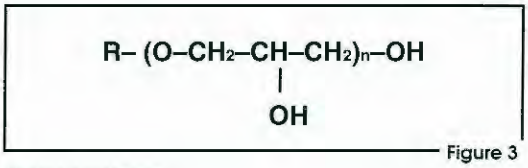

Figure 3

Polyglycerol ether

Other important vesicle forming agents are ceramides and sphingolipids in general.

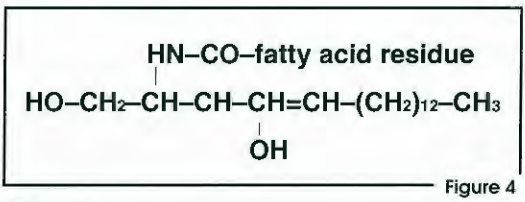

Figure 4

Ceramide

The dicarboxylic acid diesters of sucrose (1) constitute also an interesting group of substances (Fig. 5)

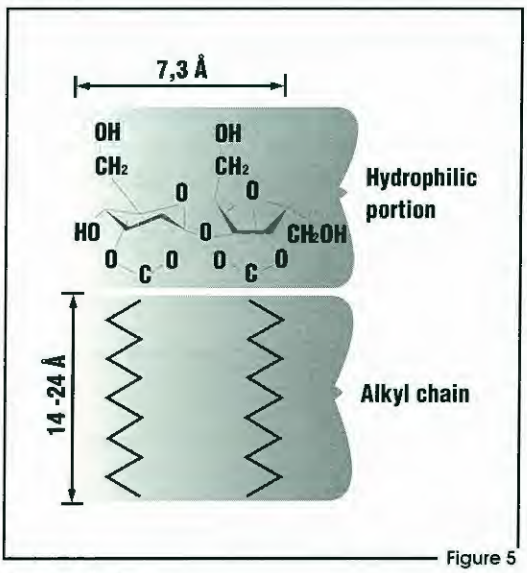

Figure 5

Sucrose diesters
(Y. Ishigami and H. Machida - 1989)

All membrane-forming amphiphiles possess a very low critical micelle concentration (cmc) of ca. 10^{-8} mol/l and less compared with ca. 10^{-3} mol/l for normal surfactants. The low critical micelle concentrations of these substances are

probably an important reason for the kindliness of these substances to skin, since the aggressivity of a surface–active substance is generally related to the concentration of free molecules.

From the point of view of availability, standardization and available literature data, phospholipids take first place amongst the liposome raw materials and are followed by niosome raw materials.

The "mechanism of action" of nonloaded ("empty") liposomes

The complex nature of the properties of liposomes can best be demonstrated for liposomes made up of polyunsaturated phospholipids.
Like phospholipids interact with proteins, glycoproteins, glycolipids and cholesterol in the cell membranes (2) (Fig. 6):

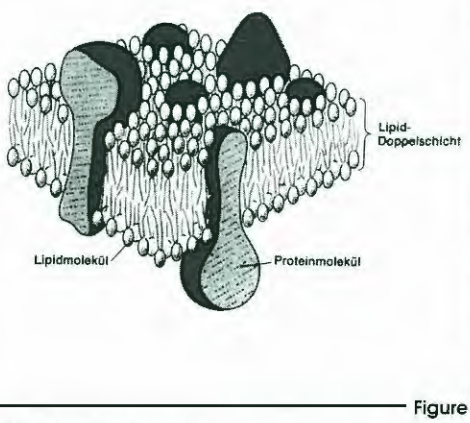

Figure 6

Model of cell membrane (A. Bruce et al. - 1986)

the same interactions come into play when phospholipids — and this applies especially to liposomes — are applied to the skin, i.e. they readily form associates with the proteins, carbohydrates and lipids to be found at the surface of the skin and in the skin. This explains the 4–phase potential effect of the phospholipids (Fig. 7).

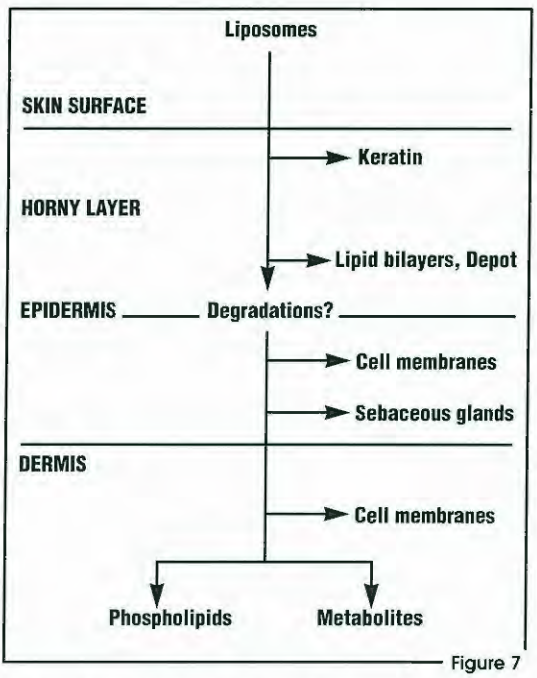

Figure 7

Potential effects of liposomes on the skin (schematically simplified)

1. In the first phase the phospholipids are bound superficially to the keratin of the horny layer (3) (cf. 4). This process is responsible for the spontaneous feeling of the skin being coated after the application. This film lipophilizes the surface of the skin and the film cannot be removed at all with water and only slowly with detergents.
However, this strong affinity to keratin results in the destruction of some of the liposomes. The same thing probably occurs at the lipid bilayers of the horny layer. There layers which are formed as an "intercellular cement" by the kerati-

nosomes (5) and whose composition is very complex (6) carry out an important barrier function and exert a disproportionate effect on inibition of transepidermal water loss.
It is important to realize this in order to decide whether to aim for just a support of the mentioned functions of the horny layer with a low dose level or whether to aim to produce further effects by means of a higher dose level (see below). Most liposomal cosmetics are likely to affect the horny layer by means of a phospholipid–keratin interaction and by a deposition in the lipid bilayers.
2. In the second phase the remaining unbound phospholipids, or possibly liposomes, are probably introduced into the deeper layers of the skin (7).
Here again the origins of the phospholipids observed.
Whether this mechanism actually involves the direct uptake of liposomes (9), which is discussed so often, or only occurs after their breakdown into individual phospholipid molecules or even their degration into individual components is not as yet clear.
The penetration of the phospholipids has been confirmed in a study made in the Institute für medizinische Balneologie und Klimatologie of the University of Munich (10) (11) (Figs. 8, 9).
In this study a liposomal concentrate which was loaded with monoclonal antibodies was applied to porcine skin in vivo. After 40 minutes it was possible to demonstrate the presence of the antibody complex in both the epidermis and the dermis by specific coloration (APAAP method) (Fig. 8, reddish coloration). The antibody alone

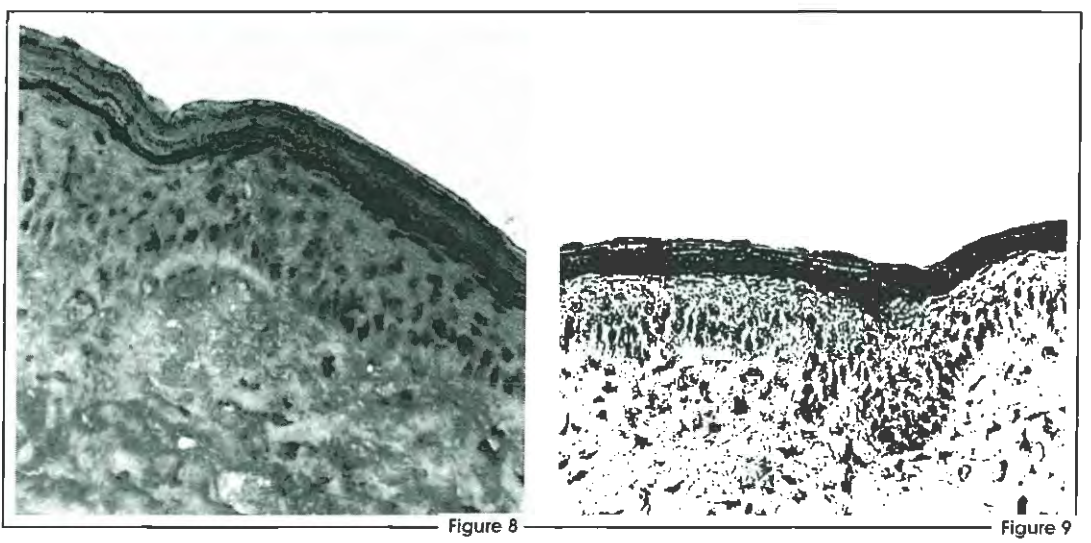

Figure 8 Figure 9

Figs. 8 and 9: Sections through porcine skin, magnified ca. 280–fold.
Fig. 8: Liposomal formulation with antibodies; Fig. 9: Control without liposomes (C. Artmann and H. Pratzel - 1988)

from membranes make themselves felt, for they are rapidly taken up again by the cell membranes. Bonnekoh et al. (8) have been able to demonstrate witb human HaCaT keratinocytes in vitro that an exogenous addition of soya phospholipid liposomes is very rapidly internalized, with a fluidization of the membrane being cannot penetrate the skin (Fig. 9).
The penetration of polyunsaturated nonliposomal phospholipids into the skin had been demonstrated earlier by means of radioactive labelling (12).
3. In a third phase the chemically bonded linoleic acid in polyunsaturated phospholipids can

possibly supplement the function of the sebaceous glands (Fig. 7). Some of the free linoleic acid is certainly produced by partial hydrolysis of the phospholipids taken up into the horny layer and distributes itself as such in the epidermis.

It is known that undersupply of the sebaceous glands with essential fatty acids leads to increased blackhead and pimple formation (13).

4. In a fourth phase the body can utilize the essential fatty acids not just as a source of energy by oxidative degradation but also to synthesize other polyunsaturated fatty acids (Fig. 10).

Thus, for example, linoleic acid released by phospholipases can lead via gamma–linolenic acid (6, 9, 12–C18:3) and dihomo–gamma–linolenic acid (8, 11, 14–C20:3) to arachidonic acid (5, 8, 11, 14–C20:4) with its metabolites and alpha–linolenic acid (9, 12, 15– C18:3) via eicosapentaenoic acid (5, 8, 11, 14, 17–C20:5) to docosahexaenoic acid (4, 7, 10, 13, 16, 19–C22:6) and its metabolites (14).

Systemic effects can certainly be excluded in any possible topical absorption; the decades of experience with phospholipids (lecithins) and highly unsaturated native oils confirm this view. Lecithin has been awarded GRAS status (generally recognized as safe) by the FDA and is registered for use in pharmaceutical, cosmetic and food applications (15).

To summarize, it must be emphasized once again that the "mechanisms of action" described

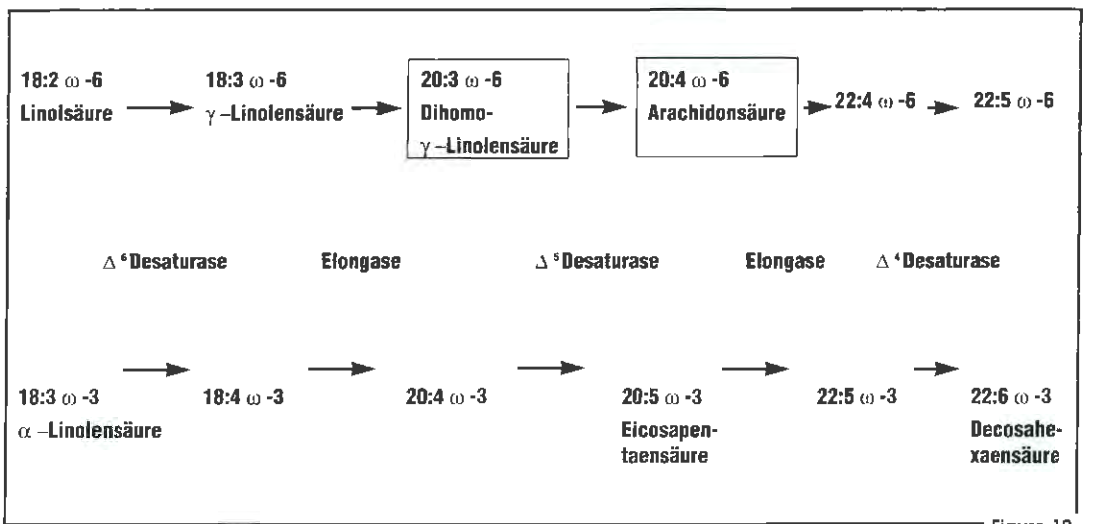

Figure 10

Metabolism of linoleic acid and alpha-linolenic acids (S.Fischer-1987)

here of empty liposomes on and in the skin are still subject to many open questions and that further biological results will be required to demonstrate the soundness of this concept for the dermatological field.

Until now there are no exact results concerning the penetration of intact topically applied liposomes through the skin into the living tissue. Neither has it been demonstrated whether suitable "classical" phospholipid formulations exhibit comparable effects, this also applies, in particular, to the penetration–enhancing effect of loaded liposomes. But what has been demonstrated is that "comparable" classical phospholipid formulations are very difficult to realize, since the "normal state" for phospholipids is of their nature in the form of liposomes.

Loaded liposomes

When "loaded" liposomes are employed for topical application the effects are those of the phospholipids and of their "load".
The storage basically occurs at two sites: Hydrophilic substances in the aqueous interior of the liposome and lipophilic and amphiphilic substances in the membrane.
In the case of water–soluble substances inside the liposomes, losses by leakage must be expected, particularly of low molecular weight substances. However, this leakage can be counteracted by ensuring that the outside phase contains similar concentrations to those enclosed in the liposomes. It should be remembered in this context that even a 10% dispersion of liposomes (calculated as dry residue) represents a very tight packing of the liposome spheres. The following picture is an electron micrograph of a 1% (!) liposome dispersion (Fig. 11).

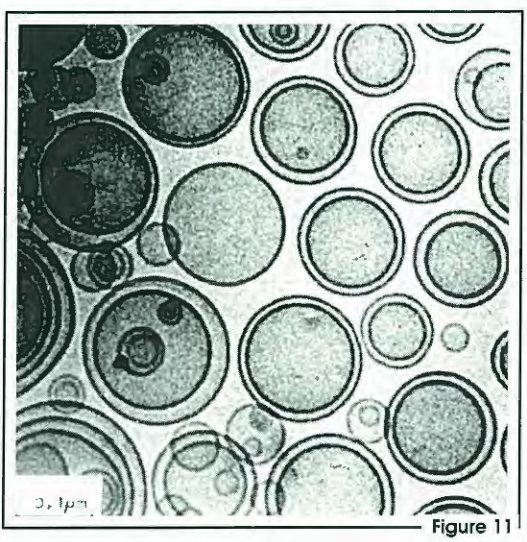

Figure 11

Cryofixed liposomes; 1% dispersion

Thus, separation from the water–soluble substances present in the outside phase is usually unnecessary and also too expensive in most cosmetic and dermatological applications.

It is the purpose of loaded liposomes, in addition to exerting their intrinsic effects, to transport their loads to the site where they are to exert their cosmetic or dermatological effects (Fig. 12). If the horny layer is the target then the distribution behaviour in this layer has priority. If transport is to take place into a deeper layer of the skin then the penetration–enhancing properties of the liposomes, respectively of their phospholipid components, are to the fore. In the case of steroids, retinoids etc., which can only exert their effect after appropriate absorption, this is the most important prerequisite along with a certain depot effect of the horny layer.

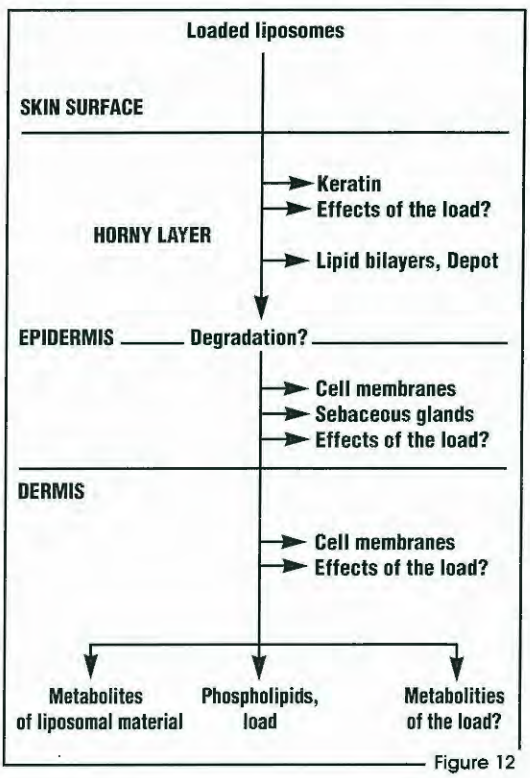

Figure 12

Potential effects of loaded liposomes in the skin (schematically simplified)

Dermatological applications of liposomal formulations

The most important groups of substances which are being investigated at the moment for the local treatment of dermatological disorders with the aid of liposomal systems are probably:
Antimycotics (and topical antibiotics in general);
antiseptics should perhaps also be included here.
Corticosteroids
Retinoids
Another potential field of application are liposomal bath oils with dermatological activities:
1. The treatment of large areas of skin is very simple.
2. The drying–out of the skin, which is usually a problem in such preparations embloying normal surfactants, is reduced.
The fields of wound healing and, in particular, treatment of sun damage (sunburn) must also be mentioned.

Cosmetic applications of liposomal formulations

The following types of preparation are to the fore:
1. Skin–care preparations with empty or moisturizer–loaded liposomes. Further potential effects are skin smoothing and supplying linoleic acid to the sebaceous glands.
2. Liposomes loaded with other special skin–care agents.
3. Sun–protection formulations with UV absorbers being optimally distributed in the horny layer and showing a certain "water resistance".
4. Liposomally encapsulated radical scavengers and related substances of the vitamin E, superoxide dismutase (SOD) or flavonoid type etc.
5. Liposomal formulations of tanning agents such as tyrosine, dihydroxyacetone etc.
6. Fitness frictions.
7. Skin caring after–shaves.
8. Very mild cleansing lotions, which simultaneously provide a skin–care base.
9. Care rinses for the scalp and hair.
10. Treatment of maternal stretch marks.
11. Bath oils.
12. Lotions for use after bath and sauna.

Lipid–rich systems

Today the most often used formulations are liposomal gels. The demonstration of liposomes in gels can be achieved very precisely by means of the electron microscope (16) (Fig. 13).

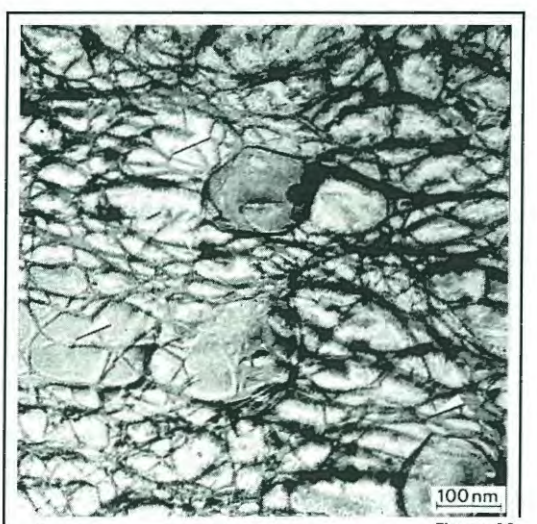

Figure 13

Electron micrograph of a liposomal skin–care gel after freeze fracture preparation (T. Müller, J. Röding, H. Lautenschläger - 1989)

The electron micrograpb (Fig. 13) illustrates liposomes in a gel matrix of xanthan gum and aloe vera.
Problems of compatibility with surfactants very often appear, when liposomal dermatologicals

are formulated as creams. Exchange processes take place which are often, in the end, detrimental to the liposomes. These processes become particularly apparent during stress tests at elevated temperature.

For this reason some manufacturers of cosmetics suggest a two-phase treatment for their customers: firstly, application of the liposomal formulation followed by the usual day or night cream. From the point of view of bioavailability of the liposomes this is certainly a good recommendation.

On the other hand, lipid–rich liposomal systems are of particular interest for cosmetics. The capacity of classical liposomes for lipids of the triglyceride type is not sufficient for the amounts required for skin care. When it is remembered that with very few exceptions the concentrations employed for liposomes do not exceed 1% and frequently lie below this.

Some very simple oil–in–water creams with very low proportions of emulsifiers have been described in the literature. Thus, for example, a liposome dispersion can be stirred into a cream base made up of 10% paraffin oil, 0.5% polysorbate, 0.5% sorbitan mono–oleate and 85% water without the liposomal system being destroyed (17).

Instead of using a small amount of emulsifier similar results can be obtained with suitable gel forming agents, such as certain polyacrylates. In these formulations which have a cream–like consistency for oil concentrations of up to 10% it is possible to avoid additional emulsifier completely. The liposomes can be seen distinctly alongside the oil droplets in an electron micrograph of such a formulation (Fig. 14).

A further new possibility for realizing lipid–rich liposomal systems involves specific mixtures of naturally occurring vegetable phospholipids which are able to stabilize oil up to a proportion by weight of 1:1. However, such vesicles no longer take up the typical spherical shape but are partly more reminiscent of a propeller, in whose centre a tiny droplet of oil is to be found (Fig. 15).

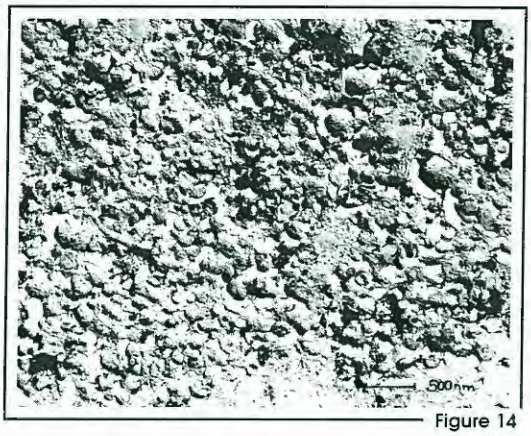

Figure 14

Electron micrograph of a liposomal gel with 2% liposomes (calculated as a dry substance) and 5% dispersed wheat–germ oil after freeze etching

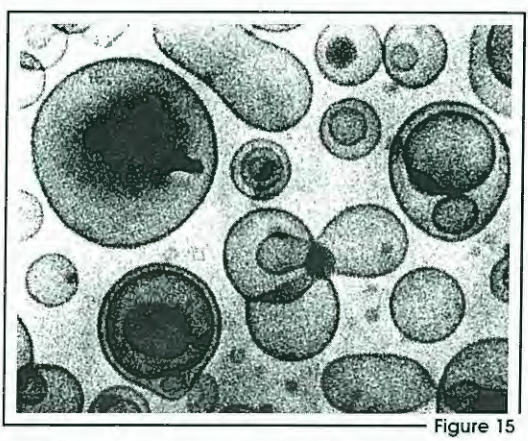

Figure 15

Cryofixed propeller–liposomes, 1% dispersion (calculated as a dry substance) (18) (J. Röding, 47th Annual Meeting of the EMSA, San Antonio, Texas, USA - 1989)

Whether this type of liposomes is an ideal base for lipid skin care is still open to question. They are likely, however, to be ideal carriers for lipid–soluble agents. In the ideal case these formulations have the advantage of being able to avoid the use of emulsifying or gel–forming additives, so that the mobility of the vesicles is not restricted.

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THE NEWEST COSMETIC TECHNOLOGIES

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KEY WORDS: *Vitamin A; NMF; PCA; Native Collagen Fibrils; Collagen Sheets; Hydration Index; Soothing Index; Acne Therapy; Gelatin–Glycine; Oral Cosmesis; Skin pH Change; Skin Aging; Betacarotene.*

Synopsis:

We use skin features as indices compared to other surfaces, nor can skin cleansing lenther be formulated as a dish–washing product. Moreover in Cosmetic Dermatology specialized "non irritating" cleasing products are used. Using particular cleaning lathers it is possible to verify changes in skin and mucous membranes pH making also evident bacterial or fungal invasion. Topical application of GLA have opened new ways for a scientific treatment of striae distensae cutis, such as a proper topical application of vitamin A seems to ensure the correct functioning of the mucosecreting epithelial cells. New experimental data suggest that PCA (Pirrolydone Carboxilic Acid) level in the skin may be directly affected by oral gelatin–glycine.
These and other cosmetic product, if correctly used, may be very helpful to the Dermatologist the Gynecologist and the Pediatrist by resolving medical–aesthetic problems without their patients taking oral drugs too much.

Riassunto:

La cute è uno dei nostri metri di bellezza e dobbiamo, quindi, adoperarci per detergerla e trattarla nel miglior modo possibile fin dalla prima giovinezza. Per questi motivi nella Dermatologia Cosmetologica vengono utilizzati speciali detergenti con una così elevata tollerabilità da esser considerati "non–irritanti" attraverso l'uso di particolari detergenti, che cambiano colore con il variare del pH cutaneo o delle mucose si può diagnosticare ad esempio la presenza di microrganismi patogeni.
L'applicazione topica dell'acido gamma–linolenico ha aperto nuovi orizzonti per una terapia cosmetica più mirata delle striae distensae cutis, così come l'uso topico dell'etil citrato e dell'etil lattato nell'acne, mentre un appropriato uso topico della Vitamina A può essere di utile ausilio per stimolare le mucose vaginali a secernere la giusta quantità di mucoproteine. Di recente interesse, infine, sono i rapporti riscontrati tra l'assunzione orale di gelatina–glycina e l'idratazione dello strato corneo.
La Dermatologia Cosmetologica, quindi, se correttamente utilizzata può essere di valido aiuto sia per il dermatologo che per il ginecologo per il pediatra per risolvere tutti quei problemi estetico–medici che non possano altrimenti essere affrontati con il solo ausilio dei farmaci.

The skin, with an area of about 2m and an average weight of 6.6 lbs., is the largest and heaviest organ of human body.

We judge age by skin, identify people by their skin, and use skin features as indices of beauty. Traditionally, to take care of the body means to take care of the skin, along with its appendages. Attempting to retard aging and to enhance beauty leads us to take care of the skin much more than any other organ.

Among the important things which we must learn are how to clean the skin well and how to protect it from damaging UV rays. When you are 16 years old your future is already clearly defined.

By that age people who clean too much and who like long exposures to the sun shall have already set the stage for trouble. (1,2,3)

Our skin, moreover, cannot be compared to other surfaces, not can skin cleasing lather he formulated as a dish–washing product.

In Cosmetic Dermatology we use specialized cleansing products possessing such greatly reduced skin irritations as to be considered "non–irritating". (4)

These cleansing products, with protein–simulating chemical structures, have their ideal pH action situated between 5 and 6, as in the normal skin.

New cosmetic compunds leave the skin cleaned and hydrated.

Moreover, using particular cleaning lathers recently introduced into the cosmetic market, it is possible to verify changes in skin and mucous membranes pH. (5,6,7)

Such pH change can document efficacy before, during and after a pharmacogynecological local or systemic therapy against pathogenic organism.

Such new cosmetic products, can make evident bacterial or fungal invasion, or the efficacy of a the therapeutic regiment against them, by a simple color change of the cleansing water used.

Cosmetic intervention may also be intended to corrent effects deriving from age and illness, and also to slow down or reserve some damage caused by chronic ambient microtraumas.

By going deeper into the knowledge of cutaneous biological mechanisms we are allowed an approach more clearly aimed at retarding future aesthetic problems.

The cosmetologist, to meed customers requests, developed may new formulae. Keeping his store of knowledge up to date, he is able to use more sophisticated and active raw materials.

As a result, moisturizing and protective creams and gels containing vitamins, collagen and elastin have been prepared.

A proper topical application of vitamin A, in a cosmetic form, seems to ensure the correct functioning of the mucusecreting epithelial cells.

This stimulates or induces the formation of mucoproteins and other mucus substances. (8)

Use of this type of vitamin A gel may provide a beneficial antikeratinizing effect on the oestradiol–induced vaginal keratinization. (9)

More recently, the cosmetic use of alkyl esters, such as ethyl citrate, seems to be useful in acne therapy.

Data from recent studies suggest that these alkylesters, hydrolized by lipoases of bacterial origin instead of the triacylglycerols, inhibit propionibacterium acnes from liberating the comedogenic free fatty acids from sebum. (10,11)

Growth of aerobic and anaerobic gram–negative organisms is also suppressed.

This harmless cosmetic acne therapy may be used instead of benzoyl peroxide and retinoic acid, both of which are photosensitizing chemical compounds.

Finally, the topical applications of some new organic compounds from silicium (silanols), which are probably precursors of collagen and elastin, coupled with the cosmetic use of gamma–linolenic acid, have opened new ways for a scientific treatment of striae distances cutis.

Interesting studies have been carried out on linolenic acid, gamma–linolenic acid and beta–carotene indicating that they are very acti-

ve in reducing the inexorable progress of skin aging. (12,13)
As active cosmetic principles employed orally or topycally they oppose the development of free radicals.
Ultraviolet rays accelerate the process of skin aging by developing free radicals which interact at the cellular level with proteins, lipids and DNA. (14)
They thereby initiate many different types of damage, some of which often turns into skin cancers. Appropriate cosmetic products can intervene at different levels to slow down, limit and reverse damage deriving from photoaging.
Present knowledge allows us to state almost certainly that UV protection has a fundamental part in preventing or, at least, slowing down the process of skin aging. (14,15)
The protective function is mailny performed through the filtering power of organic molecules absorbing UV radiations, or through the reflecting power of organic pigments which the cosmetic cream leaves on the skin. (16,17,18)
Aged skin is also dehydrated and alipidic, deprived of natural mousturizing factors (NMF) and of the skin surface lipids which are indispensable in keeping skin smooth and hydrated. (19,20) Other elements deeply associated with aging are increased skin wrinkles and decreased cutaneous immunologic competence.
Hence the cosmetic use of hydrotopes (water co–ordinating agents) such as mucopolysaccharides, PCA (5–pirrolodoncarboxylic acid) sodium salt, amino acids, such as glycin and prolin, and complex mixtures of natural carbohydrates, such as collagen and elastine, is rapidly increasing because all are active compounds for liking water to the stratum corneum. (21,22)
Well formulated cosmetics delay *perspiratio insensibilis*, help to retain water in the stratum corneum and to restore the surface lipid film.
This lipid film is in fact, the indispensable regulater of water exchanges between the dermis and the surface skin layers.
For testing the activity of moisturizing and sebum–normalizing cosmetics specific "hydration" and soothing indices are suggest.
These indices are directly correlated to the individual biotypological conditions of the skin.
The hydration index is the radio between the water retention in the surface layer of a treated skin area prior to treatment the result is multiplied by a factor 10.
The soothing index is the ratio between the sebum content of surface layer of a treated skin area and of the same skin area prior to treatment the result is multiplied by a factor 4.
These indices may be measured by the use a computer supported system called Dermotest hytech. (23, 24, 25).
More recent studies carried out on biological collagen sheets, which can improve the degree of hydration of the skin, are also very interesting.
By use of these biological sheets, composed of soluble and insoluble native collagen fibrils, it is possible to obtain restoretion of the moisture in the surface layers of the skin, varied in degree according to the quantity of native soluble collagen present in the sheet. (26)
Such sheets may also be very useful as support and active carrier of both biological and chemical materials for pharmaceutical purposes.
In fact, they may be enriched with active compounds, steadily held by fibrils by means of chemico–physical bonds, and therefrom slowly and progressively released to the skin structures.
These collagen sheets, appropriately treated, may provide useful physiological cosmetic therapies in some inflammatory conditions of genital mucosa.
These collagen sheets, appropriately treated, may provide usefull physiological cosmetic therapies in some inflammatory conditions of genital mucosa.
New experimental data suggest that the Pca level in the skin may be directly affected by oral route of gelatin–glycine. (27, 28, 29).
The improvement in observed hydration and

elasticity of stratum corneum is increased by about 40% after 60/90 days of treatment.
On the basis of these studies treatment by oral gelatin–glycine would seems to a usefull complement to cosmetic use for dry and aged skin.
Severe cuticular damage to the hair, described amongst 120 children engaged in intensive swimming pool training schedules, was probably due to the prolonged exposure to chlorinated water. (30)
Regular use of newer protective hair creams and shampoos may retard such assaults by swimming pool water.
Lastly, permanent waving solutions and depilatory substances should be carefully used.
If not, they may cause the hair to fracture of the skin, especially when depilatories are used on the face and breasts, to be irritated.
These and other products, if correctly used, may be very helpful to the Dermatologist or the Gynecologist by resolving medical–aesthetic problems without their patients taking oral drugs too much.

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EPIDERMAL MOISTURE AND SKIN SURFACE LIPIDS THROUGHOUT LIFE AS PARAMETERS FOR COSMETIC CARE

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KEYWORDS: *Moisturizing Creams; Skin Hydration; Casual Level Measurements; Hydration Measurements; Skin Surface Lipids.*

Synopsis

Aging of the skin is clinically accompanied by increased dryness. Determinations of skin surface lipids and of epidermal moisture were performed in 160 females with normal skin on the forehead and the cheek. The values of 80 females, who were regular users of cosmetic care products were compared with those of age–matched non–users. No significant differences of skin lipids and hydration existed between both groups. In the group of females over 60 years not utilizing cosmetic care products statistical evaluation showed a significantly decreased hydration of the horny layer in comparison to the control group. Supply of the skin with moisturizers thus should be a major aim of cosmetic care.

Riassunto

L'invecchiamento della pelle é clinicamente accompagnato da un incremento della secchezza cutanea. Sono stati controllati i lipidi di superficie e l'idratazione cutanea di 160 donne con cute normale a livello della fronte e delle guance, raggruppate in due gruppi di 80 soggetti. Un gruppo utilizzava normalmente cosmetici mentre l'altro era rappresentato da soggetti non utilizzatrici di creme. Non sono state riscontrate differenze significative tra i due gruppi sia sui parametri sebometrici che nell'idratazione di superficie. Nelle donne con età superiore agli anni sessanta non utilizzatrici di cosmetici é stato riscontrato un decremento significativo dell'idratazione dello strato corneo rispetto al gruppo di controllo. Lo scopo principale che debbono, quindi, raggiungere i prodotti cosmetici sembra essere quello di reidratare la cute.

Introduction

One of the essential components of attractive skin is the water content of the stratum corneum. This content depends on exogenous factors such as humidity and temperature and on endogenous factors such as perspiratio sensibilis and insensihilis and the natural moisturizing factor — a composite of amino acids, salts and other water soluble components like urea, sodium lactate and others. A decrease of the water content of stratum corneum leads to dry skin and may even cause the xerotic eczema. Together with the skin lipids, the water binding substances form the hydro–lipid film of the skin. At present, the interactions between skin lipids and moisturizing substances of the horny layer are not fully understood. Nevertless, a major aim of cosmetic skin care is to supply skin with suhstances imitating the natural hydro–lipid film.

Clinically one of the first symptoms of aging of the skin is increasing dryness. Determinations of sebum and hydration have heen performed in order to investigate possible changes of both paramters during the different periods of life. In fact, significant decrease of sebum with proceeding age has been described. (1) However, the importance of sebum for the appearance of the skin is not undisputed. The skin of babies is nearly devoid of sebaceous gland lipids but, nevertheless, serves its functions well and is not "dry" at all. Moreover, the role of stratum corneum lipids is yet not fully understood. Their involvements in the cornification and desquamation processes have been discussed. (2) While the clinical impression of dry skin increases continuously with age, the composition of the stratum corneum lipids remains constant from 50 years of age on. (2)

From previous investigations of the water content of the stratum corneum no common trend could be derived. No change in moisture content of tbe horny layer with continuous aging was found by Gloor and Frödin et al. (3,4) However, moderate decrease of hydration in aged skin was reported by Potts et al. (5) The contradictory data prompted us to study hydration of the stratum corneum in different age groups in females with normal skin. In addition, the casual levels of skin surface lipids were determined.

Methods

Test subjects

The measurements were performed in a group of 80 females, who were regular users of various cosmetic care products, the results were compared with those of 80 age matched control subjects not using cosmetic preparations in order to evaluate possible differences. Four groups of age were tested in this total of 160 females. Each group consisted of 20 users of cosmetics and 20 non-users. The groups were: 18–30 years, 31–45 years, 46–60 years, and 61–75 years of age. All subjects were healthy and had clinically normal skin. On the day of the examination, skin had not heen washed and nothing had been applied to the face. The forehead and the cheeks were used as test areas.

Measurements

The measurements were performed under standardized external conditions between 11.00 a.m. and noon. Room temperature was 21° C and humidity 40–45%. The instrument used for measurements of hydration of the stratum corneum was the Corneometer CM420 (Scbwarzhaupt Medizintechnik GmbH 5000, Cologne, FRG), which acts by measuring capacitance. For measurements of the casual level of skin surface lipids the Sebummeter SM 410

(Schwarzhaupt Medizintechnik GmbH 5000, Cologne, FRG) was used, which provides photometric measurements of the light permeability of a lipid contaminated foil.

Results

Overall evaluation of hydration revealed no significant differences between users of cosmetics and non–users (Table I).

Table I

COMPARISON OF HYDRATION AND LIPIDS BETWEEN TREATED AND NON–TREATED SUBJECTS

	TREATMENT VALUE			NON–TREATMENT VALUE			P–VALUE
	n	mean value	SD	n	mean value	SD	
HYDRATION							
Forehead	80	76	±24	80	73	±20	NS
Cheek	80	89	±13	80	86	±14	NS
LIPIDS							
Forehead	80	200	±99	80	179	±96	NS
Cheek	80	127	±98	80	104	±76	NS

SD – standard deviation
NS – no significance

No significant decrease of hydration and lipid values between treatment and non–treatment group.
Statistical evaluation according to Wilcoxon 2–Sample–Test.

In the group of non–users of cosmetic care products significant changes of epidermal hydration were observed only on the forehead at different periods of life. However, no significant changes of hydration were found in the cosmetic group in both sites in the face (Table II).

Table II

COMPARISON OF HYDRATION AMONG THE DIFFERENT AGE GROUPS IN TREATED AND NON–TREATED SUBJECTS AND TREATED AND NON–TREATED SUBJECTS WITHIN THE SAME GROUP OF AGE

Age group	<30 years			31–45 years			46–60 years			>60 years			p–value
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	
FOREHEAD													
Treatment values	20	74	±25	20	84	±22	20	69	±26	20	78	±21	NS
Non–treatment values	20	73	±17	20	83	±18	20	78	±18	20	59	±21	p<0.01*)
p–value		NS			NS			NS			p<0.05**)		
CHEEK													
Treatment values	20	91	±13	20	91	±9	20	84	±16	20	89	±11	NS
Non–treatment values	20	83	±17	20	88	±10	20	91	±14	20	83	±15	NS
p–value		NS			NS			NS			NS		

SD - standard deviation
NS - no significance

*) Significant change of hydration throughout the different groups of age within non–treated subjects in the forehead. Statistical evaluation according to Kruskal–Wallis–Test.
**) Low significant lower level of hydration on the forehead in the non–treatment group in comparison to the treatment group over 60 yrs. Statistical evaluation according to Wilcoxon 2–Sample Test.

Comparison of hydration values of cosmetic users and non–users within the same age group revealed a significant decrease in non–users above 60 years of age against the age matched users of cosmetic care (Table II). Hydration parameters of the groups younger than 60 years showed no significant differences between users and non-users.

The statistical evaluation of skin surface lipids showed no significant differences between the groups of utilizers of cosmetic care and non–utilizers within the same age. Significant variations of skin surface lipids were found at the different ages in both groups (Table III). In addition, for the total of users and non–users independent of the age for skin lipids no significant differences became evident (Table I). Comparison of the 4 age groups showed significant changes of the levels of skin surface lipids and of hydration. Distinctly lower levels of both parameters were to be found in the eldest group in comparison to the younger groups.

Table III

COMPARISON OF LIPIDS BETWEEN THE DIFFERENT AGE GROUPS IN TREATED AND NON–TREATED SUBJECTS AND BETWEEN TREATED AND NON–TREATED SUBJECTS WITHIN THE SAME GROUP OF AGE

Age group	<30 years			31–45 years			46–60 years			>60 years			p–value
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	
FOREHEAD													
Treatment values	20	195	±70	20	228	±84	20	232	±133	20	145	±76	p<0.05*)
Non–treatment values	20	213	±87	20	211	±85	20	166	±94	20	126	±98	p<0.001*)
p–value		NS**)			NS**)			NS**)			NS**)		
CHEEK													
Treatment values	20	141	±96	20	163	±91	20	137	±121	20	69	±55	p<0.01*)
Non–treatment values	20	119	±67	20	128	±68	20	96	±83	20	72	±75	p<0.05*)
p–value		NS**)			NS**)			NS**)			NS**)		

SD - standard deviation
NS - no significance

*) Significant changes of skin surface lipids throughout the different age groups within treated and non–treated subjects. Statistical evaluation according to Kruskal–Wallis–Test.
**) No significant differences of skin surface lipids between treated and non–treated subjects within the same age groups. Statistical evaluation according to Wilcoxon 2–Sample Test.

Discussion

Similar to sebum, which shows different levels in various locations, also hydration of the horny layer may show variations according to the anatomical site. In previous measurements of skin hydration mainly the lower arms or the legs were used as test areas. In our study, which focused on the comparison between cosmetic users and non–users 2 sites in the face were selected. The statistical overall evaluation between users of cosmetic care and non–users, disregarding age showed no significant differences between both groups for moisture and lipids. However, the decrease of hydration on the forehead in the over 60 years old females, who used no cosmetic care products was a significant finding. This finding shows that at least in some locations water content of the stratum corneum decreases from 60 years on and is a target for the use of moisturizers.

The decrease of skin surface lipids with age is partly due to reduced sebaceous gland function. This is in accordance with the results of sebum investigations at various ages, showing a significant decrease with increase of age.(1) In addition, a decrease of epidermal lipids caused by the thinning of the epidermis in aged persons may be contributory to the diminution of skin lipids.

The absence of a difference in skin lipids between the groups utilizers of cosmetic care products and non–users indicates equal skin condition with regard to lipids in both groups, and no effects of cosmetic preparations on skin surface lipids. The significantly lower water content of the stratum corneum in females over

60 not utilizing cosmetic in comparison to regular users accentuates the importance of moisturizers for cosmetic care.

Recent studies have shown that intercellular lipids — mainly sphingolipids in combination with other neutral lipids — play an important role in the establishment or maintainance of water retention properties in thestratum corneum.(11) Topical application of isolated intercellular lipids was demonstrated to repair previously impaired water retention properties.(12) Moreover, the positive effects of preparations of liposomes of the stratum corneum lipids have been reported.(13) Developments of new technologies, like the liposome technique, could reduce the cleft between scientific knowledge and its practical application. Thus, products closely imitating the natural moisturizing factor most closely could be created and the decrease of epidermal moisture in aged persons could be equalized.

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SKIN MOISTURIZING FACTORS: METHOD OF DETERMINATION

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Synopsis

The usual protective function of the skin is directly related to the protective action of the surface lipid film and to its water contents.
The surface lipid film covers the skin as barrier against the aggressions of external environment. The water is indispensable in keeping the skin smooth, elastic, and hydrated.
Cosmetic products are required either to keep the cutaneous hydrolipidic film unchanged, or to restore it through the proper contribution of sebum–like lipids and water, which is the only plasticizer of the corneal layer.
In order the best use the vast knowledge now being acquired in Cosmetic Dermatology, standardization techniques have been investigated for different problem areas. Our current objective in such standardization, applied to the hydrolipidic film, is to link the use of a proper cosmetic product to previously determined corrective factors. These factors are named "hydration index" and "soothing index" respectively, depending their capability to give to skin the right amount of water or of lipids sufficient to retain or re–establish a proper balance.
In order to establish each index we employed a computer–supported system named Dermotest Hytech to measure surface sebum and skin hydration. This system is made up of Sebumeter SM 810 PC and Corneometer CM 820 PC connected to a personal computer using proprietary software.
This system makes sebum data directly available in µg/cm2 and cutaneous hydration in CV (Corneometer Values). From this, we have developed each index.
The Hydration Index (HI) is the ratio between the hydration present in a treated skin surface area, monitored for temperature and humidity (t=22° C, RH ≥, 50%), and the same when not treated. For convenience the result is multiplied by 10.
The Soothing Index (SI) is the result of dividing the read–out value of a treated skin surface area by the value from the same area when non treated. This result is multiplied by 4.

Riassunto

La normale funzione protettiva della cute è strettamente legata all'azione protettiva svolta dal film lipidico di superficie che la ricopre come una barriera, difendendola dalle aggressioni dell'ambiente esterno, e dal suo contenuto di acqua, indispensabile per mantenerla morbida elastica ed idratata.
Compito dei prodotti cosmetici è di mantenere inalterato o di reintegrare il film lipidico cutaneo mediante l'apporto calibrato dei lipidi sebo-affini e dell'acqua, considerata unico plastificante dello strato corneo.
Per utilizzare nel migliore dei modi le vaste conoscenze acquisite nel settore della Dermatologia Cosmetologica, si è cercato di standardizzare il riconoscimento dei diversi tipi cutanei, legandolo direttamente ad un adatto cosmetico, mediante l'utilizzazione di precisi fattori di correzione. Tali fattori vengono denominati rispettivamente "indice di idratazione", se in grado di apportare alla cute la giusta quantità di acqua, o "indice di emollienza", se in grado di apportare lipidi in quantità sufficiente al suo riequilibrio.
Per la misurazione sia del sebo di superficie che dell'idratazione cutanea ci si è serviti di un sistema computerizzato denominato Dermotest Hytech dato dall'unione del Sebumeter SM 810 PC e del Corneometer CM 820 PC, opportunamente collegati ad un PC mediante un adeguato programma di utilizzazione. Utilizzando il Dermotest Hytech é stato possibile ottenere direttamente sia i valori sebometrici espressi in µg/cm che i valori della idratazione cutanea espressi in CV (corneometer values).
Si definisce, pertanto, indice di idratazione il rapporto tra lo strato di idratazione di una cute trattata a temperatura e umidità controllata (t = 22° C RH ≥ 50%), rispetto alla stessa cute non trattata moltiplicando il risultato per un coefficiente dieci. L'indice di emolliente si ricava dividendo il valore del casual level cutaneo di una cute trattata per l'analogo valore della stessa cute non trattata, moltiplicando il risultato per un coeffciente quattro.

Introduction

One of the major efforts in cosmetic dermatology is to keep a youthful appearance to the skin. This is chiefly accomplished by helping to retain a necessary amount of moisture in the stratum corneum. For this reason the so–called "emollient" and "moisturizing" cosmetic products are not formulated simply to act as lubricants, but also to preserve or to restore cutaneous homeostasis.
Well formulated cosmetics delay water evaporation *(perspiratio insensibilis)* and, thereby, help to retain water in the stratum corneum and to restore the surface lipid film. This lipid film is, in fact, the indispensable regulator of water exchanges between the dermis and the surface skin layers. (1-14).
In order to develop methods for testing the activity of moisturizing and sebum-normalizing cosmetics, specific "hidration" and "soothing" indices are suggested. These indices are intended to be directly correlated to the individual biotypological conditions of each skin tested. (15,16)
The "hydration index" is the ratio between the water retetion in the surface layer of a treated skin area and of the same skin area prior to treatment. The result is multiplied by a factor 10. Testing is done under standardized conditions of temperature (t=22° C) and relative humidity (RH≥50%).
The "soothing index" is the ratio between the

sebum content of the surface layer of a treated skin area and of the same skin area prior to treatment. The result is multiplied by a factor 4 (15).
These two indices make it possible to balance the use of moisturizing and emollient creams according to the index values obtained (16).

Materials and Methods

Materials

CLEANSING LOTION
Water, cetereth (and) isopropyl myristate, isoctyl stearate, sorbitol, glycerin, propylene glycol, tocopheryl acetate, retinyl palmitate, imidazolidynil urea, fragrance, ethyl linoleate (and) ethyl linolenate, methyl paraben, desamidocollagen, EDTA.
HI-5 Gel
Water, methilgluceth-10, soluble collagen, PEG-40 hydrogenated castor oil, PEG-13 octanoate, carbomer 934, sodium glycine, hydrolyzed animal protein, tocopheryl acetate UVA-filter, fragrance, quaternium-15.
HI-10 Cream
Water, PEG-8-C 12-18, isopropylheptanoate, sorbitol, ceresin, sorbitan sesquioleate, hydrogenated castor oil, borago oil, desamidocollagen, glycerin, fragrance, sodium PCA, witch hazel extract, imidazolidynil urea, UVA-filter, cyclomethicone, ethyl linoleate methyl paraben, lecithin, trisodium EDTA.
HI-20 Cream
Essential fatty acids, phospholipids, benzophenone, A, E vitamins, borago oil, in a sebumlike carrier.
SI-5 Gel
Water, methyl gluceth-10, soluble collagen, PEG-40-Hydrogenated castor oil, cetearyl octanoate, sodium glycine, UVA filter, fragrance, tocopheryl acetate, carbomer 934.
SI-10 Cream
Water, sodium PCA, cethyl dimethicone copolyol, cetyl dimethicone, poliglyceryl oleate, hexyl laureate, cyclomethicone, glycerin, isoprophylanolate, retinyl palmitate, squalene, sodium chloride, cetearyl octanoate, tocopheryl acetate, linoleic and linolenic acid, quaternium-15.
SI-20 Cream
Water, jojoba oil, ciclomethicone, octyl stearate, caprylic capric acid triglyceride, dimethicone copoliol squalano, PCA sodium, glycerin, soluble collagen , UVA-filter, tocopheryl acetate, retinyl palmitate, fragrance, methyl and propyl paraben.

Surface sebum and skin hydration are measured by the use of a computer–supported system called Dermotest Hytech. This system is made up of the Sebumeter SM 810 PC and the Corneometer CM 820 PC which are connected to a PC through proprietary software. The Dermotest Hytech reports sebum data in $\mu g/cm^2$ and reports the skin hydration in Corneometer Values (CV) by direct readout.

Methods

60 women aged 22 to 33 were divided into six group of ten people:
Group 1:
"Hyperlipidic" group with a sebum level of 720 ± 42 µg/ cm2.
Group 2:
"Normolipidic" group with a sebum level of 300 ± 53 µg/cm2.
Group 3:
"Alipidic" group with a sebum level of 175 ± 26 µg/cm2.
Group 4:
"Normohydrated" group with a mean hydration level of 117 ± 16 CV.
Group 5:
"Dehydrated" group with a mean hydration level of 72 ± 13 CV.

Group 6:
"Very dehydrated" group with a mean hydration level of 30 ± 11 CV.

Four weeks before, and during all the treatment period, drugs and diet foods were prohibited. In the ten days before treatment, all subjects used no cosmetics except a cleansing lotion provided by us, and a different creams to be applied twice a day (AM and HS) after using the cleansing lotion and abundant rinsing.
The mean values for surface sebum and skin hydration were taken from each subject by carrying out four separate measurement in adjacent areas on the forehead. Measurements were taken between 8:30 and 10:30 a.m. under standardized conditions. This procedure is based upon the method of Saint Leger and Levecque as modified by Borroni et al, (17,18).
With these values as bases, the subjects were divided into the 6 groups, each group being given the corrent cosmetics for their skin category. In particolar, the first, the second and the third group were given similary formulated cosmetics enriched with increasing amounts of lipids. The fourh, the fifth and the sixth group were given substances well known to be active in skin hydration (native collagen PCNa* and organic silicone derivatives).
Before starting our tests, studies that allowed us to balance our formulations were carried out both "in vitro" and "in vivo".
These reduced empirical evaluation as much as possible.
Soon after the use of selected cosmetic cream, delicately applied in the quantity of a fine film, sebum and skin hydration were measured again. Result are listed in Figures 1 and 2.
The reference invoices for the "soothing index" (lipidic state) have been obtained from the mean values of each group by means of the following formula:

$$\text{"SOOTHING INDEX"} = \frac{\text{VALUE AFTER}}{\text{VALUE BEFORE}} \times 10$$

The formula for the "moisturizing index" is the following:

$$\text{"MOISTURIZING INDEX"} = \frac{\text{VALUE AFTER}}{\text{VALUE BEFORE}} \times 4$$

Therefore for each group of individuals the mean obtained values are:

Group 1:

$$\frac{376}{743} \times 10 = 5 \text{ soothing index}$$

Group 2:

$$\frac{310}{310} \times 10 = 10 \text{ soothing index}$$

Group 3:

$$\frac{363}{182} \times 10 = 20 \text{ soothing index}$$

Group 4:

$$\frac{116}{92} \times 4 = 5 \text{ hydrating index}$$

Group 5:

$$\frac{114}{46} \times 4 = 10 \text{ hydrating index}$$

Group 6:

$$\frac{118}{26} \times 4 = 20 \text{ hydrating index}$$

This system has enable us to correlate various skip types with correction methods appropriate to them. This new experimental method, called Dermotest, utilizes colored diodes to provide simple and fast sebum and skin hydration measurements. After 15, 30, 60 and 90 days, readings were taken in order to verify a correlation

* Pyrrolidone carboxylic acid sodium salt

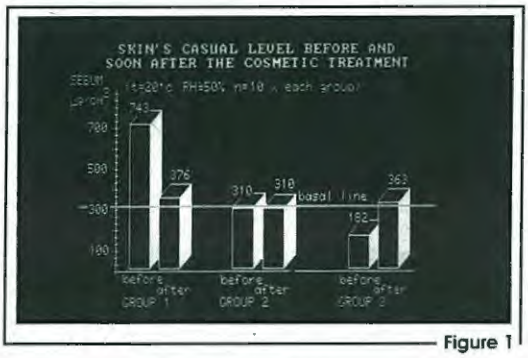

Figure 1

Sebum values before and soon after the cosmetic treatment

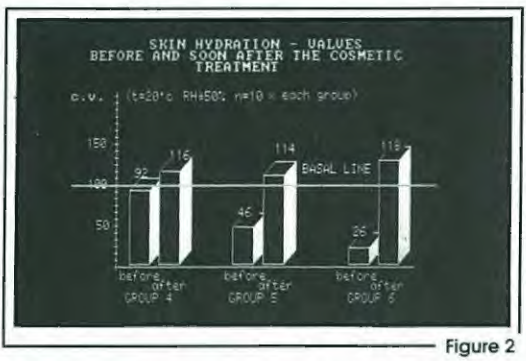

Figure 2

Skin hydration ***(corneometer values)*** *measured before and soon after the cosmetic treatment*

between the correction indices originally obtained by Dermotest, and the results obtained after the use of the cosmetic selected for that individual. Results are shown in Figure 3-8.

Results and Comments

As shown in Figure 3-8, the cosmetics which were selected for use normalized all the skin types tested. Positive effects were observed during the first 30 days. After 60 days, both the dehydrated skin and the skin with depleted or excess lipid content returned to normal mean values. It is interesting that a gradual decrease in average levels was noted in the first group (Hyperlipidic), with high sebum values. (Fig. 3) A normalization of the surface lipid film was observed in the third group (alipidic) after only 30 days of treatment. (Fig. 5)

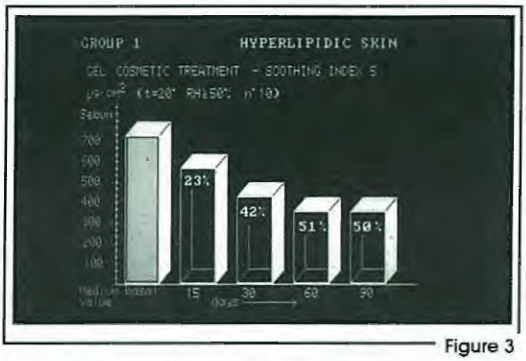

Figure 3

Group 1 - Hyperlipidic Skin
Cosmetic Gel Treatment - Soothing Index 5

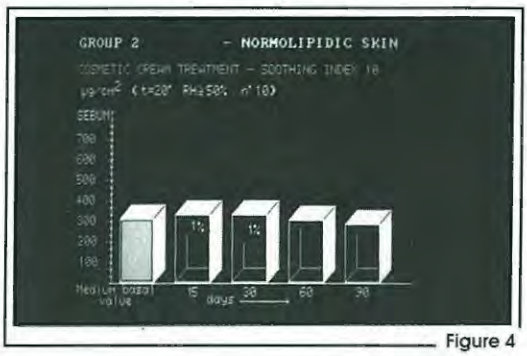

Figure 4

Group 2 - Normolipidic Skin
Cosmetic Cream Treatment - Soothing Index 10

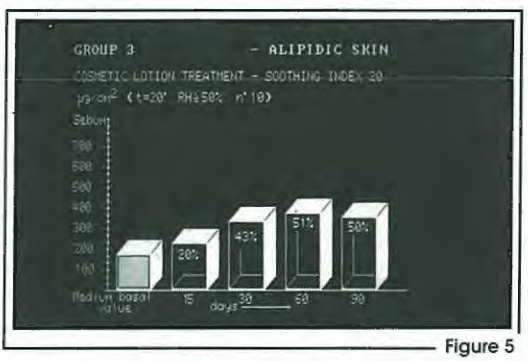

Figure 5

Group 3 - Alipidic Skin
Cosmetic Lotion Treatment - Soothing Index 20

In the final 2 groups, made up of individuals with dehydrated to very dehydrated skin, simi-

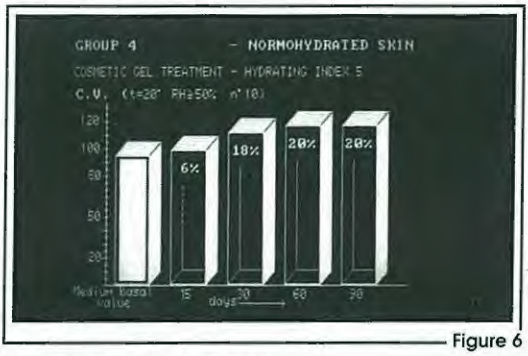

Figure 6

Group 4 - Normohydrated Skin
Cosmetic Gel Treatment - Hydrating Index 5

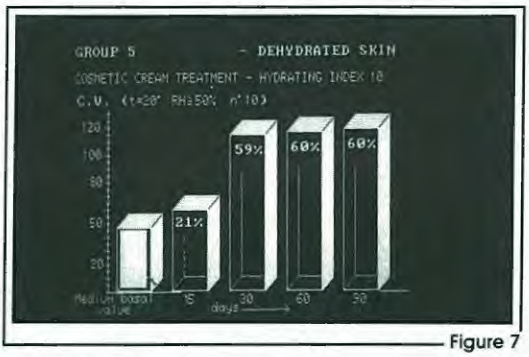

Figure 7

Group 5 - Dehydrated Skin
Cosmetic Cream Treatment - Hydrating Index 10

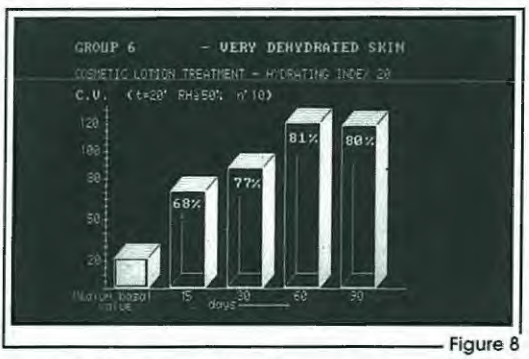

Figure 8

Group 6 - Very Dehydrated Skin
Cosmetic Lotion Treatment - Hydrating Index 20

lar results were obtained soon after 30 days of treatment. In these the skin returned to normal mean values, keeping the hydration up to the end of tests (Fig. 7,8).

Supported by these first results proving the effectiveness of our correction indeces, we keep on doing our experiments in order to evaluate more throughly the activity of different lipidic and moisturizing materials.

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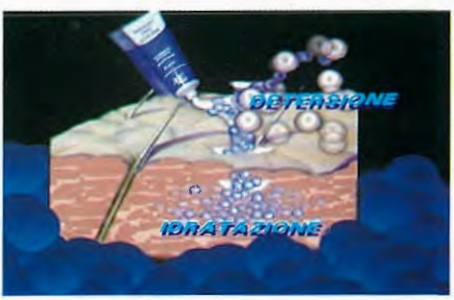

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