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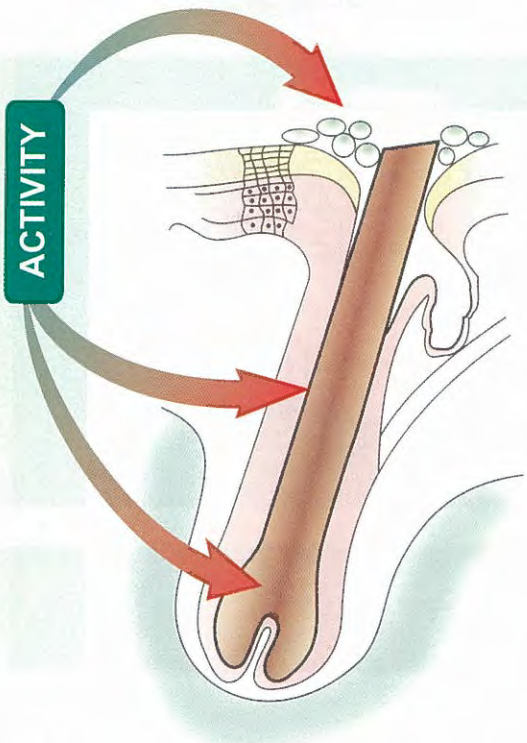

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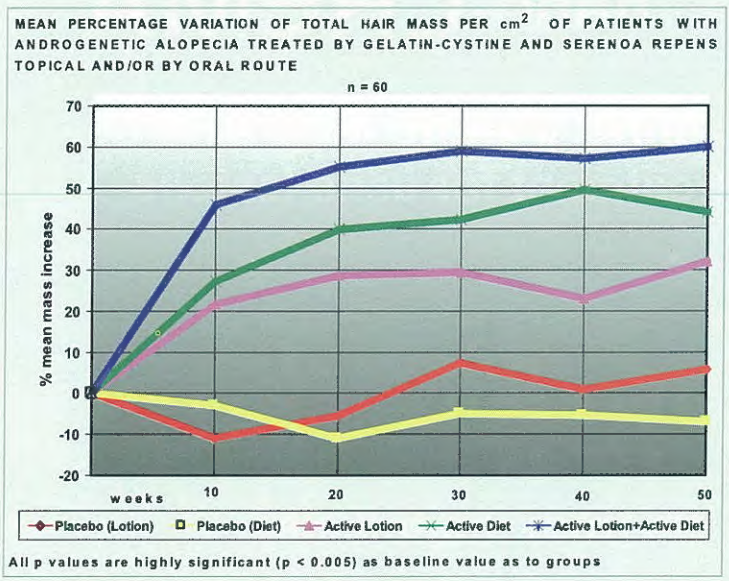
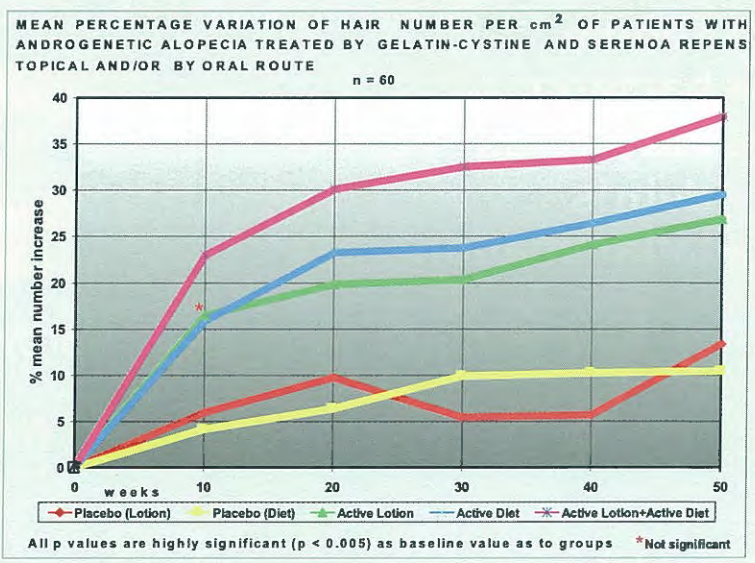


38%

increase in hair number



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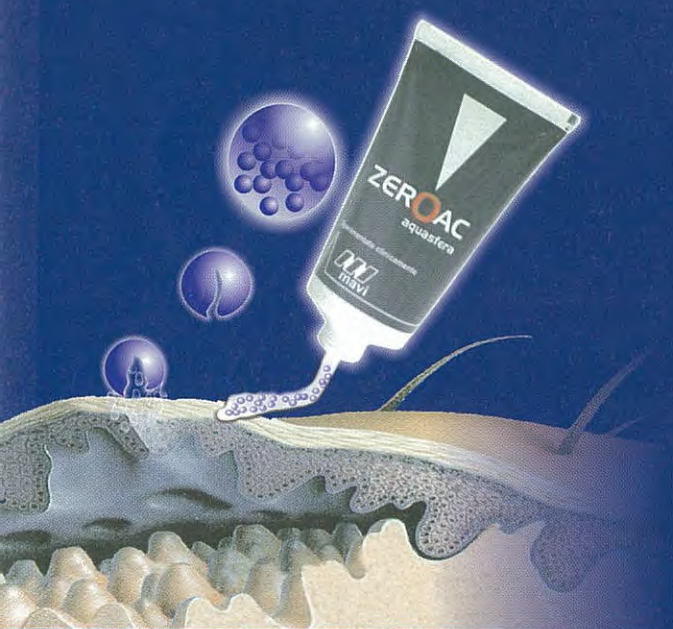

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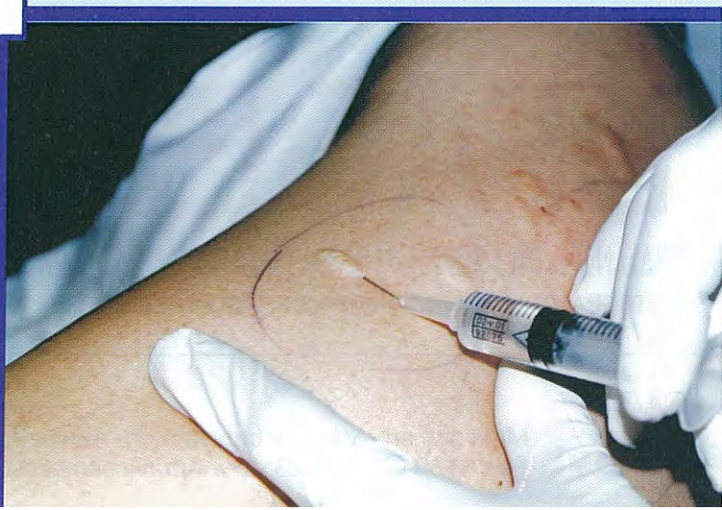

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Quarterly Review of Cosmetic Dermatology

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Quarterly Review of Cosmetic Dermatology

Contents

J. Appl. Cosmetol. 22, 65-76 (April/June 2004)

EPIDERMAL & DERMAL PROTEIN AND ENZYMES: WHAT'S NEW

Mario Vaccaro, Fabrizio Guarneri, Giuseppina Cutroneo*, Claudio Guarneri, Olga Barbuzza*, Biagio Guarneri

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Key words: *Basement membrane; Laminin; Fibronectin; Integrin; Actin-associated proteins; Signaling pathways;*

Summary

A detailed analysis and a systematical classification of the proteins synthesized in the various organs, along with their functions, their mechanism of action and their reciprocal interactions, have ever been an objective of the medical science, always looking for a better knowledge of the human body. But the research in this field has really developed only in the last decades, thanks to the concurrence of several factors: the discovery of new fundamental clonation and amplification techniques for genic sequences and derivative proteins, the exponential increase of the power of electronic calculators, the close collaboration between researchers of different disciplines (clinicians, chemists and biochemists, mathematicians, engineers). The effort in basic research has led to important practical results, like the comprehension of the molecular mechanisms that underlie several diseases, and, in some cases, the achievement of a proper therapy.

The skin, main interface between the organism and the outside world, is a physical barrier: it needs, for this reason, a large set of structural proteins, capable of assuring elasticity and firmness, impermeability to micro-organisms and potentially noxious chemical agents and selective permeability to other substances, both exogenous and endogenous. But skin is not a inert barrier: it carries out its function also by mechanisms of active defense, aimed to eliminate potentially dangerous agents. These mechanisms require the synthesis of a wide spectrum of proteins, some acting directly (lytic enzymes), some as a part of intra- and intercellular metabolic processes that allow cells to achieve complex activities (like phagocytosis).

Moreover, like all interface structures in biology (cell membranes, for example), the skin is used by the organism to acquire "information" from the external environment, useful for the activation of proper reactions. So, cutaneous cells have to be able to produce several proteins, fit for receiving "signals" of various kind from the environment, eventually elaborating them, and transducting them to the organism.

Riassunto

L'analisi dettagliata e la catalogazione sistematica delle proteine prodotte nei diversi organi ed apparati, nonché delle loro funzioni, del loro meccanismo d'azione e delle loro reciproche interazioni, ha da sempre interessato la scienza medica, in cerca di una sempre più approfondita comprensione del corpo umano. Ma è in periodi relativameute recenti che tale attività di ricerca si è sviluppata in maniera notevole, grazie alla concomitanza di numerosi fattori quali la scoperta di fondamentali tecniche di clonazione e amplificazione di sequenze geniche e relativi prodotti, l'incremento esponenziale delle capacità di elaborazione dei dati da parte dei calcolatori elettronici, la stretta collaborazione fra studiosi di diverse discipline (clinici, chimici e biochimici, matematici, ingegneri). L'impegno profuso nella ricerca di base ha portato ad importanti risultati pratici, quali la comprensione dei meccanismi molecolari alla base di diverse malattie e, in alcuni casi, la realizzazione di una adeguata terapia.

La cute, principale interfaccia tra il mondo esterno e il resto dell'organismo, svolge in primo luogo funzione di barriera fisica: necessita dunque di una vasta gamma di proteine strutturali in grado di garantire allo stesso tempo elasticità e solidità, impermeabilità a microrganismi ed agenti chimici potenzialmente nocivi e selettiva permeabilità nei confronti di altre sostanze, esogene o endogene. Ma la cute non è una semplice barriera inerte: la sua funzione viene svolta anche attraverso meccanismi di difesa attiva, volti all'eliminazione delle potenziali fonti di pericolo. Tali meccanismi richiedono la produzione di una vasta gamma di proteine, alcune agenti in maniera diretta (enzimi litici), altre facenti parte di complesse catene metaboliche intra- ed intercellulari che rendono le cellule capaci di realizzare attività complesse (come ad esempio la fagocitosi).

Infine, come tutte le strutture di interfaccia del mondo biologico, quali ad esempio le membrane cellulari, la cute è utilizzata dall'organismo per acquisire "informazioni" dall'esterno e consentire la messa in atto delle reazioni opportune. Le cellule cutanee devono quindi essere in grado di produrre un insieme di proteine atte alla ricezione di "segnali" di varia natura, alla eventuale elaborazione degli stessi e alla loro trasduzione verso l'interuo dell'organismo. Un continuo scambio di segnali biochimici si verifica, ad esempio, tra i diversi tipi cellulari cutanei e il sistema immunitario, sia in condizioni fisiologiche che in corso di alterazioni della funzionalità della barriera, e ciò contribuisce in maniera rilevante sia all'omeostasi delle difese organiche sia alla preparazione ed attuazione, ove necessario, di una adeguata risposta immune.

INTRODUCTION

Detailed analysis and systematical classification of the proteins synthesized in the various organs, along with their functions, their mechanism of action and their reciprocal interactions, have always been an objective of medical science. But research in this field has really developed only in the last decades, thanks to the concurrence of several factors: the discovery of new fundamental techniques of clonation and amplification, the increase of the power of calculators, the collaboration between specialists of different disciplines.

The resulting improvement of our knowledge is really impressive, and many practical results are now evident: comprehension of the molecular mechanisms underlying incurable diseases allowed to setting of proper therapies. But, obviously, much has yet to be done: researchers are well aware that too many questions are still unanswered. New and ambitious projects were thus started. The best known is the Human Genome Project, aiming at the decodification and comprehension of the whole genetic code of *Homo sapiens*. The first phase of this research, as clamorously announced by mass-media, is nearly completed, and will be the first step to the next, much more complex task of the interpretation of the data available.

Another project, sustained by the National Center for Biotechnology Information (NCBI) of Bethesda, USA, less widely known but surely not less important with regard to its consequence and application, is the realization of a data base of all known proteins. Commenced some years ago, it has produced a large database, containing amino acid sequences and information regarding thousands of proteins.

The available data on the human set of proteins show the variety of the metabolic activities in the skin. The search engine "Entrez Protein" of the National Center of Biotechnology Information reports approximately 1500 different proteins synthesized by cutaneous cells - a very large number, although some of these are found associated only to genetic alterations or tumors. This large number of proteins is due to the variety of skin functions. The skin, main interface between the organism and the "outside world", is a physical barrier. For this reason, it needs a large set of structural proteins, capable of assuring elasticity and firmness, impermeability to micro-organisms and potentially noxious chemical agents and selective permeability to other exogenous and endogenous substances. But skin is not an inert barrier: it performs its function also by mechanisms of active defense, aimed at eliminating potentially dangerous agents. These mechanisms require the synthesis of a wide spectrum of proteins, some acting directly (lytic enzymes, for example), some acting as a part of intra- and intercellular metabolic processes that allow cells to achieve complex activities (like phagocytosis). Moreover, like all biologic interface structures, the skin is used to acquire "information" from the external environment, useful for the activation of proper reactions. Thus, cutaneous cells are able to produce proteins fit to receive different "signals" from the environment, elaborating, and transducting them. For example, an uninterrupted exchange of biochemical signals occurs between skin cells and the immune system, both in physiological conditions and in the event of an alteration of the barrier function, and this plays a remarkable role in the homeostasis of organic defenses. Many proteins synthesized by skin cells are critical elements in the metabolic pathways that make this possible. Antigen presentation to the immune system, for example, requires proteins to capture the exogenous substance (membrane receptors) other proteins to process it (lytic enzymes) and still more proteins to trigger a correct response of immunocompetent

cells (MHC complex and many different co-expressed membrane molecules).
The wide variety of skin proteins, the complexity of their structure and their reciprocal interactions, as well as the difficulties in determining the role of each of them, both in physiological and pathological conditions, have always obliged each group of researchers to focus their attention and efforts on a limited number of "targets".
In this short report, we will try to show, as completely as possible, the "state of the art" of the research on some proteins involved in the basic functions of cutaneous cells (adhesion, proliferation, migration, differentiation). We will present studies by our group both in normal skin and in the course of different skin pathologies characterized by altered cell proliferation.

PATHWAYS INVOLVED IN CELL-EXTRACELLULAR MATRIX (ECM) SIGNALING

The ability to synthesize extracellular matrix was an essential stepping stone during the early evolution of multicellular life. Synthesis and degradation of ECM proteins are critical not only for proper embryonic and postnatal development but throughout adulthood. In turn, any aberrant communication between cells and their surrounding ECM can lead to a pletora of human diseases, for example, atherosclerosis, arthritis, renal or lung fibrosis, genodermatosis, and cancer.
This review is an up to date perspective of multiple proteins and pathways involved in cell-ECM signaling focusing on laminins, fibronectin and their cytoskeleton receptors (including integrins and actin-associated proteins). The term "signaling" shall include all forms of cell/cell and cell/ECM communication, leading to a wide array of different cellular responses, including adhesion, migration, invasion, proliferation, growth arrest or apoptosis.
In the past years, much has been learned about the structure and function of ECM receptors. A growing number of distinct matrix receptor classes have been described. Evidence is accumulating that complexes between receptors and their ECM ligands do not appear to be a one to one reaction, instead clusters of multiple ligands and signaling receptors interact with each other. Specific cellular responses result from the integration of multiple incoming signals. The best characterized matrix receptors are the integrins, heterodimeric proteins consisting of two non-covalently bound subunits, named alpha and beta subunit. In the human genome, 24 alpha chains and 9 beta chains have been found. From approximately 200 heterodimers that could form theoretically, only about 25 have been identified so far in vivo. Integrins are receptors essential for cellular adhesion to a huge variety of ECM proteins including vitronectin, fibrinogen, fibronectin, collagens, laminins, tenascins and thrombospodins or to cellular receptors such as VCAM 1, and ICAM. They also mediate cell adhesion, migration, invasion, proliferation and have a multitude of intracellular effects on the organization of the actin-containing cytoskeleton as well as roles in a variety of signaling processes. A complex series of steps leads from initial integrin interactions with an extracellular ligand to transmembrane effects on the localization of cytoskeletal molecules or signaling molecules, to the activation of signaling pathways, and to eventual regulation of gene expression.
Laminins are heterotrimers constituted by the association of 3 different gene products, the α, β and γ chain. They are a family of multifunctional non-collagenous glycoproteins which are ubiquitous in basement membranes, where they exert structural and biological functions. Through the interaction of newly forming lami-

nin with the integrins, a whole series of messages concerning the morphogenesis processes is transmitted from the extracellular matrix to the nuclear compartment (via the cytoskeleton). **Fibronectin** is one of the key molecules promoting cell migration and can regulate keratinocyte growth through its receptor α5β1.

Recent studies have suggested that in human epidermis the adhesion of the keratinocytes to the basement membrane (BM) occurs not only at the hemidesmosomes but also at the adherens junctions. At these sites, a series of transmembrane proteins connects the BM molecular components to the structure of cytoskeleton. In particular, at hemidesmosomes integrin α6β4 connects directly to the intermediate filaments, while, in correspondence with the adherens junctions, the integrins α3β1 and α2β1 link themselves to the microfilaments of actinin through a protein complex – namely actin-associated proteins (talin, vinculin, α-actinin). Apart from the mechanical linkage between the keratinocytes and BM, the adherens junctions, transfer fundamental signals from the ECM to the nuclear compartment, thus regulating the principal biological functions of the cells (adhesion, proliferation, migration, differentiation).

It seems clear that quantitative or qualitative alterations in the pathways involved in cell-ECM signaling and/or in their genetic regulation could be the basis of acquired of inherited skin pathology.

Previous studies suggested the possibility that in psoriasis may indeed have disturbed cell-ECM signaling which precede and possibly precipitate the hyperproliferative state.

It is known that in psoriasis:

1. α5β1 integrin is overexpressed relative to normal skin;
2. fibronectin, which is normally located in the dermis below the basement membrane, could penetrate the dermal-epidermal junction and is present between basal keratinocyte;
3. large regions of discontinuous immunostaining for laminin α1 chain were observed, mainly in correspondence to the apex of the dermal papillae; in the same regions, clusters of keratinocytes appeared markedly reactive;
4. these modifications were correlated with the well-known loss of the polarized expression of integrins (α6β4, α3β1 and α2β1) and the alterations in actin-associated proteins distribution (as it can be seen, there is an almost total lack of reaction against talin, vinculin and α-actinin in the basal layer and an increased positivity in the suprabasal layers).

These findings support the existence of a marked upheaval of cell/matrix adhesion structures in psoriasis.

It has to be underlined that:

1. the keratinocytes express α5 integrin only under physiological conditions characterized by epidermal proliferation, such as during tissue development;
2. the fibronectin, one of the key molecules promoting cell migration, can regulate keratinocyte growth through its receptor α5β1;
3. the laminin α1 chain, expressed only by newly forming epithelial cells, can interfere with cell adhesion and polarization, basement membrane formation and cytomorphosis processes.

Extending these observations to the skin cancer proliferation and progression, our data suggested the existence of a functional deficit, probably genetically transmitted, which affects the synthesis and/or secretion of laminin (laminin α1 chain in basal and squamous cell carcinomas, laminin α2 chain in melanoma). This deficit would explain the loss of the adhesion to the basement membrane and the alterations of the polarized distribution of integrins and actin-associated proteins, with consequent hyperproliferation, perturbed cell differentiation, tumor progression and cancer spread. The variable distribution of integrin receptors possibly reflect

impaired tumor-matrix interaction, and may relate to the much more malignant phenotype.
In conclusion, morphofunctional approach gives us a privileged point of view on the molecular mechanisms underlying hyperproliferative conditions of skin. However, we know that our results only in part explain clinical observations, and we think that only the integration of all data coming from clinical, pharmacological and basic research will lead us to the understanding of currently obscure aspects of nature. As in other fields of human life, cooperation in biomedical science is the key for a real and useful progress.

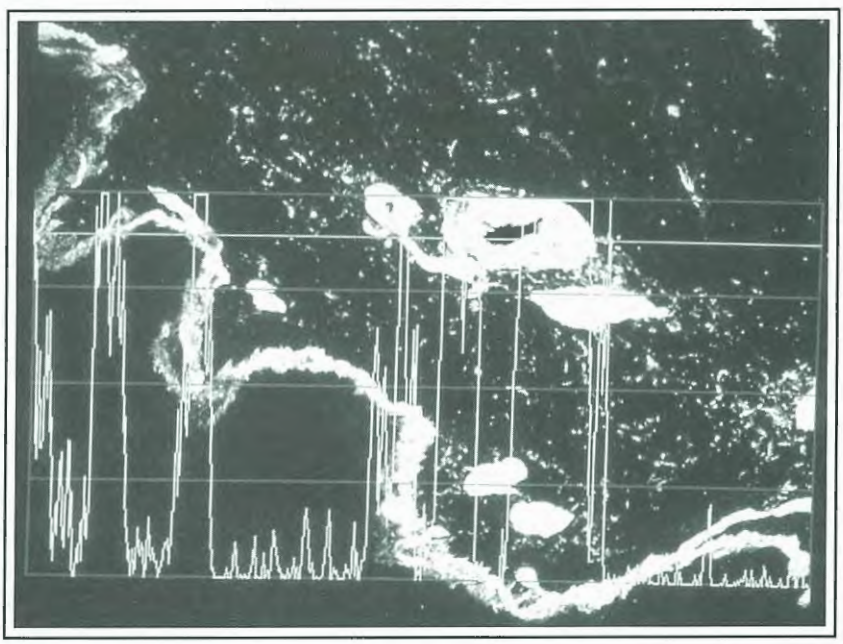

Fig. 1 Normal skin - Immunofluorescence staining of laminin. Confocal image, obtained in 'overlay' mode, demonstrates the regular and continuous distribution of this protein in the basement membrane zone.

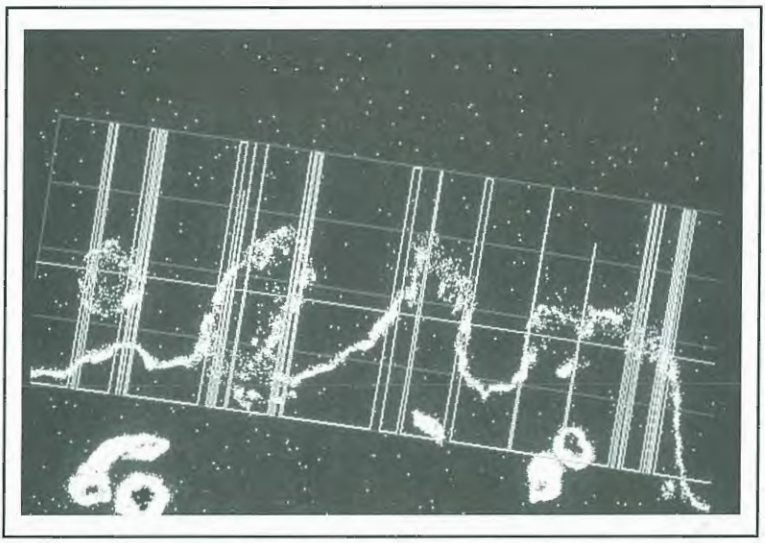

Fig. 2 Normal skin - Immunofluorescence staining of type IV collagen. Confocal image, obtained in 'overlay' mode, demonstrates the regular and continuous distribution of this protein in the basement membrane zone.

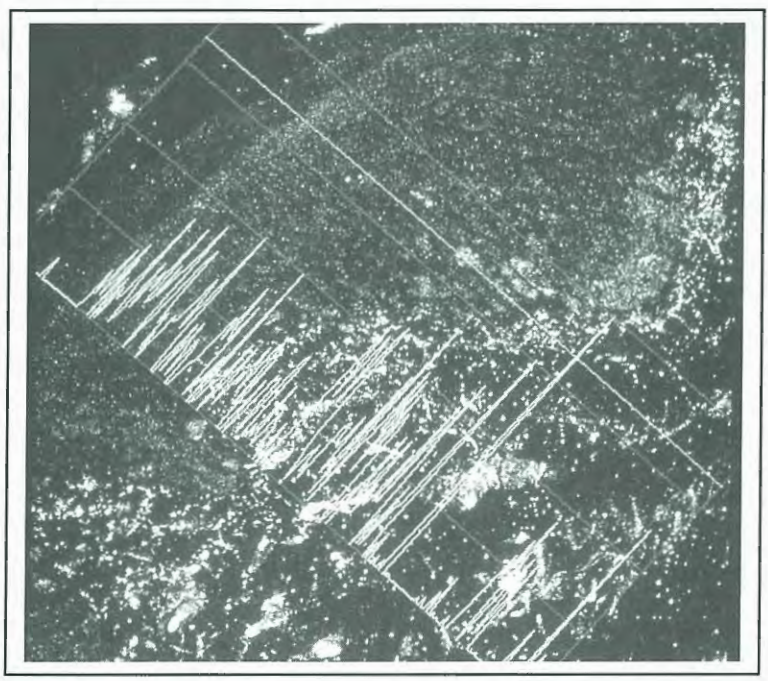

Fig. 3 Normal skin - Immunofluorescence staining of plasma fibronectin. Confocal image, obtained in 'overlay' mode, demonstrates the restricted distribution of this protein in the dermis.

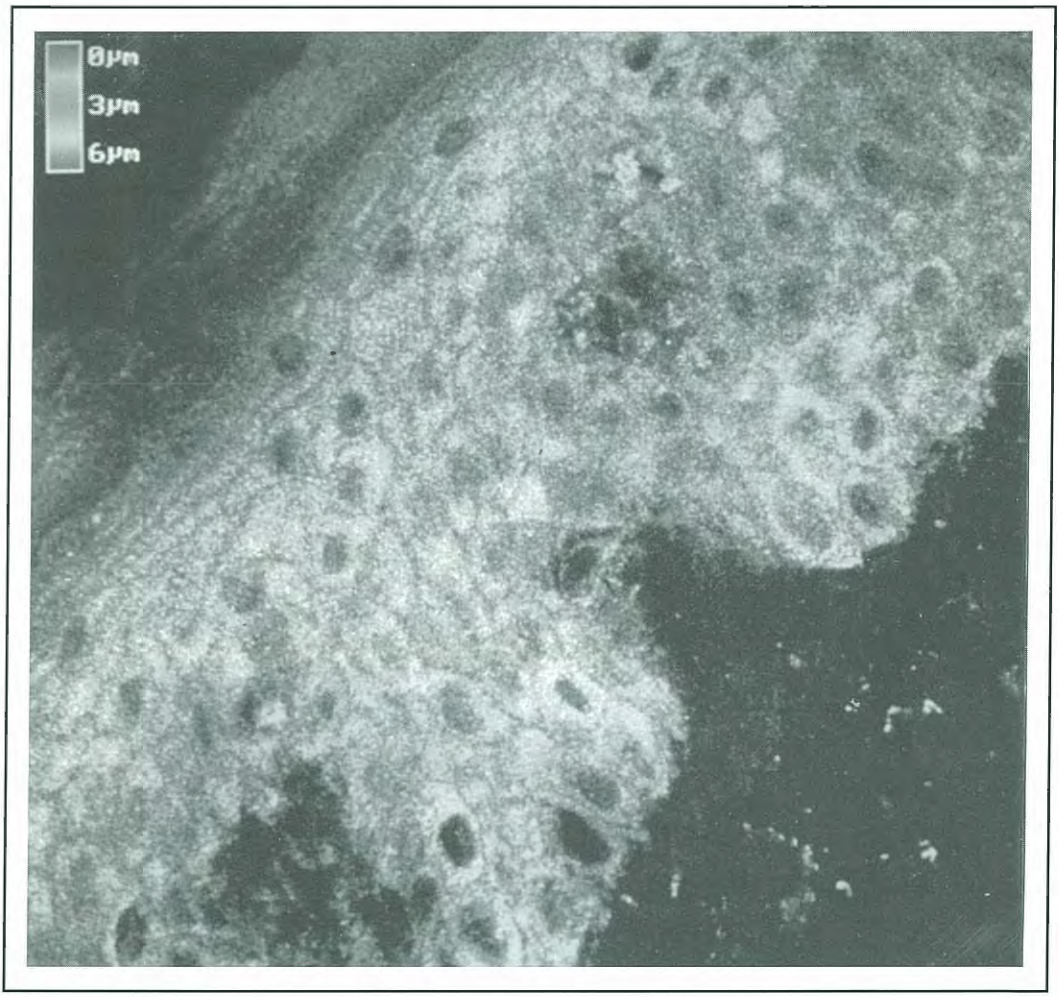

Fig. 4 Normal skin - Confocal image, obtained in 'depth coding' mode. Immunofluorescence staining of talin

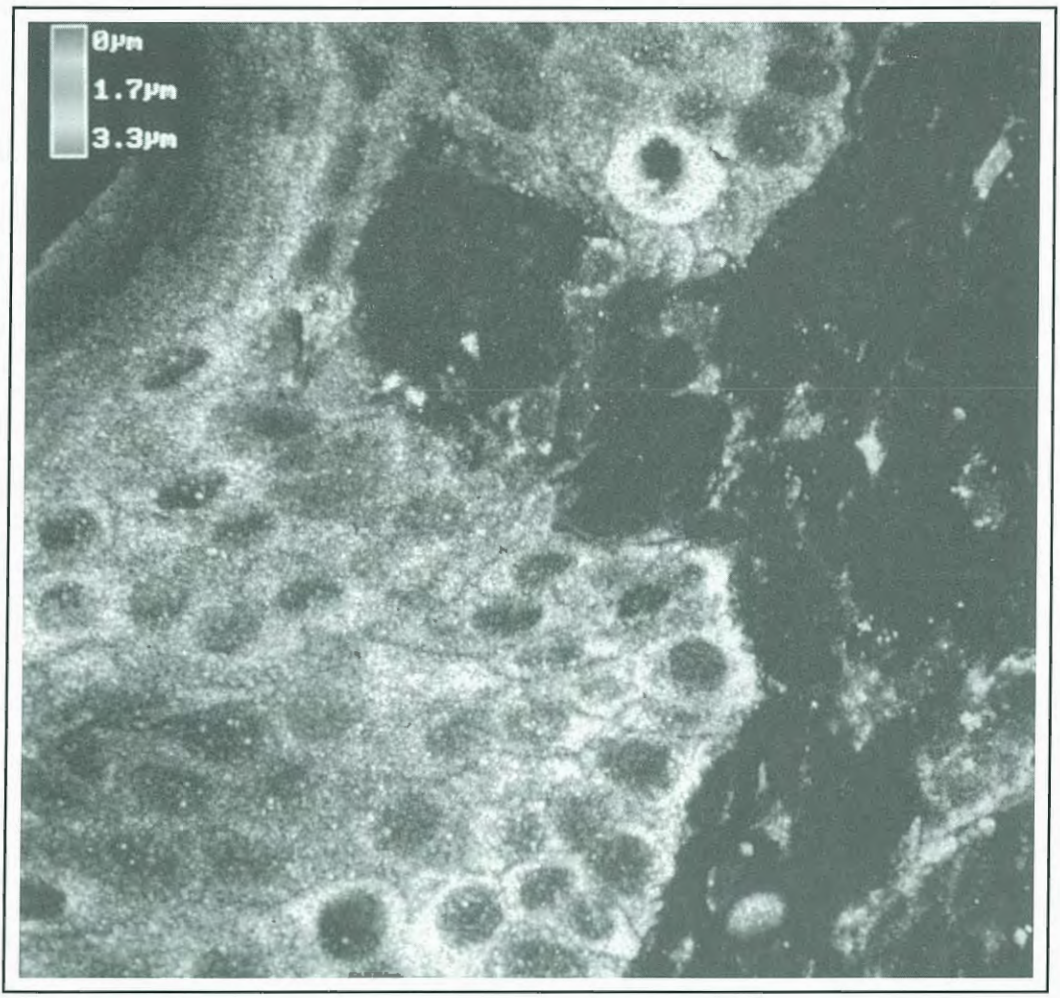

Fig. 5 Normal skin - Confocal image, obtained in 'depth coding' mode. Immunofluorescence staining of vinculin

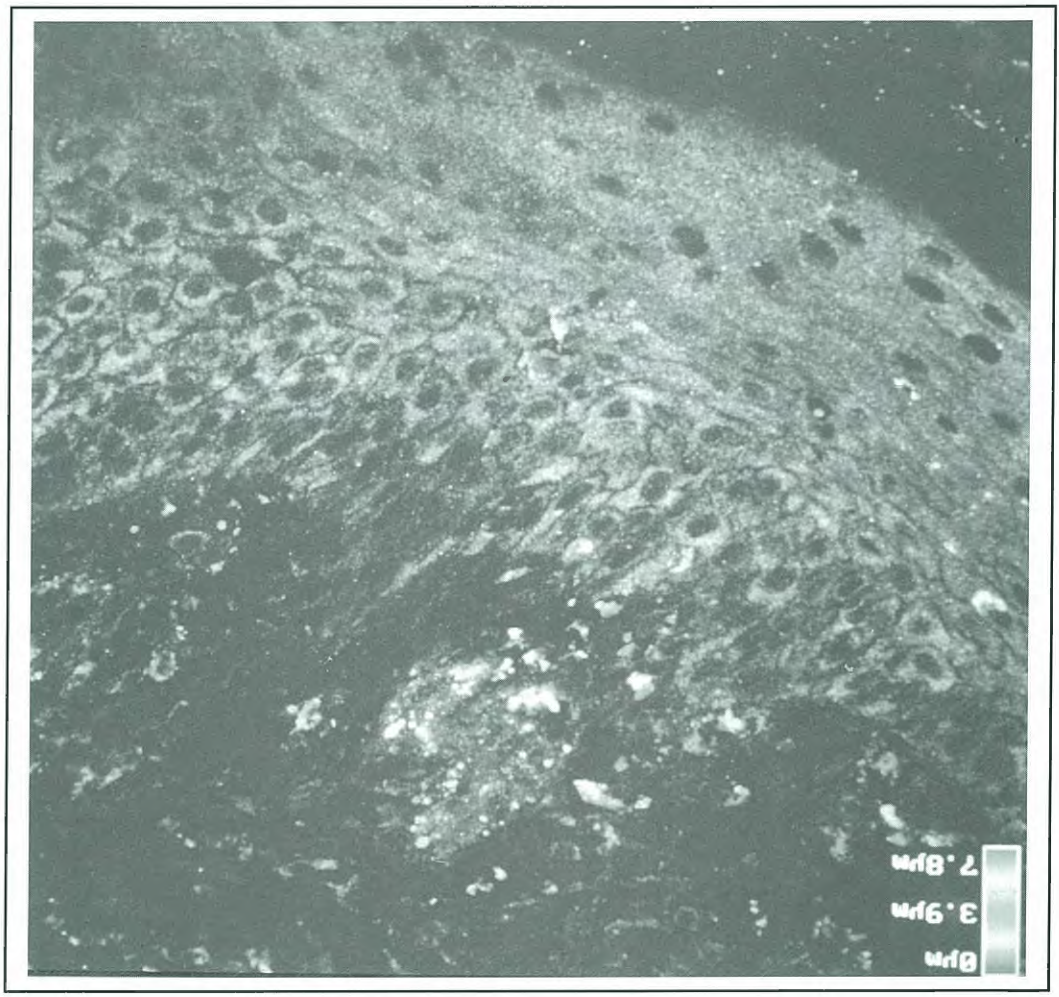

Fig. 6 Normal skin - Confocal image, obtained in 'depth coding' mode. Immunofluorescence staining of α-actinin

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SOLUBILITY OF TITANIUM DIOXIDE IN COSMETIC FORMULATIONS

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Key words: *Titanium dioxide; solubility; α-hydroxycarboxylic acid;*

Summary

Titanium dioxide was found to be unstable, i.e. soluble, in the presence of α-hydroxycarboxylic acids in o/w emulsions or in cosmetic formulations.
The amount of dissolved titanium(IV) was determined and/or monitored using UV spectroscopic method.

Riassunto

Attraverso questo studio è stato dimostrato come il biossido di titanio sia instabile in presenza degli acidi α-idrossicarbossilici, nelle emulsioni o/w o nelle formulazioni cosmetiche.
La quantità di titanio (IV) dissolto è stata determinata e monitorata usando il metodo della spettroscopia a UV.

INTRODUCTION

Anatase, rutile and brookite – three minerals found in nature - represent three crystalline forms of the titanium dioxide. Anatase and rutile have found numerous practical applications. For many years these two TiO_5 forms gained a widespread interest due to their chemical and physical properties, i.e. very high reflectivity and photocatalytic and surface reactivity with various organic compounds. Titanium dioxide is a high-melting, non-toxic compound, resistant to popular chemical reagents[1]. The high refraction coefficients: 2.7 for rutile and 2.5 for anatase result in their most popular applications as a white pigments in various industries including cosmetic industry[2,3]. Particles of titanium dioxide smaller than 100 nm are practically transparent to visible light due to the low particle size/incident radiation wavelength ratio; however, they can reflect, scatter and/or absorb UV radiation. Therefore titanium dioxide in its microfine form is applied in UV protection cosmetic products.

The studies of durability of cosmetic o/w emulsions have been carried out at the Department of Chemistry, Warsaw University of Technology. Relatively fast pH changes have been observed in preparations containing titanium dioxide on addition of lactic or citric acid. As no significant information concerning reactions of titanium dioxide with diluted a-hydroxycarboxylic acids have been found in the literature, the studies have been undertaken with the goal to clarify the observed phenomenon.

MATERIALS

Titanium dioxide rutile (Kronoss) and titanium dioxide P25 (Degussa) were used. Cosmetic raw materials for emulsion preparation have been obtained from Cognis company. All solutions have been prepared using analytical grade chemical reagents and distilled water.

METHODS

pH changes in titanium dioxide suspensions in α-hydroxycarboxylic acids solutions as well as pH changes in emulsions containing titanium dioxide were followed. The concentration of titanium(IV) ions dissolved in α-hydroxycarboxylic acid solution and in emulsion water phase has been determined by the derivative spectrophotometry and hydrogen peroxide spectrophotometric method. Every several days a 5 cm^3 sample has been taken out from the examined suspensions or emulsions. Titanium dioxide has been centrifuged off or filtered off carefully and the concentration of titanium ions in the filtrates has been determined. In case of emulsions water phase has been separated by incubation, freezing and finally centrifuging the sample.

Method of derivative spectrophotometry [4]

Concentration of titanium ions in solutions was determined using their complexes with α-hydroxycarboxylic acids. In order to establish dependence between the titanium ions concentration in the examined solution and the absorbancy of UV radiation, a calibration curve for titanium(IV) with appropriate α-hydroxycarboxylic acid has been prepared. Spectra were recorded for the range 220 – 360 nm using HITACHI U-3300 spectrophotometer. The spectrum points have been collected with 1 nm step. A 1cm cuvette has been used. From the dependence of the solutions' curve shape on pH, the location of isosbestic point (radiation wavelength at which pH does not influence the value of the second derivative of absorbancy) has been determined. Fig. 1 shows that for citric acid solution the isosbestic point occurs at 309 nm.

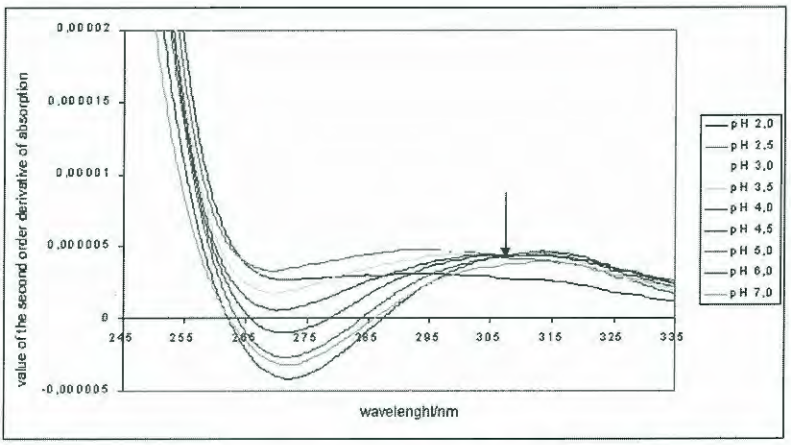

Fig. 1 Second order derivative of the UV absorption spectra of the titanium(IV) complexes with citric acid at various pH values. Isosbestic point at 309 nm.

Titanium(IV) concentration in the analysed samples was determined using the second order derivative of the calibration spectrum (calculated with Savitzky – Golay's algorithm with 51 points). This procedure eliminated the adverse effect of the samples turbidity.

The second order derivative of the UV absorption spectra of the titanium(IV) complexes with citric acid at various concentrations are shown in Fig. 2.

The following equation of the calibration curve has been derived from the second order derivative of the spectra at the wavelength of 309 nm:

$$y = 5{,}47553E\text{-}05x+5{,}61133E\text{-}06$$

Similarly the equation of the calibration curve for the second order derivative of the absorption spectra of titanium(IV) and malic acid complexes has been derived for the wave length of 314 nm:

$$y=2{,}74486E\text{-}05x+7{,}227334E\text{-}0$$

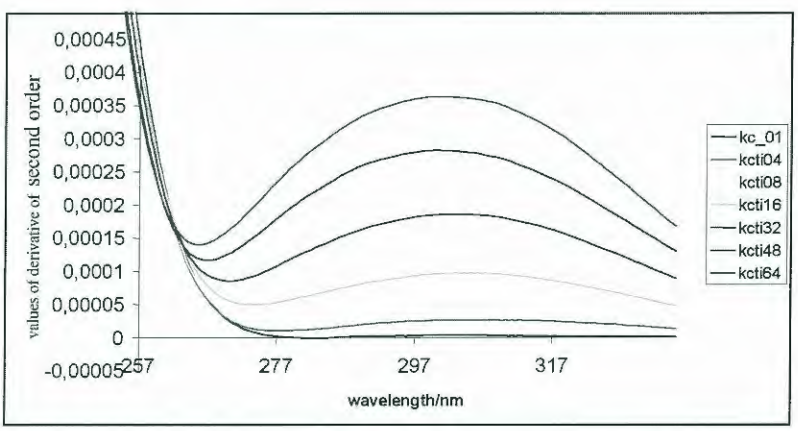

Fig. 2 The second order derivative of the UV absorption spectra of the titanium(IV) complexes with citric acid at various titanium(IV) concentrations.

Spectrophotometric method with hydrogen peroxide [5]

In order to compare the results obtained by the method of derivative spectrophotometry, samples have been analysed by the spectrophotometric method with hydrogen peroxide after 68 days of incubation. The peroxide method of the titanium(IV) determination is based on the formation in the acidic medium the orange coloured complex $[TiO \cdot H_2O_2]^{2+}$.

The calibration curve for titanium(IV) with hydrogen peroxide has been prepared. The samples have been submitted to mineralisation and then the absorbance of their solutions has been measured using SPECORD M40 spectrophotometer at the wave-length 410 nm. 5 cm^3 cuvette were used.

pH was measured with a digital pH-meter.

RESULTS

pH examination of ready cosmetic preparations containing TiO_2 [6]

The examination was started by checking the behaviour of a ready cosmetic preparations – o/w emulsions of the type of the liquid face powder – marked as e1 and e2. These preparations contained, among others, titanium dioxide and small amount of citric acid added before an emulgation process. Various amounts of citric acid were added to the samples and the pH changes were recorded (Table I).

Table I

Amount of added citric acid per 100g emulsion

Sample symbol	Volume of 1% citric acid
	[cm3]
e101, e201	0
e102, e202	6.25
e103, e203	8.75
e104, e204	12.50

The observed pH changes in e1 samples are shown in Fig. 3. The changes for the e2 samples were almost the same.

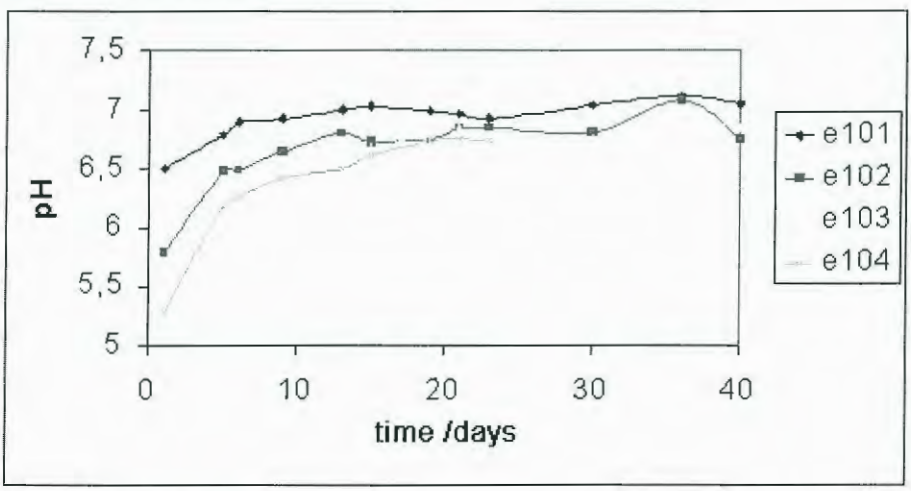

Fig. 3 pH changes in e1 emulsions.

In both preparations pH had been rising up to the almost neutral value. Separate studies of the model systems shown the existence of the strong interactions between titanium dioxide and a-hydroxycarboxylic acid. Therefore the investigations of the suspensions containing different concentrations of titanium dioxide and α-hydroxycarboxylic acid were undertaken.

TiO_2 suspensions in diluted α-hydroxycarboxylic acid

pH changes and changes of the concentrations of dissolved titanium(IV) in titanium dioxide suspensions in diluted solutions of citric, malic and lactic acids have been examined. Titanium dioxide suspended in diluted acid has been placed in a closed flask equipped with a magnetic stirrer. The composition of the samples is shown in Table II.

The examined samples of highly diluted citric and malic acid solutions showed a slow pH increase similarly as in the case of cosmetic emulsions e1 and e2. For solutions containing 0.3 – 0.4 % acid, pH remained stable or only slightly changed (Figs. 4 and 5).

Table II

Composition of titanium dioxide suspensions in diluted citric or malic acid.

Sample symbol	Sample composition (per100g emulsion)
kctiz1	1g TiO_2,
	0.03g citric acid
kctiz2	4g TiO_2,
	0.38g citric acid
kjtiz1	1g TiO_2,
	0.04g malic acid
kjtiz2	4g TiO_2,
	0.27g malic acid

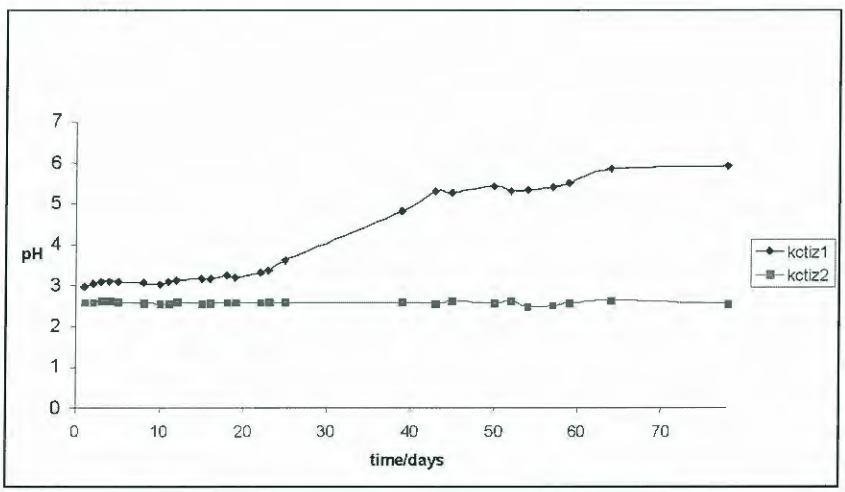

Fig. 4 pH changes in suspensions containing titanium dioxide and various amounts of citric acid.

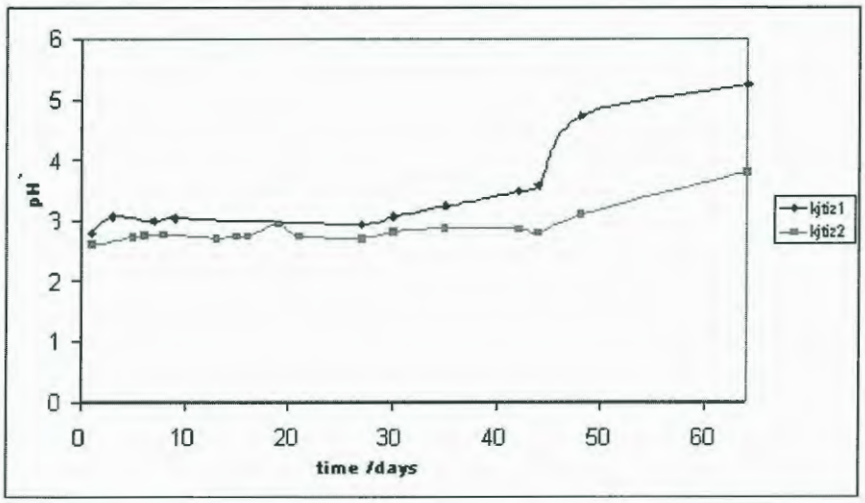

Fig. 5 pH changes in suspensions containing titanium dioxide and various amounts of malic acid.

UV absorption spectra of the collected samples after precise separation of the undissolved titanium dioxide, very similar to the calibration spectra, were used for the determination of the concentration of the titanium(IV) ions. The observed changes in concentration of titanium(IV) ions in examined suspensions determined by the derivative spectrophotometry method are presented in Figs. 6 and 7.

In all four experiments, irrespective of the initial concentration of the α-hydroxycarboxylic acid and the content of the titanium dioxide, an increase of concentration of titanium dissolved in water has been noted.

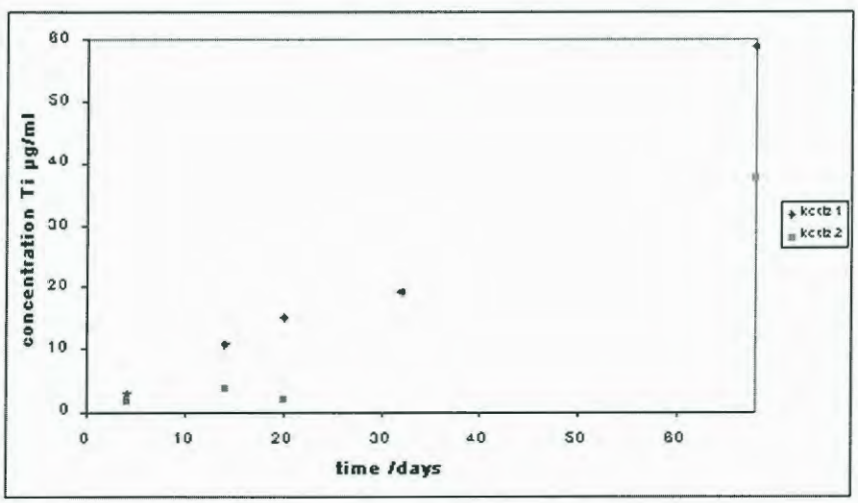

Fig. 6 Changes of the titanium(IV) concentration for the titanium dioxide suspensions in malic acid.

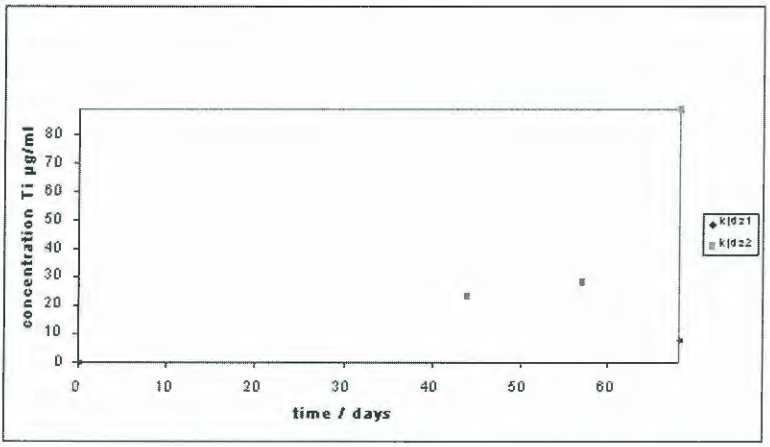

Fig. 7 Changes of titanium concentrations in suspensions of titanium dioxide in malic acid.

Table III

The formulation of the o/w emulsion

	Trade name	INCI Name	Amount [g]
oil phase	Cutina MD	Glyceryl Stearate	8
	Eumulgin B1	Ceteareth-12	1
	Eutanol G	Octylododecanol	4
	Isopropyl Myristate	Isopropyl Myristate	4
	Paraffin Oil	Paraffin Oil	4
aqueous phase	aqueous phase	Water	Water 77

Emulsions containing TiO_2

Similar measurements have been carried out for cosmetic emulsion. The o/w emulsion was prepared according to the formulation shown in Table III.

The same as before amounts of the titanium dioxide and citric acid were added to the above mentioned emulsion yielding four samples marked as kctie1, kctie2, kjtie1, kjtie2 (Table IV).

Table IV

Composition of the emulsion samples containing titanium dioxide and α-hydroxycarboxylic acid.

Sample symbol	Sample composition per 100g emulsion
kctie1	1g TiO_2,
	0.03g citric acid
kctie2	4g TiO_2,
	0.38g citric acid
kjtie1	1g TiO_2,
	0.04g malic acid
kjtie2	4g TiO_2,
	0.27g malic acid

Time dependent pH changes in the examined o/w emulsions containing titanium dioxide and citric acid are shown in Fig. 8. Emulsion marked as e0 contained neither the titanium dioxide nor the acid. Its pH decreased with time significantly. Thus the only slight pH increase observed for the samples containing titanium dioxide and citric acid most probably reflects the significantly larger pH increase when corrected for the blind sample behaviour. The similar changes have been observed for samples with the added TiO_2/malic acid.

The concentration of the titanium(IV) ions dissolved in water phase of the emulsions has been determined by the derivative spectrophotometry method. The results are shown in Figs. 9 and 10. The amount of the titanium(IV) dissolved in samples collected after 68 days of the experiment has been determined spectrophotometrically by hydrogen peroxide method.

CONCLUSIONS

The above described experiments have shown that titanium dioxide suspended in diluted solutions of citric, malic or lactic acid (for lactic acid a similar series of measurements has been done, reported elsewhere) dissolves via the acids water soluble complexes. The similar effect is taking place in the o/w emulsions upon the above listed acids addition. The concentrations of titanium(IV) measured in samples kept for 68 days vary from several to tens of mg/ml (Table V).

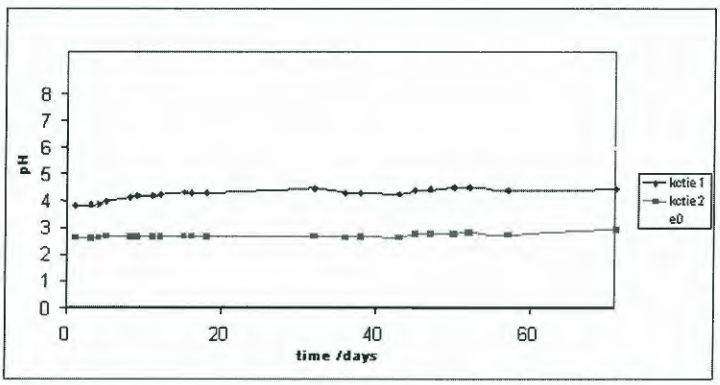

Fig. 8 The pH changes in time in emulsions containing titanium dioxide and citric acid.

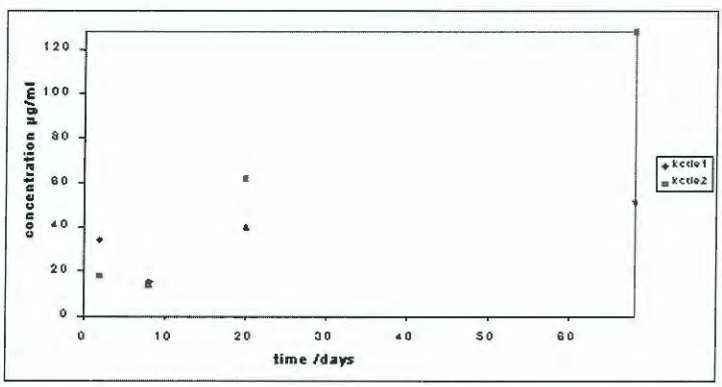

Fig. 9 Changes in the titanium(IV) concentration in aqueous phase of emulsion containing titanium dioxide and citric acid.

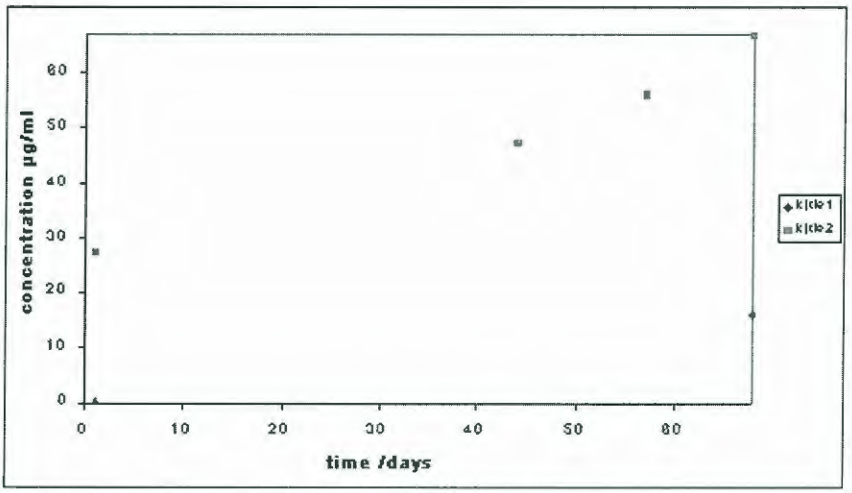

Fig. 10 Changes in the titanium(IV) concentration in aqueous phase of emulsion containing titanium dioxide and malic acid.

Table V

The titanium(IV) concentrations in samples after 68 days

Sample symbol		68th day, conc. of Ti^{V} [µg/ml]
Citric acid	kctiz1	40.99
	kctie1	51.39
	kctiz2	37.57
	kctie2	84.68
Malic acid	kjtiz1	8.10
	kjtie1	15.97
	kjtiz2	88.99
	kjtie2	61.02

In the case of added citric acid, titanium(IV) concentrations determined for 0.03% acid soln-tion (kctiz1) and for 0.38% acid solution (kctiz2) were quite close to each other. For malic acid (kjtiz1 and kjtiz2) an increase in acid concentration by one order of magnitude resulted in an increase of concentration of dissolved titanium also by one order of magnitude.

In three out of four cases the measured concentration of the titanium(IV) dissolved in aqueous phase of the o/w emulsion was even higher than in a model suspension of the titanium dioxide in an acidic aqueous solutions.

The studies confirmed that titanium dioxide reacts with a diluted a-hydroxycarboxylic acid both in model aqueous TiO_2/α-hydroxy acid suspensions and in o/w emulsions. Similar reactions, when occurring in a cosmetic preparation, might destabilise ready products formulated with the above said components.

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A SPECIAL PILL-MASK TO RE-HYDRATE THE SKIN AFFECTED BY ATOPIC DERMATITIS

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Key words: *Atopic dermatitis; Chitosan; Triamcinolone; Pill-mask; Lamellar emulsion;*

Summary

Atopic dermatitis (AD) is a common condition affecting the 10% of infants, whose problematic cutaneous cell-mediated immunity, make them prone to skin infection by viruses, bacteria and fungi.
We aimed to investigate the efficacy of an innovative self-preserving polysaccharide-based lamellar emulsion enriched with a chitosan-derived moisturizing and anti-inflammatory compound as an alternative treatment for AD.
The study was an 8- week prospective, randomized, open, parallel-group trial with 36 children. 15 (group A) and 12 subjects (group B), pre-washed by a bath oil, were applied twice a day within 3 minutes with 5 mg/g of a chitosan-derived compound solubilized in a lamellar active emulsion by a special imbibed pill-mask (group A), or a carrier emulsion (group B). A third group C of 9 children was treated with a petrolatum ointment for the same period. After one week of cosmetic treatment, all the groups were treated, once a day, with triamcinolone 0,1% ointment.
A clinical score assessing erythema, scaling, crusting and pruritus was performed at baseline and every 2 weeks thereafter on a visual analogue scale.
After 4 weeks from the starting point, a major improvement averaging of 58% was observed in the group A versus group C; 82% of group A vs. group B and 64% of group C vs. group B.
This novel *cosmetic therapy* used in AD, seems useful to reduce corticosteroids dosage avoiding their side effects, and to improve skin hydration decreasing skin dryness also in people with sensitive skin.

Riassunto

La dermatite atopica (DA) è una condizione patologica comune che interessa il 10% dei bambini la cui compromessa immunità cellulare li rende predisposti ad infezioni cutanee causate da virus, bat-

teri e funghi.
Come trattamento alternativo in caso di DA, si è voluta controllare l'efficacia di un'emulsione lamellare innovativa autopreservabile a base di polisaccaridi, arricchita con un composto derivato dal chitosano ad attività idratante ed antinfiammatoria.
36 bambini divisi in 2 gruppi, A (formato da 15 soggetti) e B (formato da 12 soggetti), sono stati sottoposti ad uno studio di 8 settimane consistente in pretrattamento con un olio e successiva applicazione (2 volte al giorno) di 5mg/g del composto in studio applicato mediante una speciale compressa di tessuto denominata "pill-mask" (gruppo A) o del solo veicolo (gruppo B: di controllo).
Un terzo gruppo, C, formato da 9 bambini, è stato trattato con olio di vasellina per lo stesso periodo. Dopo una settimana di trattamento cosmetico, a tutti i gruppi è stato applicato, una volta al giorno, un unguento a base di triamicinolone allo 0,1%.
Tutti i bambini sono stati valutati clinicamente, al giorno iniziale e alle successive 2 settimane, controllando i parametri clinici di intensità dell'eritema, desquamazione, numero delle lesioni eczematose e prurito.
Dopo 4 settimane dall'inizio del trattamento è stato riscontrato un miglioramento del 58% nel gruppo A rispetto al gruppo C; dell'82% del gruppo A rispetto al gruppo B e del 64% del gruppo C (vasellina) rispetto al gruppo B (veicolo).
Questa innovativa terapia cosmetica della DA sembra rappresentare una valida alternativa per ridurre sia il dosaggio che gli effetti collaterali propri dei corticosterodi.
Infatti, l'emulsione lamellare utilizzata sembra essere anche in grado di aumentare l'idratazione cutanea riducendo lo stato di xerosi presente spesso nei soggetti con cute cosiddetta "sensibile".

Atopic dermatitis (AD), a common skin disease affecting from 10 to 15% of children in many parts of the world, accounts for 4% of pediatric emergency care visits and its prevalence is rapidly increasing (1-9).

This inflammatory disease, displaying mainly pruritic eczema and dry skin, may be accompanied by dyshydrotic hand and foot eczema, abnormalities in keratinization including follicular keratosis, and a tendency to develop microbial infections of the skin, which include impetigo, folliculitis, furuncles, and an increased frequency of viral infections (10).

Although no one would disagree that eczema results in interactions between genes and environment, the relative contributions seems to be about 50% each one (11).

Finally in AD, there is a marked disease in water-holding and barrier functions, accompanied to a subjective sensation of itch, which leads to a desire to scratch (12-14). Until now therapy is highly unsatisfactory.

The used topical and systemic corticosteroids retards inflammation but the benefit-risks relationship is far from satisfactory. Therefore in large part because of this lack of effective and safe therapy, most patients with AD don't seek medical care, but "get by" with a multitude of non-prescription remedies.

AIM

The aim of this study was to investigate the efficacy of an innovative cosmetic treatment on patients affected by AD with the objective of restore the disrupted barrier re-hydrating the skin at a normal level, and reducing the use of corticosteroids and their consequent negative side effects.

MATERIAL AND METHODS

For cleansing:

1. Bath oil: Hydrogenated Polydecene, Silica Dimethyl Silylate, Oleth-3.

For treatment:

2. Pill-mask: pre-imbibed tissue
3. Pill-mask solution (active A): tocotrienols, hyaluronic acid and ATOBIOL®
4. Lamellar Gel (active B): Aqua (Water), Hydrogenated Polydecene, Propylene Glycol, Atobiol, Pentylene Glycol, Cetyl PEG/PPG-10/1 Dimethicone, Tocotrienols
5. Petrolatum ointment (control)
6. Triamcinolone 0.1% ointment

As it is known, bathing enhances the effects of moisturizers and topical steroids. But it is fundamental to apply the cream within 3 minutes to prevent evaporation from the *stratum corneum.* As a matter of fact the skin of patients AD affected, rapidly dehydrates and the barrier cracks. Therefore the *3 minute rule* is very important.

TREATMENT METHODOLOGY

The study was an 8-week prospective, randomized, open parallel-group trial with 36 children, divided in three sub-groups: 15 subjects (group A), 12 (group B) and 9 (group C) all pre-washed by a bath-oil.

Within 3 minutes from washing, was applied twice a day a special pill-mask (ACTIVE A) imbibed with an aqueous active solution of tocotrienols, hyaluronic acid (HA) and 5 mg/g of a patented chitosan-based anti-inflammatory compound named ATOBIOL® (Group A), and soon after the lamellar Gel B or only the lamellar gel enriched with ATOBIOL (5 mg/g) (ACTIVE B, Group B).

A third group of 9 children was treated with a petrolatum ointment for the same period (group C - control). After 8 days of cosmetic treatment, all the groups were treated, two times a week, with triamcinolone 0,1% ointment, continuing the treatment at home applying the sole lamellar gel twice a day.

METHODOLOGICAL SCHEME

FOR THE FIRST 8 DAYS

1. Phase: - to clean the treated face by the bath oil
2. Phase: - to apply within 3 minutes on wet skin the imbibed pill-mask (ACTIVE A) for at least 15 minutes + ACTIVE B gently massaging (group A)
   - to apply the lamellar gel (ACTIVE B) on wet face gently massaging until absorbing (group B)
   to apply the petrolatum ointment gently massaging (group C - control)

TAB. I

CLINICAL EVALUATION

A clinical score assessing erythema, scaling, crusting, and pruritus was performed, always by the same dermatologist, at baseline (day 1), at day 8th and every 2 weeks thereafter on a visual analogue scale (0 = absent; 1 = mild; 2 = moderate; 3 = severe (Tab. II).π

No patients used other topical treatments within the 2 months of the study period, or systemic drug or diet supplements within also the 4 weeks before starting the study.

The obtained results are reported on Fig. 1 and 2.

ERYTHEMA

0 = absent	
1 = mild	(<10% surface area)
2 = moderate	(erythema in macules and patches)
3 = severe	(generalized erythema > 50% surface area)

PRURITUS, SCALING, CRUSTING

0 = absent	
1 = mild	occasional scratching and scaling
2 = moderate	scratching continuously and some scaling and crusting
3 = severe	hard continuously scratching – excoriation, scaling crusting.

TAB.II

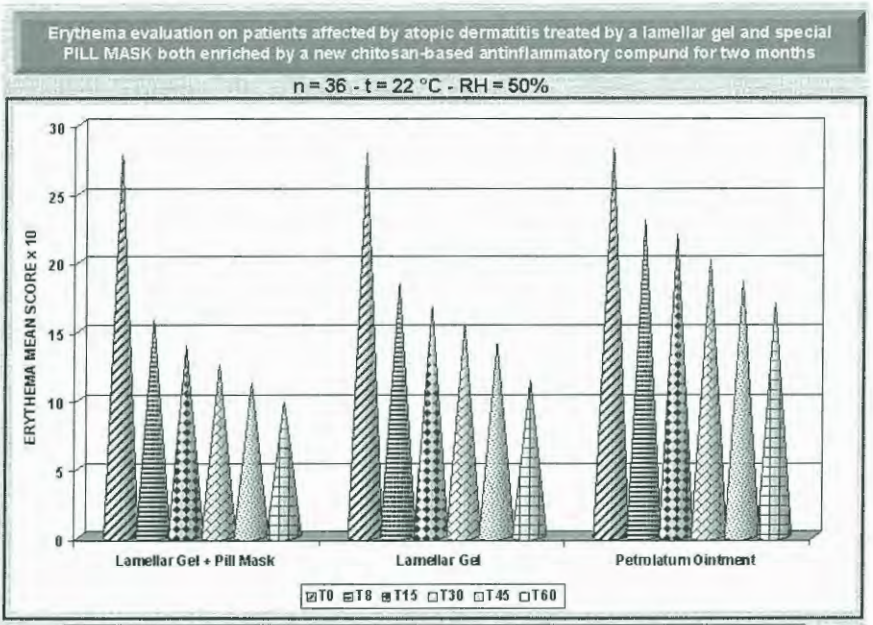

Fig. 1 ALL p VALUES ARE HIGHLY SIGNIFICANT (p<0.005) AS BASELINE AND AS TO GROUPS 346

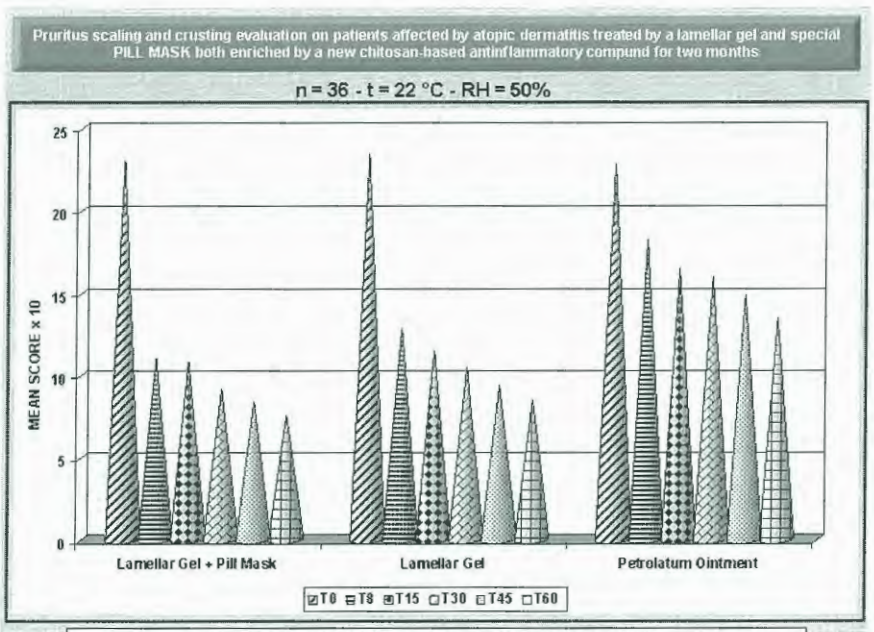

Fig. 2 ALL p VALUES ARE HIGHLY SIGNIFICANT (p<0.005) AS BASELINE AND AS TO GROUPS 347

BIOPHYSICAL EVALUATIONS: 3C SYSTEM METHODOLOGY

Quantitative measurements of skin hydration, surface lipids and TEWL were performed according to Cardillo and Morganti method (15,16) before the 1st day (baseline), after the first 8 days of pre-treatment (end of treatment) and at 15 and 60 days of treatment, always in the morning from 8 and 11 a.m. on skin cleansed the night before.

This computerized methodology collects up to 10/15 measurements over 25 second sampling period and records the mean values, automatically standardizing the environmental conditions (RH = 50% t = 22°C).

To alleviate the possibility of the patient physiologic state, the other major factor-influencing rate of water loss, it was asked to rest in the testing room for 30 minutes before measurements.

Possible site-to-site variation was eliminated by random selection of treated sites.

Skin hydration was assessed by measuring total capacitance of the horny layer and the values are expressed in 3C arbitrary units; *skin lipids*, observed by a special frosted plastic foil, are measured photometrically and expressed as $\mu g/cm^2$; *TEWL* was measured by a special 3C probe. It consists of a cylindrical open chamber measuring system, diameter 14 mm., height 10 mm. and two sensor units, containing a thin capacitance film transducer placed at 3 and 7 mm. distance from the skin.

TEWL is calculated digitally as $g/m^2 \cdot h$.

The instrument probe was always held perpendicular to the skin surface and allowed to equilibrate for 20 seconds.

All the obtained results are expressed as mean values of the measurements performed on four different right or left skin areas (cheek, forehead, chin and nose).

The obtained results are reported on Fig. 3,4 and 5.

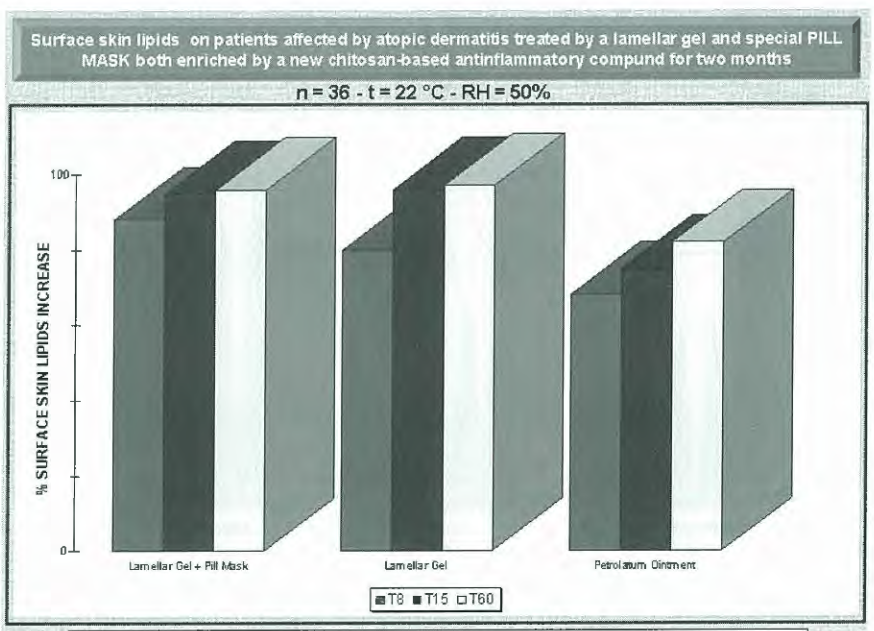

Fig. 3

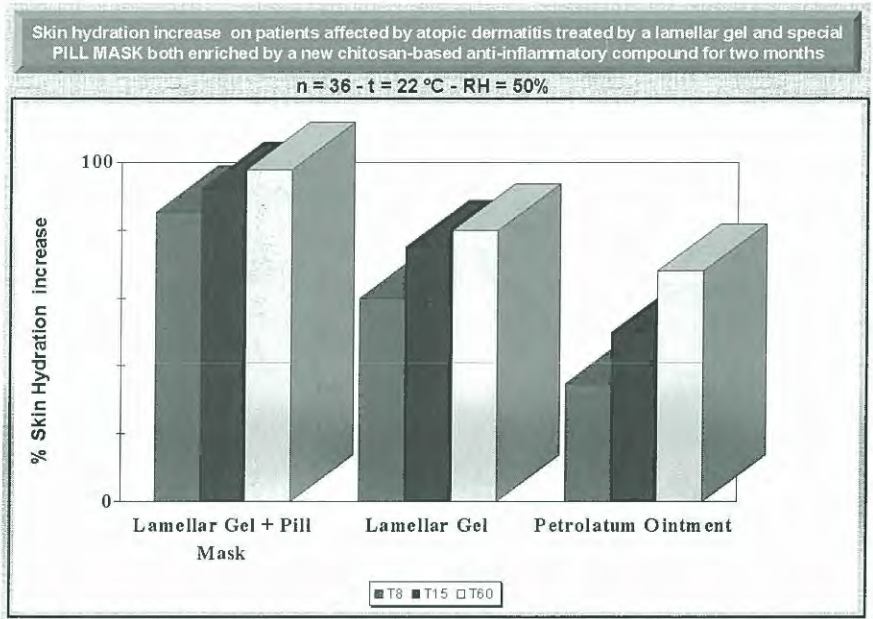

Fig. 4

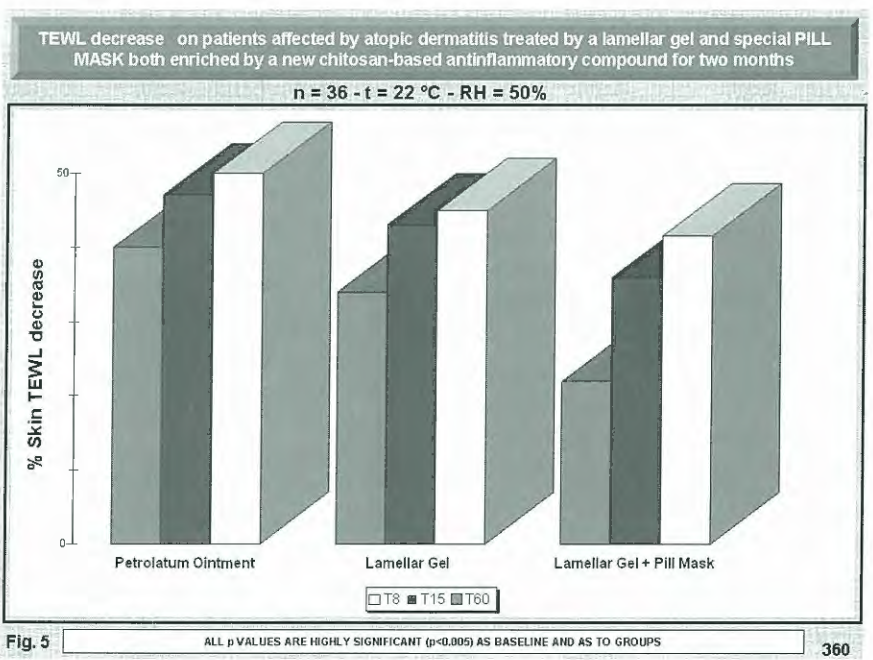

Fig. 5

360

PILL-MASK APPLICATION

The pre-imbibed pill-mask is applied on the entire cleansed face for 15 minutes. The complete imbibition period of the dry pill requires 1 minute of time operating (Fig. 6).

Fig. 6

STATISTICS

The Chi-square test and the Fisher exact test were used for statistical analyses. AP value less that 0.05 was considered significant. The Bonferroni correction was made when appropriate.

DISCUSSION

Both the gel and the pill-mask proved a strong anti-inflammatory and re-hydrating activity on atopy affected subjects treated following the methodology above described.

In fact, while the active principle used performed completely its activity, as reported also in one of our previous studies (17), the methodology used for pill-mask contributed remarkably in decreasing many symptoms usually accompanying AD.

As clearly shown on Fig. 1 and 2, the treatment with the sole gel or in combine with PILL-MASK/gel decreased the erythema appearance (Fig.1) from 59 to 65%, and the pruritus-crusting from 66 to 64% (Fig. 2) after 60 days therapy, differently from the usual petrolatum treatment which improves of about 30% only.

The use of this special cosmetic therapy gave results higher of above 25%. Why?

Probably that is due to the intense anti-inflammatory and reparatory activity performed by the new active principles used, and to the high re-hydrating activity performed both by pill-mask and by the constant use of the lamellar gel.

As observed, the treatment with pill-mask only, during the first 8 days of therapy (that is to say before using corticosteroid) improved the erythema appearance from 35 to 44% and pruritus/crusting from 24 to 52%, providing a high capacity in restoring the barrier activity.

Comparing figure 3 to 5, it can be observed a remarkable increase in hydration (+ 85%) and in surface skin lipids (+ 88%) with a consequent decrease in TEWL (- 40%).

Continuing the cosmetic therapy together with the biweekly use of corticosteroid, skin hydration values increase up to 98% using pill-mask/gel, and up to 80% using the sole gel,

while surface skin lipids increase respectively of about 97% in both treatments, and the high values of TEWL recorded in patients affected by AD decreases of about 50%.
In this case also, the control treatment by petrolatum recorded values lower from 30 to 40%.
In conclusion, we deem important to underline the surprising results obtained using corticosteroid only twice a week.

CONCLUSION

This novel *cosmetic therapy* used in AD, seems useful to reduce corticosteroids dosage avoiding their side effects, and to improve skin hydration decreasing skin dryness also in people with sensitive skin.

ACKNOWLEDGEMENTS

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Beijing must be visited ! An important International Congress on Dermatology was the right occasion

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Beijing is a city requiring a lot of time and different journeys to be entirely visited.
Whatever is the duration of the journey, Beijing is a city that reserves emotions, expecially if visitors can immerse themselves among thousands of Chineses, divided in 56 different etnias. This big metropolis, always Imperial City, has changed during the history. These changes influenced or modified its structure (Fig. 1).

Fig. 1 Area of the center of Beijing dedicated to typically ortiental sapore shopping

The old axis north-south dividing and characterizing the Ancient Beijing has been modified in east-west, as to underline the progressive economic boom of the New China.
Beijing is divided by the long Chang an Je, 40 kms, along which the sun rises on the eastern suburb area, cuts the Hatamen at the enter of the Forbidden City at midday, and paints of red all the skyscrapers of the western area during sunset.
Entire areas of the city have been pulled down to give space for example to the big Tienammen Square or to modern crystal buildings and skyscrapers characterised by the typical Chinese style (Fig. 2).

Fig. 2 Beijing two styles: ancient and modern.

The city preserves a charm made up by its history and its daily life, and just visiting it you can feel it. It remains the capital of the Popular Chinese Republic, even if it has no more the power of the ancient capital of the most vaste empire in the world.
Why does the Forbidden City extend all along the north-south axis?
Because a Taoist, descended from Heaven, as city architect, divided Beijing in different area all limited by walls, following the universe har-

mony.
The Great Wall protected the empire at north, while the city was protected by big open walls placed on the four cardinal points and by enormous Doorways as unique access.
In the middle, fifth cardinal point for Chinese, the walls protect the Emperor and his Court, while little streets of the center (hutong) were for common people.
Following Yin and Yang phylosophy, Yin, north, represents the barbarian dangerousness coming from north, while Yang, south, represents sun heat, security and life. (Fig. 3).

Fig. 3 *View of the famous Great Wall built in the 220 a. C. by the first emperor of Qi Dinasty, Gin Shi Vang Di*

So, buildings opened to south all along the axis (hatamen) that from the Belltower and the Arrow Tower (north), through Tienammen Square, arrives to Quiensenmen Door (south).
15 milion of inhabitants live in Beijing nowadays, and if the demographic control stopped the urban expansion, the new economic development draws milion of people inside the city.
A few years ago living arond the third ring-road was like living in the country-side, today living after the forth ring-road is like living in the center town. All along this area you can find lots of new excellent hotels, the Olympic Village is almost finished while the Nationality Chinese Park is ready.

In this Park, 400.000 mq, all the typic buildings of the 56 different etnia were reproduced (Fig. 4).

Fig. 4 *The Drum Tower and the Rain Bridge of Dong nationality (Nationalities Park) in Guizhou area.*

All along this park there is a revival of the old traditions of all these etnia. (Fig. 5).

Fig. 5 *Typical Bay nationality residence in the area of Yunnan*

Social and religion cultures are at the basis of the different architectures and traditions characterizing the ethnic minorities, according to different geographic areas and clima very important for the building materials (Fig. 6).

Fig. 6 The so-called Celestial Column of Orongen nationality

Fig. 8 Mosque area

Different religion traditions characterized the architecture culture even in the same geographic area. Tibetan people, living in Gansu area, developped an architecture strictly linked to Lamaism (Fig. 7).

Fig. 7 Tibetan typical residence

Each flat has a separatly area dedicated to religion. Man and God can not be divided, they must live together. But there is not just this religion culture in that area, infact you can meet lots of Muslims and their Mosque where they go praying every Friday. (Fig. 8).

Thus different religions are at the basis of different architectural styles. (Fig. 9).

Fig. 9 Buddhist Pagoda in the area dedicated to the Dai nationality, always in the area of Yunnan

Right in the middle of this Ethinic Park there is the National Etnia Museum, showing the entire 6000 years Chinese People history.
There you can follow all the transport development: for example starting from the little coach hauling by hands characterised by wooden wheels till the building of the binnacle necessary for the passenger privacy, and the utilising of animals to haul it. But you can also see all the

staff for the daily human life, different from etnia to etnia, from era to era.
It is thanks to these always new discoveries that Beijing, capital of the north and very important city for the wonderfull Chinese history, every year becomes always more beautiful and different from the other capitals.
One of the peculiar characteristics of Beijing is its gardens and the way with which green has been organized and maintained above all in this last 3-4 years (Fig. 10).

Fig. 10 *Roses garden view next to a catholic church.*

The management of green represents a civilization problem and the art with which gardens are treated can be compared to poetry, painting and handwriting, integrating part of the Chinese culture.
Garden should be a unique thing like a frame through which it is possible to admire nature. The view throughout this frame is a view of an ideal man in harmony with nature.
Cliffs and stones recall the mountains that constitute the skeleton of the earth, while water (ponds and streams) gives life to the arteries (Fig. 11).

Fig. 11 *Water, flowers and stones of a Chinese garden.*

Everything symbolizes the Tao, source of life, principle of every thing.
You can feel respect and love for nature everywhere, not only inside the gardens, real lung and soul of the city, but also along the center and suburb streets coulored and fitted out with thousands of roses framed by boxwood following the Italian style of '700.
It is a pity that this garden treatment is no more carried out in Roma. During this trip, my fifth one, what really impressed me of Beijing was the way streets and gardens are well maintained, expecially if compared to the old and full of weeds roses of Piazza di Spagna in Roma!
In Beijing hundred of young people continually look after and cure green areas starting from the airport till the center town.
A city held perfectly cleaned up and in order with patient and love as a woman everyday does with her make-up.
As for a painter the drawing of a single branch can be sufficient to recall an entire tree, a very delimited and cured garden is for Chinese the framed representation of nature (Fig. 12).

Fig. 12 *Water and flowers games in the Botanical Garden of Beijing.*

Chinese people loves nature, they demostrated it in the past and they are still demostrating it in the present through the cure with which they treat and maitain gardens and the wonderfull and cleaned cities.

I really hope that the culture of beautiful will be soon restablished in Rome, where both green areas and roads are today totaly neglected.

Flowers and gardens need continuos and loveling cures carried out by experted hands and not by precarious gardeners! (Fig. 13).

Fig. 13 *Particular of a garden*

Among particularities of Beijing suburbs, after having visited its most important momuments, there is without any doubt the Lugouqiao Bridge known as Marco Polo Bridge (Fig. 14 and 15).

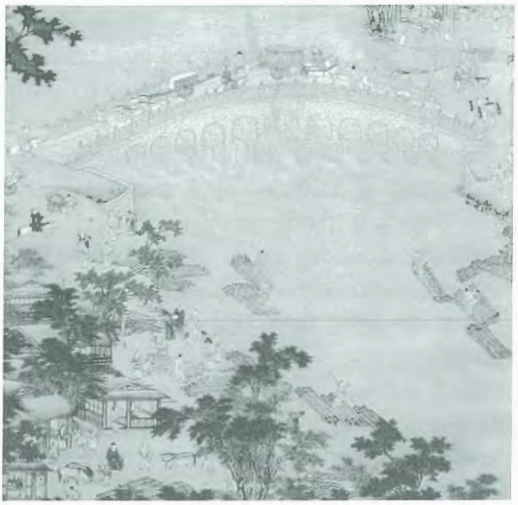

Fig. 14 *An ancient press representing Lugouqiao bridge (Bridge of Marco Polo)*

Fig. 15 *Particular of the actual Bridge of Marco Polo*

Marco Polo entered in Beijing passing for this bridge while the sunset coloured and illuminated it. It is a marble bridge, 231 meters in lenght, supported by 11 arcades enriched by 2 balusters with 485 marble statues characterized by different lions.
Build between 1189 and 1192 it was restored under Ming dynasty in 1444 and than under Qing dynasty in 1698.
In order to avoid big waves of flood to which it has been exposed for centuries, a dam up to upriver has been built. The absence of water during spring and summer doesn't give to the bridge the charm that so impressed Marco Polo.
Another curiosity to be satisfed is to visit Father Matteo Ricci known as Li Madou for Chinese (Fig. 16).

Fig. 16 Visiting Li Madou Tomb (Father Matteo Ricci) in Beijing.

He not only learned written and oral Chinese, but he tried to melt Cristian culture and Confucius one. It is thank to this attitude that he was so admired and loved by Chinese. His mortal remains lie in the garden of the Agricultural School.
The IX International Congress of Dermatology, organised by the International Society of Dermatology presided from my friend Prof. Coleman Jacobson from Dallas, USA, gave me the occasion for an ulterior trip in China.
President of this Congress and true author of it was Prof. Hong DuoChen, head of the department of Dermatology of Shenyag University, president of the Chinese Society of Dermatology and director the Immunodermatology Laboratory of the Ministry of the Health (Fig. 17).

Fig. 17 Prof. Hong-Duo Chen President of the Congress and P. Morganti General Secretary of ISCD

Thousand of important scientists from 60 different countries partecipated to this interesting meeting, held in May 19-22. They had the opportunity to listen and debate all the most important topics on dermatology: from the basic science to the most recent therapies, without forgetting the Cosmetic Dermatology and the Chinese Traditional Medicine.
During the different sessions as for example genetic, immunology and photobiology, it was discussed not only about all the patologies linked to the excessive exposure to UV rays, but also about all the disorders caused by melanogenesis alterations.
On these topics many important American researchers like Mark R. Pittelkow (Professor of Biochemistry and Molecolar Biology at Rochester USA) and my friends Prof. J. Uitto

(Skin Biology and Dermatology Department of Jefferson Medical College of Philadelphia) and Prof. Coleman Jacobson (President of the International Society of Dermatology) took speach.

Very important topics have been carried out also by other friends like the famous dermatologist Prof. Constantine Orfanos from Berlin and Prof. Terence J. Ryan from UK known for his multiple studies carry out on the importance of skin microcircle. But also by Prof. Jean Paul Ortonne of the University of Nice-Sophia Antipolis in France, by Prof.Torello Lotti of the University of Florence and of course by many Chinese friends among which Prof. Hong Duo-Chen eminent clinical immunologist, Liu Wei Director of the Dermatology Department of Military Hospital (my co-chairman during the session dedicated to Cosmetic Dermatology) and Prof. Ricardo Galimberti from Argentina and Prof. Young Pio Kim of Chonnan University of Kwangjo in Korea met few years ago during the I Congress of Korean Society of Cosmetic Dermatology.

Many others researchers from all over the world partecipated with success to this Congress to which I am glade to have partecipated as Chairman and as organiser of the Cosmetic Dermatology session.

I feel honoured of my friendship with Prof. Hong Duo-Chen with whom I'll surely organise in China the VIII International Society of Cosmetic Dermatology Congress in 2006.

The Cosmetic Dermatology session, hold the first day of the Congress, took an important place too.

It is interesting to emphasize how also in China Cosmetic at high scientific content is appreciated as new branch of Dermatology.

All the participants, a huge number, followed and debated with interest all the topics regarding the Dermo-cosmetic aspects on skin hydratation (Fig. 18).

Fig. 18 *P. Morganti and Liu Wei chairmen of the session dedicated to Cosmetic Dermatology*

Different types of skin xerosis and their treatments are very important topics for Cosmetic Industry that is trying to solve all skin problems linked to environment and life always more stressed.

As an example damages provoked by the excessive exposure to the sun or to UV lamps are increasing but may be reduced by the use of polysaccharides able to restore immune response. Thus the interesting topic of Paolo Giacomoni (Director of Estee Lauder Clinique Laboratory of Melville, USA) lecture was exactly how to make skin more resistant against UVA and UVB rays and, probably for this reason the Clinique boot was visited from many dermatologists (Fig. 19).

Fig. 19 *Clinique stand*

Giancarlo Guglielmini of Sinerga, Pero Milan, Italy treated other damages and reported interesting studies on acne treatments based on azeloglicin (AZG), idrosoluble azelaic acid, used alone or in association to phosphatidylcholine (FC).

According to clinical data, FC and AZG, opportunely calibrated and inserted in an adapted vehicle, showed to drastically reduce both lipids and P-acnes colonies main cause of acne in young people.

Dr. Aldo Cristoni lecture (Fig. 20) treated new methodologies and showed how the pro anthocyanins can carry out an interesting activity antielastase and anti-collagenase plus their already studied antinflammatory action on skin microcirculation.

Fig. 20 *Dr. Aldo Cristoni of Indena (ME) Italy*

Microcircle modifications found in various skin pathologies, can easely be controlled by videocapillaroscopy, clearly illustrated by Prof. Humbert of Besancon, France (Fig. 21).

Fig. 21 *Prof. Humbert of Besancon (France)*

Antiaging activity carried out by alpha (AHAs) hydroxy and by polydroxy acids (PHAs) has been widely treated through wonderfull clinical photos by Prof. Ruey Yu (Fig. 22), collaborator of my friend Van Scott, USA. He showed how PHAs represent, together with the most recent Bionic Acids, the therapeutic evolution of AHAs technology.

Fig. 22 *Prof. Ruey Yu from USA*

Dr. Bouloc of French Laboratoires Vichy (Fig. 23), going back to my introductory topic on xerotic and sensible skin, underlined the born of

a new category of vehicles called oleosomes helping the penetration of active principles.

Fig. 23 Dr. Bouloc of Vichy Laboratories (France)

Oleosomes are particulary active for treatment of dry and dehydrated skin. As a matter of fact, for example, they favour penetration of ceramides making easier the altered barrier reconstruction at integrum.

Dr. O de Lacharriere of French Laboratories of L'OREAL, came back on sensible skin topic. He assumed how this particular skin aspect can have a neurological origin not necessary linked to pathological phenomena but based on sensitive epidermal nerves.

Long, interesting and constructive debates took place after each lectures of this workshop.

For several times, as Chairmen, Liu Wei and myself have underlined and emphasized as Cosmesic Dermatology has become an important branch of Dermatology and of Chemistry of course.

Clinically Correct Cosmetics, studied both *in vitro* and *in vivo* characterised by validated bioclinic methodologies reached the full maturity and can maintain in a good state skin ecosystem and result as indispensable helping of various skin pathologies.

At the end of this session and after a careful visit to the numerous stands present in the Congress hall, we assist to the official inauguration of this interesting international meeting in a hall full of people coming from 60 different nations (Fig. 24).

Fig. 24 A particular of the Congress inauguration evening

The day after Prof. Hong-Duo Chen invited all his VIP hosts to a famous restaurant of Beijing (Fig. 25) where after a luxurious, perfect and delightful dinner a wonderfull and typical Chinese show has been offered. (Fig. 26 - 28).

Fig. 25 Regal Palace Theatre Restaurant where the wonderful dinner was offered

Fig. 26 Restaurant Welcome

Fig. 28 Prof. Hong-Duo Chen drink a toast with the Italian delegation

Fig. 27 A moment of the show

The high scientific value of all the lectures and the careful organization of this Congress make this International Congress unforgettable.
Very many thanks to all organizers and *in primis* to Prof. Hong Duo-Chen real Orchestra Director!

SKIN, HAIR, AND NAILS. Structure and Function

By Bo Forslind and Magnus Lindberg
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The skin, as a biologically active organ, is the first line of defense against the hostile environment and is also an important area for interpersonal communication.
This interesting book on skin and its appendages, divided in 3 parts with 16 chapters, surely may serve as an up-date reference for all the scientists interested to this topic.
Cysteine-sulfur links and stabilizes the protein chains of the skin and its appendages, making them mechanically as well as chemically highly resistant. Functionally the skin contains low amount of sulfur with a high molecular weight proteins, meanwhile the high sulfur fractions with low molecular weight proteins characterize the keratin of hair and nails.
The cornified cell surface of the epidermal cells and the cuticular surface of the hair are both rendered lipophylic by lipids: omega-hydroxy ceramides for the skin, saturated and branched chain fatty acids for the hair.
And the similarities observed among cells of the integument skin, hair and nail are reported in the introductive **chapter 1**.
Chapter 2 is an overview of the structure and function of the epidermis in relation to barrier properties. This barrier, composed of coneocytes with a thickened cell membrane and intercellular lipids, maintains the water diffusion as a dynamic process, depending on the status and function of the skin but is influenced from the external environment.
Thus the Stratum Corneum (SC), the outermost layer of the skin, prevents water loss from the body providing mechanical protection also.
Divided in five different cell layers, the epidermal stem cells, located in the base layer, migrate toward the skin surface with simultaneous maturation and differentiation to form the corneocytes of the SC. During this differentiation the keratinocytes change their form from cuboidal to flat , changing also the content of intracellular organelles, lipid metabolism and keratin expression.
The final result is a tissue that prevents water loss by the formation of a continuos matrix of highly organized lipid lamellae, into which is embedded an extensive network of dead cells called corneocytes. These lipid lamellae, arranged in stacked bilayers parallel to the skin surface, consist of a complex mixture of lipids, ceramides, cholesterol and fatty acids, having relatively long hydrocarbon chains. This liquid-ordered lipid structure formed in cholesterol-lipid mixture, represents an important component of the skin lipid matrix that serves as a permeation route for water and other diffusing substances.
But the role of SC is to protect the body from uncontrolled passage of substance in both directions,

preventing water from diffusing out of the body to any great extent. The lipid matrix structure of SC is the topic of **chapters 3 and 4**.

In contrast to the viable layers of the epidermis where phospholipids are the major components of the cell membranes, the ceramides in SC (CER) become the major constituents of the intercellular domains among other lipids like long-chain free fatty acids (FFA), cholesterol (CHOL), and cholesterol sulfate. In addition to its exceptional lipid composition, the structure of the CER, is unusual for membrane-forming lipids, because the SC CER contain very long acyl chains and small polar head groups, which bind water poorly. Thus lamellar bodies contain precursor lipids for the intercellular matrix, as well as different kinds of catabolic enzyme. After extrusion of the lamellar bodies at the stratum granulosum – SC interface, hydrolysis of the precursor lipids converts the glycosphingo-lipids and sphyngomyelin into CER and phospholipids into FFA. The presence of these amphiphilic lipids makes possible the formation of three-dimensional structures such as the lamellae recovered between the corneocytes. In these structures, the lipids are held together by forces including Van der Waals, electrostatic, hydrophobic, and hydrogen-bounding interactions. Their packing properties depend on the size of their head group, their acyl chain length, and the degree of saturation, including also pH, temperature and pressure. In the solid state, the lateral packing of lipids in lamellae is either in a hexagonal (gel), orthorhombic (crystalline), or a triclinic sub cell.

Therefore it has been proposed that skin barrier formation may take place via a continuos process of intersection-free membrane unfolding with a concomitant cristallization of the emerging multilamellar lipid structure representing the developing skin barrier.

Thus within the intercellular lamellae of the SC there exist islands of gel phase domains surrounded by a continuos liquid crystalline phase. In this domain mosaic model, the gel phase domains are important for limiting the permeability of the SC, while the liquid crystalline phase is needed for pliability. All the difficulties involved in quantitative analysis of SC lipids together with the methodologies used, such as X-ray diffraction and electron diffraction, are reported in **chapters 5, 6 and 7** where interesting proposals are also discussed on skin barrier formation.

Chapter 8 is focused on the evolution of integument used as barrier to suit the environmental needs of specialized habitats.

All organisms, in adapting to their environment, depend on a highly structured and functional external covering, or integument. In single-celled organisms, the integument consists of a thin, fragile barrier, the plasma membrane, which separates the cell from their watery environment. In both plants and arthropods, the outer surface is known as the cuticle, a non-cellular, multilayered membrane that lies over the epidermal cells. Vertebrates have a multilayered integument and have also evolved a variety of keratinized epidermal appendages, which provide additional structural integrity. However all the different protective functions of integument depend upon its specific and structural biochemical and physiological properties.

Thus human skin, as the largest and the most complex organ system, continues to stimulate discussions in interdisciplinary scientific forums.

For all these reasons an overview of the chemical-physical composition and arrangement of integument lipids that are involved in water proofing the skin or cuticle, is interesting for understanding the property of our skin barrier.

The skin is constantly exposed to environmental factors that might influence the integrity of its bar-

rier. As a matter of fact, pharmaceuticals and chemicals may interfere with both its structure and homeostasis altering its function, hence the possibility of percutaneous penetration. Inflammatory skin disorders and skin conditions with changes in keratinization also lead to altered barrier function and penetration characteristics.

All these topics are treated on **chapter 9** where both skin diseases and altered barrier properties by solvents are discussed.

Understanding the Irritative Reaction is the topic of **chapter 10**.

Contact dermatitis is a pruritic, epidermal and dermal inflammatory reaction caused by items in contact with the skin. The cause is often repeated exposure over time to a mild or low-grade irritant.

Common examples include Irritant Contact Dermatitis (ICD) caused by soaps, detergent, oils and plants, while Allergic Contact Dermatitis (ACD) is commonly caused by metals, perfumes, rubber, preservatives and drugs.

ICD is considered to be more common than ACD but all both are often interwoven. Oxidative stress is increasingly being seen as a contributory factor.

The SC of the epidermis, composed of corneocytes and lipid lamellae, is a very effective barrier against irritants, but damage to the SC is followed by loss of water, causing the surface of the skin to become dry and cracked, thus making it easier for irritants to penetrate. The irritants themselves then increase both barrier damage and the number of antigen-preserving cells.

Although not thought to play the pivotal role in irritant reactions that they have in ACD, Langerhans cells (LC) do nevertheless exhibit significant changes in morphology and epidermal density following single exposure to irritants. Where direct disruption to cell membranes and organelles occurs, it is not unreasonable to assume this would result in the release of preformed cytokines.

Thus once a person has acquired specific sensitization to a hapten, re-exposure and presentation by the LC will attract specifically sensitized T cells, initiating the release of a cascade of cytokines. Therefore although sensitized T cells carry a high specificity for a particular allergen, the profiles of cytokine release and the dermal and epidermal inflammation seen in irritant and allergic contact dermatitis are very similar. The future challenge is to increase the understanding of the mechanisms that influence and control the recovery phase of irritant skin reactions.

Chapter 11 introduces the topic on hair. Knowledge of the structural hair unit is essential in understanding the patho-physiology of hair and hair disease. The hair unit (follicle) is divided into 4 parts: (1) Bulb: consisting of dermal papilla and matrix intermixed with melanocytes; (2) Suprabulbar area from matrix to insertion of arrector pilimuscle; (3) Isthmus extending from insertion of arrector pilimuscle to sebaceous gland; (4) Infundibulum extending from sebaceous gland to the follicle orifice. The hair follicle show intermitted activity with acyclic growth, pattern in the form of alternating active (anagen) and resting phase (catagen and telogen).

Hair growth, as cyclic event, consists of almost 90% of hairs in anagen that may last up to 2-6 years ; 1% in catagen 3 weeks and 10% in telogen 3 months.

In hair research there has been an expanding focus from the hair structure –function perspectives to a view in which the hair follicle and its function can act as a model for studies on several biological mechanisms and cellular events such as growth control, differentiation, cell signaling, programmed cell death, and gene expression.

New immunological method developed implies today new possibilities for the study of hair diseases

and disorders.

Chapter 12 focuses on the fiber cuticle and its associated surface membranes described by its chemical composition and ultrastructure organization.

New immunological method developed implies today new possibilities for the study of hair diseases and disorders.

A typical characteristic of mammalian fibers is their high degree of variability. Features such as morphology, dimensions, and surface properties of cuticle cells contribute to this variation and surface membrane depth have been subject of many studies, determining its thickness between 2 and 7 nm.

External surface features of hair fiber such as its contours, defects and damage chemical treatments and polymer coatings are observed by means of SEM (Scanning Electronic Microscopy). On the other side internal cell structure and ultrastructure including the biology of fiber formation can be observed by using TEM (Transmission Electronic Microscopy). More recent studies of the fiber surface have utilized new developments in Scanning Probe Microscopy (SPM). Moreover Atomic Force Microscopy (AFM), a form of SPM is used to obtain more information about the hair surface topography and its nano-chemical properties. Many studies on these subjects are reported in this chapter.

Although much progress has been made in elucidating the factors involved in regulating continuous pigmentation in the human epidermis, we are only beginning to understand the mechanisms involved in regulating pigmentation in the human hair follicle.

The development of the hair pigmentary unit, the biochemical regulation and loss of pigment at level of its follicle and all the related pathologies are focused on **chapter 13** where the evolutionary significance of hair pigmentation, or the molecular aspects of melanocyte aging, or the pathogenesis of canities are for example, reported.

Up today we are only beginning to unravel the mysteries of hair pigmentation in human.

Each follicle synthesizes and supports a hair and possesses the ability to partially recapitulate embryogenesis to replace this hair during the hair growth cycle.

Androgens play the major role in altering the type of human hair. The effect varies from stimulating a vellus follicle to enlarge enough to produce a long pigmented hair to the reverse transformation of terminal follicles to vellus ones causing balding.

However the knowledge of the patho-physiology of androgenic alopecia (AGA) is essential in understanding the mechanism of action of current therapeutic agents.

Thus the exact inheritance pattern of AGA and how androgens act on hair follicles is still debated. The current hypothesis for the way in which androgens act on the hair follicle focuses on the dermal papilla. The mesenchyme-derived dermal papilla plays, in fact, an important regulatory role, altering many parameters of the hair follicle and determining the type of hair produced.

On the other side a major determinant of AGA is intracellular androgen metabolism, which involves two steroid-metabolizing enzymes and androgen receptor proteins. And the androgen genetic and environmental factors influencing growth is the topic of **chapters 14 and 15**, where the latest information on etiology, clinical features and state of the art of alopecia areata (AA) knowledges are also reported.

Chapter 16 is entirely dedicated to the Structure and properties of Nails and Periungual Tissues, which received little scientific interest in the past in comparison with skin and hair. The nail unit con-

sists of keratinized product, the nail plate, and four specialized epithelia: the proximal nail fold (eponychium), the nail matrix, the nail bed and the hyponychium.
Therefore the nail is a composite cellular structure that gains its stiffness from the organization of the intercellular fibrous protein keratin, as well as from the cellular architecture of the two parts of the nail plate, the dorsal and the ventral plates.
The nail plate is a fully keratinized multilayered sheet of cornified cells adhering tightly to the nail bed.
The nail bed epithelium consists of several cell layers and extends from the lunula to the hyponychium. Nail changes such as splitting of the nail plate and brittleness are cosmetic problems, meanwhile nail disorders, such as onychomycosis, are pathological problems treated by drugs.
The biological properties and morphology of nails are reported and explained in this chapter by experimental studies carried out in the laboratories of the author.
This interesting book provides an up to date review on structure and function of skin, hair and nail, presenting the last multidisciplinary results existing in this area of cutaneous research.
Reading it may be surely of great interest to a wide group of health professionals including dermatologists, plastic surgeons, cosmetic chemists, general practitioners and students, involved in medicine and chemistry, interested to better understand the new science of Cosmetic Dermatology and Aesthetic Medicine.

P. Morganti
Editor-in-Chief

DRUG ERUPTION REFERENCE MANUAL. 10TH EDITION

by Jerome Z. Litt, Md
2004. 594 pp. 64 color figures. Hardcover. CD-rom included
ISBN: 1-84214-250-X
£120.00
Taylor & Francis Group Ed.,
London, New York
Fax: +44(0)2078422298
Website: www.tandf.co.uk

The expectations for this 10th edition of Drug Eruption Reference Manual have been absolutely satisfied. The structure of the Manual is perfect : clear and easy to consult.

Since the last edition, because of many generic drug withdrawn from the marketplace, they have been deleted from this edition.

The first part of the manual lists, in alphabetical order, 950 +generic and trade drugs with their corresponding names for easy access to the A-Z section /the main body of the Manual).

Soon after comes a listing of the various classes of drugs, and those generic drugs that belong to each class.

However the major portion of the Manual lists the 950+generic drugs, herbals and supplements in alphabetical order and the adverse reactions that can arise from their use along with the appropriate references (author, journal or book, volume and pages).

The reference are more than 25.000.

The side effects include those that primary involve the skin, the hair, the nails and the mucous membranes. Therefore the book is particularly useful for all the readers of our Journal.

The last part of the manual includes a description of the 31 most common reaction patterns observed from dermatologists all over the world via the Internet and from personal communications. Consultation of the book is really very easy.

The Generic Drug name is at the top of each page. The Trade (Brand) Name (s) are then listed alphabetically. When there are many Trade Names, the ten (or so) most commonly recognized ones are listed.

Beneath the Trade Names there is a list of Other Common Trade Names, those drugs from other countries. Then appears the Indication(s), the Category in which the drug belongs, and the Half-life of each drug, when known.

On occasion, an important or pertinent Note will follow.

Finally a CD-rom, included with the book, allows users to search the whole database in a highly sophisticated and flexible way. This interesting CD-ROM, together with the possibility of searching drugs by generic, trade or on the basis of reaction patterns, also added capacity for multiple drug searching and printing out the results.

But why Dermatologists and Cosmetic Chemists who are the predominant readers of this Journal have to know and to buy this book on Drug Eruption?

Reactions to drug are unfortunately very frequently noted but also reactions to cosmetics constitute

a small but a significant portion of the cases of contact dermatitis seen by Dermatologists.
In the last ten year study, the European and American Contact Dermatitis Groups found that about 4% of the 25,000 patients tested were identified as having reactions caused by cosmetics. Probably this is an under-representation of the true incidence because most patients who experienced reactions to newly purchased cosmetics, seldom consult a physician and just stop using the suspected cosmetic.
Fortunately in the last years a lot of toxicological and allergological studies has been done and the new cosmetics at high technology become each year more sure and almost without of side effects.
For all these reasons this interesting and complete book has to become part of the library of all Dermatologists, Cosmetic Chemists, Biologists, Physiologists and all people working in the marketing and researching areas since they are directly and indirectly involved with drugs and cosmetics.

P. Morganti
Editor in Chief

BURNS: REGENERATIVE MEDICINE AND THERAPY

By Rong Xiang Xu
2004. 152 p.,69 fig., 39 in color, 68 tab., Hardcover
CHF 227.50 / Eur 162.50 / USD 198.00 (for USA only)
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Karger AG P.O Box,
CH-4009 Basel -Switzerland
Fax +41 613061234
www.karger.com/dermatology

This unusual book has been written by a pioneering Chinese scientist, Prof. Rong Xiang Xu who created a new standard of care for burns treatments.

By this book the author offers intriguing new opinions about regenerative medicine and therapy raising the ancient dichotomy between the vitalism of Chinese medicine and the materialism of the occidental one. For these reasons its strong innovation may be disconcerting for someone.

As a matter of fact, the treatment philosophy of Traditional Chinese Medicine (TCM) urges the pursuit of regeneration as opposed to replacement of burned or diseased tissues as have a precious few western doctors who sought to apply agents to improve and accelerate the wound-healing process.

Since many controlled experimental and clinical data have supported the suggestion that the moist environment enhances epithelization in the wound-healing process, Prof. Xu has developed Moist Exposed Burn Treatment (MEBT), a therapeutic procedure based on the moist environment of the wound, using an ointment that enhances epithelial repair.

This extraordinary Medical Doctor established an entirely new theory of burns physiology upon which he built an effective burns treatment, called Burns Regenerative Therapy (BRT). This innovative methodology integrates a Moist Exposed Burn Treatment (MEBT) and a Moist Exposed Burns Ointment. (MEBO). The therapeutic essence of MEBT/MEBO is to maintain the burns wound in an optimum physiologically moist environment through the use of a natural designed ointment-MEBO.

This topical remedy, composed of natural plant extracts dissolved in a sterile and refined sesame-oil base with beeswax as a preservative, promotes burns tissue repair in an incredible affective manner. MEBO cleans the burned tissue by stimulating the discharge and removal of debris, contemporary enhancing the regeneration and repair of the residual viable tissue at the base and periphery of the burn.

Accordingly, BRT and MEBT/MEBO is distinguished from conventional surgical therapy in that dryness, excision, skin grafting and scarring as well as the excruciating pain associated with dressing changes is no longer a necessary component of burns care.

The ointment's main active substance is considered to be β-sisterol at a concentration of 0.25%. Clinical and experimental investigations by Chuanji, Yunjing and Xu have indicated that MEBO has an analgesic, anti-shock and anti-bacterial activity, promoting also epithelial repair improving and reducing scar formation. Its activity contributes to the formation of a smooth, thin, and aesthetically acceptable scar, preventing the formation of hypertrophyc scars. By comparing BRT and

MEBT/MEBO treatment with the conventional therapy based on desiccation excision and grafting, its seems to represent a superior and successfully methodology.
This is the impression the book gives to the reader throughout its 9 main chapters. This innovative therapy seems to be useful to cure burns of different causes and different areas, including superficial second-degree, deep second-degree, and full-thickness third-degree burns. It is also an ideal technique for granulation tissue, regeneration and repair of burns in muscular layer and bone, resolving also the main problem of pain in second-degree burns patients.
As a matter of fact, surgical treatments, for example, aims at saving the life without considering the problem of pain. Severe pain causes shock and wound stress regulation disturbance which can tip the scales toward multiple system organ failure and death.
At this purpose MEBO covers the wound surface, protects the wound from irritation and relieves the pain almost immediately upon application.
BRT with MEBT/MEBO methodology seems capable of mobilizing and coordinating the potential physiological energy of the system wound stress reaction.
This book provides new interesting experiences to the medical community, as well as to the chemical and industrial world interested in learning all the chemical principles of burns regenerative medicine and therapy.
Moreover it may offer to specialists innovative ways to cure patients affected by burns, giving also to cell biologists, pharmacologists and physiologists new ideas of discussion on the innovative concept of skin tissue and organ regeneration.

P. Morganti
Editor in Chief

CAROTENOIDS HANDBOOK

By G. Britton, S. Liaaen-Jensen, H. Pfander
Compiled by A.Z. Mercadante and E.S. Egeland
2003. 573 p. Hardcover
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Carotenoids, fat-soluble pigments found in fruits and vegetables, form part of the antioxidant defense system that is crucial to human health.

Oxidative damage has been implicated, in fact, in the etiology of cancer, atherosclerosis, immunological disorders, and degenerative diseases such as cataract.

β-carotene and its precursor lycopene, are polyisoprenoids and share similar initial synthetic pathway with cholesterol.

Chemical and biochemical activities of carotenoids are related to their unique structure, an extended system of conjugated double bonds synthesized in plants from mevalonate. They are tetraterpenes formed by tail-to-tail linkage of two C-20 units, and in many carotenoids the end-groups are modified into five or six-membered rings giving monocyclic or dicyclic compounds. On the other hand, lycopene, consisting only of hydrogen and carbon atoms, is an acyclic carotenoid which contains 11 conjugated double bonds arranged linearly in the all-trans form.

In addition to the all-trans configuration several mono-and poly-cis isomeric forms may be formed.

Important dietary sources of carotenoids for the human are green leafy and orange to red vegetables as well as various fruits, including oranges, tangerines, or peaches.

Carotenoids, also found in various kinds of seafood including lobster and salmon, are transported in the human body in circulating lipoproteins. Therefore the uptake of carotenoids from the diet is influenced by several factors such as dietary fat, presence of fiber, or food processing.

As vitamin E, carotenoids are absorbed via the lymphatic pathway, requiring the formation of micelles from fat and bile acids. Thus, the intestinal uptake of these compounds is improved by the additional consumption of oil, margarine or butter.

The particle size of uncooked food also influences carotenoid uptake and the bioavailability of carotenoids from pureed or finely chopped vegetables is considerably higher as compared to whole or sliced raw vegetables.

A number of biological effects have been attributed to carotenoids including antioxidant activity, influences on the immune system, control of cell growth and differentiation and stimulatory effects on gap junction communication. These effects are thought to be relevant with respect to their protective properties.

However the evidence on the importance of their role in the antioxidant network is conflicting.

One reason for this conflicting information may be that most studies have been probably done by feeding carotenoid supplements to already well-fed individuals.

Therefore carotenoid depletion studies may provide a clearer picture of whether, and when, carotenoids are important antioxidants and inform on their antiradical activity. Moreover measurements in the body of their biomarker antioxidant capacity may help to disentangle their role in disease in contrast to dietary assessment methods.
The potential biomarker antioxidant capacity (AC) describes, in fact, the concerted action of the radical scavenging properties of individual antioxidants. Thereby it can help to investigate whether antioxidants act through this mechanism, as opposed to other mechanisms such as quenching or non-antioxidant properties.
For all tbese reasons and with the number of natural carotenoid structures reported rising above 700, there is a clear need for a single reference work containing data on all these compounds.
This new Handbook includes all natural carotenoids and common isolation artefacts for which structures have been assigned up to the end of 2001.
For each compound, it provides selected key references and critically assessed information about natural occurrence and isolation, and spectroscopic data for identification.
Thougb the Handbook serves as a self-contained comprehensive reference book on the known carotenoids, it is designed to be used in conjunction with the Carotenoids series.
The numbering of carotenoids in the handbook is the same as that used throughout the Carotenoids volumes. The factual information and practical guidance given in this well received book series ideally complements the information given in the Handbook.
It is highly advisable to be familiar with the general methods and precautions for handling carotenoids, and with the isolation and purification strategies and methods as described and evaluated in Vol. 1A, and the principles, application and interpretation of the spectroscopic techniques as described in Vol. 1B, to ensure that the identifications and analyses on which carotenoids work is based are accurate and reliable.
The Handbook of Carotenoids is an important source of information for both specialists and non-specialists. It will be of great value not only to chemists and biochemists, but to all researchers whose work and interest bring them into the diverse field of carotenoids, especially those from areas of biology, food science, nutrition, medicine, Cosmetic Dermatology, horticulture, agriculture, aquaculture, ecology, and biotechnology.
A standard full-page entry is given for each compound that has been characterized unambiguously, showing:

- Common name
- IUPAC name
- Structure, including stereochemistry, when assigned
- Spectroscopic data
  - UV/Vis (with illustration)
  - MS
  - CD
  - NMR (type and references)
- Chemical synthesis (references)
- Natural sources and outline of isolation procedure
- Remarks, e.g. further spectroscopic data, stability, properties, derivatives

• Selected key references

For completeness, those compounds which did not meet the required criteria for unambiguous structural assignment are listed separately with proposed structures, brief notes and key references.

This well organized book full of technical information on carotenoids is an important source of information for all the chemical, and medical community who wish to have in their own library an up do date book on carotenoids.

Carotenoids handbook will be useful also for students, who have interest in this important subject and for marketing managers since every year new biological activities of these interesting natural compounds are discovered.

P. Morganti
Editor in Chief

PHOTOAGING

By D.S. Rigel, R.A. Weiss, H.W. Lim and J.S. Dover
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Intrinsic aging is a natural process defining the progressive loss of the characteristics acquired during development which results in an increasing number of deviations from the ideal state.
It has both genetic and metabolic bases that converge to a dynamic oxidative stress, particularly in the skin.
Chemical aging is manifested by changes in the structure in micromolecular aggregations; extracellular aging is manifested by progressive cross-linkage of elastin and collagen fibers; intracellular aging is manifested by changes in normal cellular components by accumulation of substances such as lipofuscin within cells.
Photoaging or extrinsic aging is a similar process that superimposes to intrinsic aging, and it is the consequence of long term exposure to UV radiation from sun.
The effects of these radiation on cellular DNA can be rationalized in terms of direct interactions of UVB radiation with pyrymidine and purine nucleobases on one hand and photosensitive reactions mediated by UVA and visible light on the other.
However DNA bases can still absorb photons from the lower part of UVA spectrum, generating abnormal cyclobutandipyrimidines compounds.
Another important parameter to be considered is that UVA photons are able to penetrate deeply into epidermis layer, than higher-energetic UVB.
Thus, besides accelerating biological processes involved in intrinsic aging, photoaging is more susceptible then intrinsic aging to rise to skin cancers.
Photoaging or aging are caused, in fact, by a disruption of finely orchestrated molecular mechanisms that maintain skin structural integrity. The basic principles of photobiology together with aging and photoaging physiology and pathophysiology are documented and well discussed in **chapters 1 to 5** of this interesting book divided into five parts for a total of 21 chapters.
Photoprotection is the topic of **chapter 6**. Because the damages provoked by UV rays, a proper photoprotection become an integral part of the management of photoaging. Thus fabric incorporated into clothing and huts provides a convenient means of reducing ultraviolet radiation exposure, but topical sunscreens are also effective when display good photostability and protection both versus UVB and UVA.
Topical sunscreen act, in fact, by absorbing or scattering UV radiation and are widely available for general public use as consumer product. Therefore to optionally protect skin from the acute and chronic effects of UV radiation, a combination of behavior modification and use of photoprotective devices and agents is needed.
But sunscreens are just one element of photoprotection.

Therefore, because Reactive Oxygen Species (ROS) can be generated following UV exposure, the use of oral antioxidants as vitamin C, vitamin E and carotenoids has been evaluated and animal studies have demonstrated that vitamin E and, to a lesser extent vitamin C, are photoprotective in skin when topically applied or taken by oral route.
On the other hand carotenoids are among the most efficient scavengers of single oxygen and peroxyl radicals, either by physical or by chemical quencing.
Moreover the serum level of Beta-carotene and alpha-tocopherol increases upon supplementation and erythema formation significantly diminishes.
Finally, public education on photoprotection has to be also an important part of the strategy. However since oxidative stress plays a pivotal role in biological events leading to the clinical manifestations of aging and photoaging, any treatment that counteracts the effects of oxidative stress should have a therapeutic value in inhibiting the progression of aging and photoaging. The role of retinoids, vitamins, and α-hydroxy acids (AHAs) in the treatment of photoaging is the topic of **chapters 7 and 8.** AHAs and retinoids, reversing the effects of photaging are extensively used by topical applications in specific disorders, such as melasma wrinkles, lentigines, etc.
Chapters 9 to 18 are focused on the surgical/light -based therapy by chemical peels, microdermabrasion, laser, together with the use of fat transplantation and fillers. All these chemical means and technologies hold tremendous promise in rejuvenating the photoaged skin with minimal recovery time.
Modern cutaneous lasers operatoinalize the principles of selective phototermolysis. Structure in tbe skin serves, in fact, as chromophores that preferentially absorb certain wavelengths of light, which are unique to a given laser.
Chromophores that are targeted frequently include oxyhemoglobin in vascular lesions, melanin in pigmented lesions, and water in all cells.
The location and extent of the thermal injury (thermolysis) depends on the intensity duration and wavelength of the laser light.
Chemical peelings involve the application of a chemical exfoliant to wound the epidermis and dermis for the removal of superficial lesions and improve the texture of skin.
Various basic chemical agents are used to produce varying effects of light to superficial, medium to deep chemical peels through differences in their ability to destroy skin.
Superficial peeling is truly an exfoliation of the Stratum Corneum (SC) on the entire epidermis and very light peeling agents include low concentrations of glycolic acid, 10% TCA (tricloroacetic acid) and 20% salicylic acid, a beta-hydroxy-acid.
It is important to note that TCA applications are cumulative, increasing penetration and peel depth with more quantity applied, even in low concentrations.
Repetitive superficial TCA peels are useful for treatment of dyschromias and superficial skin lesions such as lentigines, ephelides and thin seborrheic keratoses as well as fine surface texture.
Microdermabrasion that offers patients a simple relatively inexpensive treatment for photoaging with rapid recovery time, may be used in conjunction with other approaches to improve treatment results.
The depth of treatment, and therefore the degree of injury produced during microdermabrasion is dependent upon several variables including crystal type particles flow rate, vacuum pressure, skin thickness, rate of movement across skin surface, and number of passes.

Botulinum, toxin A, (BTX-A), fat transplantation and different skin fillers, are used for treatment of rhytides and other signs of photoaging.
As a matter of fact, the face is the center of human communication, social interaction and the perception of attractiveness.
Fillers are used to fill in lines and folds on the face and can mimic a mini-face light under the right circumstances.
By these techniques, scars from acne, surgery and trauma can be improved also.
The advantage of fat transplantation is the ability to harvest, use and then freeze a large quantity of material.
This makes it possible not only to fill in deep hollows but also to perform a mini-face lift and fill in surgical areas in other parts of the body as well as plump up the hands to make them more youthful.
The disadvantages are the need for a surgical procedure, even though it is performed with local anesthesia, the need for touch-ups of heavy movement, and the need for a local anesthesia prior to injecting fat.
On the other hand BTX-A addresses the underlying muscular activity responsible for the development of wrinkles and folds. This toxin in combination with other facial rejuvenational procedures such as surgery, soft-tissne augmentation, and ablative and non-ablative laser resurfacing prolong and enhance benefits.
The last three **chapters 19, 20 and 21** are respectively dedicated to treatments of photoaging in Asian and Afro American patients, and to connected legal consideration in all those kind of antiaging treatments.
Asian skin, for example, is more likely to develop adverse reactions such as postinflammatory hyperpigmentation following laser surgery and intense pulsed light source treatment.
On the other hand in patient with skin type IV and V, repigmentation is impredictable and dermabrasion may worsen the hyperpigmentation.
The treatment of photoaged skin has evolved from a field with a primary medical orientation to one that is increasingly geared toward the cosmetic patient.
Scarring and pigmentary changes are the most common complications that occur in the cosmetic treatment of photoaged skin due too often to a medical malpractice.
At this purpose it is important to note that where there are two or more recognized methods of diagnosing or treating the same condition, a physician does not fall below the standard of cure by using any of the acceptable methods, even if one method turns out to be less effective than another method.
Although the standard of care may vary from country to country, it is typically defined as a matronal standard by the profession at large.
In such a situation, reccomandations, guidelines, and policies regarding varying treatment modalities for different clinical situations published by nationally recognized boards, societies, and commissions establish the appropriate standard of care. However in most situations the standard care is neither clearly definable nor consistently defined.
In the end it is the physician community that establishes that standard of care.
In the future, an increased number of modalities for the diagnosis and treatment of photoaged skin will become available, increasing the number of legal considerations.
An understanding of this trend will help both the patient who seeks treatment for photoaged skin and

the physician who treats it.
With these words ends this interesting book that, guiding and assisting clinicians in the selection of the best antiaging treatments together with their risk /benefit ratio of reviews the different types of photodamages, reporting the last rejuvenation procedures to be used.
The book Photoaging represents an indispensable tool for all medical doctors and cosmetics chemists who wish to better know and understand the role played by UV radiation at level of human skin as well as the emerging techniques used today for the best treatment of photoaging.

P. Morganti
Editor in Chief

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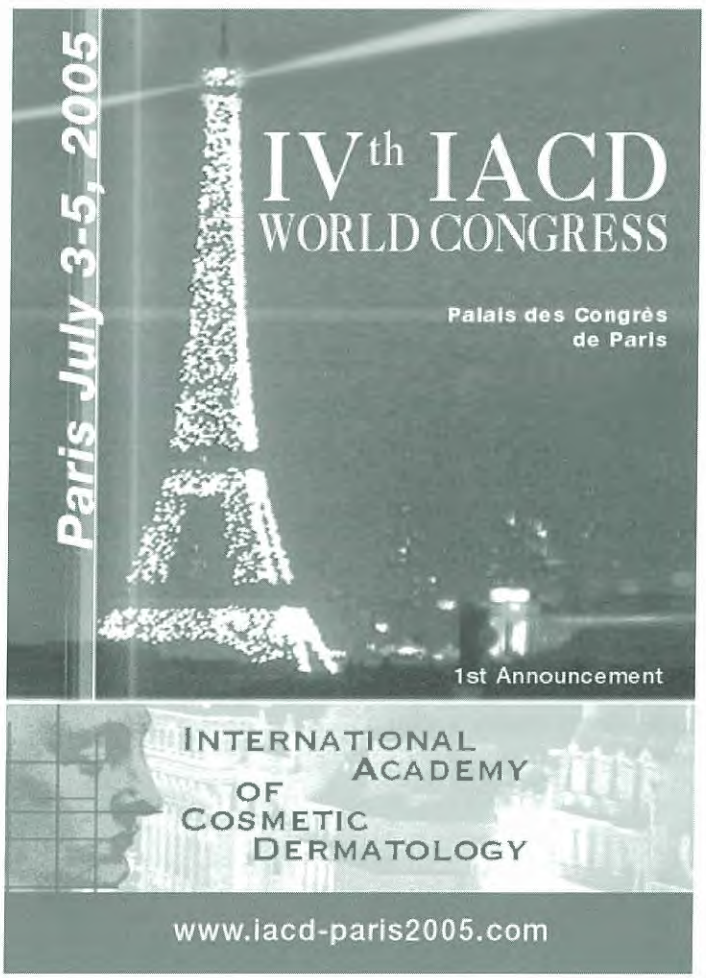

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International Society of Pharmacovigilance Annual Meeting 2004 – 6-8 October 2004, Dublin, Ireland

'Pharmacovigilance – Current and Future Challenges'

Local Organiser – Ms Niamh Arthur, Pharmacovigilance Co-ordinator
Chairperson, Scientific Committee – Dr Jürgen Beckmann
ISoP President - Prof Giampaolo Velo

Conference Topics
☆ Landscapes in Pharmacovigilance
☆ Medication Errors
☆ Risk Management Plans
☆ Future challenges
☆ Training and Education

An overlapping session with the **WHO Annual National Centres Meeting** will be held on the afternoon of the first day.

CALL FOR ABSTRACTS
Abstracts for both oral and poster presentations are invited. Closing date for submission is 15 July 2004. Abstracts should be submitted using the link on the IMB website www.imb.ie under 'Pharmacovigilance'.

For further information, please contact:

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www.imb.ie /Pharmacovigilance

The aim of the International Society of Pharmacovigilance is to provide an international forum for all those with an interest in the clinical and scientific aspects of drug safety, - and not only full-time pharmacovigilance professionals. Our Society consists of members from industry, governmental agencies, research and academic bodies.
Information about ISoP and its activities may be obtained from the website
www.isoponline.org

The VII ISCD International Congress
FIRST ANNOUNCEMENT

International Society of
Cosmetic Dermatology
Application & Research

THE INTERNATIONAL SOCIETY OF COSMETIC DERMATOLOGY
in collaboration with
ACCADEMIA DI STORIA DELL'ARTE SANITARIA

PRESENTS

The New Frontiers of Dermo-Cosmetology: Efficacy, Stability and Safety
4-6 November, 2004
Roma, Italy

The International Society of Cosmetic Dermatology (I.S.C.D.) a non profit scientific association founded in 1980, is focusing on creating a synergy between Cosmetic Chemists, Dermatologists, Biologists, Plastic Surgeons and all the Scientists involved in the study of Cosmetic Dermatology by means of diffusing and exchanging scientific information and promoting a real scientific knowledge transfer from Academia to Industry and vice versa.
The main objective of this VII International Congress

The New Frontiers of Dermo-Cosmetology: Efficacy, Stability and Safety

is to promote and enhance the efficiency of worldwide research in the field of **Cosmetic Dermatology,** giving about the latest information on the development of science and technology in the new fascinating area of wellbeing.

CALL FOR PAPERS

We have the pleasure to invite you to participate at this happening as attendee or as a speaker giving your personal contribute to its success!

→ Follows

This meeting will include 8 different Sessions:

1. The Skin Barrier in Normal and Pathological Conditions
2. Cosmetic Delivery to the Skin
3. Biological Function and Efficacy of Cosmetic Ingredients
4. Efficacy and Safety of Cosmetics: the Evaluation Methodologies
5. Thermalism and Cosmetology
6. Plastic Surgery and Medical Devices for wellbeing
7. Nutraceuticals : the Cosmetic Connection
8. The worldwide role of Medical Doctors and Beauticians in SPA

GENERAL INFORMATION

Venue: The Congress will take place at SALA LANCISI, in the Monumental and Historical S. SPIRITO HOSPITAL in Roma, Italy.

For registration, free communications and posters

send your request by E-mail at:
secretariat-congress@iscd.it

The official language of the meeting is English. Italian-English translation is planned for the scientific sessions in dependence of sponsor support.

The social program will include a reception at Parliament Hall "Del Cenacolo" and a banquet. For accompanying persons there will be excursions in outside and underground Roma and its environs. Post-Congress tours will include Napoli, Capri, and Pompei-Ercolano.

Technical Exhibition Suppliers of raw materials Products and service will find the opportunity to meet with an estimated 800 medical and chemical specialists from worldwide different countries.
It will take place within the Conference Centre.

Hotel accommodation and transport: all categories of accommodation will be offered at the more convenient price.

The official flight carrier is Alitalia that with its sky team and code-sharing partners covers the whole globe.

Weather: November is not cold in Roma. The medium temperature is o18/20 °C

FOR FURTHER INFORMATION

www.congress.iscd.it

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Philippe BERBIS
Marie BEYLOT-BARRY

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Date clef

12 novembre 2004

Date limite des pré-inscriptions et de règlement avant augmentation des droits

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