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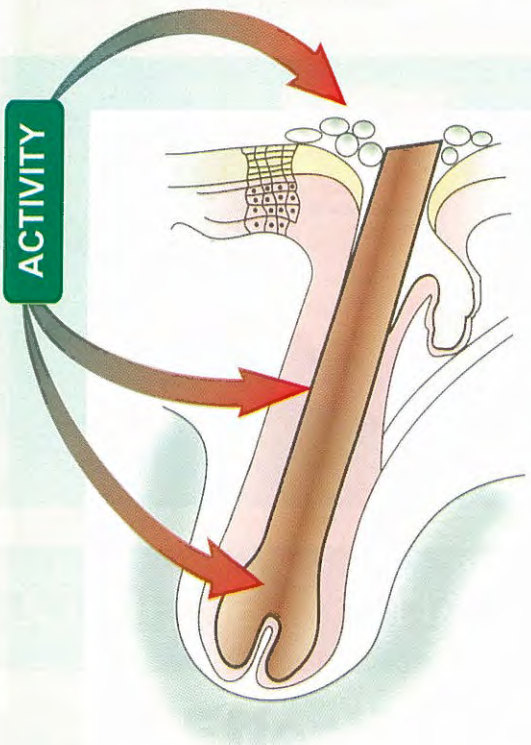

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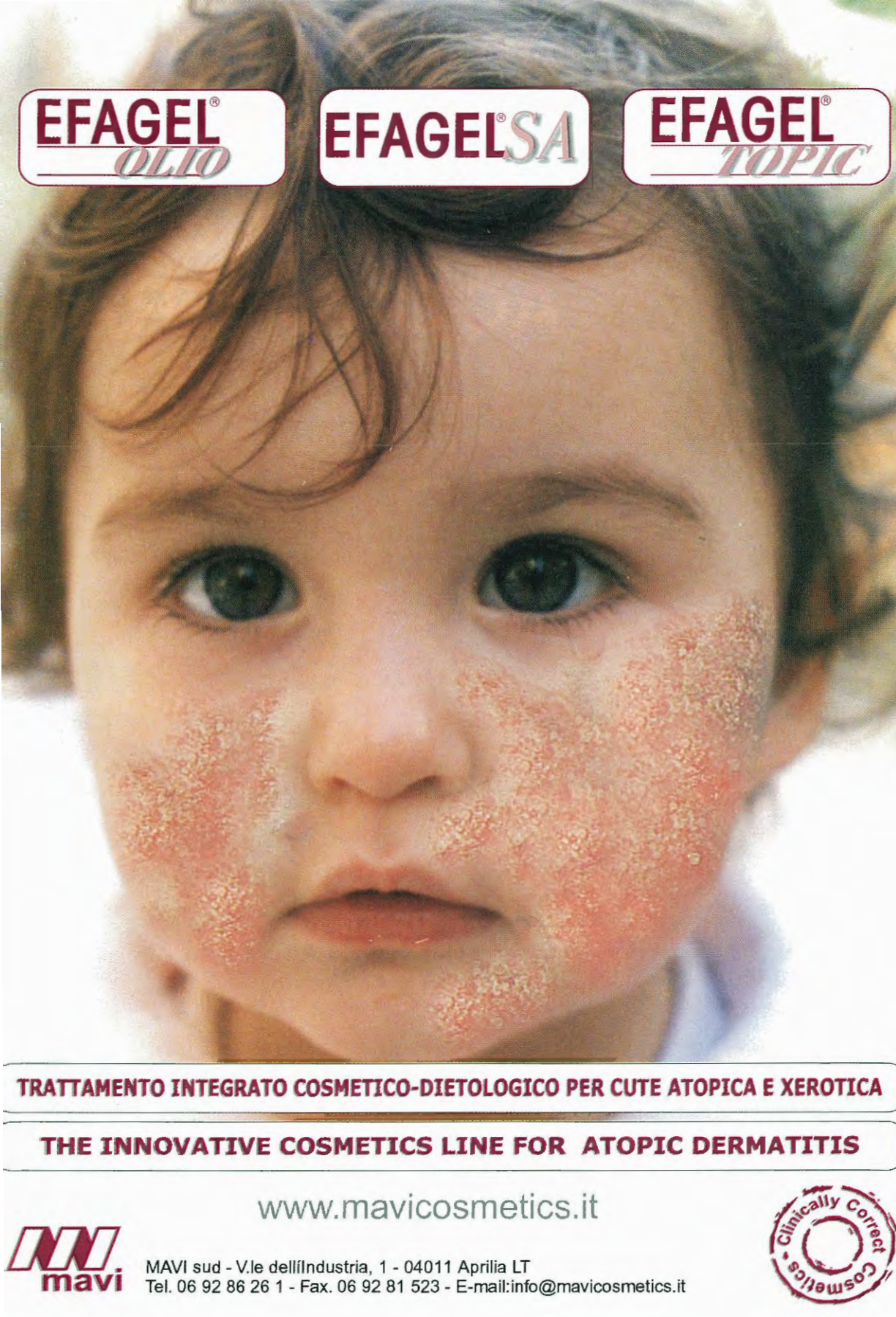

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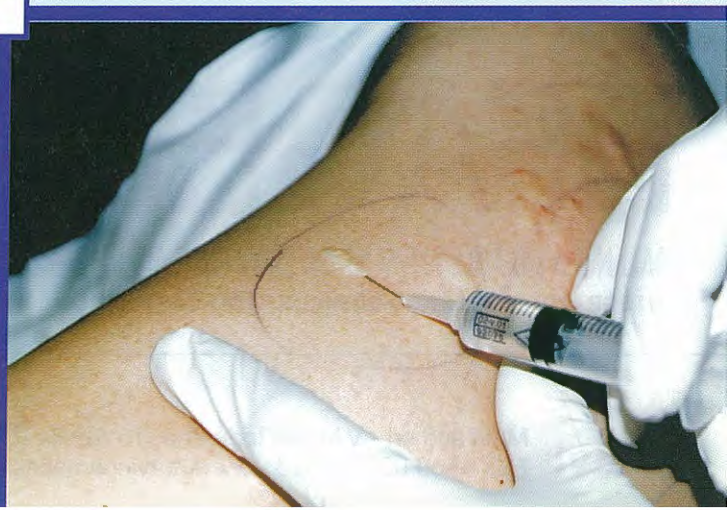

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Contents

J. Appl. Cosmetol. **22,** 125-132 (July/September 2004)

BIOREVITALIZATION AND COSMETIC SURGERY OF THE FACE: SYNERGIES OF ACTION

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Received: *March, 2004*

Key words: *Polydeoxyribonucleotide; PDRN; Biorevitalization; Aesthetic surgery;*

Summary

Polydeoxyribonucleotide (PDRN) is used in aesthetic medicine as a skin revitalyzing agent as well as to correct depressed scars and striae distansae.

The purpose of this study is to evaluate the effect of PDRN in stimulating skin biorevitalization of the face in women who underwent to a complete face-lift or a mini lifting procedure, not only to improve the cosmetic appearance but also to create more suitable conditions to better tolerate surgery. 15 female patients with an age ranging from 28 and 58 years (mean age 46) who had to undergo to a mini lifting procedure (10 patients) and a complete face-lift (5 patients) were treated in four sessions preoperatively, once a week, with intradermal administration of PDRN. Four more sessions, again on a weekly basis, were carried out starting from day 15 post-operatively. During the week before surgery and the two weeks following it, a home therapy consisting of one i.m. PDRN vial a day was offered to the patients. In all treated patients scar healing was normal, with no evidence of diastase and/or delayed scarring. Morevover the skin showed a good eutrophication and the suture stitches were removed a few days earlier than in the case of the traditional protocol (on day 10 instead of day 12). The patients' subjective evaluation was positive in all cases and extremely positive in 35% of them. The results of the study reveal a trophic and revitalizing action of PDRN on the skin which is therefore useful to improve the cosmetic appearance of the face and to create those conditions that assure a better tolerability of the stress due to surgery, and to reduce the healing time.

Riassunto

Il Polidesossiribonucleotide (PDRN) viene utilizzato in medicina estetica sia come rivitalizzante della cute che nella correzione di cicatrici depresse e di striae distensae. Scopo di questo studio è la valutazione dell'effetto del PDRN nel favorire la biorivitalizzazione della cute del volto in pazienti sottoposte ad intervento chirurgico di lifting completo o minilifting, non solo per migliorare l'aspetto estetico ma anche al fine di creare un ambiente più adatto a tollerare l'intervento chirurgico.
15 pazienti di sesso femminile di età compresa fra i 28 e 58 anni (media 46) che si sottoponevano ad un intervento di minilifting (10 pazienti) e lifting completo (5 pazienti) sono state trattate in quattro sedute pre-operatorie, una volta alla settimana, con infiltrazioni intradermiche di PDRN.
Altre quattro sedute, a cadenza settimanale, sono state eseguite successivamente all'intervento, a partire dal quindicesimo giorno postoperatorio.
Nella settimana prima dell'intervento e nelle due settimane successive, le pazienti hanno effettuato una terapia domiciliare con PDRN, una fiala intramuscolare al giorno.
In tutti i casi trattati la cicatrizzazione è stata normale, senza evidenze di diastasi e/o ritardi di cicatrizzazione. Inoltre la cute ha mostrato una buona eutrofizzazione ed i punti di sutura sono stati rimossi qualche giorno prima rispetto al protocollo tradizionale (10° giornata vs 12°).
Il giudizio soggettivo delle pazienti è stato positivo in tutti i casi, ed estremamente positivo nel 35% delle pazienti.
I risultati dello studio depongono a favore di un'azione trofica e rivitalizzante della cute da parte del PDRN, utile pertanto sia al fine di migliorare l'aspetto estetico, sia di creare un ambiente favorevole in grado di meglio sopportare le sollecitazioni dovute all'intervento chirurgico, riducendo anche il tempo di guarigione.

INTRODUCTION

Polydeoxyribonucleotide (PDRN) is the active ingredient of a preparation used in medicine as wound healing, antidystrophic and skin revitalizing agent. It consists of low molecular weight DNA fractions and it is constituted by polymers of deoxyribonucleotides whose length ranges from 50 and 2000 base pairs. PDRN therefore supplies deoxyribonucleotides, deoxyribonucleosides as well as purine-pyrimidine bases. Many studies in international literature show that nucleotides and nucleosides stimulate cell growth of several types of cells (1-7), they also promote and accelerate the synthesis of nucleic acids (8-9), and wound healing of both cutaneous and mucous tissues (10-13). These effects seem to be attributed both to the stimulation of salvage pathways, for the neosynthesis of nucleic acids with a low energy consumption (14-19), and by the activation of type A2 purinergic receptors (8, 20-22).

In various *in vitro* studies PDRN showed its trophic action on several cell types (23) and its effect on the growth of human fibroblasts in primary cultures (24-27). It also stimulates the secretion activity of collagen proteins and of other proteins of the extracellular matrix (24). Thellung (28) demonstrated that PDRN acts by activating A2 purinergic receptors. In fact he showed that by pre-treating cell cultures of fibroblasts with DMPX, an A2 receptor antagonist, the effect on both cell proliferation and metabolic activation is reduced in a statistically significant way, which is proved by a dramatic decrease of intracellular calcium release, while the A1 receptor antagonist has no effect.

The results of *in vitro* studies can reasonably explain the therapeutic effect of PDRN that was highlighted in several clinical studies, with respect to postphlebitic ulcers (33), burns (34), depressed scars (29-30), skin repair areas explanted by means of dermotomy (35-36), and corneal riepithelisation after Photorefractive Keratectomy (PRK) (37).

This study was carried out by evaluating the action of PDRN as an agent promoting the biorevitalization of the face not only to improve its cosmetic appearance, which is fundamental, but also to create more suitable conditions to better tolerate a lifting or a mini-lifting.

PATIENTS AND METHODS

From june 2002 and september 2003 (for a total of 18 months) 15 female patients with an age ranging from 28 and 58 years (mean age 46) were involved in the study using the following exclusion criteria: smokers, women suffering from autoimmune diseases or treated with systemic drugs with cutaneous trophic action. Patients presented skin phototypes II and III according to Fitzpatrick classification. The material used was Polydeoxyribonucleotide (PDRN, Placentex Integro, Mastelli), a dose of 1 vial (3 ml) was administered in each session. The protocol required the enrollment of patients with an indication for a mini lifting procedure (due to ptosis of the middle and lower third of the face and neck, total = 10 patients) and for a complete face-lift (due to ptosis of the whole face and the neck, total = 5 patients).

Four sessions were carried out pre-operatively once a week and infiltrations were stopped one week before the scheduled date of surgery. They were carried out according to these techniques: a "crescent-like" infiltration on the frontal region, a "net-like" infiltration on the chin region, and a "micropomphus-like" one on the pre and retro-auricolar anterior cervical region.

After surgery, starting from day 15 post-operatively four more sessions were carried out once a week on the same previously treated areas using the same infiltration techniques.

In the periods wheu patients were not treated with subcutaneous infiltrations, (the week before and the two weeks after surgery), a home daily treatment with one intramuscular vial of PDRN was offered to them (fig 1).

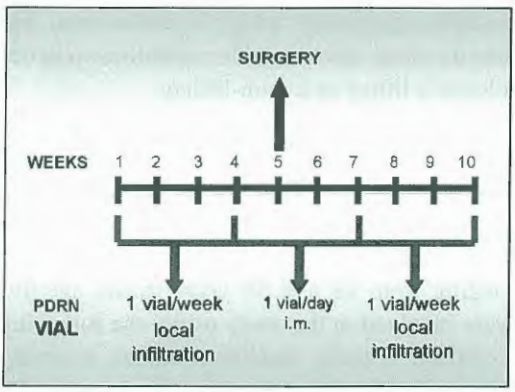

Fig. 1 Protocol of treatment. PDRN local infiltration, once a week: four sessions pre-operatively, and, 15 days after surgery, four more sessions of infiltrations. PDRN, daily intramuscular administration: in the week before and in the two weeks after surgery.

RESULTS

In this personal experience no complications occured with respect to infections and hematomas either pre or post-operatively. When undermining the tissues intra-operatively, a good elasticity of the skin tissues was observed offering better traction and anchoring of the skin flaps. All treated cases showed normal wound healing with no evidence of diastase and/or delayed scarring. Conversely, suture stitches were removed a few days earlier than in the case of the traditional protocol (day 10 vs day 12). The skin showed a good eutrophication and a post-operative satisfactory outcome due to a better traction on the skin. In this case history the scarring adjustment was good, with no clinical evidence of pathological scars especially hypertrophic ones (fig 2-3).

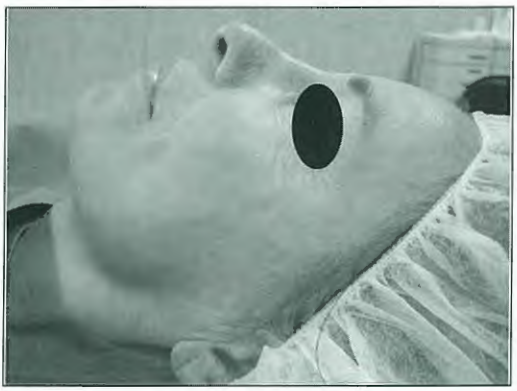

Fig. 2 Patient before treatment.

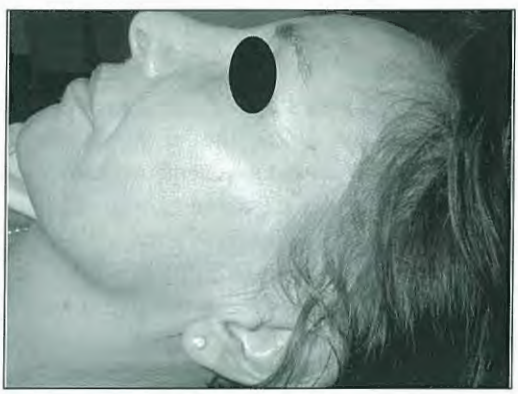

Fig. 3 Patient after treatment. The patient has been submitted to temporal lifting procedures associated to PDRN administration.

DISCUSSION

Evidence of the effect of skin biorevitalization and eutrophication was previously shown by several researchers who used infiltrations of PDRN for various applications in aesthetic medicine.

PDRN was used in a clinical trial on 20 patients with severe post-acneic scars. Intradermal administrations on the scar lesion were repeated once a week for a period of 8 weeks. The results were satisfactory in almost all patients. In 5 cases, in

particular, a flattening of the prominence of the lesion was achieved and 6 months after the end of the treatment the results had not changed (29). Rantuccio (30) treated another 20 patients presenting depressed scars with the same infiltrating method and obtained a flattening of some scars and a reduction of others, with a marked improvement of the general appearance.

As far as the treatment of skin striae is concerned, Rossi (31) treated 30 patients whose mean age was 32,8 years by administering PDRN intradermally, with the micropomphus technique along the whole length of the stria. Infiltrations were carried out every 2 weeks for a total of 7-8 sessions. An improvement was obtained in all the cases especially in the more recent striae. The one-year follow-up showed no regression of the obtained cosmetic results. Always in the treatment of striae, Follador (32) used a protocol that associated local application of 70% glycolic acid with PDRN therapy, administered by intralesional infiltrations and combined with intramuscular treatment for the 3-5 days preceeding the out-patient sessions for a total of 9-10 sessions. This treatment was administered to 14 patients. Results were good in all the cases and excellent in 6 of them.

The results obtained in this trial confirmed the effectiveness of PDRN in stimulating skin revitalization that improved both the cosmetic appearance and the quality of scarring in lifting and minilifting surgery. Results were mainly based on the positive judgement (and on the extremely positive judgement in 35% of the cases) expressed by the patients who underwent surgery, as well as on the evaluation of the surgeon who worked on a skin which was considered more trophic, elastic and more able to tolerate the stress due to surgery, thus reducing the healing time. In fact, suture stitches could be removed two days earlier than in the case of standard surgery.

The combination of local infiltration therapy with systemic administrations seems to be an important factor for the final outcome.

Integrating the results of this study with the previous clinical trials carried out by various researchers in the field of easthetic medicine, we can conclude that PDRN showed a valid and sure eutrophicating and revitalizing effect on the skin of treated patients.

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THE ANTIOXIDANT NETWORK OF SKIN AND EYE. EFFICACY OF CAROTENOIDS

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Key words: *Carotenoids; Lutein; Ascorbic acid; Lycopene; Oxidative stress; Visual activity;*

Summary

The continued exposure to solar radiation results in acute ocular disturbance and there is a tendency for eye lens transmittance to decrease as a function of increasing age.
Thanks to the high presence of oxygenated carotenoids, lutein and zeaxantbin, the macula lutea may filter tbe damaging blue light and UV, quenching the photochemically-induced reactive oxygen species (ROS).
The aim of this study was to control the activity performed by antioxidant diet supplements based on different mixture of carotenoids oxygenated and not oxygenated (enriched with vitamins C and E) in the UV-induced oxidative stress of skin and eye.
A randomized double-blind study was carried out for 8 weeks on 40 photoaged healthy volunteers aged 62-68. Oxidative stress was evaluated in blood serum by the D-ROMS test before and after oral intake of diet supplements based on carotenoids and oxycarotenoids, vitamins enriched.
Visual surveillance testing was evaluated by Perimetry, Dark Adaptometry, Photostress, CSF and VER tests.
Both caroteoinds and oxycarotenoids are able to reduce of 30/35% ($p<0.005$) the ROS content in blood serum. Moreover oxycarotenoids only seem to increase visual activity from 40 to 100% during the study period.

Riassunto

La continua esposizione alle radiazioni solari provoca acuti disturbi oculari che peggiorano col progredire dell'età allorquando diminuisce l'attività svolta dal cristallino.
Grazie all'elevata presenza dei carotenoidi ossigenati (ossicarotenoidi), quali la luteina e la zeaxantina, la macula lutea è in grado di filtrare la luce blu e gli UV dannosi riducendo la produzione di radicali liberi (ROS) indotti fotochimicamente.
Lo scopo di questo studio è stato valutare l'attività svolta da un integratore alimentare a base di differenti mix di carotenoidi, ossigenati e non ossigenati, arricchiti con vitamine C ed E, nei confronti dello stress ossidativo causato dagli UV sulla pelle e sugli occhi.
Uno studio randomizzato in doppio cieco è stato condotto per 8 settimane su 40 volontari sani di età compresa tra i 62 e i 68 anni affetti da chiari segni di fotoinvecchiamento cutaneo.
Lo stress ossidativo presente nel siero del sangue è stato valutato con il D-ROMS test prima e dopo l'assunzione degli integratori alimentari a base di carotenoidi e ossicarotenoidi, arricchiti con vitamine.
La capacità visiva è stata valutata con i test Perimetry, Dark Adaptometry, Fotostress, CSF e VER.
Secondo i risultati ottenuti sia i carotenodi che gli ossicarotenoidi sono in grado di ridurre del 30/35% ($p<0.005$) il contenuto di ROS nel siero del sangue.
In particolare durante il periodo di studio i carotenoidi ossigenati sembrano aumentare la capacità visiva dal 40 al 100%.

INTRODUCTION

For the eye, to fulfil its main function, the vision radiation must penetrate the anterior ocular tissues and be transmitted to the retina for absorption (1).

But the continued exposure to solar radiation represents a hazard to the integrity of both skin and ocular tissue, resulting in acute ocular disturbance together with photo-aging and skin cancer. As a matter of fact, there is ample documentation of solar retinopathy and development of cataracts (2,3), and there are also many evidences of chronic solar dermatosis, photodermatitis and photocarcinogenesis (4).

Moreover the optical tissues of the eye offer filtration effects, important in restricting exposure of the inner tissues to energy.

On the other, there is a tendency for lens transmittance of the eyes to decrease as a function of increasing age (5,6).

Finally it become apparent that oxygen free radicals and singlet oxygen in excessive amounts may play a key role in skin photo-toxicity and in the cataractogenic process, by initiating lipid peroxidation, protein cross-linking and enzyme inactivation (7,8).

Macula lutea, in the centre of the retina, seems to be the light-guardian of our eye (9,10).

Thanks to the high presence of oxygenated carotenoids, such as lutein, the macula may filter the damaging blue light, quenching the photochemically induced reactive oxygen species (ROS) (11,12).

For all these reasons antioxidant supplementation with dietary carotenoids seems to have a possible role in protecting, preserving and treating age-related oxidative stress both in human eye and skin (13,14)

AIM

The aim of this study was to control the activity performed by antioxidant diet supplements based on different mixture of carotenoids oxygenated and not oxygenated (enriched with vitamins C and E) in the UV-induced oxidative stress of skin and eye.

MATERIAL AND METHODS

Product A: lutein (15 mg), ascorbic acid (60 mg), tocopherol (30 mg) in gelatin capsules

Product B: carotenoids (13 mg), lycopene (2 mg), tocopherol (30 mg), ascorbic acid (60 mg) in gelatin capsules

Product C: starch in gelatin capsules

Test Procedure

In vivo

40 healthy volunteers, (25 women and 15 men) age range 62-68, all affected by skin photoageing were selected for the study and randomly divided into 3 groups.

To each group of 15 people was given sufficient capsules of product A or B for 2 months of treatment. 10 untreated volunteers, considered as control, received only starch-capsules (product C).

Neither the operator nor the subjects were able to identify the product, and each subject took 2 capsules per day for two months.

10 weeks before starting the study, the subjects suspended all drugs or diet supplement taken by oral route.

The subjects, subdivided in three groups, received in a randomized way, the diet supplement A, B or C to be taken twice a day (morning and evening) for 2 months:

I group 2 caps a day product A (oxygenated

carotenoids, lutein)
II group 2 caps a day product B (non- oxygenated carotenoids)
III group 2 caps a day product C (starch)

Test Evaluation

Blood was taken weekly in the morning between 8 and 11 for all the study period in a dermatological department, meanwhile the visual surveillance tests were done by specialized ophthalmologists.

Oxidative stress measurement

Being free radicals extremely reactive and short lived, fast flow techniques, such as spin trapping, are generally used: a diamagnetic organ molecule, called the spin trap, reacts with the radical to be detected, producing a secondary but more stable radical called spin adduct, which is more readily detectable by EPR (15).
Recently a simpler method was developed, the D-Roms test (16) already used in our lab (17,18) and in others (19,20). This method is based on a property of transition metals. In the presence of peroxides, transition's metal catalyze the formation of free radicals, which are then trapped by an alkylamine. The alkylamine reacts, forming a coloured radical detectable at 505 nm through a kinetic reaction, which is linear up to 500 Carratelli Units (U.Carr). One U.Carr is equal to a hydrogen peroxide concentration of 0,08% mg.
In our study, free radicals, (expressed in U.Carr), were photo-metrically evaluated on the blood serum of all the subjects by a spectrophotometer, according to Carratelli et al. (19).
The reagents used were the chromogens R1 (an alkylamine) and R2 (a pH 4,8 buffer).
A volume of 10µl free serum, added to 1mL R2 and soon as after to 10µl R1, was gently mixed and incubated in a cuvette for 1 min. at 37°C. The resulting deep red colouring was photometrically detected at a wavelength of 505 nm. In a short controlled time, the colour changes becoming red again after 1 min. The observed difference, ΔA is multiplied by K factor 9000. Thus
1 U. CARR = $\Delta A \times K$
Normally, the level of free radicals in the blood is in the range of 250-300 U. Carr (16). Carratelli has suggested ranges (in U.Carr values) that correspond to levels of oxidative stress (Table 1).

Table I

Carratelli's baseline U.Carr Values, indicating relative levels of Oxidative stress

U.Carr value	Oxidative stress
300 – 320	borderline oxidative stress
320 – 340	slight oxidative stress
340 – 400	oxidative stress
400 – 500	heavy oxidative stress
above 500	very heavy oxidative stress

Carratelli's methodology has been controlled elsewhere and validated by EPR (16,19,20).

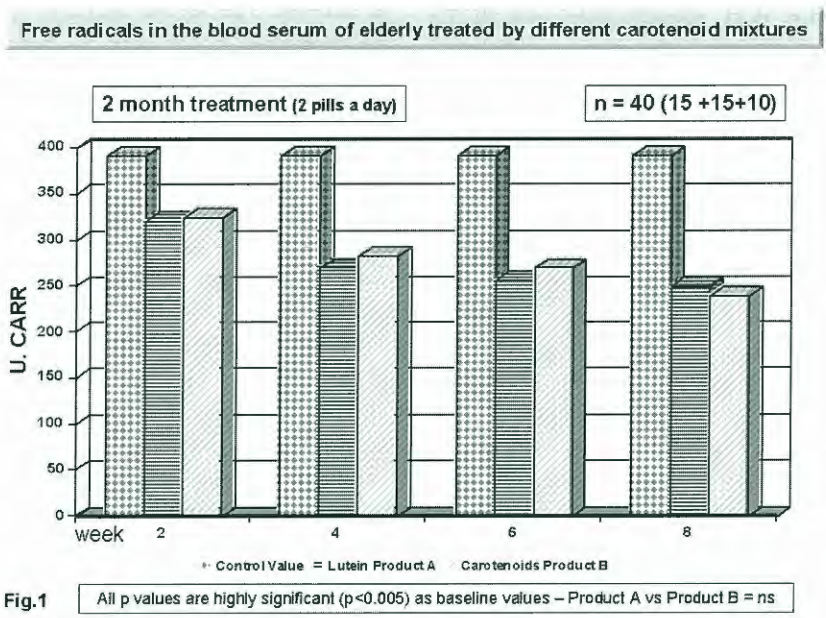

Fig.1

The obtained medium results are reported in Fig.1

Visual surveillance testing

By different visual surveillance tests and according with our reported results (14) we wished to control the visual and skin activity supported by our diet supplements.
At this purpose, we used five different non-invasive well-known techniques:

1. The Perimetry (21), as useful for documenting general changes in the extent and relative sensitivity of the visual field.
2. The Photostress test (22): by the bright light used this method creates an after image that temporarily reduces the visual activity.
3. The Dark adaptometry (23): useful to control the development and progression of diseases causing night blindness.
4. The CSF (control sensitivity function) (24): useful to measure the central visual resolution capability.
5. The VER (visually evoked response) (25) as useful electroencephalograph recording for objectively determining the effects of macular disease.

The obtained results are reported on Fig. 2 and 3.

Statistical analysis

The statistical analysis was conducted using parametric (ANOVA variance and analysis) and non parametric (CH, square) tests, and all the data reported represent the mean ± SD of 3 determinations of each blood serum sample.

RESULTS AND COMMENT

As we had formerly demonstrated with other studies (14, 17,18), all carotenoids seem to have a positive influence towards the ROS present in the blood serum and to be positively and strongly influenced from the temporary presence of other antioxidant compounds, such as vitamins C and E, as it is clearly shown in figure 1.
In fact the assumption of the mixtures of carotenoids or oxycarotenoids, such as lutein, both enriched with vitamins C and E, is able to reduce in the same way (about 30/35%; $p< 0.005$) the verified ROS content in the serum blood of the health volunteers.
Moreover all the carotenoids seem to regularly decrease the ROS content present in the blood serum after 2 months of dietary intake.
What is clearly evident is their different metabolic activity. The regular increase of carotenoids are recovered in the skin 24 hours after their ingestion (26), oxycarotenoids are recovered in blood serum and in the eye's mucous just after half an hour as demonstrated elsewhere (27).
On other controlled blood parameters, it was in fact verified about a 40% increase of plasma lutein soon after the ingestion and after a two-week of treatment and 100% at the week 8 with product A only (Fig.4).
Moreover, according with other studies (28-30), it was shown a clear relationship between the global visual function and the lutein supplement action from all the subject tested (Fig.2).
In fact, it was also verified a continuous increase of macular pigment density, a better general visual acuity, visual resolution capability, together with a more rapid dark adaptability from about 40 to 100% ($p<0.005$) during the study period. (Fig. 2 and 3).

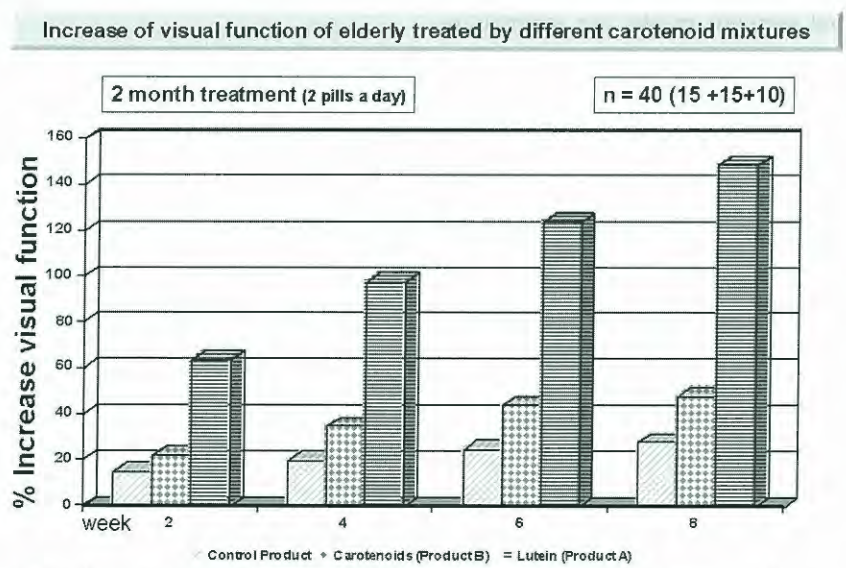

Fig.2 All p values are highly significant ($p<0.005$) as baseline values and as to groups

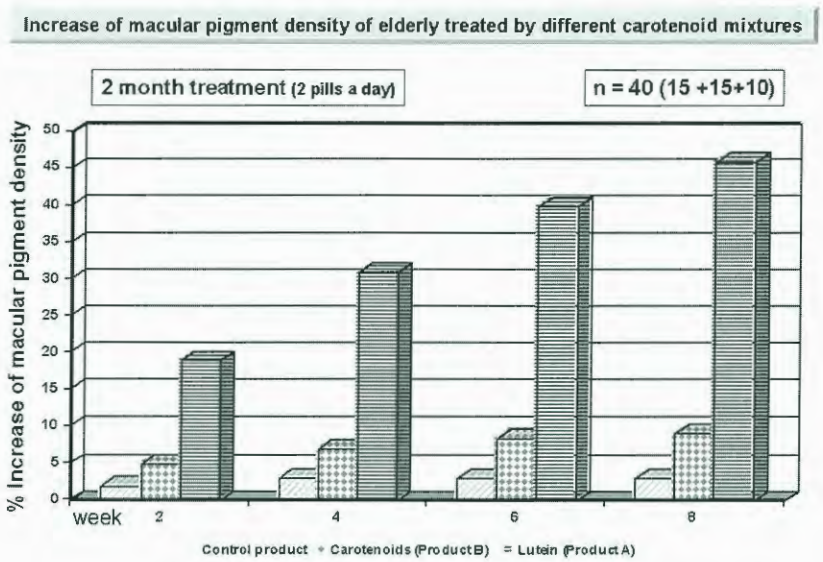

Fig.3 All p values are highly significant ($p<0.005$) as baseline values and as to groups

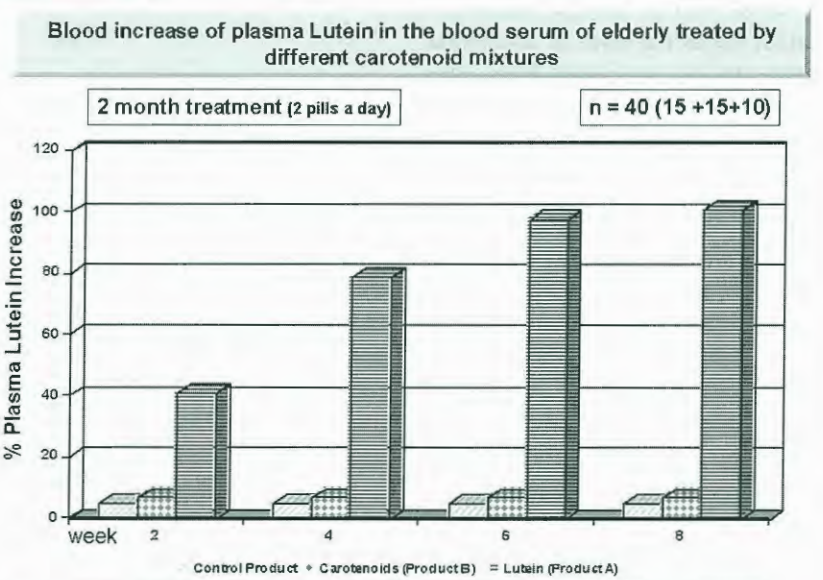

Fig.4 All p values are highly significant ($p<0.005$) as baseline values and as to groups

What seems to be more interesting (Fig.3) is the macular pigment density verified by the heterochromatic flicker photometry (31) the contemporary high increase of lutein recovered in both the eyes.

CONCLUSION

How clearly reported by this study, carotenoids seem to be an interesting dietary supplementation useful to decrease the degeneration of both the skin and the eye mucous provided especially by the increase of ROS in the environment. Is to be underlined also the difference activity verified between the normal carotenoids mix (product B) and oxygenated carotenoids such as lutein (product A).

The first (product B), accumulating at level of derma should be active against the excessive ROS increased by the UV radiations and dangerous for the skin cells.

Meanwhile the second (product A) is surely more active to protect the eye from the aggressive blue and UV-light.

As a matter of fact lutein, recoverable in the plasma blood, seems to deposit preferentially at level of the yellow spot of the eye meanwhile other carotenoids deposit at level of skin strata. These first data are also supported from other new experimental results recently obtained (27).

From all the obtained results we still have to study in depth the amount-efficacy ratio of carotenoids taken as diet supplement and we have to point out the increase of their efficacy when they are associated with other antioxidant components (vit. A, E and C)

In fact, although is quite evident the increase of activity due to the presence of other compounds with an antioxidant activity, we haven't still make clear the real dose-efficacy, above all of lutein. We've obtained similar results using both 2,5 mg (14) and 15 mg of lutein (this study), even if we've noticed a quickest efficacy with the 15 mg amount.

Therefore, more research is needed to better define the dose-efficacy of lutein and the carotenoids diet intake necessary to counteract the negative effect of pollution, UV rays and ageing.

ACKNOWLEDGEMENTS

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COSMETIC APPLICATION OF MICROFINE TITANIUM DIOXIDE

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Key words: *Titanium dioxide; Pigment; UV filter; Semicoductor; Sensitizer of photoreaction; Penetration; Stratum corneum.*

Summary

The properties of titanium dioxide account for a broad use of this substance as a white pigment in numerous branches of industry, including cosmetic industry, as well as UV filter and semiconductor sensitizing photoreaction. Interaction of the TiO_2 particle and electromagnetic radiation are discussed. During the 1980-s and 1990-s numerous papers concerning semiconductor photocatalysis have appeared. They presented titanium dioxide as an active UVA and UVB absorber in result of which its surface became the source of free radicals – reactive oxygen species (ROS). The examples of these results are reported. Determination whether or not titanium dioxide can penetrate through *stratum corneum* during normal application of cosmetic products containing this compound is very important because of a risk of side-effects. Some papers of TiO_2 penetration in *stratum corneum* are reported.

Riassunto

Le proprietà del biossido di titanio giustificano l'uso diffuso di questa sostanza come pigmento bianco in numerosi settori dell'industria, incluso quello cosmetico, così anche come filtro UV e semiconduttore sensibilizzante delle fotoreazioni.

L'interazione tra le particelle di biossido di titanio e le radiazioni elettromagnetiche sono state in discussione.

Durante gli anni 80 e 90 sono apparse diverse pubblicazioni riguardanti semiconduttori fotocatalitici. Il biossido di titanio viene qui presentato come in grado di assorbire attivamente le radiazioni UVA e UVB, in questo modo la sua superficie diventa sorgente di radicali liberi - specie ossigeno

reattive (ROS).
Esempi di questi risultati sono stati riportati nel lavoro in oggetto.
La determinazione del fatto che il biossido di titanio sia in grado o meno di penetrare attraverso lo strato corneo durante l'applicazione di prodotti cosmetici che lo contengono, è molto importante per via dell'eventuale rischio di effetti collaterali.
Sono stati riportati alcuni lavori che riguardano la penetrazione del biossido di titanio attraverso lo strato corneo.

INTRODUCTION

Titanium oxides, due to their variety of structure, properties and ultimate functionality, appear as fascinating non-organic solid compounds.
Titanium Dioxide TiO_2 is very stable, insoluble in water and non-volatile, chemically and biologically passive. It appears in three different crystalline forms: rutile, anatase and brookite.[1]
The first two, rutile and anatase are the most interesting. Their crystalline structures could be described as chains of TiO_6 octahedra, in which each Ti^{4+} ion is surrounded by six O^{2-} ions. Both structures differ from each other by the level of similarity to a regular octahedron and an arrangement of octahedrons in chains. In rutile lattice structure each octahedron is in contact with ten neighbour ones sharing 2 edges and 8 corners, in the case of anatase – each octahedron is in contact with eight neighbour ones sharing 4 edges and 4 corners.[2] As a result of those differences, distances between atoms, electron structure and physical properties of those substances differ as well[3]. Both oxides have a very high reflectivity of light, they can absorb UV radiation and show surface activity in relation to numerous organic and non-organic compounds. They can be prepared in the form of particles of diameter between several and several hundred nm, colloidal systems and thin layer films. The properties mentioned above account for a broad use of titanium dioxide as a white pigment in numerous branches of industry, including pharmaceutical, cosmetic and food industry, as well as UV filter and semiconductor sensitizing photoreaction. Such variety of applications of one compound is possible because an interaction between that substance and electromagnetic radiation as well as results of that interaction depend on radiation wavelength, size and shape of particles and a characteristic of their surface.

INTERACTION OF PARTICLES AND ELECTROMAGNETIC RADIATION

Electromagnetic radiation, i.e. transport of energy in space includes waves between 10^{-14} m and several thousand km in length. The most interesting for us, ultraviolet radiation is associated with wavelengths between 280 – 400 nm and a visible light's range between 400 – 760 nm. As indicated in Fig. 1, electromagnetic radiation can interact with the matter in various ways. It can alter a direction by deflection or scattering on a surface of the matter particles; it can be absorbed, transmitted and refracted while passing from one medium into another.[4]

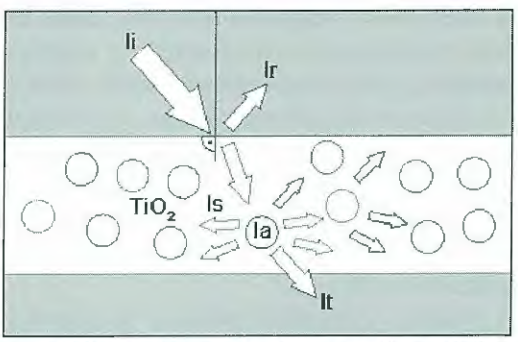

Fig. 1 Attenuation of electromagnetic radiation by titanium dioxide. Ii – incident radiation, Ir – specular reflectance from surface, Is – radiation scattered by the particle, Ia – radiation absorbed by the particle, It – radiation transmitted through the layer of TiO_2.

The scattering of radiation by homogenous particles has been described in Rayleigh's theory and Mie's theory. The conclusion of Rayleigh's theory is that for matter particles that are very small in comparison to the wavelength of the falling radiation (10-20 times smaller than the wavelength) the scattering intensity is inversely proportional to the power four of the wave-

length.

The dependence concerning homogenous matter particles of any size can be derived from Mie's theory. Assuming that the thickness of the layer showed in Fig.1 equals ***l***, and the concentration of spherical particles in a suspension equals **c**, then the intensity of the radiation that falls on that layer and the transmitted one expresses the following dependence:

$$\log I_i/I_r = qcl$$

In this reasoning the intensity of specularly reflected radiation at the surface has been ignored considered as very low. Symbol ***q*** designates the extinction coefficient, which is the sum of scattering coefficient ***qs*** and absorption coefficient ***qa***.

$$q = qs + qa$$

The coefficients can be calculated on the basis of Mie's theory where the following values are taken into account: a wavelength of a falling radiation, a size of scattering particles, refractive indices of the substance and its environment. The extinction coefficient of particles consists of two parts: a real and an imaginary one. The latter one is responsible for absorption. Both parts of extinction coefficient change along with radiation wavelength.[4,6]

A chemical compound molecule in a ground state has its valence electrons at HOMO orbital (highest occupied molecular orbital). After absorbing an energy quantum equal to the difference of energetic levels between HOMO and LUMO (lowest unoccupied molecular orbital) orbitals, an electron passes to LUMO orbital and the particle transforms into an excited state.

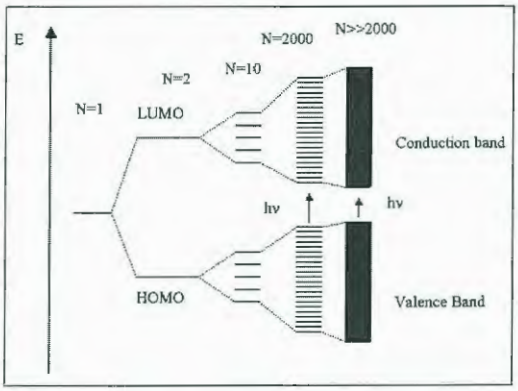

Fig. 2 Change in the electronic structure of a semiconductor compound as the number N of monomeric units increases: N=1 - atomic orbitals, N=2 - molecule, N=10 - cluster, N=2000 - Q-size particle, N>>2000 - semiconductor.

Fig. 2 illustrates a scheme model of energetic differences between HOMO and LUMO orbitals for semiconductors as number N of monomeric units in the particle increases from unity to more than 2000 units.[7]

For many compounds, an increase of number N in a particle means a decrease of energy necessary to photoexcite the particle. For rutile and anatase particles the energy difference ($h\nu = E_{bg}$) between HOMO and LUMO orbitals amounts to 3.0 eV and 3.2 eV respectively, which is in accordance with UV range of wavelength. It means that titanium dioxide has an ability to absorb UV radiation and transform into the excited state. Free electrons e^- and gaps h^+ appear then in a semiconductor particle.[8]

TITANIUM DIOXIDE AS A COSMETIC RAW MATERIAL

White pigment

According to definition, pigments are solid molecules insoluble neither in water nor organic solvents; they reflect and scatter electromagne-

tic radiation within a range of UV spectrum and visible light spectrum. Titanium dioxide, the white pigment of exceptionally high refractive index (2.7 – 2.5), has been used in cosmetics industry as a component of colour cosmetics for decades. The average diameter of particles of those pigments amounts to 220 – 250 nm and more. They absorb and scatter UV and visible radiation in such a way that total effect of attenuation of radiation is similar within the whole range of the examined spectrum (Fig.3).[4]

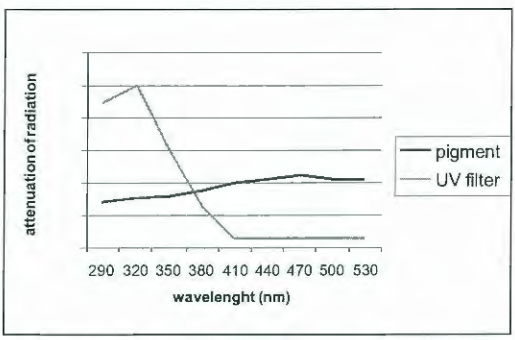

Fig. 3 The spectra of microfine TiO_2 and pigmentary TiO_2 (schematic comparison).

UV radiation filter

Microfine titanium dioxide was introduced into the market at the beginning of the 1990-s. Microfine term refers to pigments whose particle diameters are between 20 – 100 nm. The pigment particles that are much smaller than visible radiation wavelengths, become practically transparent within visible range. On the other hand they attenuate UV radiation in a much more effective way. On the basis of Mie's theory the extinction coefficient q can be calculated as a function of a wavelengtb and an average size of particles. The results of such approximate calculations for molecules of different diameters and for two chosen wavelengths are shown in Table I.

The data show tbat particles of microfine titanium dioxide attenuate UV radiation due to absorbance and scattering. For the wavelength at 310 nm it can be clearly noticed that the smaller particle's diameter, the bigger participation of absorption coefficient. A very small particles, i.e. 20nm of diameter and less, should behave according to Rayleigh's theory and scatter the shortest range of falling radiation in the most effective way.

Table I

The attenuation of radiation due to absorbance and scattering in the UVA and UVB regions for different particle size of titanium dioxide.[4]

Average particle size	310 nm (UVB)		360 nm(UVA)	
nm	% qs	% qa	% qs	% qa
20	7	93	50	50
50	37	63	83	17
100	48	52	86	14
220	54	46	70	30

Pigmentary titanium dioxide is not suitable for UV protection though (from a point of view of cosmetics users) as it effectively interacts with a visible light. Formulations containing these particles are white and non-transparent.

TITANIUM DIOXIDE AS A SEMICONDUCTOR - SENSITIZER OF PHOTOREACTION

Destruction of chemical compounds and biological material

Absorption of electromagnetic radiation photon whose energy is equal or higher than $h\nu = E_{bg}$ (Fig.2) results in the promotion of an electron e from the valence band to the conduction band. At the same time in the valence band there is created the positively charged gap $h+$.[2] Recombination of e^-h^+ pair can take place on the particle surface or inside it. The energy snrplus is emitted then in the form of heat and the excited molecule resumes its ground state. The other sequence of events is also viable: the electron and positively charged gap independently face the particle surface, where the electron reduces the electron acceptor molecule A *to* A^-, *a* h^+ oxidizes the electron donor molecule D *to* D^+. (Fig.4) [2]

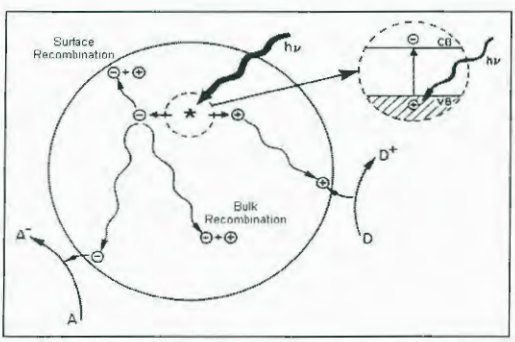

Fig. 4 *Processes in the semiconductor particle.*

Photocatalytic reactions occurring on titanium dioxide particles as the Fig. 4 indicates, has been broadly used in practice for removing organic and non-organic pollution from water and air and destruction of biological material. [8]
Typical particle size of catalyst is 30 nm. The titanium dioxide activity can be modified by changing properties of its surface. The increase of catalysis effectiveness is usually achieved by deposition of other semiconductors, noble metals, colour organic compounds on titanium dioxide particles.[2] In order to inhibit undesirable activity, the surface is covered with aluminium oxide, zirconium oxide, silicon oxide or other compounds.

EXAMPLES OF PROCESSES AND REACTIONS INDUCED BY UV RADIATION WITH A PRESENCE OF TITANIUM DIOXIDE USED IN COSMETICS

At the end of the 1970-s titanium dioxide started being considered as an effective and safe physical sunscreen as it was thought to be able to reflect and scatter rather than absorb visible and UV radiation.[9] During the 1980-s and 1990-s numerous papers concerning semiconductor photocatalysis have appeared. They presented titanium dioxide as an active UVA and UVB absorber in result of which its surface became the source of free radicals – reactive oxygen species (ROS). Therefore interest has been raised concerning the safety of titanium dioxide applications in cosmetics.

Bio-molecules, cell and tissue cultures in vitro

There is no doubt that amino acids, purine and pyrimidine bases, DNA and RNA particles, enzymes placed in suspension containing titanium dioxide and exposed to UV radiation undergo degradation as most of organic compounds in such conditions do.[10] In studies concerning genetic material damages, water solutions of citosine, thymine, uracil as well as ade-

nine, guanine and titanium dioxide P25 (80% anatase, 20% rutile; average particle size 20 – 40 nm) saturated with oxygen have been exposed to a mercuric lamp's radiation (over 290 nm UVA + UVB). Similarly DNA and RNA particles have been irradiated with radiation 310 – 400 nm in water suspension with and without titanium dioxide. Researchers observed that decomposition of examined nucleic acids has been occurring 500 – 800 times more efficiently with titanium dioxide.[11] The authors of a paper concerning inactivation of horse radish peroxidase wrote: "clearly the presence of TiO_2 does not protect the enzymes from damage, but rather, it helps inactivation to occur much more efficiently".[12]

Examination of the influence of irradiated titanium dioxide on animal cell and tissue cultures leads to less univocal conclusions. The influence of various types of titanium dioxide (anatase 21 nm, anatase 255 nm, rutile 255 nm, rutile 42 nm) on cell cultures has been examined *in vivo*. Samples have been exposed to radiation similar to the natural sunlight. It has been observed that titanium dioxide sensitised by radiation has damaged DNA and caused chromosome structural aberrations in mammalian cell cultures. Genotoxic activity was dependent on radiation intensity, concentration and type of dioxide – the most active was anatase 21 nm, the least rutile 41 nm; anatase 255 nm was active also without radiation.[13] In the other paper the authors have not observed a negative influence of titanium dioxide on genetic material of normal and cancer human cells, but the conditions of the examination were different (TiO_2 microfine anatase: UVA 360 nm). The authors showed that the same dioxide protects cells against the effects of UVC 254 nm radiation.[14] The differences in titanium dioxide activity are associated with a crystalline form and particle size. It has been observed that anatase exposed to radiation of wavelength 370nm usually generated more hydroxyl radicals than rutile and amorphous form; for anatase the most active was the form in which crystal size was around 30 nm, for rutile around 90 nm.[15]

It should be stressed that all quoted studies have used titanium dioxide with uncovered surface.

METHODS OF COMPARISON OF ACTIVITY OF DIFFERENT OXIDES

Titanium dioxide particles can be covered with zirconium oxide, aluminium oxide, silicon oxide and many organic compounds. Those additives influence surface properties of titanium dioxide and change its photocatalytic activity.

There are not many studies that compare photocatalytic activity of modified surface dioxides in a systematic way. Comparison of different materials' activity is usually based on examination of oxygenation reactions of model systems or indication of free radicals concentration generated by radiation influence.

The example of the first approach to this issue can be oxygenation of acetaldehyde to acetic acid with a presence of several types of photocatalysts and UV radiation of wavelength 360 nm.[16] The compounds used in the studies are listed in Table II:

Table II
Sample of titanium dioxide

Sample	Crystalline form	Average size	Type of raw material	Non-organic covering	Organic covering
A	Anastase 70% rutile 30%	21 nm	Microfine	None	None
B	Anastase	410 nm	Pigment	None	Polyhetylene or methicone or dimethicone or STPM*
C	Rutile	30-50 nm	Microfine	Al_2O_3	Lecithin or dimethicone
D	Rutile	180-800 nm	Pigment	None	Poliol

*combination of esters of glycerine, octyldodecyl myristate and dimethicone

It appeared that in this reaction the most active catalyst was pigment B with non-covered surface, then oxide A. Covering pigment B with polyethylene decreased the activity by four times and with dimethicone or combination of organic compounds the activity almost disappeared. Similar behaviour has been observed with oxide C – in this case there was no non-covered sample and fairly low activity of the sample covered with Al_2O_3 has been compared with several times lower activity of the same type of oxide covered with lecithin and dimethicone. Other results have been obtained in tests of oxygenation of corn oil and squalen in water-ethanol suspension. The samples have been irradiated with a lamp imitating the sunlight. It has appeared that under an experimental condition the double bonds were protected against oxygenation by titanium dioxide covered by aluminium oxide and silicon dioxide or aluminium oxide and glycerine. The samples covered with aluminium hydroxide and stearic acid, dimethicone, aluminium oxide and stearic acid appeared to be oxygenation promotors, sometimes more effective ones than dioxide sample with non-modified surface.[17]

Photoactivity of titanium dioxide samples can be compared by indication of, for instance, concentration of singlet oxygen [18] or hydroxyl radical by a method of spectroscopy.[15] It has been observed that in the first case titanium dioxide covered with methylhydrogen polysiloxane and irradiated with a xenon lamp was not photoactive in ethanol suspension. However the authors at the end of their article wrote sentence that sounded like a warning: "Because TiO_2 has been used as a potent sunscreening agent, biologic significance of the photodynamic properties of this compound to generate singlet oxygen and super oxide anion should be taken into account for preventing oxidative damage of the skin."[18]

PENETRATION OF TITANIUM DIOXIDE MOLECULES THROUGH STRATUM CORNEUM

Determination whether or not titanium dioxide can penetrate through *stratum corneum* during normal application of cosmetic products contai-

ning this compound is very important because of a risk of side-effects.[19] The studies examining this subject have been published since the mid-1990s. Penetration of microfine titanium dioxide (average molecule size 20 – 60 nm) suspended in water, polyethylene glycol and castor oil through a rabbit skin has been examined and some titanium dioxide ability to pass percuta neously particularly from oily suspension has been observed.[20] Several papers concerning penetration of dioxide through human epidermis *in vivo* and *in vitro* have been published.[21,22,23] Titanium dioxide penetration has been studied by a method of tape striping. Atomic absorption spectrometry (AAS) and transmission electron microscopy (TEM) have been used to analyse the obtained samples. The presence of micropigment molecules has been observed in the succeeding 10 – 12 layers of *stratum corneum*. It has been also observed that the form of examined compound had a significant influence on penetration effect: the compound from oily suspension penetrated deeper than from a water suspension; the greatest effect could be obtained by liposomes application.[22,23] Possible photocatalytic activity of titanium dioxide particles within *stratum corneum* raises understandable suspicions that only partially can be dispelled by the results of the studies on durability of covering TiO_2 with aluminium oxide. (Aluminium oxide appeared to be permanently bound to the surface of examined TiO_2 samples and a ratio between aluminium and titanium has not been changing either in formulation preparing process or in particles that penetrated into *stratum corneum* of epidermis.)[24]

CONCLUSION

Titanium dioxide, depending on particle size, can scatter and reflect visible light and/or UV radiation.

The particles of TiO_2 smaller than 100 nm are practically transparent for a visible light, and because of their ability to scatter radiation of shorter wave-length they have been broadly applied as UV filters. However the initial convictions that titanium dioxide is chemically and biologically passive and that it does not penetrate through the epidermis in topical applications are not entirely compliant with some experimental data published during the last decade.

Titanium dioxide absorbs UV radiation and heat emission is not always the only effect of this absorption; frequently as an active semiconductor it initiates occurring free radicals (ROS - reactive oxygen species predominantly), that can be harmful for both components of cosmetics and the skin the preparation is applied on.

Publications concerning photoactivity of titanium dioxide particles with modified surface sometimes show contradictory data regarding effectiveness of different covering substances. The reason of this can be that the experimental conditions of particular studies cannot be compared to each other straight forwardly or the authors did not include all possible factors influencing the activity of titanium dioxide as a photocatalyst in their conclusions. The number of reports concerning penetration of small titanium dioxide particles into *stratum corneum* of epidermis is also increasing.

The problems that microfine titanium dioxide creates for chemists, technologists and physiologist are sure to be broadly studied in the future.

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ITCH. Basic Mechanisms and Therapy

By Gil Yosipovitch, Malcom Greaves,Francis McGlone and Alan B. Fleischer
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Itching may be a cardinal symptom of general medical significance that substantially impairs the quality of life.

It is predominant symptom of inflammatory skin disease and can best be defined indirectly as a sensation, which leads to a desire to scratch. Moreover it is also critical feature of many dermatological disorders such as atopic eczema, dermatitis herpetiformis, and often psoriasis.

On the other hand, severe itching can occur as a consequence of more dryness of skin.

This book, divided in six parts and 35 chapters, presenting a concise discussion of the basic aspects of itch, various diseases in which itch constitutes a major problem, and methods employed in its diagnosis and management, represents surely an interesting source of information for both the medical and research community.

Part I, with its first introductory chapter, contains a proposed clinical classification of itch, based on an improved understanding of its neurophysiology. Thus this first chapter provides four different definitions of itch, such as neuropathic itch, due to dryness or damage, pruritoceptine itch due to skin inflammation as a consequence of pathology located at any point along the afferent path way; and neurogenic itch, originating centrally without psychological abnormalities.

However itch is unpleasant sensation that can be reduced by the pain induced by scratching and therefore it is intimately linked to the desire to scratch.

Beyond the direct interaction of pain and itch, a remarkable similarity of central sensitization phenomena exists for the two perceptions. Although the responses in itch units reflect the pruritic potency of pruritic mediators, such as histamine-positive mechano – insensitive C-nosiceptors, the strong activation of these units by capsaicin and bradykinin seems to contradict this specific role. These substances are, in fact, mainly algogenic and not pruritogenic.

At this purpose our latest understanding of the interaction of pain and pruritus has led to new ideas about central mechanisms of the itch sensation.

Thus the development of non invasive techniques such as a functional magnetic resonance imaging (f MRI) and positron emission tomography enables new approaches to the questions of an itch center in the brain and the relation of the sensation to the scratch response.

As a matter of fact, the activation of the prefrontal cortex correlates directly with the subjective perception of itch intensity. Moreover a prominent influence of psychological and cerebral factors on skin inflammation has been also suggested. Thus activation and deactivation of the prefrontal cortices by means of appropriate stimuli has revealed further insight into emotional, motivational, and

behavioral consequences of itch. Therefore, a more differential understanding of the central nervous processing of itch would lead to the development of new specific antipruritic drugs.
An understanding of the sensory functions, in general, and itch, in particular, is not possible without knowledge of the skin nerve anatomy and the distribution of the neuropeptides and receptors in normal and diseased skin.
The skin is equipped, in fact, with an effective communication and control system designed to protect the organism in a constantly changing environment.
For this purpose, a dense network of highly specialized afferent sensory and efferent autonomic nerve branches exists in all cutaneous layers.
This sensory system contains receptors for touch temperature, pain and, of course, itch. Thus pruritus is a cardinal symptom of many dermatological disorders, attributed for example to a high density of nerve C-fibers within the epidermis, or due to an incomplete arrangement of intercellular lipid lamellae in the stratum corneum (SC).
The impaired barrier function in the skin support, in fact, the entrance of irritants and itchy agents. But more studies are necessary to understand the direct connection between the different epidermal receptors systems and peripheral nerves and their role in itch.
All the 13 chapters of **Part II** are dedicated to review the basic mechanism of itch.
On **Part III** and **IV**, are reported all the new techniques addressed for the evaluation of the patient with itch, such as micro dialysis and questionnaires.
In the context of the itch research these techniques has been mainly used, in fact, as clinical research tools, which can be applied in patients.
At this purpose intradermal micro dialysis is an elegant tool easily to study the interaction of mediators, nociptors, inflammatory cells and vasculature in human skin in vivo. Moreover pain measurement with questionnaires is also important part of the armamentarium of patient monitoring and evaluation.
Epidemiology and Characteristics of Itch, is the topic of Part IV where several skin diseases and systemic diseases are discussed such as atopic dermatitis, post burn itch or psoriasis associated with seborrheic dermatitis, (sebopsoriasis), or neurophatic itch.
As a matter of fact, it is well established that the skin inflammation can cause itch, but it is not generally realized that damage to peripheral nerves as well as damage to brain or spinal cord may be followed by itch. Moreover, it is also to be remembered that like the pain, the subjective perception of itch is a complex emotional experience influenced by many factors, not only by severity of the disease.
Finally, several chapters of **Part V** and **VI** address the most up-to-date therapeutic developments, including new drugs and psychological approaches.
Thus many opioid receptor antagonists such as Naloxone and Naltrexone are reported as active drugs to diminish pruritus. The natural alkaloid capsaicin and other members of the vanilloid receptor family are reported for a symptomatic antipruritic and analgesic therapy.
The topical application of Zangrado, extract from an Amazonian latex, seems to relieve itch due to insect bites, stings and plant reactions, suppressing the activation of sensory afferent nerves. Determining its real mechanism of action may be important to provide new information on the basic mechanisms of itch and pain.

Finally, topical tacrolimus has demonstrated its ability to decrease the severity of itching in a large cohort of study subjects with moderate to severe atopic dermatitis. It may be an alternative agent to the chronic use of corticosteroids, either topically or systemically.
However, psychogenic and psychosocial factors play also an important role in the etiology of pruritus.
Itching and scratching often appear in patients suffering from depression but itching itself can exacerbate emotional states, such as tension. Moreover, not only emotional states but also different personality dispositions are implicated in the reporting of itch adding to the notion that interplay between psychological factors and itch may exist at several different levels.
Thus there is room for greater awareness of the emotional aspects of dermatological phenomena on the part of patient with skin complaints and of their dermatologists.
This awareness may be fostered by clinical teamwork and joint scientific studies and publications.
To conclude this interesting book of itching and its neuropathophysiology and molecular basic, provides a complete base of understanding of this "unpleasant sensation provoking the desire to scratch ", giving an up-to-date knowledge of all the latest researches on itch together with their clinical and therapeutic aspects.
This book, compiling by leading specialists worldwide known, may be useful not only for dermatologists and non dermatologists who treats itching, but also for neurophysiologists, pharmacologists and all the medical and chemical community interested on Cosmetic Dermatology.

P. Morganti
Editor-in-Chief

PHYSIOLOGY OF THE SKIN II

By Peter T. Pugliese
2001. 383 p. Hardcover
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Allured Publishing Corporation, Ill, USA
Fax +1 630/6532192
e-mail: www.SkinInc.com

The best way to review this interesting book of the friend Peter, is to entirely report all the introduction that describes where the book really going.
This second edition of Physiology of the Skin has been revised and updated with the addition of 11 new chapters.
This book is written for estheticians, to help them understand current scientific developments and prepare for future developments in science.
Many new subjects have been added, including basic chemistry and an introduction to biochemistry. The topic of immunology is covered in sufficient detail to allow the serious student to explore the subject further. While the subject of molecular chemistry will grow increasingly important, it is not an appropriate topic for a small book on physiology. The field of enzymology, however, is an area of biochemistry that estheticians will apply often in their practices, both in exfoliating treatments and in specific treatments for acne and other skin conditions.
The book is organized in two sections—Science and Application. I strongly recommend that you read the Science section first, if even lightly. This will provide you with a basis for understanding the latter chapters in Applications. A brief description of the chapters follows.
Chapter 1—*"Behavior of Normal Skin"*
Even advanced professionals need to review material from time to time, for as waves against the sand, our shoreline of knowledge constantly is being eroded. Several new concepts are presented, as well as many old ones seen from a different point of view.
Chapter 2—*"The Desquamation Process"*
An entirely new chapter with up-to-date information on the enzymes of the stratum corneum responsible for exfoliation, this information will prepare you for new exfoliation treatments and help you understand the complexity of the stratum corneum.
Chapter 3—*"The Appendages"*
A review with new information on some of the functions of the appendages and some surprises as to how hair really grows!
Chapter 4—*"The Lymphatic System"*
A good grounding in the physiology of the lymphatic system is necessary. While knowledgeable estheticians are a leg up on other profes-sions, when it comes to the lymphatic system, there always is more to learn.
Chapter 5—*"Pigmentation"*
Always complex and unpredictable, melanin will be a major contender for your time and interest. Understanding the melanocyte and chemistry of melanin is a step up on this pathway.

Chapter 6—*"Basic Chemistry of Life"*
This chapter provides the foundation for biochemistry, introducing atomic particles, pH and chemical reactions.
Chapter 7— *"A Biochemistry?"*
Protein, carbohydrates and lipids make up the stuff of life. An appreciation of the structure and reactions of these substances, as well as knowledge of enzymology, is essential to understanding the new science in esthetics.
Chapter 8—*"Free Radicals and the Skin"*
A complex chapter, but necessary information if you want to understand antioxidants, ultraviolet radiation and the fundamental processes of life.
Chapter 9—*"Sun's Effect on the Skin"*
A tan may look healthy, but it indicates damaged skin! Read all about it here.
Chapter 10— *"Herpes-type Viral Infections"*
Fever blisters, shingles and a lot more—how to tell what that little blister means.
Chapter 11—*"Elastin: The Youth Protein"*
No protein in the body adds more to our appearance than elastin. Saggy cheeks and droopy eyes mean poor elastin. Elastase is the culprit. Learn how to combat this effect.
Chapter 12—*"The Biological Role of Oxygen"*
A subject dear to my heart. More nonsense is written about oxygen than is written in political campaigns. These are the known facts backed by science and presented in a manner that can be understood easily. The section on applications will contain some basic scientific information; such is the case with
Chapter 13—*"Immunology and the Skin Care Specialist"*
The basics of immunology are tough, but like any meat, it is digestible if taken in small chunks. As you read this chapter make sure you understand each concept before going to the next. Much of the new science of skin care will relate in some fashion to immunology.
Chapter 14—*"How Wrinkles Develop"*
While a great deal is understood about wrinkle formation, the last word has not been written. Working in esthetics we must contend with wrinkles, hut the wrinkle is only a more obvious manifestation of the serious problem of aging. Both problems are dealt with in this chapter.
Chapter 15—*"Biology of Acneic Skin"*
The pathophysiology of acne slowly is becoming known. Using the information we have on this subject helps to apply effective therapy.
Chapter 16—*"Sun-related Disorders"*
This chapter builds on information gathered in Chapters 8 and 9. Many skin problems relate to ultraviolet damage, some are quite obvious and others are very subtle. Your knowledge in the area will be expanded to help you recognize and understand several sun-related conditions.
Chapter 17—*"Systemic Lupus Erythemato-sus"*
Lupus is a very complex, multifaceted disease that is yielding its secrets bit by bit. You will see a significant number of clients with lupus and this chapter will take you into the pathophysiology for a better understanding of how best to handle this problem.
Chapter 18—*"Males and Females: Physiological Differences"*
As much as some liberals would deny, there are biological differences of great magnitude between

men and women. Failing to appreciate the physiological differences could blind you to the needs for varied treatments between the sexes.

Chapter 19—*"Estrogens and Phytoestrogens"*

The biochemistry of estrogens and phytoestrogens is found in this new chapter, and it also includes information on hormone receptors and how phytoestrogens work and their benefits to estheticians.

Chapter 20—*"Menopausal Skin"*

Menopause induces a major physiological change in women and skin is a very critical target of these changes. This chapter will explain the basic physiological changes and offer some remedies to help your client through this period.

Chapter 21—*"New Concepts in Aging"*

Aging is one of my favorite subjects and each year it becomes more interesting to me. Is aging a disease, or is it natural to undergo aging changes? Actually, scientists are divided. I see aging as a disease, something we can slow, or reverse.

Chapter 22—*"Supplements and Beyond"*

A wide range of nutritional supplements are available now, so what to take, and how to take them are questions of importance. A new class of agents called nootropics are designed to increase brain power. This chapter leads you into some exciting new areas.

Chapter 23—*"The Power of Chemical Peels"*

Chemical peels are here to stay. New peels are available today and some old ones have been "souped-up." The more you understand about peeling chemistry and physiology, the more versatile and effective you will be using peels.

Chapter 24—*"Cellulite"*

There is new scientific evidence that cellulite is a condition related to estrogen. This chapter outlines the information on what can be done to combat cellulite.

Chapter 25—*"Phytotherapy"*

This chapter is an introduction to the use of plants unesthetics. While phytotherapy requires year soft raining to use, just a little knowledge will help introduce you to the proper use of plants and help avoid the pitfalls of improper use.

Chapter 26—*"Sterilization"*

This last chapter deals with the everyday problems of how to keep equipment clean and sterile. This discipline will help you avoid problems and make your life as an esthetician easier.

It is written for beautician, easy to read, the book will be useful for cosmetic chemists, for marketing managers of cosmetic and consumer skin products and for all the students who wish to better understand the skin and its appendages. A deeper knowledge of the skin is fundamental is food for all people involved with our wellness.

And in full agreement with the author reading the book, " gives you the opportunity to digest the material and understand it before proceeding to the next fact ", if the reader can't understand some subject immediately, has " to go over it again ".

P. Morganti
Editor-in-Chief

DERMATOTOXICOLOGY. Sixth Edition

By Hongbo Zhai and Howard I. Maibach
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This entirely reviewed 6th edition of Dermatotoxicology is been added with six new interesting chapters such as the one dedicated to sensitive skin or to iontophoresis.
The revisions of old chapters and the new ones added clearly describe the up-to-date knowledge of dermatotoxicology, giving, to the reader all the fundamental information on the mechanisms of action of toxicants on skin.
Dermatotoxicology is in fact the science that deals with skin related to toxicity.
This edition is also divided in two parts respectively of 26 and 27 chapters. Moreover at the beginning of each chapter a general content is reported to facilitate the consultation.
The main topic of **Part I**, "concepts" ,describes the primary function of skin as barrier between the well-regulated *milieu interieur* and the outside environment, elucidating how this complex structure may affect penetration of toxicants.
Part II, "methods", contains a compendium of methodologies employed by experienced investigators to identify various toxic potentials.
The stratum corneum (SC), which is comprised of approximately 40% lipids, 40% protein, and 20% water, constitutes the rate-limiting barrier to the transport of the most chemical across the skin. Therefore chemical must first partition into the SC before entering the deeper layers of the skin, the epidermis and dermis, to reach the vascular system. Thus the predominant diffusion path of the molecule toxicant crossing the SC follows a tortuous route and has to cross a number of hydrophilic and lipophilic domains.
Understanding the process of chemical positioning into the SC becomes important in developing an insight into its barrier properties and transport mechanisms. And a subject not covered in earlier editions is the potential applications for powdered human stratum corneum (PHSC) in substitution of its intact membrane.
PHSC contains, in fact, both intact corneocytes and intercellular lamellae, and thus retains SC' original physical – biochemical properties. Moreover, the greater surface area of PHSC enhances solute penetration. Therefore this *in vitro* model offers an easy methodology for the determination of chemical partitioning into the SC and may be useful in many skin research areas. By this new *model* has been possible to demonstrate as protein domain of SC seems to play an important role in the absorption of water. As the SC contains protein, lipids and various lower molecular weight substances with

widely differing properties, the many available binding sites display different selective affinities with each chemical. Thus, the degree of maximum binding or of equilibrium varies with molecular structure. Therefore the solubility limit of a compound in the SC is important in determining the degree of partitioning.

When water is employed as the vehicle, the chemical partition PHSC/W increases with increasing lipophilicity of solute. Conversely, the protein domain of the SC governs the absorption of hydrophilic compounds. Moreover, in addition to partitioning into these two domains, some amount of chemicals may be also taken into SC as the result of water hydration, called sponge domain.

The anatomical and physiological changes associated with aging disease or chemical damage may also affect the barrier function and/or specific anatomical component of skin. Thus a knowledge of how these processes affect each structure's integrity, then gives one a perspective on how the absorption of chemical may be modified.

We know that occlusion may increase percutaneous absorption of applied components. In environmental and occupational scenarios, the chemical to which an individual is exposed is a fraction of their occurrence in the environment. But the effect of one chemical modulating absorption of a second mixture component is not known.

A brief review into factors that should be considered when chemical mixtures are topically applied to skin is reported from chapter 1 to 7.

Sensitive skin is the topic of chapter 8. The number of individuals declaring their skin as *sensitive* is high and is estimated at 50% with a clear dominance of women. A common statement of these individuals is that they have discomfort when using some cosmetic products, and the reason is difficult to define. Up-to-day there is no possibility to prove this statement with objective methods. However with the last classification reported on this chapter, it can be stated that there is neither any significant correlation nor any significant coincidence between individuals with a sensitive skin and individuals with an *irritable skin*. Only a minority of individuals with a sensitive skin or irritable skin can be identified as *stingers*.

Light-induced dermal toxicity studies and light-activated reactions that are produced in skin constitute a significant segment of the 6th edition also.

Phototoxicity is in fact mainly produced by chemicals that are activated by the ultraviolet area of the electromagnetic spectrum. Thus phototoxic events are initiated when a photoactive chemical enters the viable elements of the skin and becomes excited by appropriate UV radiation that penetrates skin. In some cases the photo-excited drug transfers its energy to oxygen, exciting it to the single oxygen state, which is cytotoxic. In other cases, oxygen may not be involved and light-activated chemical reactions that are produced in skin may result in phototoxic or photoallergic skin reactions. But systemic effects of percutaneous absorption are also to be considered whenever a potentially toxic chemical makes contact with skin. Adverse effects may be insidious and require special insight when chemicals are involved whose toxic potential is discovered to follow chronic skin contacts, for example, in an occupational setting.

Twelve chapters (from 9th to 20th) deal with topical and systemic effects from skin exposure to UV and xenobiotic chemical.

UVR is the carcinogenic factor in UVR and various aspects of this subject are treated in chapter 21st. The good news is that among cancers, skin cancer is believed to be one of the most preventable mali-

gnancies. Sunscreens and educational efforts may be an effective method to reduce UVR-induced photodamage. Additionally, many naturally occurring compounds such as antioxidants present in the diet have potential for human benefit. For example, green tea has been suggested as an adjunct to sunscreen to present photodamage, and a diet low in fat may reduce actinic keratosis and non-melanoma skin cancer. Thus, life style change could dramatically reduce the incidence of skin cancers.

Water: is it an irritant? This is the topic of the chapter 25. An irritant is defined as any agent, physical or chemical, capable of producing cell damage. Therefore everything can be irritant, including water, if applied for sufficient time and in sufficient concentration. Water is a ubiquitous irritant, and exerts its irritancy through different mechanisms. The irritancy of water under occlusion has long been recognized. But even contact with pure water will also produce physiologic changes of the skin, and these changes might be involved in some pathological processes. Thus, water, being an unconventional irritant may irritate the skin in a way other than dermatitis.

Skin disorders caused by cosmetics in China is an additional new chapter of this 6th edition.

In China cosmetic contact dermatitis and allergic contact dermatitis are a major problem involving about 70% of the cosmetic skin disorders.

Primary irritant contact dermatitis is induced by deodorants, whitening agents and epilation etc. Allergic cosmetic contact dermatitis is mainly caused by the ordinary cosmetics and usually located over the face and neck, especially in adult women. These related disorders are more preeminent in the Dermatologic clinics, accompanying the promotion of life level in China.

Cosmetic safety is concern of both the cosmetic manufacturer and the dermatotoxicolologist, meanwhile risk assessment and risk management has entered the province of the environmentalist.

These are the topics treated in Part II, where guidelines and methodologies to determine cosmetic safety are reported. As this purpose *in vitro* and *in vivo* percutaneous absorption method are used. But the European guidelines for skin absorption studies require that material remaining in the viable skin layers be considered as systematically observed.

The toxic manifestation of topically applied substances may induce, in fact, immediate phenomena (primary irritation), delayed phenomena (sensitization), phenomena which require an additional vector (phototoxicity) and systemic phenomena (paraquat toxicity). Such reactions cannot occur unless the toxic agent reaches a viable part of the skin going through the SC with accompanying intercellular lipid structure disruption. Thus, Electron Parmagnetic Resonance spin labeling is the sight method for monitoring the structural change in intercellular lipids induced, for example, by topically applied surfactants.

However, chemicals that undergo significant metabolism in skin may exhibit greater or lesser biological activity than predicted simply by skin penetration studies. As a matter of fact, skin metabolism studies are difficult to accurately conduct *in vivo* because of systemic metabolism that take place before samples are collected in the blood, urine or other sites.

On the other hand, in vitro, studies create other problems isolating the skin from the metabolic activity in the rest of the body. But, *in vitro*, studies may be the only ethical way to obtain human skin metabolism data for chemicals with safety concerns.

However, skin penetration is the first act in dermatotoxicology because chemicals, that gain entrance into the body via the skin route and adversely affect the skin or produce systemic effects, must first be absorbed into the living components of skin. And transdermal therapeutic systems (TTS) pro-

vide an effective method to deliver certain drugs through skin.
Currently TTS are useful for delivering small lipophilic molecules and many compounds do not meet these requirements. Thus, new techniques are being developed to allow the transfer of hydrophilic charged drugs through the skin. *Active* transdermal drug delivery involves utilizing external driving forces on the SC in order to allow penetration of molecule of interest. These electrically-assisted methods include iontophoresis, phonophoresis, electroporation, magnetophoresis and photochemical waves. Finally hydrating agents and chemical enhancers also increase pore size of the skin enhancing drug delivery.
The SC may also be removed or bypassed utilizing ablation, microneedles or follicular delivery media, such as liposomes, ethosomes, transferosomes and niosomes. Many other fundamental information on the mechanisms of action of toxicants on the skin and new approaches to evaluating dermal toxicity are reported on this sixth edition of dermatotoxicology.
Thus, the revisions of old chapters and the additional chapters provide on up-to-date assessment of the progress in this fundamental field of dermatotoxicology.
This six edition represents an important reference book for use by the medical and chemical community engaged and by all scientists.
The book will be also interesting for occupational physicians, regulatory authorities, students in biology and cosmetic chemistry, marketing managers of consumer products, and all scientists who are concerned with minimizing the occurrence of toxicant-induced skin disease.

Editor-in-Chief
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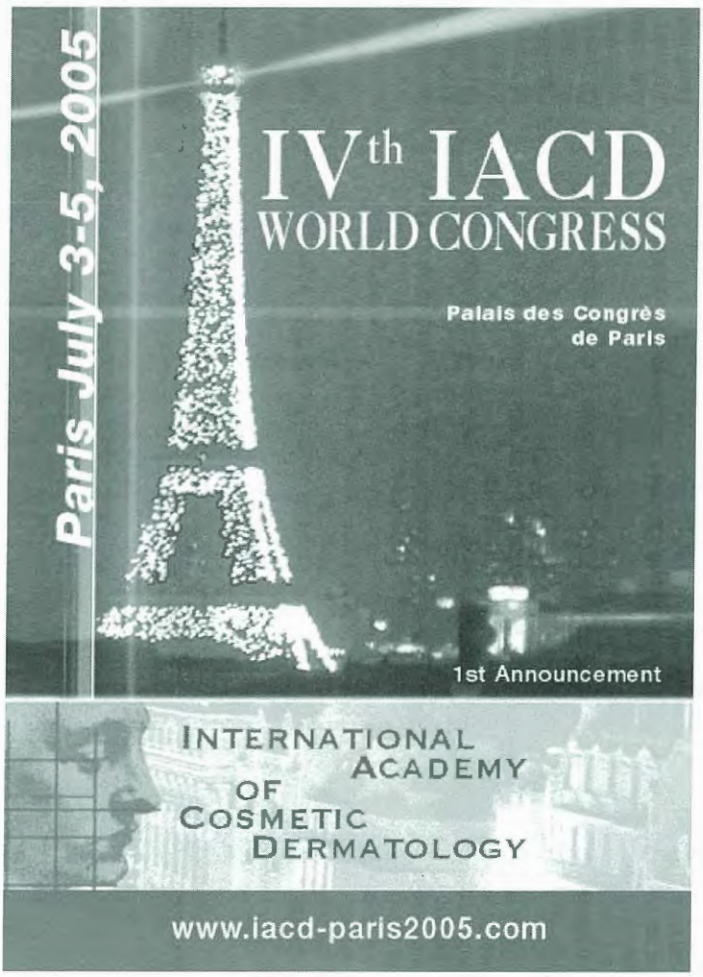

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