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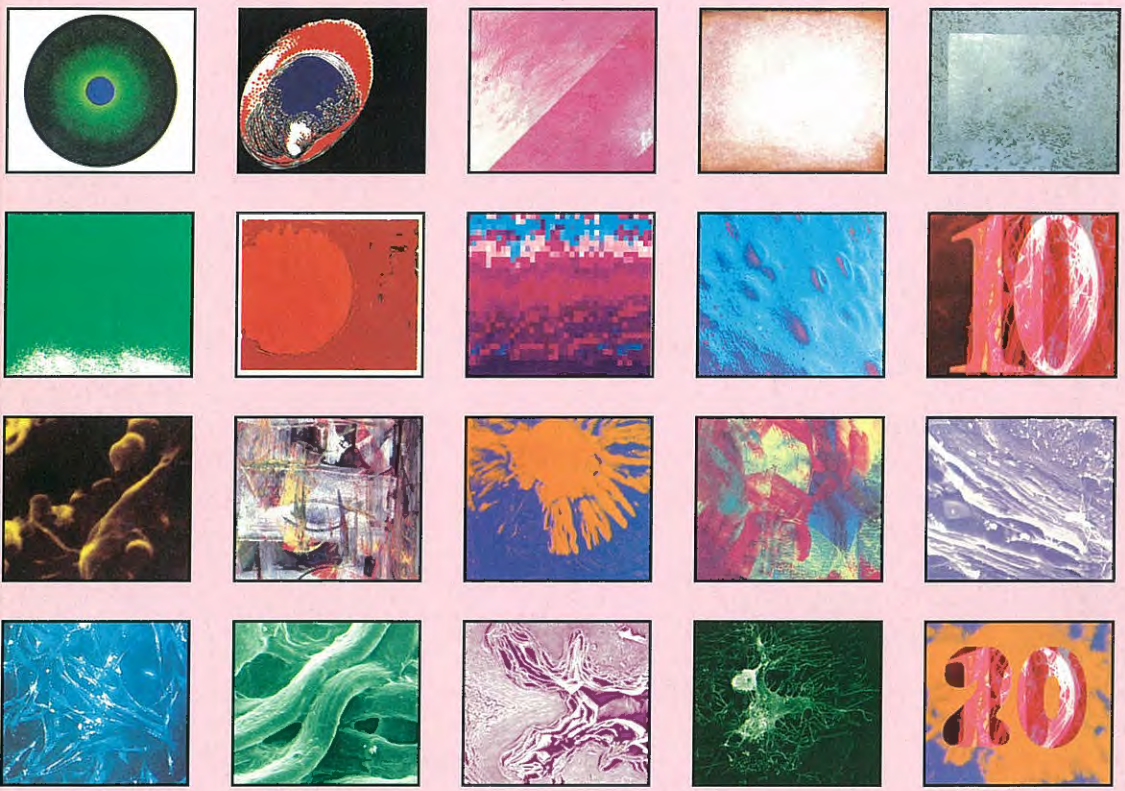

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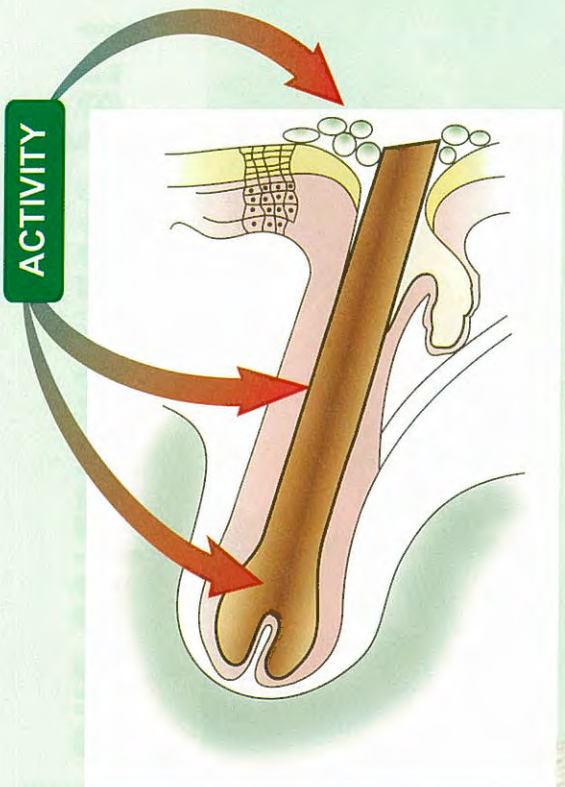

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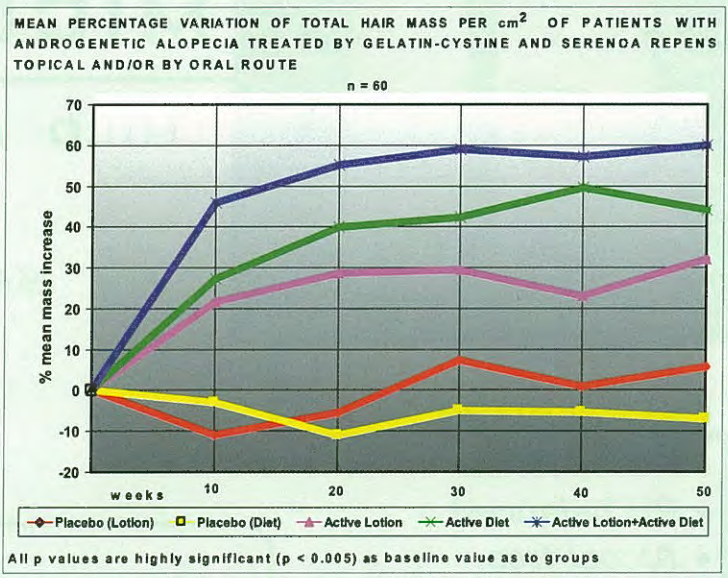

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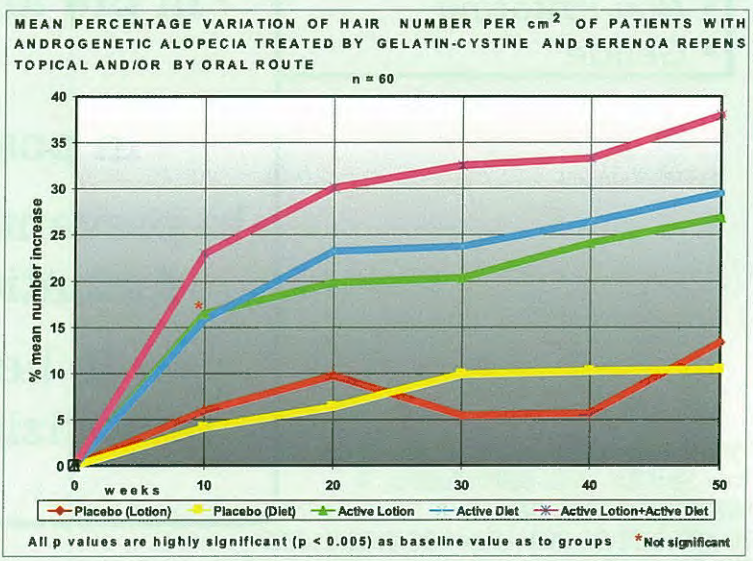

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Contents

J. Appl. Cosmetol. **20**, 219-225 (October/December 2002)

Chitosan Conjugated CLA Gel For Treatment of Stable Chronic Psoriasis Vulgaris

Allan Lassus[1], Jan Wadstein[2], Erling Thom[3]

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Received: *February, 2002*

Key words: *Conjugated linoleic acid, Chitosan, Psoriasis Vulgaris*

Summary

A new gel containing Conjugated Linoleic Acid (CLA) used in adult patients with chronic stable psoriasis vulgaris, showed promising therapeutic results. The duration of the study was 4 weeks. Forty patients were included; 20 received in a randomised manner treatment with the new gel and 20 got placebo. The study was carried out as a double blind trial.

Thirty-eight patients concluded the study according to the protocol. The two withdrawals were in the placebo group and were due to deterioration of the disease. The treatment with the CLA gave significant improvements in the psoriasis disease while the results in the placebo group were not significant.

The results were judged through clinical evaluation by the investigator (AL) as well as with objective measurements using Dermascan C. A significant correlation between the subjective clinical evaluation and the objective measurements is observed.

The tolerability was good in both groups. However, several patients in both groups were of the opinion that the vehicle had a drying effect on the skin. Based on these observations it is recommended that the present vehicle should be changed in order to avoid the drying effect on the skin.

Riassunto

Un nuovo gel contenente acido linoleico coniugato (CLA) utilizzato per pazienti adulti affetti da una forma cronica e stabile di psoriasi vulgaris, ha mostrato di possedere una promettente attività terapeutica.

La durata dello studio è stata di 4 settimane. 40 pazienti suddivisi in 2 gruppi di 20, selezionati in modo casuale, sono stati trattati in doppio ceco con il prodotto in studio o con il placebo. 38 pazienti hanno concluso la terapia in accordo al protocollo. 2 pazienti appartenenti al gruppo del placebo hanno interrotto la terapia per il peggioramento osservato.

Il trattamento con CLA ha fatto registrare buoni miglioramenti che non si sono avuti con il placebo.

I risultati ottenuti sono stati valutati clinicamente e con l'uso del Dermascan C.

Buona è stata sia la correlazione tra i risultati dell'indagine soggettiva e quella oggettiva, che la tollerabilità del prodotto e del placebo. Comunque molti pazienti di entrambi i gruppi hanno affermato che il veicolo provocava loro secchezza cutanea. Dati questi giudizi si stanno studiando veicoli alternativi.

INTRODUCTION

Psoriasis is a common, genetically skin disorder. Between 80 to 90 percent of the patients suffer from localised, stable plaque-type lesions. This patient group is commonly treated with topical steroids, calcipotriol or home phototherapy. Patients with severe, widespread lesions are usually treated with ambulatory phototherapy or oral therapy such as retinoids, cyclosporin or methotrexate. In rare cases hospitalisation is needed. The pathogenesis of psoriasis is still unclear. High amounts of saturated fatty acids, e.g. arachidonic acid, in psoriatic epidermis may be of importance. In a pilot study oral administration of chitosan conjugated CLA had a beneficial effect on psoriasis of the stable type. The aim or the present study was to evaluate the effect of topically used chitosan conjugated CLA of chronic psoriasis plaques in a placebo-controlled way.

MATERIAL AND METHOD

The study was carried out as a randomised vehicle (placebo) controlled study in
40 patients with chronic stable psoriasis. The administration of the formulations was randomised meaning that half of the patients received the active preparation and the other half received the vehicle (placebo). The duration of the treatment was 4 weeks and the formulations were applied b.i.d. (in the morning and in the evening during the study period.

Investigational formulations

The patented formulation (approved June 5 2001;Norwegian patent no. 310176) used in this study were made according to a formula developed by one of the authors (JW). The conjugation is made as follows: 100g CLA (Tonalin 80,Natural ASA Norway) is heated to 70°C under pressure with 30 g Chitosan (Chitoclear 400,Primex AS Norway). When conjugation has taken place (milky appearance of the solution) it is cooled down to 50°C and the other ingredients are added. Retinyl palmitate (RA) is conjugated with chitosan in the same way as for CLA. The gel base is of a standard type and is used as placebo. Other ingredients are Vitamin E as stabiliser and preservative and lactic acid used for pH adjustment. to 6.5.
To our knowledge this is the first gel containing CLA and RA conjugated with chitosan. Substances sensitive to oxidation, as both CLA and RA are can be successfully protected through conjugation. It has further been shown that skin penetration of the active compounds (CLA and RA) is improved when the substances are used in a conjugated form.
The CLA gel and the placebo gel were produced by Regina Cosmetics AB, Halmstad Sweden.
Polar PHARMA OY Espoo Finland delivered the drugs in similar containers to keep the blindness. The appearance and cosmetic properties of the two gels were identical. Code envelopes accompanied the drug deliveries. The code envelopes should only be opened in emergency situations. All envelopes, opened and unopened should be returned to the sponsor at the conclusion of the study.

Efficacy measurements

The investigator (AL) carried out the clinical evaluation the patients with respect to the psoriasis disease initially, after 2 and 4 weeks using a 4 –point scale (0=absent, 1=mild, 2=moderate and 3=severe). The following items were scored: Crnsting,thickness erythema and itching.
Dermascan C (Cortex,Århus,Denmark) was used for measuring crusting and acanthisis (mm). Erythema index was measured using a photospectrometer.

Ethics

The study was carried out in accordance with the Hong Kong (1989) amendment to the Decla-

ration of Helsinki (1964). The study was monitored in accordance with GCP (Good Clinical Pratice) standards. The trial protocol, the patient information and the informed consent form were approved by an ethics committee before enrolment of any patient into the study.
All patients signed an informed consent before inclusion in the study.

Statistical methods

A significance level of 5% was used in the tests and two-tailed tests were applied. Mean was used for estimation over continuos and near continuos variables

RESULTS

Forty Caucasian patients were included in the study, 25 males and 15 females with an average age of 56.0 years. All patients fulfilled the requirements for participation and all gave their informed consent before being included in the study. Two patients in the placebo group did not complete the study according to the protocol due to deterioration of the disease. The investigator therefore decided to withdraw these patients from the study and start alternative treatments. This decision was taken after the 2 week control for both patients. One patient in the group treated with the CLA gel stopped treatment after 2 weeks due to complete healing.
Demographic data for the two treatment groups are presented in Table I.

Table I.
Demographic data for the two treatment groups. Average values with SD in brackets.

PARAMETER	CLA GROUP	PLACEBO GROUP
Gender	11 males / 9 females	14 males / 6 females
Age (years)	58.4 (8.8)	53.6 (70)
Duration of the disease (years)	22.7 (3.4)	23.9 (3.1)

The two treatment groups are comparable with respect to demographic parameters at baseline. The patients in the CLA group are somewhat older than in the placebo group, but the difference is not statistically significant ($p>0.05$). The patients in both groups had had psoriasis for more than 20 years (22.7 years and 23.9 years in the two groups, respectively).
Table II lists the medical background history at inclusion.

Table II.
Medical background history at inclusion; Number of patients.

	CLA GROUP	PLACEBO GROUP
Onychopathia (Y/N)	10 / 10	12 / 8
Arthopathia (Y/N)	7 / 14	8 / 12
Concomitant disease (Y/N)	6 / 14	2 / 18

As can be seen from the table, the distribution of patients with and without onychopathia, arthopathia and concomitant disease is similar in the two treatment groups. There is no significant difference in any of the parameters between the groups.
All patients fulfilled the inclusion criteria in the study protocol. With respect to concomitant disease, none of the patients had diseases and/or pharmacological treatments conflicting the inclusion criteria. Based on demographic data (Table I) and the medical background history (Table II) the two patient groups are well matched at the start of the study, and no significant differences are found in any of these parameters.
None of the patients had received treatment for their psoriasis within 2 weeks prior to entering the study. The majority of the patients had previously been treated with topical steroids and phototherapy.

Table III lists parameters describing the severity of the psoriasis disease at inclusion in the study. As can be seen from the table, the different parameters are quite similar expect for the grade of itching, which is reported to be significantly higher in the group receiving CLA treatment ($p<0.05$). However, for the other parameters it is no significant difference in the psoriasis disease at baseline.

Table III.

Psoriasis related parameters in the two groups of patients at baseline. SD in brackets. N=20+20.

CLINICAL EVALUATION	CLA GROUP	PLACEBO GROUP
Grade of crusting	2.1 (0.3)	2.0 (0.4)
Grade of thickness	2.6 (0.3)	2.6 (0.4)
Grade of erythema	2.7 (0.5)	2.8 (0.5)
Grade of itching	1.2 (0.2)	0.8 (0.3)
DERMASCAN MEASUREMENTS		
Munro's microabscesses	2.20 (0.4)	2.35 (0.3)
Acanthosis (mm)	0.44 (0.1)	0.49 (0.2)
Subepidermal oedema	0.25 (0.1)	0.25 (0.2)
Erythemal index	20.3 (2.4)	18.3 (2.1)

The conclusion to be drawn when using the data from Tables I-III is that the two patient groups are clinically comparable with respect to demographic data, medical background history and the severity of the psoriasis disease. The only deviation observed is that the grade of itching is significantly higher in the group receiving CLA treatment.

In Table IV we have listed the development of the disease during the 4 week treatment period in the two treatment groups based on the clinical evaluation. As can be seen from the table, it is an improvement in all the 4 clinical parameters evaluated in the CLA group. The improvements are statistically significant as compared to the baseline values for all parameters in the CLA group, but not in the placebo group where the changes are negligible or not existing. The improvement in the 4 clinical parameters in the CLA treated group is sizeable amounting to 40-50% as compared to baseline situation.

Table IV.

The development of the psoriasis disease during the treatment period based on the clinical evaluation. SD in brackets.

GROUP	PARAMETER	BASELINE (week 0)	At week 2 0 - week 4	At week 4	Diff. Week	p-values
CLA group	Grade of crusting	2.1(0.3)	1.2(0.1)	1.2(0.1)	0.9	p<0.05
	Grade of thickness	2.6(0.3)	1.8(0.1)	1.6(0.1)	1.0	p<0.05
	Grade of erythema	2.7(0.5)	1.8(0.1)	1.7(0.1)	1.0	p<0.05
	Grade of itching	1.2(0.2)	0.6(0.1)	0.6(0.1)	0.6	p<0.05
Placebo group	Grade of crusting	2.0(0.4)	1.9(0.3)	2.0(0.3)	0	ns
	Grade of thickness	2.6(0.4)	2.6(0.4)	2.4(0.4)	0.2	ns
	Grade of erythema	2.8(0.5)	2.7(0.4)	2.6(0.3)	0.2	ns
	Grade of itching	0.8(0.3)	0.5(0.2)	0.6(0.2)	0.2	ns

In table V we have listed the measurement done by Dermascan C and the erythermal index at baseline and throughout the study. When comparing the baseline values for the two groups, no statistical significant difference in any of the parameters can be found. Also from this point of view, the two groups are clinically comparable.

However, as can be seen from the table, it is a significant improvement in the four parameters in the CLA group during the treatment period, while this is not the case with the placebo groups where none of the changes reach statistical significance.

Table V.
The development of the psoriasis disease during the treatment period based on Dermascan C measurements and erythemal index.

GROUP	PARAMETER	BASELINE (week 0)	At week 2	At week 4	Diff. Week 0 - week 4	p-values
CLA group	Monro's microabsesses	2.20	1.16	1.25	0.95	p<0.05
	Acanthosis (mm)	0.44	0.34	0.36	0.08	p<0.05
	Subepidermal oedema	0.25	0.11	0.11	0.14	p<0.05
	Erythemal index	20.3	17.3	18.3	2.0	p<0.05
Placebo group	Monro's microabsesses	2.35	2.2	2.0	0.15	ns
	Acanthosis (mm)	0.49	0.40	0.46	0.03	ns
	Subepidermal oedema	0.25	0.26	0.23	0.02	ns
	Erythemal index	18.3	17.7	18:2	0.2	ns

In table VI the results from the investigators' global assessment of the two groups of patients are listed. As can be seen from the table, 15 patients in the CLA group were evaluated as having effect of the treatment and 5 patients to have no effect. It is impressing that 9 patients (45%) were rated as completely cured/almost cured. After all, these patients had had psoriasis in average for more than 20 years. The results in the placebo group show that 6 patients bad effect while 14 had no effect.

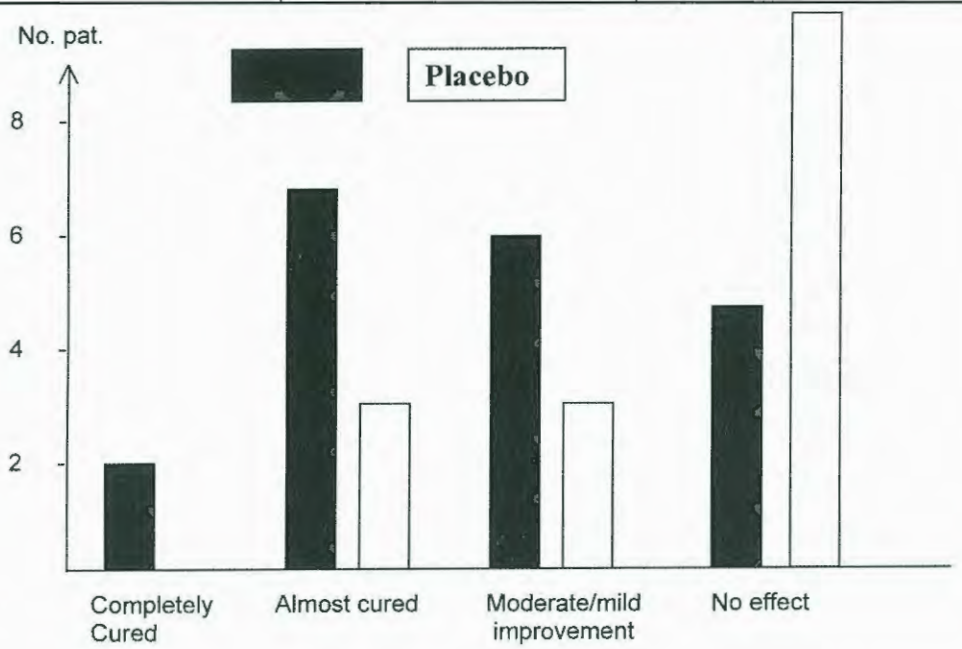
A comparison of the results in the two groups of patients is highly statistically significant in favour of the CLA treatment ($p<0.001$).

The results from the clinical evaluation by the investigator during the study (weeks 2 and 4) and the objective measurements carried out at the same visits, are highly correlated to the investigator's global evaluation of the status of the disease at the end of the study. The results show an improvement in the CLA groups, but not in the placebo treated group.

Based on the results from this study, the CLA gel seems to be an interesting treatment alternative for patients with psoriasis. As mentioned later in the report (Tolerability), some changes need to be made in the present galenical formulation in order to avoid the drying effect this formulation has on the skin.

Table VI.
Clinical judgement by the investigator at the conclusion of the study (Number of patients).

RESULT	CLA GROUP	PLACEBO GROUP
Completely cured	2	0
Almost cured	7	3
Moderate/mild improvement	6	3
No effect	5	14



TOLERABILITY

No severe adverse events of the treatment were reported in either of the two groups. However, a number of patients reported that the gel had a drying effect on the skin. In the placebo group, 14 patients reported a drying effect on the skin, while one reported pruritus and another irritation. Both the last ones can of course be related to the drying effect. In the CLA group, 16 patients reported a similar drying effect. The lesson to learn from this is to add more lipids to the gel in order to avoid the drying effect. From the above mentioned it is obvious that the present concentration of CLA in the gel in itself is not able to reduce the drying effect. Other galenical formulation techniqnes have to be considered in order to avoid this effect on the skin and give the gel an improved dermatological tolerability.

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Tibetan Medicine: An Effective Botanical Treatment for Peripheral Vascular Disease (PVD)

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Summary

The botanical formula Badmaev No. 28, which originated in Tibetan medicine, provides an instructive example of how a nutriceutical has evolved from an ancient concept into a contemporary application through scientific research. This developmental pathway has led to a standardized nutriceutical with clinically proven efficacy in tbe treatment of peripheral vascular disease (PVD). During the 1970s systematic scientific investigation begun in Switzerland and resulted in six double-blind clinical studies on the cardiovascular use of this formula. The formula's mechanism of action has been described in Tibetan tradition, based on three groups of botanical and mineral ingredients: (1) main acting ingredients, (2) auxiliary ingredients, and (3) components that moderate the action of the first two groups and facilitate gastrointestinal absorption of the formula. Based on the preclinical, clinical and laboratory studies several mechanisms of the formula relevant to alleviation of tbe pathomechanism of PVD have been discussed; for example, increase in threshold for platelet aggregation, lowering total blood cholesterol level, lowering levels of low-density lipoproteins (LDL) while increasing levels of high- density lipoproteins (HDL), and prevention of lipid peroxidation. Also, recently performed studies have shown that the formula can exert actions as a biological response modifier by alleviating vascular inflammation. The latter mechanism may be particularly important in light of the inflammatory nature of atherosclerosis.

Riassunto

La formulazione botanica di origine Tibetana, denominata Badmaev N. 28, dimostra come, attraverso la ricerca scientifica, sia possibile realizzare un moderno nutriceutico partendo dalla medicina tradizionale. Attraverso studi continui iniziati in Svizzera nel 1970 e realizzati attraverso 6 studi clinici a doppio ceco, è stato infatti, possibile ideare un nutriceutico attivo nelle patologie vascolari periferiche (PVD).

Il meccanismo d'azione della formulazione riportato dalla tradizione tibetana è basato sull'uso di tre gruppi di sostanze di origine botanica e minerale: (1) i principali ingredienti attivi, (2) gli ingredienti ausiliari, e (3) i componenti che moderano l'azione dei primi due gruppi facilitando l'assorbimento gastrointestinale della formula. Basandosi sui numerosi studi di laboratorio, studi pre-clinici e clinici vengono discussi i diversi meccanismi in grado di alleviare la patologia delle PVD; per esempio, l'incremento della aggregazione piastrinica, l'abbassamento dei livelli globali di colestero-

lo, e delle lipoproteine a bassa densità (LDL), l'incremento del livello delle lipoproteine ad alta densità (HDL), e la capacità di prevenire la perossidazione lipidica.
Di recente è stata anche dimostrata la capacità di questa formulazione di ridurre i processi infiammatori vascolari particolarmente importanti nell'aterosclerosi.

BRIEF HISTORY OF TIBETAN MEDICINE IN ASIA AND EUROPE

Tibetan medicine has aroused the interest of Western physicians during recent years, principally because of claims of its practical value1. Tibetan doctors of the Tibetan Medical Institute at Dharamsala, India, are by now well known visitors to American and European universities, where they have lectured on theory and practice of Tibetan medicine. However, there is great difficulty in communicating the concepts of Tibetan medicine to the West. One reason often given for this difficulty is the overall difference between these two medical cultures and philosophies*.

As a Western physician, my interest in Tibetan medicine stems from the fact that four generations of physicians in my family, educated in European schools, have combined Western medical concepts with those of Tibet in their practice (1,2,3,4,5,6,7). Knowledge of Tibetan medicine was acquired in our ancestral home in the Asian part of Russia, the Buryat Republic. This is one of the few places outside of Tibet where Tibetan culture has continued to flourish (3,7).

Tibetan medicine is rooted in ancient traditions. Its first written document is approximately 1,300 years old (8,9). The consensus among Tibetologists is that this medical system was developed under the influence of the medicine and philosophy of India. However, at least at the beginning of the Tibetan Empire, that knowledge was primarily Western (i.e. Greek) and secondarily Chinese in origin (10).

The Tibetan Empire, which lasted from the seventh to the ninth centuries, extended south to the plain of the Ganges, north to Samarkanda, and included part of China (8). The vast and culturally varied territory of that empire had an impact on the development of Tibetan medicine. Buddhism was brought from India to Tibet, providing a philosophy that has become essential in medical education and knowledge in that country (8,9). Symbolically, Buddha occupies an important position in the medical hierarchy of Tibet. One of his titles there is "Supreme Physician" and he is often thought of as the "Tibetan Aesculapius".

The Tibetan king Ti-song-De-tsen invited in VIII century AD Padma-Sambhava, a famous Buddhist teacher from the College of Nalanda, in India, to Tibet. The three kings who ruled the Tibetan Empire were, in chronological order, Song-tsen Gam-po, Ti-song De-tsen and Rolpachon. They are regarded as the most prominent figures in Tibetan history. In addition to the introduction of Buddhism, their reigns were highlighted by a medical convention which took place between 755 and 797 AD, at Samye, southeast of Lhasa, the capital of Tibet (11). During that meeting, renowned physicians from Persia, Greece, India, China, Afghanistan, Nepal, East Turkestan and Kashmir translated their medical works into the Tibetan language.

The eighth and ninth centuries have also been remembered in the history of Tibetan medicine through the work of a physician known as the "Elder gYu-thog Yon-tan mGon-po" or as the "Excellent Protector". During the 120 years of his life, the Elder earned the reputation as a charismatic teacher. He was probably the first to compile the scattered texts on Tibetan techniques of diagnosis and treatment (12,13). One of his descendants, the "Younger gYu-thog Yon-tan mGon-po" is credited with adding a broad knowledge to the canon textbook of Tibetan medicine the yGyud-bzhi. In fact, the original of the yGyud-bzhi (pronounced Zud-shi, meaning"Four Roots") was brought to Tibet from

"I taught my patients that I do not cure illness, but that I remove the causes of disease. I taught them that the aim of mankind is consciousness, will, and good deeds – only these things can bring realization to the aims of humanity. I instruct them that nothing but conscious collaboration with nature can yield health and well-being."

(Dr. Vladimir Badmaev, Sr.)

India during the active period of the Empire. According to one source, the book was written originally in Sanskrit in the fourth century. Most likely, the translation into the Tibetan language was accomplished in the eighth century by Vairochana , with the assistance of the Tibetan physician, Zla -ba mNon-dgha (9). That translation was presented to Padma -Sambhava, the famous teacher of Buddhism, who became skeptical whether the yGyud-bzhi could readily be understood and appreciated by a majority of the physicians of that time. In the late nineteenth and early twentieth centuries that ancient work was translated from Tibetan and Mongolian into Russian by my granduncles Dr. Alexander Badmaev and Dr. Peter Badmaev (14) (A).

Historically, medical education in Tibet has been based on a highly structured system, with Buddhist monasteries functioning as medical schools (9). The first medical college in Tibet, Kong-po-menlung, was built in the eighth century at Lhasa. Among medical schools established since then, the best known are the Chagpori Medical College, built in the seventeenth century, and Mentsi Khang built in 1915 , both in Lhasa. Since 1959, the Tibetan Medical Institute, at Dharamsala, India, is the center recognized as upholding this medical tradition.

Tibetan medicine has also been practiced in Mongolia, where it was introduced in the year 1235 by the physician, Sakaja, who cured Godon, the ruler of that country, of a form of paralysis (15). The Mongolian people, in recognition of the Tibetan contribution to their medical knowledge, as well as the teachings of Buddhism in Mongolia, awarded the ruling priest-prince of Tibet in 1547 the Mongolian title of "Dalai-Lama," meaning "Ocean Priest" (16). In the eighteenth century, Tibetan medicine was brought from Mongolia to the Asiatic part of Russia, and both that medicine and Buddhism have flourished in the Buryat Russian Republic.

Unlike Ayurveda and Chinese medicine, Tibetan medicine came to the attention of the West relatively recently, in the middle of the nineteenth century. The pioneers were Alexander Csoma de Koros, a Hungarian "hero of learning, " who had spent years in seclusion in Tibetan monasteries studying the language and Tibetan medical treatises (17). The other pioneer was my ancestral, Buryat physician, Dr. Sul-Tim-Badma, who, in recognition of his medical skills, was invited in 1850's to the European part of Russia by the then governor of Siberia, Muraviev Amurski. Later, Dr. Sul-Tim-Badma settled in St. Petersburgh and changed his name to Dr. Alexander Badmaev (2,3).

Alexander was soon followed to St. Petersburg by his younger brother Dr. Peter Badmaev, whose Buryat name was Zham-saran. Both Alexander and Peter are well recognized figures in the latest Russian history for their ties to the last two emperors of Russia. They both become court physicians to the Czars (18,19).

THE PRINCIPLES OF TIBETAN PHARMACO-THERAPY

According to the tradition carried in my family, herbal treatments have a certain regimen (18). The treatment usually starts with a digestive formulation because, in Tibetan medicine, disease is considered primarily a derangement of nutrition. After the initial treatment, and to correct the suspected nutritional pathology, the appropriate treatment of any secondary disease is then instituted. Nutrition is central in the theory and practice of Tibetan medicine. According to that concept, prevention of disease can be accomplished by seasonal adjustment of the menu to comply with changing nutritional requirements. The taste of the food is the single most important consideration in defining proper nutrition and preventive medicine during the seasons of the year. Tibetan pharmacotherapy has been based on the concept of proper nutrition, and in fact herbal and mineral formulae, as passed down in my family tradition, were referred to as

a "condensed food" for a specific disease condition.

The Tibetan herbal formulations as practiced in my family have been composed of several herbal and/or mineral ingre-dients. These have been arranged based on triadic philosophy derived from Ayurveda into three therapeutic groups of ingredients occurring in each formula:

1. the main acting ingredients,
2. the ingredients which support the main action, and
3. the ingredients that prevent any untoward effects of the first two groups and increase gastrointestinal bioavailability of the active principle

COMPARISON RESULTS OF THERAPEUTIC No. 28 VS PHARMACEUTICAL DRUGS

Compound name	Duration of treatment	percent increase maximal walking distance
28	12 weeks (Hurlimann)	54%*
" "	16 weeks (Schrader)	98%
" "	16 weeks (Samochowiec)	93%
" "	16 weeks (Drabaek)	97%
" "	16 weeks (Wojcicki)	103%
" "	16 weeks (Smulski)	112%
Pentoxifylline		
[Trental]	24 weeks (Porter)	58%
" "	4 weeks (Volker)	40%
" "	24 weeks (Porter)	33%
" "	8weeks (Bojan)	47%
" "	24weeks (Lindgarde)	50%
" "	90 days (Chacon-Quevedo)	25%
Neftidrofuryl		
[Praxilene]	24 weeks (Phole)	70%
" "	12 weeks (Maass)	54%
Buflomedil		
[Loftyll]	12 weeks (Trubestein)	97%
" "	90 days (Chacon-Quevedo)	28%
Bencyclan		
[Fludilat]	6weeks (Holle)	34%
Nifedipine	90 days(Chacon-Quevedo)	21%

* Hurlimann study assessed pain free walking distance see references

(Badmaev V, **Essentials of Complementary and Alternative Medicine** 1999)

TAB. I

THE EVOLUTION OF TIBETAN PHARMACO-THERAPY

This system of herbal and mineral formulae has been continuously developed and used for over 100 years with each formula known by its numerical designation, e.g. Badmaev formula No. 28, Badmaev formula 179, Badmaev formula No. 269 etc. The partial list of these formulae and their clinical indications have been described elsewhere (1). In 1969, Karl Lutz a Swiss industrialist and my father Dr. Peter Badmaev, Jr. founded the Switzerland based company Padma AG. 4 (1,18) This company (name Padma derived from the family name Padma or Badma, which means Lotus Flower) was established to scientifically and commercially explore the Badmaev's know-how and clinical experience of the formulae. The first products that were clinically studied, registered with the Swiss IKS and introduced to the market place included Badmaev formula No. 179, Padma Lax; and Badmaev formula No. 28, Padma 28. 1 (18)

The formula 28 is one of the best clinically tested traditional multicomponent formulations known. The usefulness of the formula in the treatment of peripheral vascular disease (PVD) was first clinically evaluated by Hurlimann20 in late 1970's. Subsequently, five double blind trials of the formula in PVD have followed [Tab. 1]. In addition to the cardiovascular the anti-inflammatory and the immune system modulating mechanisms of the formula have been reported [Tab. 1] (20).

The formula (N° 28) was fortified recently with a minute amount of black pepper extract (standardized for 58% alkaloid piperine-Bioperine®) which has been shown in clinical studies to increase the bioavailability of broad range of nutritional compounds [Fig. 1, Fig. 2] (21,22).

The consensus among the participants of the January, 1999 conference on Bioavailability of Dietary Supplements organized by The Office of Dietary Supplements (ODS) of the National Institutes of Health (NIH), Bethesda, Maryland (USA) was that bioavilability (term involving efficiency of absorption as well as utilization of a nutrient(s)) is crucial to the health benefits of a supplement. The nutritional role of black pepper extract for fat and water soluble nutrient bioavailability was discussed during that conference.

The formula 179 - a gastrointestinal formula, has been tested in a 4 week open field study in Switzerland by four independently working physicians1. A total of 52 patients of both genders presenting with irregular gastro-intestinal (GI) functions manifested by constipation, flatulence, feeling of fullness, heartburn and belching participated in these studies. The 43 participants reported a significant ($p<0.001$) GI improvement after using No. 179.

No. 179 eliminated gas in 80% of patients, heartburn in 83%, abdominal fullness in 76% and constipation in 74%. The 85% of patients reported relief within one week after taking 1 to 3 tablets per day. Those patients who had no history of laxatives use or previously used mild laxatives benefited most from therapy with No. 179. While typically the whole formula is more effective than the individual herbs, one of the most active gastrointestinal components of No. 179 was shown to be Terminalia chebulae, fam. Combretaceae and derived gallotannins compounds. (Fig. 3, Tab. II, Tab. III)

The formula No. 96 and related No. 269 were tested in vitro with the MDCK epithelial tissue culture cell line for its traditionally recognized anti-viral effect27,28. The results indicate that the formula is active in protecting epithelial cells against damage caused by influenza virus. Traditionally it is believed that "lymph factor" plays an important role in the mechanism of No. 96 and No. 269. The phenolic compounds abundantly present especially in formula No. 269 have been found to regulate two important parameters of the immune system in human, i.e. in-

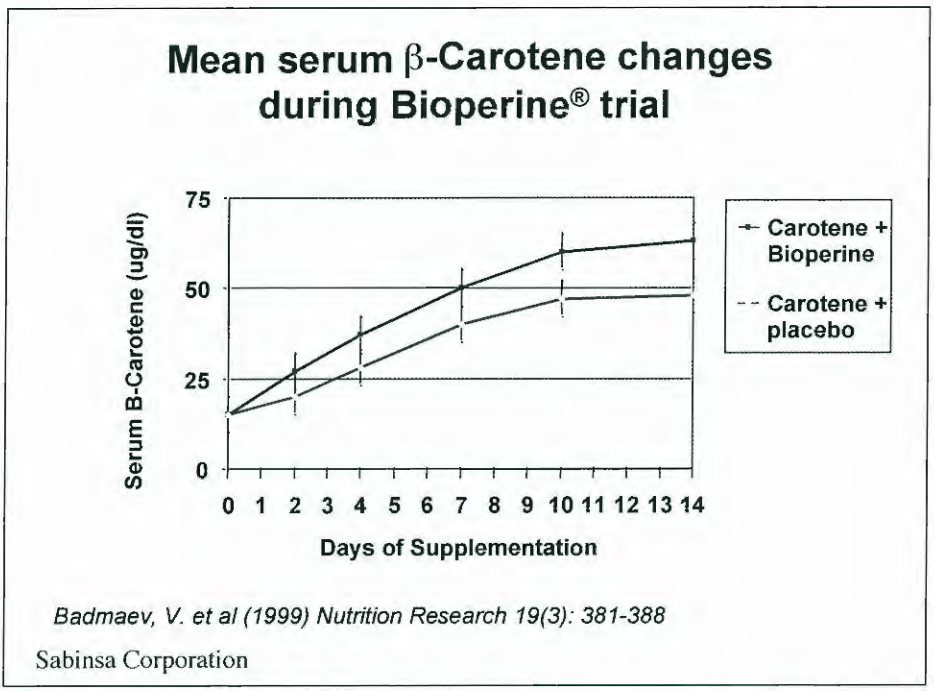
Mean serum β-Carotene changes during Bioperine® trial
Serum B-Carotene (ug/dl)
75
50
25
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Days of Supplementation
Carotene + Bioperine
Carotene + placebo
Badmaev, V. et al (1999) Nutrition Research 19(3): 381-388
Sabinsa Corporation

Fig. 1

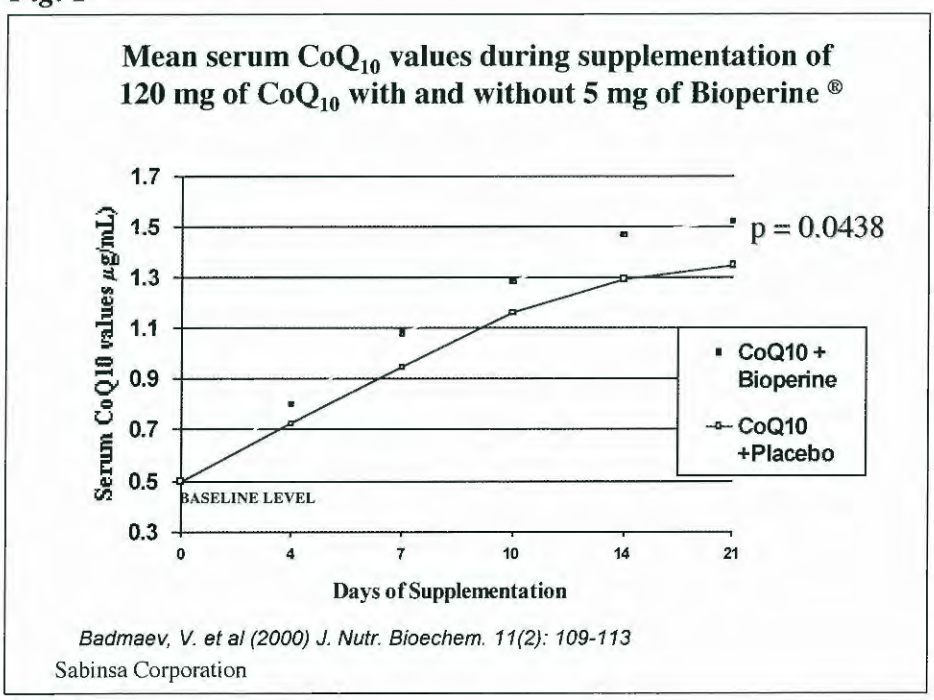
Mean serum CoQ10 values during supplementation of 120 mg of CoQ10 with and without 5 mg of Bioperine ®
Serum CoQ10 values µg/mL)
1.7
1.5
1.3
1.1
0.9
0.7
0.5
0.3
BASELINE LEVEL
0
4
7
10
14
21
Days of Supplementation
p = 0.0438
CoQ10 + Bioperine
CoQ10 +Placebo
Badmaev, V. et al (2000) J. Nutr. Bioechem. 11(2): 109-113
Sabinsa Corporation

Fig. 2

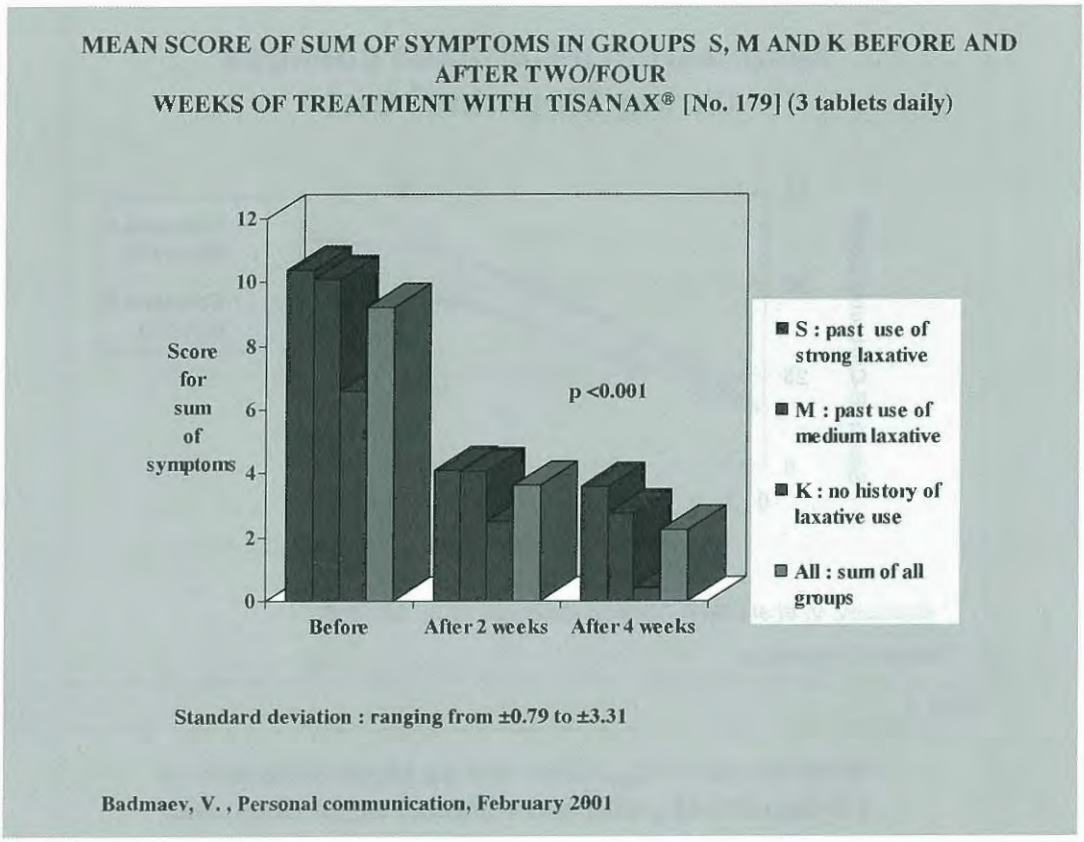

Fig. 3

terleukin-12 (IL-12) and protein compounds inhibiting apoptosis (IAP). In the 34 week study a group of 40 elderly patients (>70 years old) of both sexes received daily 500 mg of phenolics from turmeric, known as curcuminoids. As a result of this regimen the serum levels of IL-12 significantly increased and IAP levels gradually decreased (Fig 4. and Fig 5). There were no objective or subjective reports of any untoward reactions due to the treatment.(Badmaev V, Personal communication, February 2001).

TIBETAN THERAPY IN THE CONTEXT OF TIBETAN MEDICINE

Herbal therapy plays an important, but not primary, role in the overall approach to the treatment of a disease in Tibetan medicine. Before prescribing any specific formulation to a patient, a physician makes sure that a patient understands the overall approach to the disease. According to this approacb none of the techniques devised by man against any disease could be as helpful as the body 's own means of fighting the disease. These natural means should be

RESPONSE OF ANTACID AND AMLAKI IN ULCER DYSPEPSIA				
THERAPY	**INITIAL**		**4 WEEK TREATED**	
	PAOmEq/h	**Symptom score**	**PAOm Eq/h**	**Symptom score**
Antacid	18.33±4.26	4.20.±0.45	15.0±3.06	0.40 ±0.55*
Amlaki	22.80±5.27	4.60±1.34	16.0±3.19	0.60±0.84**

PAO:Peak acid output, *p<0.001, **p<0.01

Chawla, Y.K. et al. (1982) Ind. J. Med. Res. 76(Suppl):95-98.

Tab. II

RESPONSE OF ANTACID AND AMLAKI IN NON ULCER DYSPEPSIA				
THERAPY	**INITIAL**		**4 WEEK TREATED**	
	PAOmEq/h	**Symptom score**	**PAO mEq/h**	**Symptom score**
Antacid	20.01±3.06	4.40.±0.63	14.7±9.0*	1.53 ±0.65*
Amlaki	20.56±4.17	5.0±1.22	15.5±4.04*	1.61±0.84**

PAO: Peak acid output, *p<0.001, **p<0.01

Chawla, Y.K. et al. (1982) Ind. J. Med. Res. 76(Suppl):95-98.

Tab. III

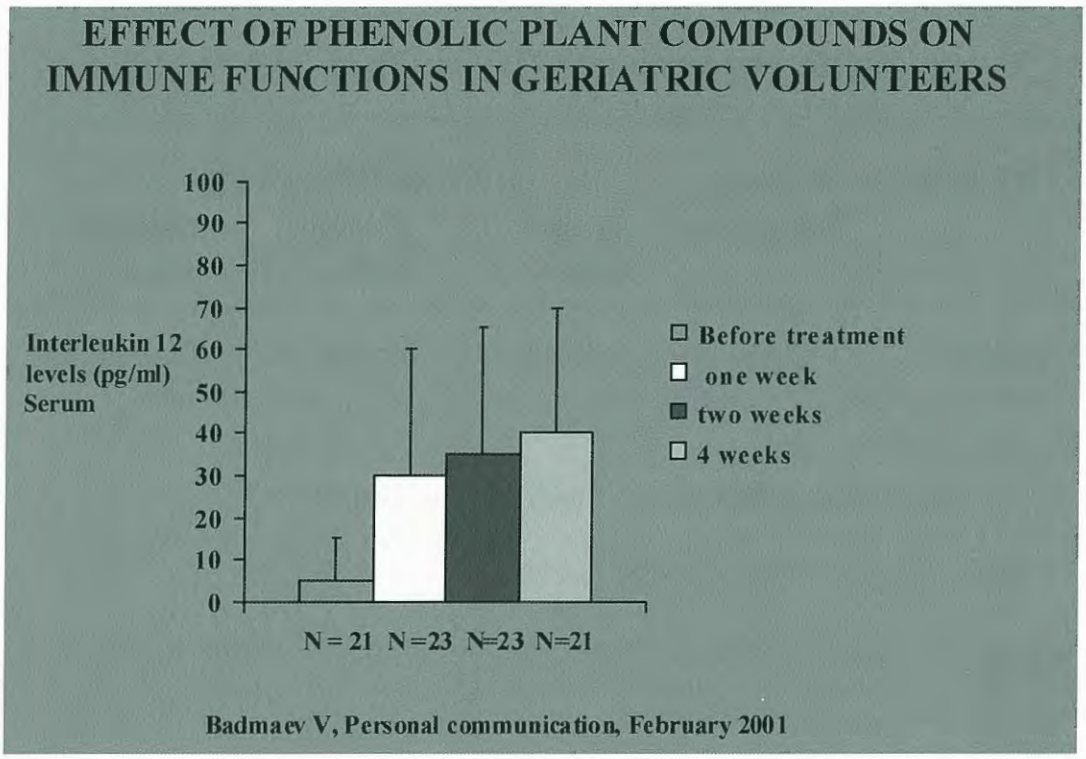

Fig. 4

supported, during critical moments, by specific treatments. But, in the first place, the patient should be maintained in good shape by: 1) proper nutrition, 2) good life-habits, 3) proper adjustment to the seasons of the year, and 4) awareness by the individual of his/hers physical and psychological predispositions. In order to fulfill these four conditions of well-being a man should guide himself/herself with awareness, will power and compassion. These three aspects, based on the triadic philosophy derived from Ayurveda, are named in Buryat language Chi, Schara and Badahan corresponding to Vata, Pitta, Kapha in Ayurveda.

In modern medicine there is, regrettably, little recognition of moral values as a means of disease prevention and treatment. Indirectly, this void in contemporary western medical practice is becoming recognized and the role of family physician by some is being restored and enlarged so that a patient is approached on a more personal level. The communication with a patient in Tibetan medicine is a critical part of a visit to the doctor's office. Physician recommendations, given to a patient during office visits, are not only to be acknowledged but also understood by the patient. Thus, the patient acquires a sense of health-care philosophy, and can identify with it and could further propagate it. This simple approach results in an efficient system of preventing disease in the first place. This approach to a health care has been referred in my family tradition as "Synthesis Medicine" 1.

THE FUTURE OF TIBETAN MEDICINE

Introducing Tibetan medicine and integrating its principles into the Western medical practice can

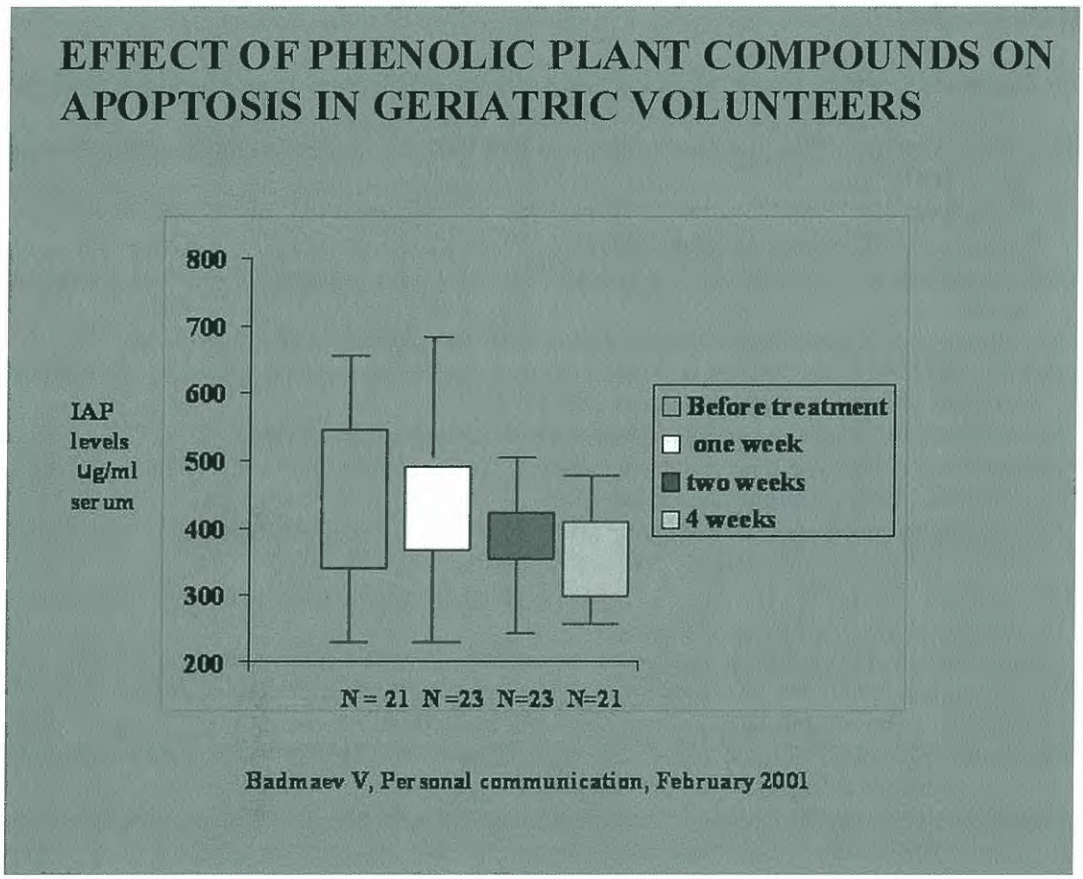

Fig. 5

improve existing healthcare considerably in many ways. It is not only a matter of advanced technology that allows people to be and feel healthier. Despite tremendous advancement in medical technology we, as a society, are not healthier. It suffices to observe that the work of man, his thoughts and the outcome of his deeds, are chiefly directed towards destruction and based on short-sighted goals. Today, economic and political life has become a kind of thoughtless game of chance; the cult of the power of the group and the State has overshadowed the real aims of humanity. Regrettably the delivery of modern health care became an integral part of this bureaucratic and technocratic system.

The medical tradition as known to me stresses an unusual approach to health care, where a man should guide himself with moral values, with the ultimate goal being compassion. As unusual as it may sound, however, to recognize moral values as a means of well-being and an integral part of the treatment method would be a meaningful step towards better medicine. Perhaps we should go back to the past and only then to the future.

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(A) Badmaev, Badmayev, Badmajeff, Badmajew – different spelling of the same name.

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The cosmeceutical Pycnogenol®

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Summary

Pycnogenol® (PYC) the extract of French maritime pine bark (Pinus pinaster), possesses various unique biochemical properties, which in combination designate it as fascinating cosmeceutical. PYC is one of the most potent natural antioxidants with demonstrated ability to neutralise all species of oxygen radicals. Its ability to reduce the vitamin C radical and to protect vitamin E from oxidation helps to prolong the bioactivity of these vitamins. Women suffering from hyper-pigmentation (melasma) experienced significant reduction of pigmentation intensity and affected skin area size after 1 month supplementation with PYC.
PYC strongly binds to collagen and elastin and this inhibits their enzymatic degradation. its improvement of microcirculation supposedly supports better oxygen and nutrient supply as well as better detoxification of the skin. These unique properties render PYC a fascinating cosmeceutical to support a healthy and juvenile looking skin.
Research has shown that PYC displays a pronounced anti-inflammatory activity. In human volunteers oral supplementation with PYC was able to increase the minimal erythema dose in response to UV exposure. In vitro experiments have established that PYC constituents inhibit NF-kB-controlled expression of inflammatory mediators such as adhesion molecnles and cytokines. These findings suggest an application of PYC for protection against photoageing of the skin.

Riassunto

Pycnogenol® (PYC) è un estratto di Pinus Pinaster della costa francese, particolarmente ricco in procianidine. Per la sua forte attività antiossidante è in grado di riciclare e prolungare l'azione della vitamina C, è sicuro nell'uso e privo di effetti allergizzanti se utilizzato per via topica o per via sistemica.
Le procianidine si legano in modo stabile alle fibre di collageno della pelle proteggendo PYC dalla degradazione provocata dai radicali liberi o da enzimi.
Inoltre l'uso di questo estratto aiuta a prevenire gli effetti "invecchianti" provocati dalla luce del sole, neutralizzando i radicali liberi e ridncendo conseguentemente i fenomeni infiammatori.
Preso per via orale da volontari sani, PYC è stato in grado di ridnrre l'eritema indotto dagli UV in maniera dose-dipendente. Si è visto con uno studio che questo estratto è in grado di interagire con NF-kB espressione dei mediatori dell'infiammazione prevenendone l'ossidazione.
In un altro stndio si è visto che la forte attività antiossidante esplicata da PYC era in grado di ridurre

i fenomeni di iperpigmentazione in donne colpite da cloasma se utilizzato in dosi di 75 mg/giorno. Sembra, inoltre, che PYC migliori la microcircolazione aumentando la produzione dell'NO endoteliale diminuendo la relativa dilatazione dei capillari. Si verifica così un maggior apporto di ossigeno e di nutrienti che migliorano notevolmente l'aspetto della cute.

INTRODUCTION

Pycnogenol® (PYC) is the standardised, water-soluble extract of the bark of the French maritime pine (Pinus pinaster). It consists of the phenolic constituents taxifolin and catechin, and oligomers of the latter, the procyanidins. Furthermore, it contains phenolic acids: p-hydroxybenzoic, protocatechuic, gallic, vanillic, p-coumaric, caffeic and ferulic acid [Rohdewald, 2002]. Pycnogenol® is the trademark of Horphag Research Ltd., UK. PYC is available world-wide as a food supplement, used primarily for its potent antioxidant activity and its values for maintaining a healthy cardiovascular system.

PYC has been demonstrated to inactivate essentially all oxygen free radicals [Elstner & Kleber, 1990], and has been found to be one of the most potent, natural free radical scavengers [Noda et al., 1997]. It is able to reduce the vitamin C radical, and thus recycles vitamin C back to the bioactive form [Cossins et al., 1998]. In presence of PYC, vitamin E is protected against oxidation [Virgili et al., 1998]. Furthermore, it up-regulates intracellular activities of GSH, GSH peroxidase, superoxide dismutase and catalase, thus reinforcing cell-own antioxidant protection [Wei et al., 1997]. Oral supplementation with PYC significantly enhances the antioxidant capacity in humans [Devaraj et al., 2002]. Metabolisation studies have revealed a peak urinary excretion of the smaller constituents 2 hours after consumption, while larger constituents peak around 8 h post consumption [Grosse-Düweler & Rohdewald, 2000].

PYC has been extensively researched for its safety, it has a very low acute toxicity, no chronic toxicity, no mutagenicity, teratogenicity and perinatal toxicity and it is non allergic [Rohdewald, 2002]. In clinical studies dosages of up to 360 mg PYC have safely been taken. In rare cases a mild stomach discomfort occurs which can be avoided by taking PYC together with food.

In addition to being a powerful antioxidant, it possesses two further basic biochemical actions. It also enhances production of endothelial nitric oxide (NO) which is the underlying mechanism for improvement of micro-circulation as well as prevention of platelet aggregation. An improved micro-circulation supposedly is advantageous for the skin as well, as supply with oxygen and nutrients and removal of waste products will be enhanced.

The affinity of PYC to collagen and elastin has been proposed to be the mechanism responsible for strengthening of capillaries as well as for its use as an internal cosmetic.

RESULTS AND DISCUSSION

Solubilised collagen, elastin, powdered skin and ovalbumin were incubated with PYC in a concentration of 0.2 mg/ml and unbound PYC was determined photometrically. It was found that it displays a high binding affinity with 33.9% of added PYC being bound to collagen and 41% bound to elastin, respectively. As expected from the ubiquitous presence of collagen and elastin in skin, 37.9% of PYC were found to be bound to powdered skin. As unspecific control protein ovalbumin was tested and only 2.1% of PYC were fonnd to bind [Grimm & Högger, 2002]. This demonstrates the very specific affinity of PYC to the most important structure elements of skin and blood vessels.

To assess protection of collagen and elastin from degradation the free amino groups of these proteins were exhaustively succinylated. Degradation of collagen and elastin was quantified by determination of developing amino groups by colour reaction with 2,4,6 trinitro benzosulfuric acid at 450 nm. Degradation of collagen by matrix metalloproteinase -1 (MMP 1, collagenase 1) was inhibited by PYC in a dose dependent manner (figure 1) [Grimm & Högger, 2002]. Corresponding results were obtained showing that it inhibits degradation of elastin by MMP-2 and MMP-9.

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Aesthetic Medicine and Cosmetology between East and West

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Summary

Aesthetic medicine, together with Cosmetic Dermatology, is today a new medical discipline which is widely represented and legally recognized within the Chinese territory. "It is the new science which concerns itself with the role played by beauty in nature for a better life", as was stated by Professor Peng Qing Xing, in his role as Chairman, at the opening of the 2nd World Congress on Aesthetic Medicine and Cosmetology which has recently taken place in Beijing.
As a matter of fact, Aesthetic/Cosmetic Dermatology has had in China a considerable boost, especially in the course of the last few years, both with the opening of new medical-aesthetic wards in the main hospitals and with the opening of medical dispensaries devoted to this new medical discipline.
An interest for aesthetics and the harmony of the body has always been characteristic of Chinese culture and has always been an integral part of their natural medicine.
This Congress has made the modern trends in Chinese medicine official, a kind of medicine that has always known how to wisely join their great naturalistic tradition to pharmacology's modern advances.
Such was the birth of Cosmetic Medicine with all its related branches, such as Cosmetic Surgery, Cosmetic Dermatology, Dentistry and traditional Chinese Dermocosmetics.
All these new scientific branches naturally stem from the classic branches of Plastic Surgery, maxillofacial Surgery, Dermatology and of traditional Chinese Medicine.

Riassunto

La Medicina Estetica e la Dermatologia Cosmetologica sono nuove branche della disciplina medica ampiamente rappresentate e legalmente riconosciute sul territorio della Repubblica popolare Cinese. Rappresentano "la nuova scienza che pone in evidenza il ruolo che la bellezza svolge per un vivere sano e felice" secondo quanto affermato dal Prof. Peng Quing Xing, in qualità di Presidente, all'apertura del II Congresso Mondiale sulla Medicina Estetica e Cosmetologia tenutosi quest'anno a Pechino.

Infatti la Dermatologia Estetico/Cosmetologica ha avuto in Cina un vero e proprio boom. Specialmente nel corso degli ultimi anni, con la apertura di reparti specializzati presenti nei maggiori ospedali e con l'apertura di studi medici specializzati in questa nuova disciplina medica.
Questo Congresso ha posto in evidenza come lo sviluppo della medicina tradizionale cinese abbia saputo coniugare la loro grande tradizione naturalistica con lo sviluppo della moderna farmacologia.
Infatti, l'interesse per l'estetica e per l'armonia del corpo ha da sempre caratterizzato la cultura ed ha sempre fatto parte delle tradizioni cinesi.
È nata così e si è sviluppata la Medicina Cosmetologica con le sue branche quali la Chirurgia Cosmetologica, la Dermatologia, la Odontoiatria Cosmetologica e la Dermocosmesi Cinese. Tutte queste nuove branche scientifiche provengono dalle classiche branche mediche quali la Chirurgia maxillo facciale estetica, la Dermatologia e la Medicina Cinese tradizionale.

MEDICINE & AESTHETICS

The relation between Medicine and Aesthetics, which has always been at the basis of Chinese culture, is now a teaching subject in official Chinese Medicine, too. As much was claimed by both Prof. Peng Qing Xing of Beijing University and Chairman of the Congress and by Prof. Feng-Xinzhong, who is Secretary General and Head of the Department of Dermatology at Shanghai University (1,2) (Fig. 1 and 2).

Fig. 1 Prof. Peng Quing Xing, President of the Congress.

Fig. 2 Prof. Feng Xin Zhong, Secretary General of the Congress and Head of the Department of Dermatology at Shanghai University

Evidence of the above statement can be found at the Huangsi Aesthetical Surgery Hospital in Beijing where patients are treated and cured also from an aesthetic viewpoint at the expenses of the Chinese Health Care System.

As a matter of fact, in that hospital as well as in others, there are nurses-beauticians working along physicians specialized in the different branches of medicine who are able to apply, for example, masks for acneic skins to the faces of those patients admitted into day hospital, or to redefine the eyebrows' contour (Fig. 3). Also, in

Fig. 3 Nurse-beautician concentrated on remodeling eyebrows. Aesthetical Surgery, Hospital of Huangsi Beijing.

the same hospital, it is possible to find a pharmacy selling cosmetics produced by the hospital to outside patients, too (Fig.4).

Fig. 4 The Pharmacy of Huangsi - Aesthetic Surgery, Hospital of Huangsi - Beijing

TRADITIONAL CHINESE MEDICINE

Traditional Chinese medicine seeks to treat tbe whole person rather than an individual disease

entity. Therapy is based on the interpretation of signs and symptoms encompassing the philosophy of Yin and Yang and to realignement of these forces (3).
The Chinese character Yin indicates the shadowy side of a hill, Yang represents the side which is exposed to the sun.
Yin and Yang oppose each other and, although they look like opponents, they are complementary. Thus, in a healthy body, Yin and Yang are perfectly balanced, whereas in the course of a disease the balance breaks down. Yin and Yang continuously modify themselves in such a way that, in the case of an increase in the body temperature, there will be an increase of Yang, whereas the ensuing perspiration (Yin) will decrease the body fluids and thus consume Yin.
Another fundamental concept in Chinese philosophy and medicine is Qi. This concept has variously been translated into energy, material force, or vital power.
The different translations of the word Qi are due to the difficulty of correctly translating this word which takes on different meanings according to the most different circumstances.
As a matter of fact, Qi represents an energy that manifests itself simultaneously on physical and spiritual level and is in a constant state of flux and in varying states of aggregation.
Traditional Chinese physicians perceive skin diseases as a breakdown in the essential relationship between Yin nourishment and Yang activity. Such a crisis allows the subsequent invasion of the body by several pathogenic factors such as wind, heat and humidity, which further exacerbate the disease damaging Qi, blood and body fluids.
Under such circumstances Chinese herbal therapy, seeks to eliminate hostile pathogens re-balancing Yin and Yang.
As much was learned from the erudite and amusing talk given by Professors Huang Feili and Wang Wei of Beijing University (4).

NUTRICOSMECEUTICALS & CHINESE FOOD

The constant link between the body's beauty and physical and psychic strength was the leit motive of the entire Congress, which paid particular attention to a project of Italian-Chinese cooperation which I explained to an alert audience.
In fact, in China too it was proposed to organize a master in Aesthetic Medicine and Cosmetic Dermatology following the programs that will be developed from this year onwards at the faculty of Medicine – headed by Prof. Renato Lauro (5) - at the University Tor Vergata in Rome. Such talk followed the main topic, on which I gave a talk, concerning nutricosmeceuticals.
The rhythm of life is regulated by our way of life and, consequently, by our diet and by the way we externally treat our body through exercise and the use of appropriate cosmetics.
The cosmetics we use not only have to improve and optimize the skin cells' turnover, but also make our hair and the whole of our body look more pleasant and harmonious. It is in order to reach these goals that cosmetics and food supplements must be defined as clinically correct, i.e. they must be formulated and controlled in their efficacy both *in vitro* and *in vivo* through a number of methods which have been properly validated.
The correct development of these innovative cosmetics and food products undoubtedly represent an important opportunity for both researchers and companies to meet everybody's expectation: grow old in the best way (6).
My talk raised much attention precisely for the importance that nutrition has always had in Chinese culture. For the Chinese in fact the old Roman proverb *mens sana in corpore sano* has always been valid. As a matter of fact, physicians in old China knew very well and held in high consideration the close relationship

between diet and health.
In the philosophy of Yin, we find that "each of the five main organs reacts to only one out of the five tastes: sour, bitter, sweet, hot and salty that correspond respectively to the liver, the heart, the spleen, the lung and the kidneys, and each organ takes from its corresponding taste the energy to re-generate itself". Thus the physician had the hard task of accurately choosing the best food for each individual according to his/her ailment. (7).
Food was considered so important that each foodstuff was treated in pharmacology together with all those elements of animal, plant and mineral origin having recognized therapeutic effects. Still nowadays, in modern Chinese pharmacology, all produces from the animal, plant and mineral kingdom are taken into consideration and many of them are used in nutrition science: "take the five cereals as the nourishing basis, the five fruits as complements, the five meats as tonic and the five vegetables as supplements and mix together the Qi and the Wei (the flavors) in your diet: such a mixture is what helps body and mind".
The search for Taoist harmony is an integral part of Chinese cooking: foodstuffs must be fresh and every dish balanced in its tastes, flavors and even in colors. Foodstuffs must be varied in the course of a meal so that the dry, the smooth and the crunchy, as well as the soft and the saucy, may be there (Fig.5).

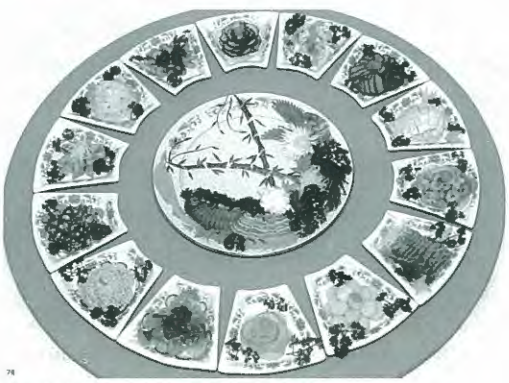

Fig. 5 Chinese food

What therefore characterizes Chinese culture is that in the course of their history the population has always been able to remain healthy in a balanced way precisely thanks to their nutritional philosophy. Chinese cooking is thus one of the most diversified in the world, like Italian cooking. The dishes available are in fact over 5000, subdivided into four main categories corresponding to as many geographical areas of the country. Northern cooking, known as Mandarin cooking, is typical of Beijing where it is possible to taste the renowned glazed duck; Southern cooking, which is also the most renowned and appreciated, is characteristic of the Canton area; Eastern cooking is typical of Shanghai and of the Yangtze regions and, finally, Western cooking that is characteristic of the Sichuan region and which is undoubtedly the hottest within the Chinese culinary tradition.
Keeping in mind mostly Cantonese cooking that the following proverb was coined: to be born in Suzhou, to live in Hangzhou, to lunch in Juangzhou (Canton) and to die in Liuzhou.
The reason why you should want to be born in Suzhou, considered the Chinese Venice, and live in Hangzhou is easy to imagine if you visit the marvelous gardens of these towns that are immersed in green areas (Fig. 6, 7).

Fig. 6 A famous bridge of Suzhou

THE AESTHETIC DENTISTRY

Prof. Ronald E. Goldstein, President of the International Federation of Aesthetic Dentistry, also gave a very interesting talk as he brilliantly explained how over the last few years in the United States several medical health providers, such as Dermatologists, Dentists and Plastic Surgeons, have been working in team with beauticians so that their patients may be completely satisfied of the results they obtain (8) (Fig. 8).

Fig. 7 Beautiful garden in Suzhou

Fig. 8 Prof. RE Goldstein, President of the USA international Federation of Aesthetic Dentistry

It is important not only to cure or substitute a cavity, but it is also very important to keep into its due consideration the gums' aspect, the regular alignment of the teeth, their color, the lips' outer look and also the general look of the face.
It is for this reason that at his Dental Clinic there are dental technicians, dermatologists, plastic surgeons, cosmetologists and beauticians who work together to obtain the best results, both clinical and aesthetic, so that the patient may be totally satisfied.
The treatments' final aim is to solve all the medical problems improving the patient's look both on the short and on the long term.
A whole session was thus devoted to the aesthetics of the mouth and teeth; among those who participated in this session were Philippe Gallon from France, Mariano Flore Rubio from Peru, Sandesh Mayekar from India, So-Ran Kwon from Korea and Luo Yipping from China (9-13).
Healthy and shiny teeth are in fact a fundamental complement to make your smile pleasant and your face aesthetically beautiful.

Mens sana in corpore sano

Such was the general catch-phrase of the Congress which was attended, as Italian guests, by Prof. Enzo Berardesca, Head of the Dermatological Department, S. Gallicano Hospital in Rome, Dr Desanka Raskovic from I.D.I. in Rome and Prof. Luigi Rusciani, who is a renowned dermatologist and plastic surgeon from the Catholic University in Rome (14-16) (Fig. 9,10).

Fig. 9 Desanka Raskovic MD from I.D.I. Hospital in Rome, giving her talk

Fig. 10 Prof. Luigi Rusciani, from Catholic University of Rome, giving his talk

Enzo Berardesca and Desanka Raskovic explained how two active principles such phosphatidylcholine and the soluble azelaic acid work simultaneously in the treatment of acne.

These two derivatives, inserted into a particular nanostructured emulsion which was patented by MAVI, have resulted active in drastically reducing both surface lipids and the bacterial colonies of *Proprionibacterium acnes*, which is the main cause of the development and advancement of acne. Its use turned out to be very interesting also during the summer given its harmlessness that the cosmetic has shown to possess, together with a total lack of side effects due to allergic photosensitization.

Prof. Luigi Rusciani also talked about his personal experiences on the use of a mixture of ascorbic acid, β-glucane and hyaluronic acid having a low molecular weight (Fig. 11).

This new medical-surgical device has shown to possess interesting properties in modifying and improving the aspect of acne scars and stretch marks as well as lengthening the time of duration of the traditional natural skin fillers.

A talk that was completely different from the others was the one given by Prof. Katsuya Takasu, chairman of the Japan Society of Liposuction Surgery. He showed to all the audience how he was able to "get 15 years younger" (17).

While he was talking in playback (?!), he explained in person the surgical interventions that his colleagues have performed on him (face-lift, liposuction of his cheeks, subchin and stomach, redistribution of his hair, peeling with phenol, etc.). Acting under local anesthesia, he described himself the various interventions.

This is how all the wrinkles disappeared from his face, his general look improved and he was able to go back in time, as was evident from the pictures that showed him the way he was before and the way he appeared to us after his intervention.

The participants of the Congress had certainly never been present at surgical operations performed by a plastic surgeon on his/her own person. This unusual presentation has characterized this innovative International Congress of Cosmetic Dermatology, too.

There were many other interesting talks that went from the cosmetic-aesthetic use of natural products that are typical of Chinese culture, to collagen fillings to modify wrinkles and skin scars to surgical operations to increase the volume of the breast or to make the shape of the eye more European-like.

What is interesting to underline is also the collaboration existing in hospitals between the plastic surgeon, the dermatologist and the beautician-nurse in order to obtain better aesthetic results respecting the patient's health.

The several thousands of people who participated in this Congress crowded the halls and listened to the talks with great interest. Even the exhibition area was well organized. The only Italian company was MAVI from Rome (Fig. 11).

Fig. 11 The booth of MAVI at the Congress Exhibition

What is interesting to underline is the peculiarity of Cosmetic Dermatology and of Chinese Plastic Surgery that is closely related to their culture and the way the Chinese live a beautiful human body completely immersed in the surrounding nature (18, 19).

It is interesting to visit in all the towns with a Chinese spirit the beautiful parks each full of flowers and plants wisely looked after (Fig. 13), and the way the Chinese conceive their home in the ancient Chinese culture.

Fig. 12 A view of the administrator's garden in Suzhou

THE CHINESE WAY OF LIVING

As a matter of fact, the home is organized around the garden in such a way as to make it possible to enjoy it from all different angles (Fig. 13).

Fig. 13 Another view of the administrator's garden in Suzhou

A particular hint must be given to the sensations that a European visitor feels every time that he/she arrives in China and makes contact with the crowd.

The Chinese you meet on the street are in great numbers and move quickly, almost running; they take small, quick steps, as graceful as felines. On the street, which is the huge stage of Chinese life, people carry out all their activities from the small hours of the morning until the moment when dusk calls everybody back home. The old neighborhoods, which are the greatest majority in town, are characterized by very small houses, one onto the other, sometimes separated by narrow alleys where a bicycle can barely pass. In Beijing, but also in Shanghai as in many other cities towns, bicycles come in great numbers and are used by this colorful crowd made up of different ethnic groups.

Older and younger women shield from the sun with small umbrellas that they insert even into the handle of their bicycles. Their complexion in fact must remain perfectly white!

It is also thanks to this way of staying outdoors that skin tumors are less spread throughout the whole of the Far East (Fig. 14).

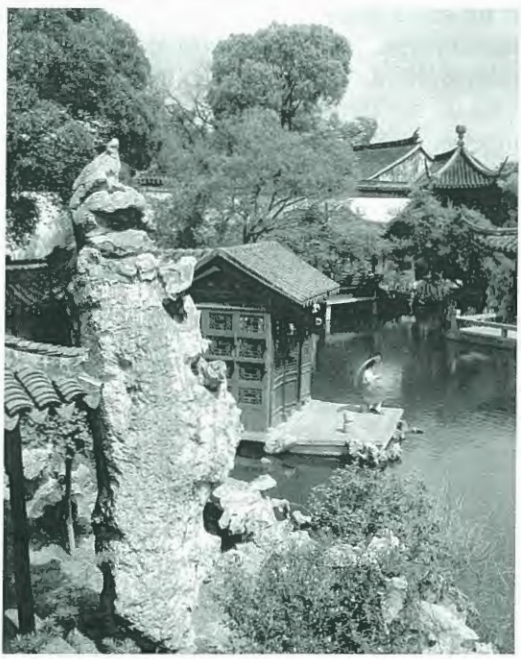

Fig. 14 Girl with umbrella. Suzhou Garden

Without exaggerating, feeling no nervousness nor stress, from dawn to dusk the Chinese strive, commit themselves, produce and consume following an ethic of life that has characterized them throughout the centuries even if - due to the events of recent modernization - a more Western-like way of life is noticeable, with all its faults.

A typically Chinese custom is to take birds in captivity out to converse. What you see in the mornings in the beautiful and well-kept parks in the towns look like a picture painted in light colors. In these parks you meet old people with their cages completely covered to protect their little birds from noises and the confusion. The wicker cages are laid on the lawn. Once the pieces of cloth are removed from the cages the birds are let to communicate and learn how their free companions whistle (Fig. 15).

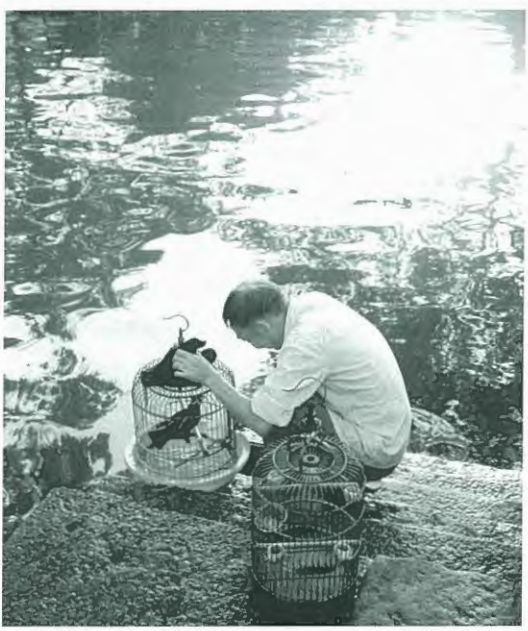

***Fig. 15** A man with his bird*

Another custom that is noticeable early in the morning in the parks is a crowd of people of all ages performing Taiji Quan.

Taiji Quan is a particular workout that is carried out by moving very slowly and which is particularly important to safeguard your health and to prevent diseases. As a matter of fact, the slow movement of all muscles moving in harmony with your breath has positive effects on the nervous system and on the cardiovascular, respiratory, osteo-articular and digesting systems and on your basic metabolism.

Chinese Traditional Medicine and Western Medicine represent in China today two different ways of treating pathologies. They can co-exist, but at any rate they must reach the goal of keeping all citizens healthy.

Aesthetic Medicine and Cosmetology also aim at treating the look of the body and the health of the spirit following the ancient Chinese traditions and the technical-scientific progress that took place, especially in the West, in the course of the last fifty years.

This is the fundamental message that was learned from this interesting Congress. About five thousand physicians and paramedics took part and about thirty companies from the dermocosmetic field participated in it. Of these only one was Italian.

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Where Cosmeceuticals and Nutraceuticals are going

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Summary

With the improvement of the average lifestyle during the last fifty years, no one wants to look or be old anymore. "What is beautiful is good".
Attractiveness in the elderly is really equated with youthfulness. Facial appearance , in fact, is one of the most powerful factors influencing interaction in many situations. Therefore, the modern cosmetic is to ameliorate and enhance the more positive aspects of appearance, while the aim of diet supplements and healthy nutrition is to improve our general well-being.
Cosmetic products (cosmeceuticals) and diet supplements (nutraceuticals) occupy today a grey area since the real activity they may have is not well defined.
Cosmeceuticals cover a wide range of products such as those aimed at diminishing wrinkles, acne marks, blotches, scars and brown spots.
Nutraceuticals cover products for reducing sugar, caffeine, salt intake, for eating less, reducing calories, stopping/reducing junk/fast food, stopping/reducing alcohol or/and fried foods. However they represent the reality of products necessary to generally prevent pathological diseases.
For these reasons it would be necessary to clearly define with appropriate laws the meaning to be given to functional dietetic products and to active cosmetics, better regulating their production and distribution, showing their real efficacy and safety carrying out more *in vitro* and *in vivo* studies.

Riassunto

Con il miglioramento dello stile di vita avvenuto negli ultimi 50 anni nessuno vuole più apparire o essere vecchio. Bello è buono e attrarre l'attenzione per una persona della terza età equivale ad essere giovane.
L'apparire sani e belli rappresenta un fattore fondamentale nelle interazioni e nei contatti sociali. Perciò, compito di un moderno cosmetico, è di migliorare ed esaltare gli aspetti positivi dell'apparire, mentre l'integratore alimentare deve esaltare lo stato di salute del corpo.
I prodotti cosmetici (cosmeceutici?) e gli integratori alimentari (nutraceutici?) occupano oggi un'area cosiddetta grigia non ancora ben definita nelle funzioni che realmente svolgono o possono svolgere categorie di prodotti che nella realtà sembrano in grado di prevenire lo sviluppo di alcune patologie oltre che migliorare l'aspetto generale dell'apparire.

I cosmeceutici sono così in grado di alleviare e migliorare patologie quali l'acne, o ridurre l'impatto negativo di cheloidi e smagliature.
i nutriceutici possono sostituire l'uso di zuccheri riducendo la quantità di calorie assunte con l'alimentazione e spesso sono anche in grado di migliorare le funzioni della cute, modulare riportando alla norma la barriera alterata da patologie quali la dermatite atopica o la psoriasi.
Per tutti questi motivi sarebbe necessario dimostrare sia l'efficacia che l'innocuità dei cosmeceutici e dei nutriceutici conducendo un maggior numero di studi sia *in vitro* che *in vivo*, come sarebbe anche opportuno definirne meglio le funzioni mediante nuove e più chiare normative.

Under the high Patronage of the Senate of the Italian Republic, the Ministry of Health, the National High Institute of Health and Regione Lazio, in the prestigious location of the CNR there took place the following international conference: "Nutri-cosme-ceuticals: a challenge for the future?" (Fig. 1).

Fig. 1 Opening Cerimony. From the left: *Prof. C. Orfanos, P. Morganti, A. Capparoni*

Organized by the International Society of Cosmetic Dermatology together with the Faculty of Medicine of the University "Tor Vergata", the Faculty of Pharmacy of the University "La Sapienza" of Rome and the Accademia di Storia dell'Arte Sanitaria, this conference was chaired by Professor **Renato Lauro**, dean of the Faculty of Pharmacy in Rome (Fig. 2), and was attended by researchers from 16 different countries and 110 speakers for a total attendance of about 500-600 participants.

Cosmeceuticals and nutraceuticals occupy today a grey area and can only claim on the packaging that they help to relieve certain symptoms.

However they represent the reality of products necessary to generally prevent pathological diseases.

Cosmeceuticals cover a wide range of products such as those aimed at diminishing wrinkles, acne and stretch marks, blotches, scars and brown spots. Moreover they may be used to complement aesthetic dermatology and surgery, combining both medical and cosmetic necessities.

On the other hand, nutraceuticals cover products for reducing sugar, caffeine, salt intake for eating less, reducing calories, stopping/reducing junk/fast food, stopping/reducing alcohol or/and fried foods.

Fig. 2 *Prof. R. Lauro speaking*

THE SKIN BARRIER

But the structure of skin is quite complex, being composed of several layers, each of which is equipped with its own arsenal of defence molecules, and the various systems differ from each other on the bases of layer's susceptibility to oxidative stress and its function.

In particular, human stratum corneum (SC), shows specific antioxidant activity, against oxidative environment injuries, including UV radiation, chemical and biochemical oxidants of exogenous and endogenous origin, air pollution and anaerobic organisms. Therefore it is generally agreed that one of the major contributions to skin aging, skin disorders and inflammatory skin diseases, involve a interconnected redox-sensitive pathways, based on reactive oxygen species (ROS).

This is what described in a clear way from Prof. **Stefano Manfredini** from Pharmaceutical Science Dept. University of Ferrara, Italy. Small variations in the basal level of ROS, play a role not only in the context of damage to biomolecules and cells, but also in inducing more complex responses such as the activation of cellular si-

gnalling pathway, culminating in modulated gene expression, as well as post translational modification of proteins. This is the reason because of 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 the medical science.

In fact, the skin performs its barrier 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), 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, 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 for receiving 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 body organic defenses.

This was another interesting theme treated from Prof. **Biagio Guarneri**, Head of Dermatological Dept., University of Messina, Italy.

THE ANTIOXIDANT NETWORK

Redox sensitive events in the skin involve direct interaction with specific receptor, and/or redox-activation of members of signalling pathways such as protein kinases, protein phosphatases, transcription factor, cytokines, adhesion molecules, and T-lymphocyte receptor.

A better comprehension of the mechanisms involved in skin oxidation, and regulation of cell response to antioxidant treatments, would be of help in the development of more powerful pharmaceutical and cosmeceutical antioxidant strategies to prevent or modulate skin disorders.

Skin is therefore an efficient barrier aggressed by both external and internal perturbations caused by oxidative stress. The antioxidant defence of the skin is constructed to face these two types of aggressions.

The external damage is determined by UV irradiation and by atmospheric pollution. The defence from these agents is mainly accomplished by a barrier of lipids and corneocytes which form the stratum corneum. The oxidation of the lipids of this stratum reduces the efficiency of the barrier causing a more pronounced water loss, and a reduction of the defence against possible infections. The antioxidant defence system in skin was the topic of Prof. **Umberto Cornelli** from Loyola University Medical School of Chicago, USA (Fig. 3).

Fig. 3 *Prof. U. Cornelli - Univ. of Chicago*

Since the enzymatic systems is not efficiently operating in corneocytes, squalene is considered to be the most powerful natural antioxidant in this compartment.

The mechanism and modern therapy for vitiligo

was another interesting topic presented at the meeting by Prof. **Yon Kee Park**, President of Korean Society of Cosmetic Dermatology.
In vitiligo-involved patients, it may causes disruption of normal social life especially in colored people. The use of the right cosmetics may be of fundamental help.
The nutri-cosmeceutical market even if criticized from some trade and/or consumer's associations nevertheless has an important ongoing annual increase of about 20%.
This increase is due to the promises this market often keeps thanks to the scientific progress both of new discovered active principles and innovative carriers able to penetrate the skin strata and/or the mucous membranes. For these reasons there is also the need to reassess the existing cosmetic and food laws and its interpretation in order to facilitate the communication of beneficial, scientifically valid information to consumers in terms they can understand.
And this was the scope of the round table "The international rules in the cosmetic and dietetic field: status quo and future prospective", organized during the Multidisciplinary Symposium on Nutri- cosmeceuticals.

EUROPEAN RULES

The round table focused on the European Union's legislation on cosmetic and dietetic products and the possible perspectives and changes that can be expected for the future.
While I stressed once again that cosmetic and dietetic products must be carefully and clinically tested before they can be defined effective and safe, **Senator Riccardo Pedrizzi** (Fig. 4) underlined that also in Italy there is a need for a cosmetic surveillance that may monitor – on a national level – a business sector that reached the considerable sum of 8500 million Euro in Italy this year.

Fig. 4 From the left: *P. Morganti, R. Pedrizzi*

All the leading members of the cosmetic and dietetic field, from both the Ministry of Health and the High National Institute of Health, had their say during the Round Table for different reasons. Dr **Colella** (Fig. 5) and Dr **Guidarelli** from the Ministry of Health (Fig. 6) underscored how the present European legislation rightly protects and safeguards consumers although a stricter cosmetic supervision is felt as necessary. Such supervision ought to be organized through a closer collaboration among all the people involved, i.e. representatives of the cosmetic business, dermatologists, pharmacists and consumers, of course.

Fig. 5 *Dr. M. Colella - Italian Ministry of Health*

Fig. 6 Dr. Guidarelli - Italian Ministry of Health

As much was claimed by Professor **Giuseppe Salvatore**, who coordinates the various laboratories of the National Institute of Health that are given the task of controlling cosmetic products. Professor **Aureli** and Professor **Gagliardi** stressed once again the need for a greater harmony among the different rules and the application of laws allowing the member states to easily control both the dietetic products and foods unifying the methods that the producing industries should put into market. Dr **Gramiccioni** (Fig. 7) pointed out how medical devices, such as some injectable and non-invasive products ought to be strictly evaluated too, bearing in mind their use associated with the topic application of cosmetic product. The use of hyaluronic acid as a skin filler is an example.

Dr **Papadia** from the Committee for a Fair Competition in Trade and Dr **Leopardi**, who is chairman of FOFI (Federation of the Italian Pharmacists) underlined the need for a stricter control on advertising that unfortunately very often, especially in the past, turned out to be deceiving for the consumers (Fig. 8).

***Fig. 8 Round Table:** Prof. G. Leopardi speaking.*

Fig. 7 Dr. Gramiccioni - Italian Ministry of Health

At the conclusion of the discussion between all the speakers and participants, Prof. Giuseppe Salvatore suggests to take in Italy following initiatives:

- census of cosmetic manufacturing, packaging and exporting industries in each region;
- drawing up of a notified ingredients form;
- drawing up of a product form;
- setting up of a method to report all undesired side effects (family doctor, dermatologist, chemist, center for antidotes) through an adequate form for data collection;
- definition of an interregional pilot program of cosmetic surveillance.

BOTANICALS AND PHYTOCOSMETICS

But other important observations came out about the need to scientifically prove the global effectiveness of herbal extracts.

Therefore, declared Prof. Salvatore (Fig. 9), the following requirements are fundamental for phytocosmetics:

- the main herb used must contain substances, which are functional in cosmetics. They must be contained in adequate quantities also in their extracts;
- the solvent and process (according to cases referred to by ratio Extracts/Crude Drug, or Solvent/Crude Drug), must be suitable in order to dissolve the active ingredients (or the

phytocomplex) and obtain an extract that can be practically used (tincture; fluid, soft or dry watery or hydroalcoholic extracts; generic glycolic, butyl or greasy extracts; supercritical extracts);
- the prepared extract must be chemically characterized and standardized in order to meet specific requirements for a constant chemical composition, a chemical and microbiological purity and stability to be used in large quantities for phytocosmetic preparations.

But the best way to make the active principles efficacious is represented by a vehicle which must have chemical-physical requisites to enhance stability, efficacy and to control the degree of penetration through the skin layers.

Fig. 9 Prof. G. Salvatore

SKIN PENETRATION

The efficay of cosmetic products, then, can be determined by the relationship established between the permeability coefficients of the SC and the structure features of the penetrants, such as the cosmetic carrier and the active principles used.

The optimization of the concentration of the active principle and its degree of activity in the right cutaneous area will make the beauty product efficacious, especially if the product has a pleasant aspect and it is easy to apply.

Therefore Delivery System affect the efficacy of cosmetics and and/or functional food and they should be considered clinically correct, when their efficacy has been proven by biological and clinical correct methodologies. At this purpose the development of novel or more active cosmetics (cosmeceuticals?) or functional food (nutraceuticals?) is one of the most exciting and promising way in which the future food and cosmetics may address the human health needs and well being and a more strict collaboration between expert researchers from both university and industry seems to be necessary.

This was the leit motive discussed during this International and Multidisciplinary meeting in the session on Percutaneous and Mucous Absorption chaired from Prof. **Howard Maibach**, famous dermatologist of the University of San Francisco, USA (Fig. 10).

Fig. 10 Prof. H.I. Maibach - Univ. of S. Francisco

According with Prof. **Maibach**, it is tacitly assumed that one mechanism of action of cosmeceutical relates to the delivery of one or more "actives" into one of more skin compartments: stratum corneum, viable epidermis, dermis, eccrine / apocrine / sebaceous glands and hair follicles. For these reasons two of the main problems confronting chemists and dermatologists have been always to obtain the right absorption of cosmetic product through the skin layer, and to prove their clinical efficacy.

CLINICALLY CORRECT COSMETICS

At this purpose the so-called clinically correct cosmetics", are beginning to be sold i.e., products whose efficacy have been demonstrated and proven safe. In fact, the interference caused by all the products topically applied to the skin, mainly on the intercellular lipids of the stratum corneum (SC) but also on the cellular membrane of all the viable skin layers, determines both the minor or major efficacy of the cosmetic principles used and, of course, the eventual undesirable side effects that might arise. These were the opinions of the research group of Mavi during this meeting.
The same opinions were also expressed from the dermatologist Prof. **Giuseppe Fabrizi**, Catholic University of Rome, Prof. **Cesare Bruno**, physiologist from University of Urbino and Prof. **Bruno Berra** (Fig. 11), Dept. of Biochemistry-University of Milan.

Fig. 11 Prof. B. Berra

The increasing significance given to appearance in human relationships has also increased the demand for facial rejuvenation procedures. This was the topic of a round table chaired by Prof. **Roberto Bracaglia**, Prof. **Luigi Rusciani** from Catholic University of Rome together with Prof. **Paolo Palombo**, Head of Plastic and Reconstructive Surgery, S. Eugenio Hospital of Rome (Fig. 12A, 12B).

Fig. 12A From the left: *Prof. P. Palombo and Prof. R. Bracaglia*

Fig. 12B *Prof. L. Rusciani*

Face lift, age spots, keloids and scars were the most interesting topics treated. Nowadays, pulsed dye laser may totally eliminate pigmented lesions as well as laser resurfacing may reduce wrinkling giving a better reconstructed derma. About scars there are a variety of usable techniques such as filler injections, serial excisions or epithelial abrasion, as stated by Prof. Palombo and Prof. **Marawali Harahap** from the Dept. of Dermatology, University of North Sumatra, Indonesia (Fig. 13). Moreover a new therapeutic approach seems also to be the use of antitbomotoxic drugs as reported by Dr. **Nicola Dell'Edera** from Rome to define the quality of the active principles, to regulate their absorption and consequently to verify the efficacy of tbe cosmetic products and/or the diet supplement is necessary

a closer collaboration between industry and university. The latter should furthermore organize special medical courses devoted to study and validate novel clinical non-invasive methodologies.

Fig. 13 Prof. M. Harahap - Univ. of North Sumatra

MASTER DEGREE IN COSMETIC DERMATOLOGY

At this regard Prof. Lauro announced an innovative European Master-degree in Cosmetic Dermatology and Aesthetic Medicine which will start contemporary in five Italian Universities in the Academic year 2002/2003 (Fig. 14).

Fig. 14 From the left: *P. Morganti, R. Lauro.*

The main objective of this two-year master is to lay the theoretic and practical basis of Cosmetic Dermatology and Medical Aesthetics as a new clinically oriented science. This Consortium of five primary Universities will be also able to organize and standardize new medical technologies useful for controlling the efficacy both of cosmetics and functional food.

Other objectives of this Consortium is also to establish more stable link with the European Industrial Compartment for developing new delivery nanometric-scale systems to utilize as carrier for skin and or mucous membranes.

Blue or marine cosmetics stands out as the latest novelty, in terms of time, that appeared on the cosmetic market following natural cosmetics, botanical cosmetics, mineral water and mad-based cosmetics.

However, can the present technological progress to be found in all fields of trade truly define these various kinds of cosmetic products or are these latter diversified for a marketing reason only? Do we really have the products and the techniques allowing us to evaluate and verify the differences – as long as there are differences – between a cosmetic product so called natural and another one deemed normal?

Are homeopathic, Chinese and ayurvedic cosmetics real categories of cosmetic products that differ from the standard?

At any rate it is sure that the use of *clinically correct cosmetics* together with a balanced diet and less "stressful" and closer to nature way of life stands as the basis for the real well being of our organism. All these fascinating topics were discussed in the course of this interesting conference whose aim was also to clarify the meaning of the following two terms: nutri/nutraceuticals and cosmeceuticals.

ACNE AND PHOSPHATIDYLCHOLINE

Thus, it has been shown, from Dr. **Desanka Raskovic** from IDI Hospital in Rome (Fig. 15), Italy, a significant decrease in the levels of linoleic acid in sebum of patients affected by acne and a contemporary and abnormal increase of squalene and oleic acid. This unbalance may be reported at normal levels by the use of an innovative nano-colloidal cosmetic gel, patented by

MAVI Co. The squalene concentration decreases drastically since the second week of treatment, while at the same time it can be noted a regular increase of the linoleic acid present in the stratum corneum lipids.

Fig. 15 Dr. D. Raskovic - IDI Hospital - Roma

Based on the combined activity of phosphatidyl-choline-linoleic acid rich and azelaoyl-diglycinate, this nano-colloidal gel was also able to strongly decrease the superficial skin lipids and the presence both of corinebacterium-acne and ROS, normally present in people affected by acne juvenilis, contemporary increasing skin hydration. In fact, according with **U. Moser**, from Roche Vitamins Europe Ltd, skin hydration and transdermal waterloss seems mostly due to the linolenic acid content in the skin. What is interesting to underline is the complete absence of side-effects recovered by the use of this gel after a three months use of the cosmetic formulation, also in presence of sun-light.

Moreover today, consumer needs for creams have dramatically changed in comparison to some years ago. Prevention gets more and more important as life conditions have changed as well as unlimited youth via repair is the dream of many people.

Mavi Booth

Clinique Booth

THE MEDITERRANEAN DIET

More active cosmetics, more efficient functional food and a better way of eating and, generally, leaving, was another live motive of this multidisciplinary meeting. It is necessary to remember, in fact, that more than 50% of adults in the United States are overweight and one in five is obese, according to the Center for Disease Control and Prevention – approximately 25% of women and 19,5% of men. These adults have a 50-100% increased risk of death from cardiovascular diseases such as diabetes, heart disease, and stroke. Genetics may account for 40-50% of obesity, but some of the environmental factors that influence obesity include attitudes toward unbalanced diet and exercise. At this purpose Prof. **Publio Viola** (Fig. 16) and Prof. Bruno

Berra from University of Milano, spoke about the solid biological role of the so-called Mediterranean Diet (MD) useful to live in a better way. Moreover fruits, vegetable and olive oil represent the base of MD, rich in antioxidant compounds. Moreover extra-virgin olive oil contains not only a balanced quantity of omega-3 and omega-6 poly-unsatured fatty acids, but also anti-oxidants compounds such as tocopherols, polyphenols and squalene in high quantity, necessary to prevent the over-all cellular oxidative damage. Furthermore topical application and oral intake of olive oil and/or carotenoids suppress UV-induced carcinogenesis and may thus be useful for the skin photo-protection.
This is the typology of natural and clinically correct cosmetic products that may be defined "cosmeceuticals" or at least cosmetic products of the new generation.

Fig. 16 Prof. P. Viola

THE UNCONVENTIONAL MEDICINE

The number of people who turn to unconventional medicine and natural products increases with each passing year in Western world to the extent average rate, of about 40%.
We increasingly turn to biological products and, together with homeopathy, Chinese medicine as well as with Ayurvedic Indian medicine are more and more widespread. These latter have a rightful place among alternative and complementary therapies.
Do we also have the bases to define and distinguish from a scientific viewpoint those cosmetic and dietetic natural products that are an alternative to the "normal and dietetic products"?
Did we define the necessary markers to control the uniformity in time and in the different lots of the phytotherapeutical extracts?
Do we have the analytical and pharmacological methods that allow us to verify the "infinitesimal" dosage and the clinical effectiveness of dietetic and homeopathic products?
Many of the researchers who attended the conference tried to give a clear answer to all these questions. Particularly interesting was the view given by Dr **Anthony Dweck** on the main plants and active principles having a vegetal origin that are used worldwide. Dr Dweck is president of the UK Society of Cosmetic Scientists (Fig. 17).
Dr Dweck highlighted the use of plants to sooth dryness of the skin and the cases of erythema caused by aggressive environmental factors and by the sun to whose rays, both positive and negative, we expose ourselves perhaps too often.

Fig. 17 Dr. A. Dweck - President UK Soc. Cosm. Scientists

The significance and the role of aromatherapy and aromachology were clearly demonstrated by Prof. **Carla Scesa**, from University of Siena (Fig. 18).

Fig. 18 Prof. C. Scesa - Univ. of Siena

The cosmetic scientists carefully analyze the potential cosmetic use of all the smelling substances able to act on the most important issue related to the achievement and conservation of the human physical and psychical well being.
The smelling molecules, in fact, not only are absorbed through the skin but also succeed in hitting the vital centres of our brain. Dr. **V. Badmaev**, from Sabinsa - USA, talked about the effectiveness of the nutriceuticals based on methods connected with the ancient Tibetan traditions whereas Dr **De Monte**, who is a scholar of Ayurvedic Indian medicine, took us back in time to six hundred years ago showing how, along with our allopathic medicine, there exist other ways to "cure" pathologies that were healed thousands of years ago through therapeutic means that take into greater consideration our "personality".
In this session of works it was inevitable for professor **Francesco Negro**, who is a well renowned Italian homeopathist, to intervene , stressing once again how important the homeopathic dilutions are in curing even very serious pathologies. It was once again underscored how the absence of side effects makes homeopathic medicine a safe medicine. However, the safety and effectiveness of both the cosmetic and dietetic products also depend on their rate of absorption, which is connected with the use of vehicles studied precisely for this purpose.
The penetration of environmental polluting substances, topic drugs and cosmetic products through the skin layers is indeed connected with a number of factors among which stand out, of course, the state of health of the skin itself and thus of the "cutaneous barrier", as well as the chemical-physical characteristics of the carriers used to this end. We have a similar problem with the absorption through the mucous membranes that concerns especially the whole digestive tract that is involved in absorbing all the products that we intake with our diet.
Consequently, the activity and the efficacy of cosmetic and dietetic products is connected with both the selection and the control of the active principles that are used because they are deemed more suitable for the goal we aim at, but also and mostly because they are inserted into suitable vehicles or carriers that allow them to reach and act in the right part of the body.

UV PROTECTION

For instance, in the case of a sun product, the screens to be used must remain stable and "active" on the horny layer because they are necessary to neutralize the negative effects of UVB and UVA rays, which hit our skin exposed to the sun or the sun-lamp.
As a matter of fact, a deeper skin absorption may cause toxic effects that are never to be underestimated. For these technical motivations professor **P.U. Giacomoni** from Clinique-New York presented: The Photosomes (Fig. 19).
These particular micro-particles have the ability to slowly yield solar filters and anti-oxidants to the skin as they are being exposed to the light.

In a similar way, all active substances making up the anti-oxidant network of our skin and/or our organism must, to the contrary, penetrate more deeply through the different layers of our skin or mucous membranes to counter the damages caused by the environmental polluting substances in excess, which cause the formation of free radicals.

***Fig. 19** Prof. U. Giacomoni - Clinique*

Dr. **I.R. Scott** (Fig. 20) and **C. Harding**, well known English researchers who have been collaborating with Unilever's research centers for years, have pointed out how important the role of NMF (natural moisture factor) is to keep the skin moisturized at the level of the horny layer.

***Fig. 20 from the Left:** H.I. Maibach, I.R. Scott.*

Dr. **Blume**, a German researcher, and Professor **Touitou** from the University of Jerusalem (Fig. 21), have talked in very precise terms about the possibility of modulating the trans-cutaneous penetration of what is applied on the skin in terms of particular liposomes or micro and nano-capsules.

***Fig. 21** Prof. E. Touitou - Univ. of Jerusalem*

Professor **Lee** instead, from the Korean University of Yonsei (Fig. 22), talked about the importance of the role played by the calcium ion in regulating the skin barrier.
Perturbation of the epidermal barrier leads to the loss of normal calcium gradients and barrier recovery is parallel to the restoration of the calcium gradient in the epidermis.

***Fig. 22** Prof. Lee - Korean Soc. of Cosmetic Dermatology*

THE PROTECTIVE CAROTENOIDS

Among the topics of the conference much emphasis was given to the so called functional

foods of the third generation, i.e. those dietary supplements that can play an important role especially in preventive medicine.
Consequently betacarotene or carotenoids were talked about mostly by Dr. **Gerritsen**, and Professor Fabrizi.
The use of carotenoids, especially if well balanced among them and associated with vitamin E and C, are apparently able to greatly decrease the free radicals that can be found in bulk, for instance, in the blood of those people who smoke heavily.
These controls have been obtained lately in a new non-invasive test that allows us to define the so called "protection factor against free radicals" (RPF).

View of the old Pharmaceutical Laboratory, Accademia di Storia dell'Arte Sanitaria - Roma

View of the old Pharmacy Laboratory, Accademia di Storia dell'Arte Sanitaria - Roma

HAIR LOSS

Another topic of the conference focused on the activity carried out by the dosed extracts of Serenoa Repens with regards to the alpha reductases that can be found at the level of the sebum on the scalp of those patients affected by androgenetic alopecia.
The Italian biologist Dr. **Fasulo** and Professor **Argenziano**, a dermatologist from the University of Naples, talked about the topic and/or systemic effectiveness of such phytotherapeutic extract.
According to Dr. Fasulo, the combined used of topic frictions and dietetic products based on Serenoa Repens and gelatin-cystine are apparently able to greatly improve those patients affected by androgenetic baldness.
Professor **Lanzone**, from Gynaecology Department of the Catholic University of Roma, talked about the beneficial effects that phytoestrogens may have in the various pathologies that are hormone-dependent (Fig. 23).

Fig. 23 Prof. A. Lanzone - Catholic Univ. of Roma

Such phytoestrogens if taken orally as dietetic products are surely beneficial during the premenopause period thus allowing a reduction in drugs taking having an estrogenic activity.
It is necessary, however, to clearly define with the appropriate laws the meaning to be given to

functional dietetic products and to active cosmetics, better regulating their production and distribution. It is necessary also to show their real efficacy and safety and to define the qualities that are ascribed to them by an increasingly aggressive – but not always truthful – marketing about their real effects.

Gala Dinner From the Left: *P. Morganti, C. Orfanos, H.I. Maibach, A. Giardina.*

For the cosmetic and dietetic products exotic and during product performance claims have become, in fact the essence of many companies' marketing plans. To be defined clinically correct or cosmeceuticals and/or nutriceuticals, it would thus appear necessary the use of the right active principles and vehicles calibrated and stable in time. It is necessary to carry out more thorough clinical studies on the end product in order to show its real effectiveness.

These and other interesting topics were presented and discussed from 120 researchers coming from universities and industries world wide during this two and half meeting, organized in a prestigious location: the Italian National Research Centre (C.N.R.) in Rome.

During the sessions coffee breaks were offered the original Italian espresso by *Caffè d'autore* Morganti, and the delicious typical pastry by the Community of Monti Cimini. Least but not last the exquisite red and white wine produced in the region of Lazio by the company Pietra Pinta were offered during the brunches.

Coffee Break From the left: *P. Morganti, B. Guarnieri, G. Borroni, G. Trevisan. The Best coffee in Roma*

Opening ceremony *- S. Spirito Hospital - Roma*

Opening ceremony *- S. Spirito Hospital - Roma*

VIEW OF THE CONGRESS LOCATIONS

Exhibition Area

Room A

Room B

Press Conference

***MS. A. Lebovich** Scientific Books Corner*

Scientific Secretariat

Hostesses

CHITOSAN IN PHARMACY AND CHEMISTRY

By Riccardo A.A. Muzzarelli and Corrado Muzzarelli
2002. pages 524 - Soft Cover
EUR 90.00
ISBN 88-86889-07-0
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VIA VALTESINO 29
63013 GROTTAMMARE (AP) Italy
Fax +39 0735735121

This book deals with all the potential and current applications of chitosan in several fields, firs of all the pharmaceutical and medical one. In five sections it reports a collection of articles all concerning chitosan and its wide range of applications. The first section begins with an interesting introduction about the discovery of chitin and a concise portrait of the discoverer.
Following we can find all articles about chitosan as a drug delivery, for example chitosan salt for colon-specific drug delivery, chitosan microspheres of ibuprofen and chitosan and trimethyl chitosan microparticles associated with diphtheria toxoid for mucosal vaccination. In this study, chitosan and trimethyl chitosan microparticles were investigated for their capacity to enhance the systemic immune response against diphtheria toxoid after nasal and oral administration.
The second section illustrates all the medical and dietary aspects.
In this section it is also reported the antimicrobial activity of chitosan that brings to a remarkable question: could chitosan be considered also a novel food preservative?
Whilst consumers are demanding reductions in the levels of synthetic preservatives used in food products, there is a need to develop new preservation systems based on innocuous antimicrobial compounds found in nature, chitosan is one of them. The third section is about the inorganic composites and polymer blends such as cellulose-chitosan, chitin-surfactant and others, and in this part there are also fascinated articles as one about the use of chitosan for paper improvements: chitosan is here contemplated as material that meets well the requirements for paper impregnation.
Another interesting article concerns chitosan possible application in textile finishing. Due to its chemical structure, chitosan has a very good adhesion and film-forming properties: it easily forms a film layer on both natural and synthetic fibres. The section four is about dye and metal ion adsorption.
Chitosan is nowadays considered even as an useful textile auxiliary to modify the surface topography thus controlling the surface-related properties of the fibres. For example in the wool finishing, chitosan has been used as a shrink-resist agent and as an agent for improving the dyeability of wool.
The last chapter is all about the chemistry aspects like synthesis of chitosan derivatives, crosslinking reaction and physico-chemical properties. In this final section some interesting articles are reported, such as one about the synthesis and macromolecular characterization of chitin derivatives, another one about the production of chitosan derivatives under shear deformation and many others.
In conclusion we can assert that this volume, so rich of articles by scientists from all over the world, could be considered a precious device for scientists and technologists, who needs to have a complete view of this versatile raw material.

P. Del Ciotto
R&D
Mavi Sud S.r.l.

TELEMEDICINE AND TELEDERMATOLOGY

By G. Burg
2003. 270 p. Hardcover
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www.karger.com
P.O. Box CA -4009 Basel (Switzerland)

This volume, organized in six parts and 40 chapters, reviews the historical and technological aspects of telemedicine reporting in detail the particular aspects of teledermatology.
Telemedicine coined as term 20 years ago, is defined by the World Health Organization (WHO) as the practice of healthcare using interactive audio, visual and data communications. It holds great potential not only to revolutionize both medical and paramedical services but also to teach students by long distance and organize the continuos medical education.
As a matter of fact, Telemedicine, including healthcare delivery, diagnosis, and treatment as well as education transfer of medical data and the discussion of legal and ethical aspects of teleconsulting, add, a new dimension to the medical and paramedical services. Moreover along with the growth of the Internet, higher speed access methods may be offered to medical education teaching and research a range of new services, such as real-time video and voice communications.
Thus in case of a medical emergency in a airplane, for example, the air traffic control center can act as a communications bridge between the aircraft and a healthcare staff on the ground.
On the other hand, Internet, because of its accessibility, offers access to unlimited amounts of information, meanwhile multimedia systems allow the end user to share, communicate and process a variety of information in an integrated manner. Thus became a necessity to organize the internet-based computerized patient record (iCPR).
With an elevated life expectancy, accustomed to international travelling, people, in fact, notably raise their demands on availability and accessibility of personal medical data and documents. An extensively documented and continuously updated health record will become in future, more and more important. Hence the necessity to record a large amount of data. But the required data rates to transmit the raw video streams data exceed by far the capacity of modern network.
Thus the goal of video and image compression algorithms is to reduce this large amount of raw data to match the capacity of the network before it is transmitted.
At the receiver the compression procedure needs to be reversed to restore the original data stream, loosing, however, a certain amount of information and quality of media.
However decompression provides a means to trade quality for compression ratio in order to allow and to adapt the bit rate of the data stream to the capacity of the transmission channel.
Dermatology is well suited for teleteaching and for reaching out dermatological patients residing in underserved areas by telecommunication equipment (teledermatology). As a matter of fact, tbe computer, as an instrument in every day work, is a well- suited tool for teaching and learning purposes, because it can reduce the costly personal presence of teachers in schools and universities. Also, many university students own a computer or have easy access to computers, as well as the Internet.
Moreover in the field of medicine, dermatology is an ideal specialty to develop multimedia-teaching

concepts, because the skin as an organ is readily accessible and visual aspects are very important.
The goal of teledermatology is therefore to decrease the costs of providing some health services, and to improve the quality of care. Its delivery service may be through store-and-forward computer-based systems, or/and real-time video conferencing systems. Diagnostic procedures and therapeutic interventions can be recommended through both approaches. Either system may have a dermatoscope and a microscope camera as additional features together with a digital camera with the right number of pixels and bytes per pixel. However video images can be transmitted preferably through digital lines for their better quality if compared to the poorer analog phone lines.
Finally computers used to transmit these images need to have the capability to deal with large, image –based files.
In conclusion opinions differ regarding whether real-time videos is requires for teledermatology or if digital images will suffice. But physicians tend to display greater comfort with their in-person diagnoses than their videoconferencing diagnosis. Patients, on the other hand, almost universally accept real-time teledermatology. However the option of telecommunicating and teleteaching medical information to students, graduates and postgraduates became more and more an important issue. Moreover in dermatology there is a special need for teleteaching tools, because the number of illness and dermatological conditions to be presented to students is limited by the number of patients visiting the hospital and the diseases they suffer from.
On the other hand, rare dermatological diseases which a doctor sees only a few times if at all in all his years of chemical practice, are hard if not impossible to show to students and other clinicians as real cases. Thus the use of teleteaching tools in order to present such cases in detail provides an excellent way of making this relevant information available despite the rareness of the disease.
What is important to underline about telemedicine is that its possibilities are not limitless, being more significant both communication and computer technology.
Nurses, dermatologists, radiographers, pharmacists, etc., are liable to be the big winners if they are open to change, making their work place changing work for them.
In fact telemedicine may alleviate some of the factors connected with increased stress and dissatisfaction for individual working in the health care industry, by reducing isolation and improving continuing education opportunities, and indirectly by improving communications within and among organizations and professionals.
Thus telemedicine is a fascinating example of how new technologies can offer new medical diagnostic and therapeutic services, or offering existing services in a way that is more convenient to the patient or the doctor. But the number of economic evaluations of this new discipline and applications is still somewhat limited.
The development of these technologies requires in fact more collaboration between medical and commercial interests.
Also if the scientific literature in this area leaves little doubt that telemedicine services can be cost saving, it is time to stop talking about serving billions, and rather spend more time and effort on high-quality evaluation of its interesting and promising group of technologies.
In modern lifestyle are merged of fundamental importance the need for personal mobility and for access to information and services, indispensable to both professional and leisure activities.
For these reason telemedicine is fast becoming indispensable in modern medicine, healthcare and education.
At this purpose many other are the aspects covered by this interesting book from telemedicine in

Ophthalmology, in Corrections, in Cardiology or Gynecology, to the secure transfer of medical data of the patients over the Internet.
Topics have been carefully treated in order to explain to the reader all the aspects covering the "novel" telemedicine world.
The detailed discussion of teledermatology all around the world from Europe to North America makes the book indispensable for dermatologists. All the data on the education in pharmaceutical sciences and web-based telemedicine application by interactive computerized technologies, makes it also interesting and useful for all healthcare professional, from the medical practitioner to the pharmacist, cosmetic chemist, healthcare manager nurse or technician.

P. Morganti
Editor-in-Chief

TRANSDERMAL DRUG DELIVERY

By Richard H. Guy and Jonathan Hadgraft
2003. 383 pages Hardcover
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This second edition of eleven chapters reports all the new increased knowledge of the mechanisms of absorption and how these can be used in the development of medicinal and cosmetic agents and innovative formulations for both dermal and transdermal delivery.

The scientific literature of skin transport has been growing rapidly because of its many applications, and because now it is also possible to get more precise information on the uptake and transcutaneous movement of molecules.

Much of the recent success in the field of skin absorption is attributable to the rapidly expanding body of knowledge in the field of Stratum Corneum (SC) barrier structure and function, and in the use of chemical and physical approaches to promote absorption, examining the feasibility of delivering molecules into and through the skin.

As a matter of fact, the skin is continuously bombarded by many chemicals from the environment or deliberately applied on the skin: dermatological to modify skin function, cosmetics to beautify and optimize skin turnover, transdermals to treat some distant organs.

It can also be found that diffusion barrier reduction may conveniently, and more elegantly, be achieved in a reversible manner via the use of chemical or physical enhancers.

Thus, skin uptake and permeation studies are useful for screening ingredients and comparing pharmaceutical and cosmetic formulations.

Many are the reasons why it is important to predict the absorption rate through the skin. For dermal drug delivery, it is desirable to choose a drug structure that has the best possible chance of arriving at the site of action. It should be remembered that compounds such as corticosteroids have a bioavailability of only a few percent.

If drugs were chosen with more favorable partition and diffusion characteristics, this bioavailability could be improved considerably.

It is also known that the composition of the topical vehicle greatly affects the rate and extent to which the drug penetrates the dermal barrier.

The Leaving potential, or thermodynamic activity of the drug in the vehicle, is therefore a major factor in the delivery process.

For transdermal delivery sufficient drug must permeate the various strata of the skin so as build up a plasma concentration, which elicits a systemic effect.

Equally, there are also chemicals, the absorption of which in significant amount is clearly undesirable.

Finally for cosmetics, such as cleansers, protectants and other products that are intended to act on the skin surface, passage through or accumulation within the skin are undesirable.

The Feasibility, assessment in topical and transdermal delivery and Evaluating the transdermal per-

meability of chemicals are the topics respectively of chapter 1 and 2.
A combined mathematical prediction modeling plus confirming in vitro data should provide the information needed to determine the feasibility of delivering a drug transdermally reasonable estimates of the amount of chemical absorption by the skin, is important for determining also safe levels of contamination.
When decisive experimental measurements are not available, predictive equations based on measurements for other compounds can provide a reasonable substitute. Many model equations developed from large and diverse databases are reported and discussed on from chapter 1 to 3.
These data together with a rich appendix, containing many permeability coefficients, provide the means to develop mechanistically relevant predictive models of percutaneous absorption.
Moreover all the permeability coefficient data examined were critically reviewed, measured in vitro and validated through human skin from aqueous vehicles.
The quality of any predictive equation of dermal absorption, using physicochemical properties of penetrating molecules, is limited, in fact, by the quality of the data used in its development. It is therefore important to review critically each measurement in the database of Kcw (SC-water partition coefficient) values prior to the development of predictive equations. And a new collection of Kcw data were critically reported on chapter 4, identifying new criteria and model of predictive evaluation.
Experimental values of SC-water partition coefficient, in fact, do not exist for many compounds with the potential for dermal absorption. Tbus there is a need for these structure-activity-based methods for estimating Kcw using more readily available parameters.
Because molecular passage is impeded by the barrier properties of skin, transdermal drug delivery offers a number of potential advantages over conventional methods, such as injectable and oral route. At this purpose a number of chemical and physical approaches to enhancing and better controlling transport across skin and/or expanding the range of drug delivered have been investigated.
Therefore the aims of chapters 5, 6, and 7 are to give an overall picture of the main features respectively of iontophoresis, electroporation and sonophoresis.
These pbysical technologies are based on two strategies: enhancing skin permeability and/or providing a driving force acting on the drug.
Iontophoresis typically refers to the transfer of charged substances through a biological membrane under the influence of an electric field.
The application of a low electrical potential gradient across the skin enhances the penetration of molecules. Its appeal resides on the direct relation that can be established between the flux of any ion present in the circuit, on either side of the skin, and the current passed. A basic iontophoresis device consists of a power supply connected to an anode and a cathode which separately contact the skin via an appropriate conducting medium. A preferred material for the electrodes is Ag/Agcl; such electrodes are reversible and do not induce pH changes in the media in contact with the skin.
The main disadvantage of these electrodes is the consumption and accumulation of chloride ions at the anode and chatode respectively reducing the flux of anionic drugs.
For practical application electrode formulations based on contactive gels are preferred. Either the electrolyte solution or the gel makes contact with the skin, thus avoiding direct contact with the electrode.
Iontophoresis, acting on the molecules themselves by a physical mechanism of transport, temporary perturbs the membrane barrier to a smaller extent and the drug delivery is less sensitive to the con-

dition of the skin, at the application site. Further benefits of this technique derive from the fast – responding and versatile administration kinetics that may be achieved. It may be useful, therefore, for safe transdermal delivery in population of uncertain barrier maturity, such as prematures and neonates.

The main limitation for iontophoresis resides nevertheless in the range of molecules for which an efficient enhancement is achievable. Ionic mobility and hence the corresponding transport number of drugs decrease, in fact, with increasing molecular weight or size, and with the presence of other ions in the vehicle.

There have therefore been attempts to combine iontophoresis with other enhancement techniques, such as chemical promoters and electroporation.

Electroporation involves the creation of transient aqueous pathways across lipid bilayer membranes by the application of short high-voltage pulses. Application of high-voltage electric field pulses has been shown to increase transport across and/or into skin for compounds ranging in size from small ions to moderate-sized molecules and macromolecules.

Moreover, orders-of-magnitude-increases in transport have been demonstrated also for hydrophilic molecules, highly charged compounds and macromolecules with a molecular weight cutoff larger than 40 KDa.

The enhancement magnitude and the onset times for transport depends on the pulsing protocols and the physicochemical properties of the molecule being transported as well as the skin model. Theoretical evidences suggest also that the transport flux increases are caused by transient changes in skin microstructure by a mechanism involving electroporation of the SC lipid bilayers.

Moreover application of high-voltage pulses to skin dramatically and reversibly increases skin permeability, inducing the creation of new, and/or the enlargement of existing, aqueous pathways in the SC. In addition local heating of the SC due to the passage of current also contributes to the phenomenon of skin electroporation.

However the contribution of electroporation and relative diffusion are dependent on the physicochemical properties of the molecule transported as well as on the formulation of the drug reservoir and, of course, on the voltage and on the pulse duration.

In conclusion, electroporation is an efficient method of enhancing transdermal drug delivery and expanding the range of compounds transdermally delivered.

As compared to other enhancing methods, electroporation could be particularly interesting for transdermal delivery of macromolecules and fast and/or pulsatile transdermal delivery.

Phonophoresis or *sonophoresis*, is defined as the use of ultrasonic energy (ultrasound) in order to enhance the topical or transdermal delivery of drugs and/or cosmetics.

Ultrasound is an acoustic vibration propagating in the form of longitudinal compression waves at frequencies beyond the human auditory range, i.e., 0.02MHz.

The intensity parameter measured in W cm-2, defines the quantity of energy conveyed by an ultrasonic wave as it passes through any given site, as the skin and this parameter is used to establish the time of exposure.

Therapeutic continuos or pulsed ultrasound is normally generated by a transducer that converts electricity to ultrasound by utilizing the piezo-electric principle. This effect describes the behavior of certain ceramic materials, which expand or contract when a voltage is applied across them.

The ultrasound emitted by the transducer propagates away from the front face in the direction in which the transducer is pointing. Since air is a poor medium for ultrasound propagation, investiga-

tions into phonophoresis require the use of an ultrasonic coupling medium energy which facilitates an effective transer between the transducer and the skin surface. The medium is either a commercially available viscous gel or an aqueous solution. The therapeutic agent may be homogeneously dispersed within the complying medium or deposited directly on the skin and the overlying complying gel subsequently added. The intensity applied is between 0.020 and 3 MHz and rarely greater.

It is important to stress that formulation design of the donor vehicle/ complying agent may radically affect therapeutic efficacy in phonophoretic systems. The combination of ultrasound chemical enhancers and/or electroporation seems to he more efficacious in permeabilizing and enhancing the absorption of different molecules through the human skin that either modality alone.

The Metabolic Approach to Transdermal Drug delivery based on the two-compartment model of human SC, is discussed on chapter 8.

In this new model, the lipids of the SC are segregated within intercellular domains, while the lipid-depleted corneocytes act primarily as spacers, while providing protection from mechanical insults. SC lipid matrix is, in fact, a two-phase system with a discontinuous lamellar-crystalline structure embedded in a continuos liquid-crystalline structure. If the crystalline areas are considered impermeable, while the liquid-crystalline areas remain permeable, and if water is located primarily in the liquid-crystalline areas, the diffusion of both hydrophilic and hydrophobic compounds would be restricted to the liquid-crystalline domain.

As a result, permeating molecules would perform a random walk in liquid-crystalline channels separated by two or more crystalline domains.

Variations in intercellular lipid content of SC interstices and membrane structure provide a structural basis for the wide variations, in permeability of different human sites. Therefore the variations in SC lipid composition over different skin sites and the relative differences in the water vapor – permeability comprise the different permeahility barrier to transdermal drug delivery, as well.

Thus the SC interstices appear to subserve both the putative intercellular transport route as well as the reservoir function of the Stratum Corneum.

The Application of supersaturated Systems to Percutaneous Drug Delivery is the topic of chapter 9.

As we have seen previously, different methods are available to enhance the diffusion of compounds across the skin. Many of these techniques can give rise to local intolerance either directly or through increased local delivery of other vehicle excipients. Supersaturation provides an alternative mechanism of penetration enhancement specific to the drug without perturbing the skin barrier.

As a matter of fact, when a supersaturated solution is placed on the surface of the skin, the concentration of drug in the SC will become supersaturated. When this appears, penetration enhancement proportional to the degree of supersaturation will occur.

Thus supersaturation can be useful in dermal and transdermal drug delivery and can lead to the application in possible adverse drug reactions. Therefore it can be used in combination of other enhancement strategies to produce synergistic effects.

On chapter 10 the Minimally Invasive Systems for Transdermal drug Delivery are reported.

These new technologies that allow delivery of drug across skin without the need for needles, require some form of energy input or are only activated by the user's actions.

For example MEMS (microelectromechanical system) provide transepidermal drug administration via microscopic silicon needles; the laser injection ablates SC transiently increasing wave formation. The objective of this non-invasive laser-enhanced optoacustic technique is to reduce the thickness of

the SC and thereby reduce the transit distance through the skin of permanent drugs or to cut holes through the SC to allow drug permeation directly into the epidermis.
During laser irradiation, the energy input, correlated to wavelength, pulse length and pulse energy, is absorbed by the components of the skin as vibrational heating. Water within the irradiated area of the skin quickly reaches its boiling point, and the resulting vapor pressure elicits a microexplosion that forms the ablation as the tissue vaporizes. The rapid loss of energy from the ablated site protects the surrounding skin tissue from the heat-induced damage.
The ability of control the level of energy imparted to the skin by laser allows this to be a well-controlled method of removing SC if the applied energy is sufficiently low.
Other kind of devices specifically developed to produce mechanical disruption of the upper skin in order to facilitate transdermal drug delivery are reported in this chapter.
In future, however, since silicon-machining technology is intimately associated with electronics manufacture, the opportunity exists to build easily and inexpensively coincident monitoring and communication systems onto MEMS drug delivery systems. These new systems will provide therapeutic benefit through safe efficacious delivery of drugs coupled with technologies easy of use and at low cost.
Transdermal drug delivery systems (TDS), marketed for systemic action and considered controlled release dosage forms, should scientifically support in vitro and in vivo claims of controlled release features and should assure in vitro as well as in vivo reproducibility.
Moreover TDS regarded as new drugs, have to be approved based on clinical safety and efficacy studies. Therefore their penetration effect should be predictable and reversible. Regulation considerations on TDS are reported and discussed on the conclusive chapter 11.
This interesting volume presenting and describing the state-of-the-art of the Stratum Corneum's permeability properties and relationship between the structure of different active compounds and their diffusion across skin membranes, full of insights on the pivotal role of the skin as well as on the risk assessment of topically applied drugs or cosmetics, provides the reader with all the scientific knowledge necessary to better understand all the problems linked with the transdermal delivery. Hence this book is an excellent source of knowledge, an ideal reference as well as an experimental laboratory guide for all people researchers and scientists, such as dermatologists cosmetic chemists, pharmacists, toxicologists, pharmacologists, and manufacturers of cosmetic and drug for the skin who intend to deeply know the various mechanisms of percutaneous absorption and skin delivery.

P. Morganti
Editor –in- Chief

SUN PROTECTION IN MAN

By P.U. Giacomoni

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The need for sun protection ranges from every day exposure to specific sun-seeking behavior such as sunbathing. Sunburn is, in fact, a common acute injury for many people especially during the summer months all around the world, when many people enjoy spending their leisure time outside and natural ultraviolet light is most intense.
Thns singlet oxygen can be produced in the skin as a result of photosensitization reactions triggered by drugs, cosmetics and plant toxins.
Moreover solar UVB and particularly UVA radiation have the ability to induce also free radical damage to skin.
Therefore chronic exposure to sunlight is the major cause of skin cancer in humans and major factor in skin aging.
For all these reasons generating demand for any product with significant sun protectors is vital in the battle against skin cancer.
Sun protection is the topic of this interesting book organized in 36 chapters, covering topics such as : The protection against the sun in ancient times, The modulation of gene expression by UV, Topical and systemic photoprotection by sunscreens and dietary intervention and therapy.
Although it is well established that excessive exposure to sunlight can lead to increased risk of Squamous and Basal Cell Carcinoma (SCC and BCC) as well as to decrease the elasticity of the skin, this should not preclude humans from being exposed to sunlight.
It is important to remember that exposnre of the skin to sunlight played and plays an important role in the evolution of vertebrate mammals. But this exposure to hands, arms and face should be from one quarter to one third of the (MED) Minimal Erythemal Dose two/three times a week, for satisfying the body's requirement.
However, lifestyles have changed in recent decades to reflect the fashion for obtaining a healthy tan by either natural solar exposure or artificial lamps. Frequent sunshine holidays, increased leisure time and weaning minimal clothing as soon as the sun shines.
Moreover there is also the possibility of increased UV-B in sunlight reaching the surface of the earth due to the depletion of the ozone layer. Thus, at the present time, it is likely that human subjects are being exposed to more UV that previously.
These seem to be the reasons for the increased development of skin cancers, initiating from a down –regulation of the immune system and a consequent DNA damage.
Therefore sun exposure and genetics play an important role in the development of skin cancer.
Childhood sun exposure seems to be a more important risk factor for BCC than sun exposure during

adulthood. Moreover, intermitted sun exposure has been postulated as greater risk factor for BCC than cumulative sun exposure.
BCC more than SCC is the most common skin cancer in East Asians.
All these negative effects of solar radiation, their effects on the skin of Asians and on the human immune system are described in the first five chapters.
In chapter 6 is discussed photoaging as related to its morphological phenotype , underlying mechanisms as well as its relationship to different molecular models of aging. The unifying pathogenic agents of photo-oxidative damage, characterizing photoaging, are UV-generated reactive oxygen species (ROS) which deplete and damage non-enzymatic and enzymatic antioxidant defense system of the skin.
ROS induce changes in gene expression pathways related to collagen degradation and elastin accumulation. A decrease in the overall ROS load by efficient sunscreens or other protective agents may represent promising strategies to prevent or at least minimize ROS-induced photoaging.
Moreover the epidemiological data suggest that sun protection will have the greatest impact if achieved as early as possible in life, and that it will be probably have an impact later in life, especially in those who had high childhood exposure to solar radiation. This topic is reviewed in chapter 7.
Aside from the skin, the organ most susceptible to sunlight-induced damage is the eye. It is constantly exposed to sunlight including ultraviolet radiation UVB and UVA and visible light that can lead to impaired vision and eventually, blindness.
Earlier diagnosis, in conjunction with ocular protection against light (sunglasses) and prescribed specific supplementary antioxidants (lutein, vitamin E), may retard or present blindness in the elderly.
Can these compounds protect also lenticular UV filters which decrease linearly over our life span?
Probably if they will be able to keep free from the proteic bounds the photo-protective UV filter compounds. These interesting topics are reported in chapters 8 and 12 where the redaction in elderly of antioxidants and antioxidant enzymes and the photo-oxidation owing from the absorption or UV radiation by aminoacids, peptides and proteins are respectively discussed.
The lens of the eye is composed of two parts that are susceptible to damage: the (outer) epithelial cells and the (inner) fiber membrane.
The epithelial cells control transport to the lens. They have direct contact with the aqueous and are most vulnerable to photo toxic damage, compromising the viability of the lens. The
Fiber membrane can be photocbemically damaged through damage to the lipids and/or to the main intrinsic membrane protein.
The UV damage to nucleic acid components and the Lipid photo oxidative damage in biological membranes are treated respectively in chapters 10 and 11.
UVB radiation induces DNA damage by direct absorption of UVB photons meanwhile UVA generates the damage through photosensitization reactions.
The final formed compounds are 12 dimeric pyrimidine photo products, upon exposure to UVB radiation and few oxidized purines and pyrimidines upon UVA irradiation.
On the other side unsaturated membrane lipids are crucial targets for 102 and free radical attack in photodynamic reactions.
Oxidative modification of these lipids play an important role in UV-induced skin cancer.
Lipid hydroperoxides (L00Hs) are, in fact, much longer-lived than free radical precursors or products. This make L00Hs potentially more dangerous because they may be able to disseminate peroxidative stress by moving from one membrane to another.

Together with many interesting photo taken by SEM (Scaring Electron Microscopy), in chapter 9 is reported the Photodegradation of human hair.
Sunlight degrades both hair proteins and hair pigments. UV irradiation results in aminoacid degradation of the hair fiber during UV exposure. The uniform distribution of a UV sunscreen, such as the water-soluble benzophenone-4, successfully, reduces, or at least retards, photo-degradation in the fiber interior and periphery during irradiation.
But UVA activates a wide range of genes implicated in the acute inflammatory response of erythema. This activation is mediated by singlet oxygen and ROS is involved in stimulating signaling cascades and transcription factor activation. Moreover UV-B can generate other intermediates that may be involved also in signal transduction and gene activation. The inflammatory response seems therefore to be loosely correlated with DNA damage.
In chapter 13 is discussed and quantified the amount of UV-induced DNA damage and the relative estimate cellular damage.
Although skin cancers appear to be related to UV radiation, new experiments are necessary to clarify if and how UVB and UVA can affect some involved genes.
Signal transduction pathways that regulate cycling, differentiation and apoptosis are fonnd to be correlated in skin cancers, as described in chapter 14.
Other forms of UV-induced genetic changes may, however, contribute to skin carcinogenesis with different wavelength dependencies.
Therefore knowledge of the full range of UV-induced DNA damage and ensuing genetic changes is of obvious importance especially for a better understanding of the etiology of the most fatal skin cancer malignant melanoma.
In vivo studies in human skin have been mainly directed towards understanding also photoaging caused by chronic exposure to sunlight and it is now well-established that induction of matrix metalloproteinases by keratinocytes and fibroblasts leads to degradation of the extracellular matrix as described in chapter 15.
Citotoxicity and morphological endpoints of exposure to UV is the topic of chapter 16.
The use of in vitro systems can be of great relevance in understanding of the pathogenic mechanisms of UV radiation changes, and to determine possible drugs capable of counteracting UV-mediated subcellular pathology.
Alteration found in structural studies can be summarized as a sequence of events mainly composed of: 1) cell retraction with loss of cell-cell interaction, 2) surface blebbing and finally 3) cell death. Morphogenesis of these events can be ascribed to oxidative modifications due to ROS formation following radiation that can modify both cell membrane and cytoskeleton.
All humans are photosensitive to solar radiation to some degree and skin photosensitivity is a consequence of several factors including genetic background, skin pigmentation and prior exposure to UVR. However, there are many situations when this normal photosensivity is increased by either disease or exposure to exogenous photosensiting chemicals, such as flnoroquinolone (FQ) and antibiotics.
The large body of information accumulated on FQ phototoxicity, the validation of simple, in vitro, screening method and the increased knowledge of structure-phototoxic activity relationship may, in the future, lead to a reduced number of phototoxic drugs reaching the market. These are the conclusive remarks reported in chapter 17 titled Drug-Induced Skin Phototoxicity.
Chapter 18 focuses on the UV-induced pigmentation in human skin.

Pigmentation is considered to have photoprotective properties in human skin, reducing the adverse acute and long-term effects of solar UVR-exposure.
This activity seems to be mainly due to the optical screening properties of melanin. Much of evidence for this is epidemiological and is based on the inverse relationship between skin cancer risk and skin pigmentation.
However further studies suggests the possibility of other defense mechanisms that may be as important as melanogenesis.
In particular, it seems possible that the ability to tan is a reflection of DNA repair capacity of the skin. And, as described in chapter 19, the Nucleotide Excision Repair (NER) is a versatile and highly conserved repair system capable of removing a wide range of DNA lesions, including cyclobutane pyrimidine dimers (CPD) and 6-4-photoproducts (6-4 PP). It is important, in fact, to preserve and protect the integrity of DNA from external and internal influences.
As matter of fact, the described lesions can interfere with essential and vital processes such as cell replication and transcription, inducing genetic alterations cause of hereditary disorders and skin cancer.
Fortunately all organisms respond to the environmental assaults by the induction, for example, of heat shock proteins (hsp). This induction is followed by a transient state of increased resistance to further stress and seems to represent an evolutionary conserved adaptive mechanism to cope with hostile environmental conditions. Expression and UV induction in skin are reported in chapter 20, where is also discussed its possible use to restore cellular function in aged tissues.
The role of protein p53 in the response of skin to UV and the effect of solar radiation on cytochromes P450 (CYPs) are respectively focused in chapters 21 and 22.
p53 plays a mediating-protecting role in human skin UV-exposed and CYPs facilitate elimination of xenobiotics. For its role the wild-type p53 gene is also called "guardian of the genoma", even if the regulation of p53 activity in human skin after a physiological relevant UV irradiation dose remains largely unsolved.
The Higb Energy Visible (HEV) portion of the solar spectrum named bleu light, is also a possible source of retinal damage causing the development of age related macular degeneration (AMD).
And the Eye protection from sunlight damage is reported in chapter 23, where a comparison of the color perception and light protection performance of several sun-glass lenses are presented.
The damage to the retina is cumulative and characterized by the sum of the damage induced and developed over time from day-in, day-out activities carried out under bright sunlight exposure, ever with "full" UV protection.
Tbe cristalline lens, in addition to absorbing UV, also tends to absorb progressively more blue light with age, becoming more yellow in appearance.
At this purpose, the protective lenses enriched with melanin seem to combine a more high eye protection factor (EPF) value with minimum color distortion, compared with normal lenses.
Clothing also is an effective source of protection against the sun.
Fabric incorporated into clothing and hats provides, in fact, a convenient means of reducing ultraviolet radiation (UVR) exposure. Therefore, standardized tests for assessing the level of UVR protection are established and this has led to the development of specially designed summer clothing and labels indicating the tested levels of UVR protection, similar to that developed for sunscreens.
All the new methods and studies on texiles are addressed on chapter 24 where are also reported the UV-protective suitability of fabrics under condition of stretching, wetting and generally usage.

Self tanning is the topic of chapter 25.
Dihydroxyacetone (DHA), binding the amino terminal groups of the free aminoacids of epidermal proteins, imparts an orange-brown color to the skin 3-10 h from the applications. The degree of skin darkening depends on the concentration of DHA and on the frequency of its application.
The DHA does not protect against UVB, but has interesting photo-protective properties against long-wave UVA and visible radiations. Its use is therefore useful to prevent polymorphous light eruptions or erythropoietic protoporphyria and to give a tanned look to fair-skinned individuals avoiding harmful sun exposures.
To avoid the risk of sunburns following excessive sun exposure, cosmetic products containing DHA are now formulated adding physical or chemical sunscreens, in order to provide UVB protection also.
But what is the skin protection activity performed by topical sunscreens?
The assessment of the photochemical and photophysical properties of a range of organic and inorganic sunscreens with respect to their efficacy and safety is reported in chapter 26.
Some undesirable aspects of sunscreens include the ability to form radicals DNA-adducts, sensitize the formation of thymine dimers and singlet oxygen that are all deleterious attributes to human health.
For all these reasons it is important to minimize the risk of producing reactive excited state or non-excited state species within sunscreen formulations. This is the reason to use the right sunscreens in the right vehicle.
Moreover the cosmetic product has to have resistance to water immersion and sand abrasion and it is necessary to know where, how often and how much is to be re-applied. The mismatch between expectation and realization may be one contributing factor why sunscreens have been reported to be a risk factor in melanoma.
Applying sunscreen in the right way is just one element of a protective strategy aimed to controlling sun exposure, which include also, seeking shade around the middle of the day and wearing clothing and wide-brimmed hats.
These topics are reported in chapters 27 and 28, where the positive effects of sunscreens, their potential dermatological and psychological risks and conditions under which sun protection becomes critically important are also reported and described.
As matter of fact, sunscreens should not be used to prolong the time spent out in the sun, but rather to minimize the damage incurred from unavoidable exposure. It is also vitally important that the mention of the uncertainty associated with sunscreens and their ability to protect humans from various pathologies should not be interpreted as discouraging their use.
Rather sunscreens are to be used as one component of a total program of sun protection. together with combination of antioxidants taken by oral route.
At this purpose several in vitro studies provide evidence that dietary antioxidants prevent photooxidative damage and may be capable of protecting against UV-induced erythema formation if systematically available over a period of several weeks.
Oral supplementation of carotenoids, tocopherol and ascorbate may be used, together with topical sunscreens, to increase the basal protection and thus increase the defense against UV-light-mediated damage to skin.
All these news are reported in chapters 29 and 30.
Reduction in total dietary fat of omega-3 fatty acid supplementation, have resulted in protection

against non-melanoma skin cancer and other markers of UV-induced tissue damage. It is in these directions that future research is likely to be most beneficial with regard to systemic protection against UV-insult.
However the rationale for an approach to systemic photoprotection rests within our current paradigm of wisdom regarding the nature of actinic damage to the skin and the mode of action of topical and systemic photoprotectants.
Therefore more active topical sunscreens and dietary manipulation offer a safe environmental approach for exploring potential strategies to combat the rising skin cancer trends and to protect the skin from other adverse UV effects, including photosensitivity disorders and photoaging.
As we have seen previously DNA damage influences extracellular signaling, through cytokine gene expression. This occurs before cell decide whether to repair or die.
Enhancement of repair of UV damage in humans and Boosting the immune system are respectively the topics of chapters 31 and 32.
Reversing DNA damage even later in life may be mitigated through restoration of the immune system, mutations initiated from childhood exposure.
The possible DNA repair has, in fact, beneficial effects on both mutation and suppression of the immune system, according to recent studies.
Besides causing mutations in DNA, UV radiation contributes to carcinogenesis by suppression immune responses to highly antigenic, newly arising neoplastic cells in the skin.
The use of antioxidants such as ascorbic acid polyphenols from green tea, flavonoids and plant polysaccharides to prevent immune damage are described.
The obtained data from humans and laboratory animals have demonstrated that the protection of the immune response is important in preventing skin cancer.
The multiplicity of sun protection strategies and agents employed (sunscreens, antioxidants, immune-regulatory polysaccharides, etc.) show that there are many ways to protect the immune response from the effects of UV radiation.
Chapter 33 is focused on Skin pigmentation enhancers.
Agents that enhance skin pigmentation have the potential to reduce both photodamage and skin cancer incidence.
An understanding by which these agents induce melanogenesis may provide important insight into potential safety issues. However tanning simulators, such as DHA, and stimulators such as l-tyrosine or propylene glycol should have a sufficient efficacy to induce a visible tan; a cosmetically pleasing tan; a minimun or lack of side effects or safety issues; and potential benefit in terms of photoprotection.
The metabolic effects of solar radiation and enhancers of energy metabolism, Sunlamps and sunbeds and Solar radiation at the earth's surface are the last three conclusive topics of this book.
The risk assessment of detrimental effects of solar and/or sunlamps and sunbeds UV radiations requires a detailed knowledge of the intensity the spectral composition and the continuos changes involved in the atmospheric constituents, due to human activities.
All the variations have a direct impact on the quality and quantity of UV radiation responsible for sunburn or even skin cancer.
Solar light results not only in DNA damage but in protein damage as well.
The interactions between DNA damage and protein damage caused by solar radiation are complex and they also involve niacin, NAD and poly (ADP)-ribove polymenase (PARP-1). The dependence

of these mechanisms on skin cell NAD content and on niacin status indicate that maintenance of an optimal niacin status in skin, especially skin exposed to sunlight, is another desirable goal.
Identifying ways to optimize the function of PARPs is likely to be very important in minimizing the deleterious effects of solar radiation on skin.
As stated in the preface this interesting book is not "another book on sunscreens " but a complete monograph concerning all the physical biological and dermatological aspects regarding sun protection and use of topical and systemic skin photoprotectants.
The beneficial and harmful effects of solar radiation are all well described and documented, the chemical effects of UV rays have been analyzed, investigating all the phenomena inducing immune-depression photoaging and carcinogenesis.
The completeness of the topics treated and of the references reported for each chapter makes Sun protection in man a real unique textbook for chemists, bio-chemists and dermatologists involved in photobiology and photomedicine.
Pharmacy, Chemistry and Medicine students who wants to enlarge their knowledge on photobiology and sciences dealing with skin photoprotection problems should read this excellent textbook.

P. Morganti
Editor in Chief

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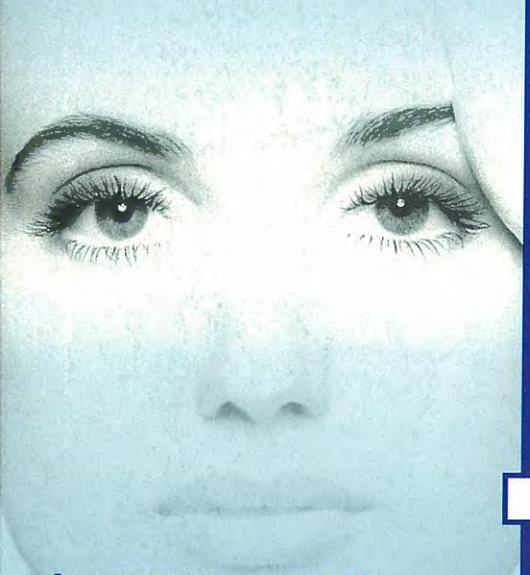

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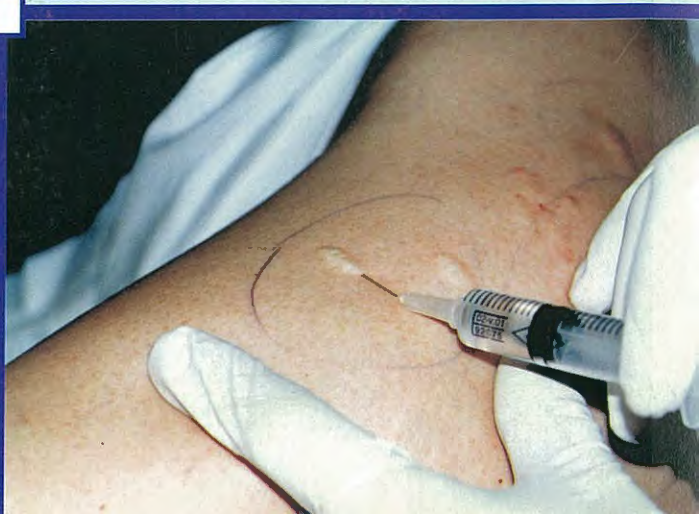

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