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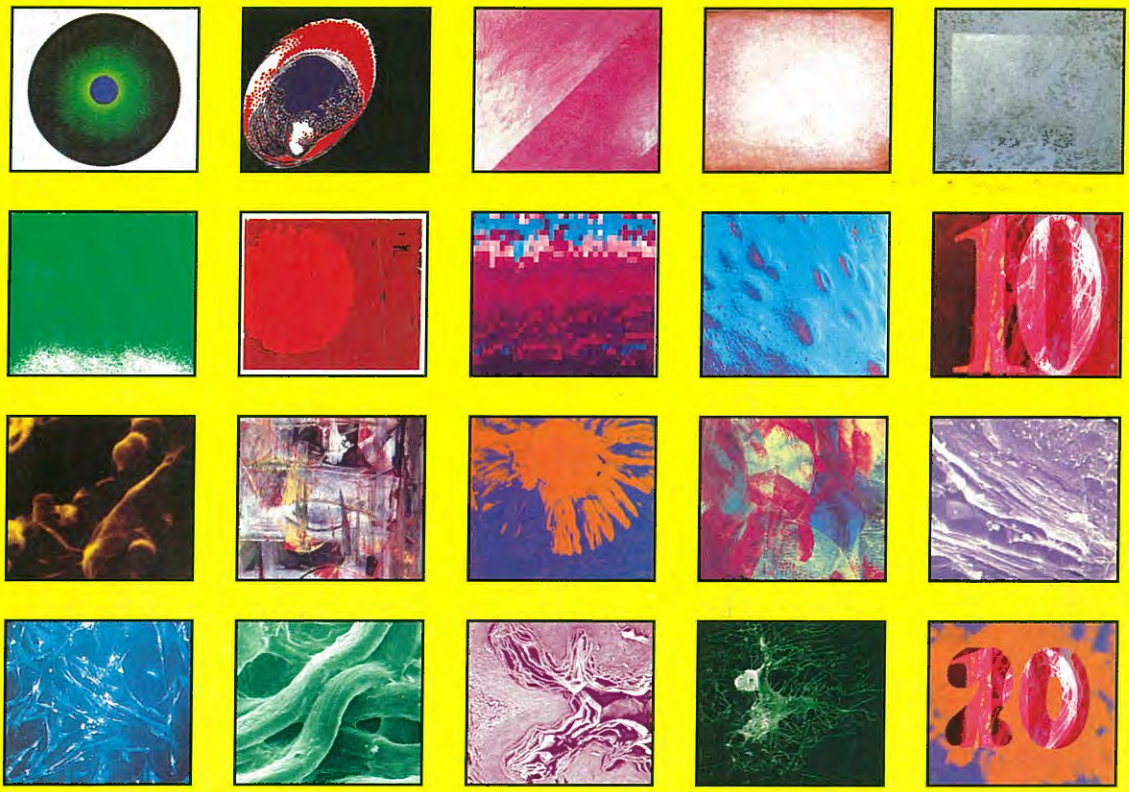

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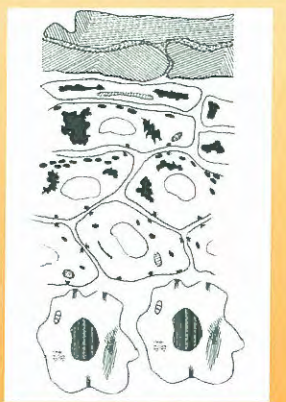

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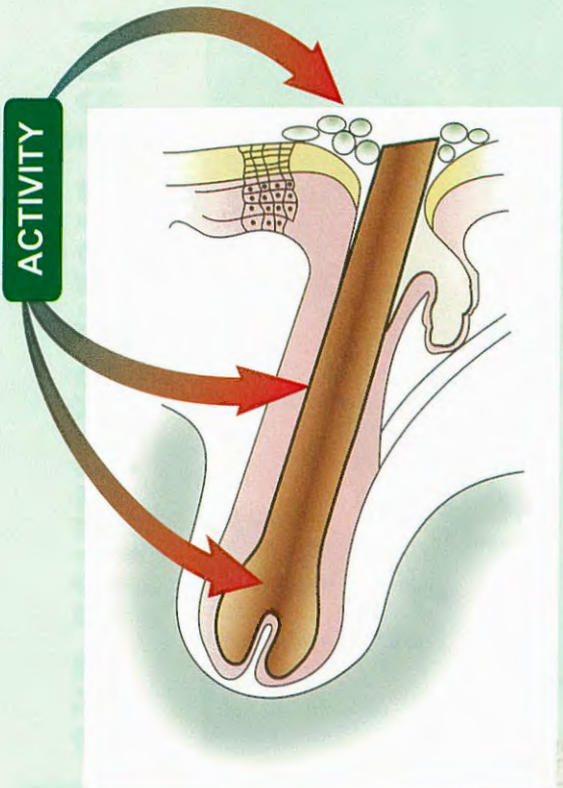

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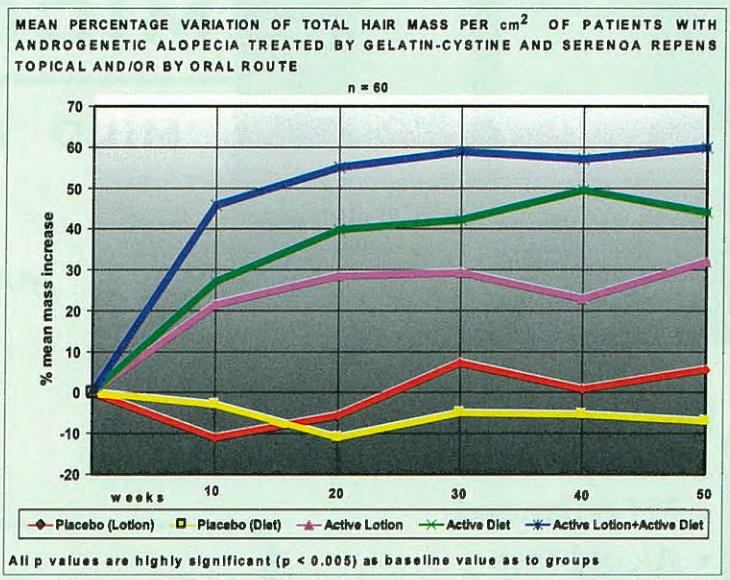

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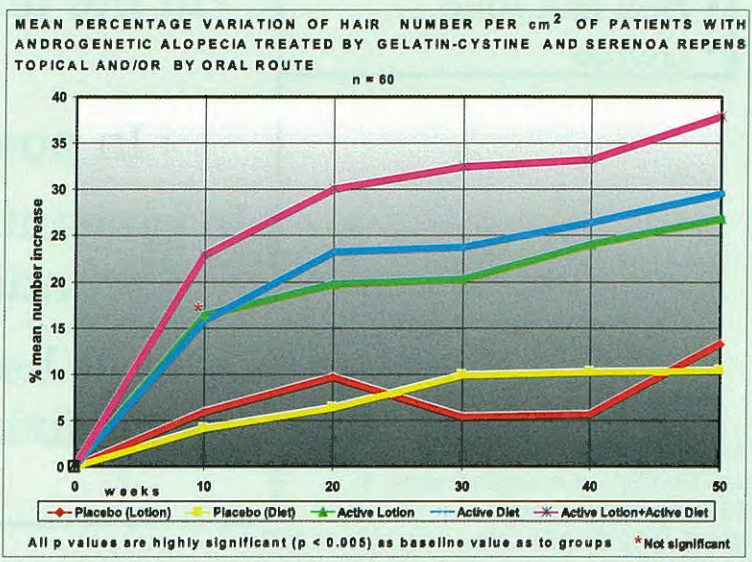

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[2] Fabrizi G, Morganti P, (1999),*SÖFW-Journal*, **125**, 2/3 :10-13

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Trimestrale di Dermatologia Cosmetologica
Quarterly Review of Cosmetic Dermatology

Contents

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ZINC NUTRITIVE AND SKIN: AN OVERVIEW

N. Cassano*, A. Amoruso, G.A. Vena

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Key words: *Zinc; Skin; Zinc Deficiency, Primary and Acquired; Oral Zinc Therapy*

Summary

Zinc is an essential trace element which participates in several biochemical pathways. It is also important for skin homeostasis, as shown by the relevant changes of skin and its appendages during the primary form of zinc deficiency, named "acrodermatitis enteropathica" (AE). Cutaneous lesions resembling AE may also develop owing to acquired zinc deficiency due to multiple causes: nutritional factors, alcoholism, malabsorption, liver cirrhosis, chronic renal diseases and other chronic debilitating disorders. In acute zinc deficiency, the skin eruption is vesico-bullous or eczematous, whereas in the chronic state parakeratotic psoriasiform lesions occur. Other signs include widespread asteatotic eczema, cheilitis, glossitis, stomatitis, alopecia, nail anomalies, and are usually associated with extra-cutaneous manifestations. The recognition of the underlying zinc deficiency is of crucial value as zinc supplementation causes regression of symptoms.

In some skin disorders, the epidermal and/or serum concentrations of zinc were found to be decreased, but the actual implications of such abnormalities are still unknown and controversial, at least for some diseases. Some evidences seem to support the implication of zinc in wound healing, prevention of UVA-induced apoptosis, sebum composition and excretion. Some reports showed a potential usefulness of oral zinc in skin diseases, such as acne vulgaris, recalcitrant warts, leprosy, decubital ulcers, amicrobial pustulosis, erosive pustulosis of the scalp, perifolliculitis capitis abscedens et suffodiens and necrolytic acral erythema.

Riassunto

Lo zinco è un oligoelemento essenziale che prende parte a numerosi processi biochimici. Esso è anche di fondamentale importanza per l'omeostasi cutanea, come è dimostrato indirettamente dal coinvolgimento della cute e dei suoi annessi durante il deficit primitivo noto come "acrodermatite enteropatica" (AE). Lesioni simili a quelle dell'AE si possono osservare in caso di deficit acquisito di zinco secondario a patologie di vario tipo: carenze nutrizionali, alcolismo, malassorbimento, cirrosi epatica, nefropatie croniche e altre malattie debilitanti croniche. In corso di deficit acuto di zinco, le lesioni cutanee assumono un aspetto vescico-bolloso o eczematoso, mentre durante gli stadi cronici si notano prevalentemente manifestazioni psoriasiformi. Altri possibili segni sono eczema asteatosico, cheilite, glossite, stomatite, alopecia, onicodistrofie, e vari sintomi extra-cutanei. L'individuazione del deficit di zinco è fondamentale in questi casi dal momento che la terapia con zinco orale consente la regressione completa di tutti i sintomi.

In alcuni disordini cutanei si è riscontrata una riduzione delle concentrazioni epidermiche e/o sieriche di zinco, ma la reale rilevanza di tale riduzione è ancora sconosciuta, per lo meno in alcune condizioni. Si è ipotizzato un ruolo dello zinco nel processo di guarigione delle ferite, nella prevenzione dell'apoptosi indotta dagli UVA, nella composizione ed escrezione di sebo. Alcune esperienze depongono per il potenziale valore terapeutico dello zinco in talune dermopatie, come acne, verruche, lebbra, ulcere da decubito, pustolosi amicrobica, pustolosi erosiva del cuoio capelluto, perifolliculitis capitis abscedens et suffodiens ed eritema necrolitico acrale.

INTRODUCTION

Zinc is an essential trace element, contained at high concentrations in shellfish, legumes, nuts, whole grain and green leafy vegetables; fruits, wine, beer and spirits contain insignificant levels (1). Zinc supply depends on the protein content of the food; protein undernourishment and intake of foods with high amounts of phytates and fibres can lead to zinc deficiency. The daily oral dose of this element should be of approximately 3mg in infants less than 6 months, 5mg in infants 0.5 to 1 year old, 10mg in children 1 to 7 years old and 16mg from the 11th year onwards. During pregnancy and lactation, women should receive 20-25mg of zinc daily (2).

The normal serum level of zinc is about 70-125μg/100mg, equivalent to 11-19μmol/l. The mean concentration, determined by atomic absorption spectrophotometry, is about 60μg/g in epidermis and 40μg/g in upper dermis, with levels much higher in the upper than in the lower dermis layers (3).There is no correlation between the tissue and serum concentrations.

BIOLOGICAL FUNCTIONS

Basic functions

Zinc participates in several biochemical and biological pathways (Table I). In particular, it is well-known that several aspects of specific and non-specific immunity are regulated by zinc (4,5): development and functionality of neutrophils and NK cells; intracellular killing, cytokine production and phagocytosis of macrophages; many functions of T lymphocytes, including activation, Th1 cytokine production, B lymphocytes help; development of B lymphocytes and production of antibodies, especially of IgG. The effects of zinc on the immune system are mostly mediated by the influence on cellnlar functions (DNA replication, RNA transcription, cell division and activation). Furthermore zinc inhibits the production of tumor necrosis factor (6). Zinc is also a cofactor for over 200 enzymes (the most important of which are listed in Table II) (7-9). It is a constituent of some nnclear hormone receptors, such as those for steroids, thyroid hormones, vitamin D and retinoids (10).

Table I.
Principal biological functions regulated by zinc.

Immunity (both specific and non-specific)
DNA, RNA and protein synthesis
Cell division and activation
Action of several hormones and enzymes
Functional integrity of membranes
Growth
Development
Neurosensory functions
Apoptosis (inhibition)
Inflammation (inhibition)
Oxidative stress (inhibition)

Table II.
Principal enzymes with zinc-dependent activity.

Alkaline phosphatase
Alcohol dehydrogenase (and other dehydrogenases)
Carboxypeptidase
Digestive enzymes
Metalloproteinases
Thymulin
Thymopoietin
Cu-Zn superoxide dismutase
DNA and RNA polymerases
Thymidine kinase
Ribonuclease

Cutaneous functions

Zinc is also important for skin homeostasis; some evidences support its role for specific skin-related processes.

In human skin fibroblasts the antioxidant effects of zinc have been demonstrated; interestingly, these effects do not appear to be mediated by antioxidant metalloenzymes (11). It was also found that zinc can protect human cutaneous fi-

broblasts against both UVA1-induced DNA damage and early/delayed apoptosis (12).
The involvement in wound healing has been also suggested. During the healing process, zinc accumulates into the skin (13). Moreover, zinc supplementation leads to an higher percentage of Langerhans' cells having dendrites in the epidermis of patients with decubital ulcers; it is likely that the increased motility of these cells may favour the healing process of the lesions (14). However, the actual value of zinc in wound therapy is still controversial (15).
Hints suggesting a potential role of zinc in skin desquamation have been provided. In fact, a 25 kDa chymotrypsin-like proteinase possibly involved in this process has been characterized in the stratum corneum; this enzyme can be inhibited by zinc ion and also by aprotinin and chymostatin (16). This finding can explain, at least in part, the squamous nature of lesions associated with chronic zinc deficiency.

ZINC DEFICIENCY

Zinc deficiency may be distinguished in primary and acquired forms (17). In turn, the primary forms can be linked to a specific defect of absorption (acrodermatitis enteropathica) or to insufficient nutrition (endemic nutritional zinc deficiency). The acquired zinc deficiency is a consequence of gastrointestinal tract disorders causing diarrhoea and malabsorption or of other diseases.

Acrodermatitis enteropathica

Acrodermatitis enteropathica (AE) is a rare disease probably inherited in an autosomal recessive fashion, which was identified in 1936 by Brandt (18) and further investigated in 1942 by Danbolt and Closs (19) who gave the name to the disease.
The link between the disease and zinc deficiency was first described by Moynahan in 1974 (20). In patients affected by AE the zinc absorption is low (2-3% compared with 27-65% in normal adults); the precise cause of this malabsorption is unknown. Probably, some cases of AE can be caused by a cellular defect in zinc metabolism rather than by a reduced absorption (21).
Clinical features. The onset of the disease is usually 4-6 weeks after weaning or can occur earlier if breast milk is not given. AE is typically characterized by vesicobullous lesions on hands, feet and periorificial areas and several systemic symptoms: irritability, photophobia, hair loss and thinning, diarrhoea, stunted growth, decreased resistance to infections and poor wound healing. Angular cheilitis is an important clinical feature which seems to be associated with the risk of relapse and needs usually more time to improve during treatment compared with other manifestations (22).
Microscopic findings. The histological findings related to the vesicobullous lesions consist in intraepidermal vacuolization and massive ballooning, with prominent epidermal necrosis and with no acantholysis. Bullous lesions seem to develop *ex novo* on unaffected areas and not on erythematous patchy lesions (23). Light and polarizing microscopy of the hair can display uneven diameter of the shafts, atypical trichorrhexis nodosa with stretched fractures, pseudomonilethrix, irregular pattern of alternating dark and bright bands (24).
Diagnosis and management. In AE the serum zinc level is significantly decreased. However, serum zinc values are not a good index of tissue zinc concentrations; in the serum, zinc is almost entirely bound to transport proteins, and its tissue availability may be regulated by multiple factors. There is a good correlation between depressed plasma zinc levels and low alkaline phosphatase activity (25).
Without proper management, the prognosis is poor and in the past a lethal outcome occurred within 4-5 years. Oral zinc supplementation, at the daily dose of 2mg/kg, induces a prompt regression of symptoms within 1 or 2 weeks. Pro-

longed therapy at least to adult age is necessary to prevent recurrence of manifestations. Anyway, a trend towards improvement with age is possible. During supplementation, it is mandatory to monitor the serum levels of zinc and copper and the immune functions in order to provide a proper dosage of zinc according to different stages. In fact, several evidences have shown that excessive zinc dosages induce low copper levels with subsequent impairment of immune function (21,26).

Endemic nutritional zinc deficiency

This form has been described in severely malnourished children, presenting with dwarfism and hypogonadism as the main symptoms (27). The deficiency is due to the peculiar diet of people from some underdeveloped countries, which consists mainly of unleavened whole grain bread with a high fibre and phytate content; secondarily, concomitant concausal factors may be represented by the habit of clay eating and frequent hookworm infestation.

Acquired zinc deficiency

Etiology. Zinc-depletion syndrome was first recognized in patients with AE-like cutaneous lesions after prolonged total parenteral nutrition for bowel disturbances (28,29). The syndrome can develop within 2-3 months in adult subjects who receive as little as 0.2 mg/day or 1.3% of the recommended allowance (30); if there is a concomitant abnormal howel function, zinc depletion can occur earlier. Premature infants are particularly prone to develop zinc deficiency, because they have negligible zinc stores, undergo rapid growth and show an insufficient absorption compared to mature infants, or because they receive mother's milk which has an insufficient zinc content. However normal neonates or growing children can also require increased zinc supplementation. Other groups at risk are pregnant women, elderly people and malnourished subjects (5-9).

All the conditions that decrease zinc absorption or increase the metal loss from the gastrointestinal tract, skin or urine are able to induce a zinc deficiency due to the limited availability of rapidly exchangeable zinc pools in the body (5-9, 26, 31-38) (Table III).

Table III.
Most important pathological conditions with risk of zinc deficiency.

Alcoholism (alcoholic liver cirrhosis and pancreatitis)
Malabsorption
Artificial nutrition
Chronic diarrhoea
Intestinal by-pass (especially in patients with poor eating habits)
Extensive burns
HIV infection
Chronic renal diseases
Chronic debilitating disorders
Sickle cell anemia
Drugs: chelating agents (penicillamine), cimetidine, diuretics (ACE-inhibitors, thiazides, chlorthalidone) and chemotherapy (cisplatin, antileukemics)

Clinical features. The syndrome includes acute or chronic forms (17,39-41). In acute zinc deficiency cutaneous symptoms resemble AE. The skin eruption is vesico-bullous or eczematous, located on hands, feet, anogenital area and at periorificial level; typical flat bullae surrounded by red-brown erythema can develop on flexural finger creases and palms. There can be also paronychial inflammation and angular stomatitis with perioral lesions sparing the vermilion border. Necrotic and burn-like lesions can be seen, as well as oozing lesions on the heels of bedridden patients. Hair growth stops and there can be a diffuse thinning of the scalp hair, possibly leading to total alopecia within few weeks.

The patients with chronic zinc deficiency show psoriasis-like parakeratotic changes on areas subject to repeated pressure and trauma; the lesions are well-demarcated, thickened and of a

brownish colour. Other skin changes include: lichenification, moderate scaling, seborrhoeic dermatitis-like lesions on the face, flare-up of acne vulgaris, delayed wound healing. In cirrhotics a widespread asteatotic eczema can occur. The hair have a poor and sparse growth and show structural changes. White, transverse bands and depressions may be observed on the nails. In severe deficiency, deep transverse depressions (Beau's lines) on the finger nails due to temporary arrest of nail growth become visible 3-4 weeks after the start of zinc supplementation.

Various degrees of systemic involvement are possible (Table IV) depending on the severity of deficiency (8,9,40). Interestingly, diarrhoea is not only a cause of zinc deficiency but also a consequence of this through still unknown mechanisms.

Table IV.
Possible systemic symptoms of zinc deficiency.

Delayed puberty in adolescents
Diarrhoea
Emotional disorders
Growth retardation
Hyperammonemia
Impaired reproductive development in males (hypogonadism, oligospermia)
Intercurrent infections
Mental lethargy
Ocular abnormalities (reduced ability to dark adapt, photophobia, optic neuritis)
Poor appetite
Taste abnormalities
Weight loss

Diagnosis. The serum zinc and alkaline phosphatase levels are low (39); between these two parameters there is a positive correlation which can be used diagnostically and to control the effects of treatment. It is also important to consider the level of plasma albumin that binds 60-70% of circulating zinc. The actual utility of measuring zinc concentrations in hair and sweat is still uncertain. Skin changes related to acute and chronic zinc deficiency must be differentiated with a great variety of vesico bullous and scaly disorders, respectively. Differential diagnosis also includes eczematous eruptions, psoriasis, stasis eczema (42), asteatotic eczema, seborrhoeic eczema, kwashiorkor, pellagra and necrolytic migratory erythema (43,44).

Management. Severe forms can be fatal if unrecognized and untreated. Therapy in adult patients is based on oral zinc sulphate tablets of 0.2 g b.i.d or t.i.d. (about 2 mg zinc/kg); similar doses on a kilogram basis are given to children. Parenterally, 0,2-0,3 mg zinc/kg/day can be used in severe acute forms. During zinc therapy serum copper and immune status should be carefully monitored. Long-term high zinc supplementation is not recommended and is indicated only for AE (40).

ZINC AND SKIN DISEASES

The role of zinc in the pathogenesis of some skin diseases has been frequently claimed, although conclusive results are available only in some instances. There are several reports suggesting the therapeutic potential of zinc for skin-related disorders. Some of these reports are however anecdotical and need to be confirmed by controlled studies.

Leprosy

In several trials the zinc serum levels and the effects of oral zinc as an immunomodulator in leprosy were studied. In all subtypes, especially in erythema nodosum leprosum, low serum zinc levels with parallel increase of serum copper were observed. Zinc therapy restored normal zinc levels but was unable to reduce copper levels (45).

In subjects with multibacillary leprosy oral zinc was administered in combination with conventional antileprosy drugs. The addition of zinc induced faster clinical improvement, rapid fall in the bacterial index, greater influx of lymphocy-

tes in the granuloma and neovascularization (46). Moreover, the adjunctive therapy with zinc in recurrent erythema nodosum leprosum caused a marked improvement in the frequency, duration, and severity of the reaction, with a significant decrease of steroid requirement (47,48).

Allergic contact dermatitis to nickel

In a guinea pig model, without zinc sulphate interventions, nickel-exposure resulted in significantly higher stimulation indices at the lymphocyte transformation test as compared to non-exposed controls (49).
Weissmann and Menné (50) reported cases of nickel dermatitis improving after oral administration of zinc sulphate. The response to zinc sulphate has been more recently studied in 15 patients sensitized to nickel (51). Zinc improved both clinical manifestations and pruritus, and abolished or reduced the majority of patch test reactions. According to the authors of this study (51), several mechanisms of action of zinc can be speculated in nickel contact allergy, including: prevention of complete antigen formation, removal or decreased absorption of nickel, and reduction of reactive oxygen species.

Acne vulgaris

Rebello et al. (52) demonstrated an inibitory effect of zinc on the lipase of *Propionibacterium* species found in human pilosebaceous follicles. They noted also a small, but not significant, fall in the free fatty acid content of skin surface lipid *in vivo* in acne patients treated with zinc. Other authors pointed out that supplemental zinc sulphate may reduce the quantity of skin-surface sebum (53).
An *in vivo* study conducted in acne patients treated with zinc gluconate suggests that this treatment can inhibit chemotaxis of polymorphonuclear cells by reducing granulocyte zinc levels (54). Recent studies support the effectiveness of zinc gluconate for the treatment of inflammatory acne (55,56).

Miscellaneous disorders

There have been some evidences suggesting a potential usefulness of oral zinc supplement in the prevention of diaper rash in normal infants (57), but this topic has not been further investigated.
In some skin disorders such as acne, psoriasis, dermatitis herpetiformis and Darier's disease, the zinc epidermal concentrations were found to be decreased, in spite of normal serum zinc levels, but the actual implications of such abnormalities are still unknown and may be non-specific (58).
Low serum zinc was also observed in children with atopic eczema; it was suspected that this finding could be regarded as a non-specific consequence of the dermatitis and that there was no indication for zinc therapy in patients with atopic eczema (59). This was subsequently confirmed by a double-blind placebo-controlled trial which demonstrated no improvement of disease activity by zinc sulphate (60).
Beneton and coworkers (61) described two young women with amicrobial pustulosis associated with autoimmune diseases, in whom the pustulosis healed with zinc supplementation. Oral administration of zinc is also considered effective for the treatment of erosive pustular dermatitis of the scalp (62,63), perifolliculitis capitis abscedens et suffodiens (64) and necrolytic acral erythema (65).
A recent placebo-controlled trial (66) has highlighted the efficacy and safety of oral zinc sulphate in the treatment of recalcitrant warts. In fact, in the zinc-treated group a complete clearance was observed in about 61% of cases after 1 month and 87% of cases after 2 months of treatment with 10mg/kg daily. A direct relationship between response to treatment and serum zinc level was observed.
Nutritional factors have been implicated in the

precipitation of systemic lupus erythematosus (SLE); among the aggravating substances, some authors include excess calories and protein, high fat, iron, L-canavanine and zinc (67). In 1979 Fjellner (68) described the case of a woman, treated with hydralazine and propranolol for 6 years, who developed multisystemic manifestations of a LE-like syndrome within one week after starting oral zinc therapy. The actual role of zinc as inducer of SLE is still obscure, although some evidences suggest the involvement of zinc in both the functionality of some autoantigens and in the activity of enzymes operating in some autoimmune reactions (69,70).

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THE HAIR IN CHILDHOOD AND OLD AGE

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Summary

More than 20 syndromes, most congenital, have hypertrichosis as a feature. An excessive growth of non-androgen-dependent hair has been reported in association with many acquired diseases and medications, some of which, as cyclosporine, can be administered also in children. Even though primary hypertrichosis is benign in most cases, it may result in cosmetic disfigurement and psychosocial trauma; a pediatric assessment is necessary to rule out associated diseases. Lanugo hair can occur in otherwise healthy individuals but can be associated with polymyositis and neoplasms. Hirsutism can be idiopathic, but often can be associated with an adrenal or ovarian cause. Thns all women with hirsutism require careful evaluation. More, growing evidence has linked hyperandrogenism to increased risk of cardiovascular disease, genital tract neoplasms, and non-insulin-dependent diabetes mellitus. An application from the study of hairs comes from oligoelements. A recent study investigating the zinc status of eighty newborn babies with neural tube defects and their mothers compared with controls found a positive association between this defects and decreased hair zinc levels. As far it concerns the color of hairs our group has demonstrated that heterochromia of the scalp hair can be a sign of pigmentary mosaicism even withont underlying malformations. The present elucidation of pathogenesis of androgenetic alopecia has lead to second generation steroidal 5α reductase inhibitors, such as Gl-198745 (a combined type 1 and type 2, 5α reductase blocker), W09704002, Turosteride, Mk-963, MK-434, Episteride, and MK-386. A variety of non-steroidal inhibitors such as zinc and saw palmetto are also under investigation . The possibility of gene therapy for androgenetic alopecia has been advanced in animal by the development of a cream capable to deliver DNA to hair follicles. Finally, the study of the stem cells of the hair follicle will give us new possibilities of treatment.

Riassunto

L'ipertricosi può presentarsi isolata o essere un sintomo di oltre 20 sindromi, per lo più congenite. Inoltre l'ipertricosi può associarsi a malattie acquisite ed anche a vari farmaci, tra cui la ciclosporina. Vashi e coll. hanno esaminato 11 bambini (7F, 4M) con ipertricosi idiopatica di cui quattro con la forma generalizzata e gli altri sette con la forma localizzata. Mentre nei primi la forma era congenita, negli altri il fenomeno si era manifestato dalla nascita fino al quarto anno di vita. Una bambina con ipertricosi diffusa aveva anche una iperplasia gengivale. È interessante ricordare che l'ipertricosi lanuginosa può osservarsi in individui altrimenti normali ma può anche associarsi a polimiosite o

a neoplasie sottostanti (carcinomi del basso intestino nelle donne, carcinomi polmonari negli uomini). Per quanto riguarda l'irsutismo, oltre alle ovvie indagini endocrinologiche, bisogna prestare attenzione ad un maggiore rischio di malattie cardiovascolari, tumori dell'apparato genitale e diabete mellito non-insulino dipendente. Un'interessante novità viene dallo studio degli oligoelementi negli annessi cutanei. Dato che è noto che un deficit di zinco può provocare negli animali difetti della chiusura del tubo neurale, 80 bambini con questo problema ed 80 controlli sono stati esaminati con la spettrofotometria ad assorbimento atomico. I livelli di zinco del capello, ma non quelli serici, dei bambini malati erano significativamente più bassi die controlli suggerendo che una supplementazione di zinco potrebbe ridurre questo problema. Nel campo del trattamento dellalopecia androgenetica si stanno sviluppando degli inibitori della 5α reduttasi di seconda generazione come il Gl-198745 (un inibitore combinato di tipo 1 e tipo 2), il W09704002, la turosteride, il Mk-963, MK-434, l'episteride, ed il MK-386.

INTRODUCTION

This paper will not focus in depth the problems oh hair diseases related with genodermatoses. These abnormalities are numerous and varied but such diseases are rare and the patients are generally cared in special centers. In this article the other causes of deficit or abundance of hairs are discussed with special emphasis on new clinical observations concerning the association of hair abnormalities with underlying diseases or with drug administration. The role of zinc as a possible indicator (when deficient) of neural tube defects and as non-steroidal inhibitor of 5α reductase, is also discussed.

CLINICAL DISCUSSION

The other causes of alopecia [1] or hypertrichosis [2] are listed in Table 1a, 1b and in Table 2a,

Table Ia
*Diffuse Alopecia **

Drug induced hair loss
Telogen Effluvium
Telogen gravidarum
Chronic Telogen Effluvium
Early androgenetic alopecia
Diffuse alopecia areata
Radiotherapy
Iron deficiency
Starvation/Malabsorption/ Crash diet
Hypothyroidism and hyperthyroidism
Chronic renal failure and hepatic failure
Syphilis
Acute lupus erythematosus
Advanced malignancy

2b. Hypertrichosis, that is an excessive growth of non-androgen-dependent hair, may be localized or generalized, congenital or acquired. More than 20 syndromes, most congenital, have hypertrichosis as a feature. Not taking into account large congenital melanocytic nevi that may be hypertrichotic and at increasing risk for developing a malignant melanoma, hypertrichosis has been reported in association with many acquired diseases (Table 1b) and numerous medications

Table Ib
*Diffuse Hypertrichosis ***

Multiple Sclerosis
Schizophrenia,
Head Injury
Encephalitis
Starvation
Anorexia Nervosa
Porphyrias
Cushing's Syndrome
Dermatomyositis
Hypothyroidism
Hyperthyroidism
POEMS Syndrome

Table 2a
*Drug induced alopecia**

Telogen Effluvium
Heparin
Warfarin
Propranalol/Metoprblol
Captopril/Enalopril
Allopurinol
Boric acid
Phenytoin
Glibenclamide
Amphetamines
Levadopa
Bromocryptine
Methysergide
Interferon
Albendazole / Mebendazole
Cimetidine
Colchicine (low dose)
Sulphasalazine
Penicillamine
Gold
Anti thyroid action
Carbimazole
Propylthiouracil
Amiodorone
Lithium
Hypolipidaemic agents
Clofibrate
Triparanol
Pro-androgen action
Oral contraceptive pill
Danazol
Testosterone
Anabolic Steroids

(Table 2b) some of which, as cyclosporine, can be administered also in children.

Table 2b

Drug induced hypertrichosis **

Minoxidil
Cyclosporine
Phenytoin
Amiodarone
Psoralens
Tamoxifen
Tiopronin
Diazoxide
Corticosteroids
Zidovudine

** *adapted from: Sperling LC (2001).*
NB: Almost all chemotherapy agents can produce generalised hair shedding.
• *from Sinclair RD, Dawber RP (2001)*

Vashi et al. [3] have reviewed generalized and localized symmetrical hypertrichosis in children in a case series of 11 prepubertal male and female (7F, 4M) patients who had idiopathic hypertrichosis. While four patients showed the generalized form the other 7 had the localized one. All patients with generalized form manifested the condition at birth while in the other group the age of onset ranged from birth to 4 years. One girl with generalized hypertrichosis had gingival hyperplasia and the girl with faun tail deformity had bony diastematomyelia with spina bifida occulta. Primary hypertrichosis, although rare in children are benign in most cases, but may result in cosmetic disfigurement and psychosocial trauma for patients and families. A dermatological and pediatric assessment is necessary in all cases to rule out associated diseases.

It should be remembered that lanugo hair (that is the fine, thin, lightly pigmented hair that covers the human fetus that is normally shed before birth) as hypertrichosis lanuginosa can occur in otherwise healthy individuals but can also present associated with polymyositis and as a rare paraneoplastic condition (colorectal cancer in women and lung cancer in men). Hirsutism (the excessive growth of androgen-dependent hair in a woman) can be idiopathic, but often can be associated with an adrenal or ovarian cause. Thus all women with abnormal menstrual cycles or with severe or sudden-onset hirsutism require careful evaluation. More, growing evidence has linked hyperandrogenism to increased risk of cardiovascular disease, genital tract neoplasia, and non-insulin-dependent diabetes mellitus.

An interesting application from the study of hairs comes from the investigation on oligoelements. As far it concerns the problem of neural tube defects it is known that folic acid supplementation has reduced the incidence of this event. Since it is known that zinc deficiency can provoke this defect in animals, a recent study [4] has investigated the zinc status of eighty newborn babies with neural tube defects and their mothers compared with eighty apparently normal newborns and their mothers. Serum and scalp hair zinc levels were analyzed by atomic absorption spectrophotometry. The hair zinc levels, but not the serum levels, of the affected babies and their mothers were significantly lower ($P < 0.001$) than the controls. Thus this study has found association between neural tube defects and decreased hair zinc levels, suggesting to investigate whether zinc supplementation would reduce the overall incidence of this defect.

As far it concerns the color of hairs, the recent paper of our group [5] has demonstrated that heterochromia of the scalp hair can be a sign of pigmentary mosaicism even without underlying recognizable malformations.

The present development in tbe treatment of some forms of alopecia is due to the elucidation of pathogenesis of androgenetic alopecia, especially with regard to the role of 5α reductase. After the first specific antagonist drugs, second generation steroidal 5α reductase inhibitors, such as GI-198745 (a combined type 1 and type 2, 5α reductase blocker), W09704002, Turosteride,

Mk-963, MK-434, Episteride, and MK-386 have been developed and are undergoing further investigation as are a variety of non-steroidal inhibitors such as zinc and saw palmetto [1]. The possibility of gene therapy for androgenetic alopecia has been advanced in animal (mice) by the development of a topical cream containing liposomes capable to deliver entrapped DNA to hair follicles.

CONCLUSIONS

The field of hair disorders in childhood and old age is presently very interesting. From one side, in children, the fine analysis of the hair can establish a diagnosis which would be otherwise delayed or misdiagnosed (e.g. trichorrexis invaginata in Netherton's syndrome) from the other side, in elderly people, hair changes can be an useful marker of an underlying disorders that can be sometimes fatal if untreated. The study of the stem cells of the hair follicle will give us new possibilities of treatment in the future both for genetic and acquired disorders.

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N-Carboxymethyl chitosan in innovative cosmeceutical products

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Summary

A line of cosmetic products of interest for dental and oral applications has been prepared with N-carboxymethyl chitosan, endowed with biochemical and microbiological significance. Moreover, a systematic survey of the use of N-carboxymethyl chitosan in emulsions has been made, and an after-sun body milk is preseted as an example of advanced cosmetic formulations.

Riassunto

È stata preparata una linea di prodotti cosmetici funzionali di interesse per applicazioni odontostomatologiche e di igiene orale; le loro formulazioni comprendono N-carbossimetil chitosano, un polisaccaride avente capacità antimicrobica e riparativa. Inoltre, è stato fatto uno studio sistematico per l'uso dell'N-carbossimetil chitosano nelle emulsioni, e viene presentato un latte dopo-sole per il corpo, quale esempio di formulazioni cosmetiche avanzate.

INTRODUCTION

Chitin supports countless forms of terrestrial and marine life since many million years (Jollès and Muzzarelli, 1999). It is the most abundant nitrogen compound and cationic biopolymer. Thanks to modern technology, its isolation and purification from marine biomasses provides today chitosan, a natural biocompatible and biodegradable polymer approved for human consumption in Italy as well as other countries (Subasinge, 1999; Muzzarelli, 2000).

N-Carboxymethyl chitosan, originally developed by Muzzarelli (1982) (see also Muzzarelli et al., 1982) is the carboxymethylated soluhle form of chitosan, carrying a glycine aminoacid on most of its units. It belongs to a family of carboxymethylated chitins and chitosans, amply tested in the cosmetic and biomedical fields (Muzzarelli, 1988; Muzzarelli et al., 1989, 1994 a, b, 1998; Mattioli et al., 1999). Among its characteristic properties, the inhibition of the bacterial growth within the oral cavity, the prevention of Streptococcus mutans adhesion to the tooth surface, and the stabilization of the local pH, permit to recommend this functional ingredient for oral care products (Tarsi et al. 1998).

The antibacterial action of N-carboxymethyl chitosan combined with its efficacy against Candida albicans, qualify it as a functional ingredient in tootbpastes and mouthwashes.

N-Carboxymethyl chitosan keeps the filmogenic ability of the parent chitosan. The flow behavior and the viscoelastic properties of N-carboxymethyl chitosan aqueous system in the sol and gel domain have been investigated by means of dynamic, steady and transient shear techniques. These gel-like properties were explained in terms of the association of ordered chains to develop a cohesive network, analogous to that in normal gels but with weaker interactions between associating chains (i.e., weak gel) (Muzzarelli and Muzzarelli, 1998).

N-Carboxymethyl chitosan as a 1.0 % solution at pH 4.80 exerts a beneficial effect in terms of emulsion stability. It is a valuable functional ingredient of cosmetic hydrating creams in view of its durable moisturizing effect on the skin. The film-forming ability of N-carboxymethy chitosan assists in imparting a pleasant feeling of smoothness to the skin and in protecting it from adverse environmental conditions and consequences of the use of detergents (Muzzarelli and Muzzarelli, 1986; Chen et al., 2002).

N-Carhoxymethyl chitosan was found to be superior to hyaluronic acid as far as lasting hydrating effects for human skin are concerned (Muzzarelli et al., 1986).

EXPERIMENTAL

N-Carboxymethyl chitosan was prepared from shrimp chitosan as previously described by reductive amination of glyoxylic acid (Muzzarelli, 1997). The characteristics of the compound were checked by infrared spectrometry and H-NMR spectrometry; these techniques provided spectra from which the degree of carboxymethylation and the degree of acetylation were calculated. By 13C-NMR, the degree of acetylation is revealed by the hand at 24 ppm, while the degree of carboxymethylation and dicarboxymethylation are obtained with the analysis of the 53, 58 and 64 ppm bands. For the quality control purposes, the degree of acetylation is determined by i.r. spectrometry on the basis of the 1650 cm^{-1} band in the chitosan before the derivatization, while the degree of carboxymethylation is determined with the 1730 cm^{-1} band, typical of the carboxyl group.

The 1.0 % N-carboxymethyl chitosan solution including 1 % Germaben II is commercially available under the trade name Chitoglycan®. For certain preparations, freeze-dried N-carboxymethyl chitosan was prepared with a Heto Drywinner freeze-drier.

RESULTS AND DISCUSSION

Dental care

Four innovative formulations including N-carboxymethyl chitosan are presented here for the first time: a toothpaste deprived of abrasive inorganic compounds, a mouth wash, a gingival gel and an artificial saliva preparation that is often sought by dentists as well as for other clinical applications.

Tooth paste in gel form with no inorganics

For this preparation, in the turbo emulsifier the water is heated at 70°C and sodium saccharin, hydroxyethylcellulose and xanthan gum are added and dispersed in 15 min (Table 1).

Table I
Composition of a tooth paste with no inorganics.

N°	INCI NAME	%
1.	AQUA	q.b. 100
2.	SODIUM SACCHARIN	0.20
3.	HYDROXYETHYLCELLULOSE	1.50
4.	XANTHAN GUM	0.50
5.	SORBITOL	30.00
6.*	CITRUS GRANDIS, GLYCERIN	1.00
7.*	N-CARBOXYMETHYL CHITOSAN	5.00
8.	POLYSORBATE-20	0.80
9.	AROMA	0.20
10.	SODIUM LAUROYL SARCOSINATE	3.00

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The temperature is lowered to 30°C, and sorbitol, citrus grandis glycerin, N-carboxymethyl chitosan, sodium lauroyl sarcosinate are added; the homomixer is operated for 10 min.
Pre-mixed polysorbate-20 and aroma are added, to obtain a clear and homogeneous product. The pH may be adjusted with the aid of NaOH.

The final characteristics of the gel are the following: pH 8.22, viscosity at 25°C 6000 mPa.s with VT-02, pale yellow color, smell and taste typical of the aroma used.
In this gel sodium lauroyl sarcosinate is used as a foaming and antimicrobial detergent; its anionic nature is attenuated by its secondary amide function, and it is therefore compatible with Chitoglycan®. Xanthan and hydroxyethyl cellulose are two other polysaccharides used as rheological additives that impart viscosity and stability to the gel.
The rationale behind the use of Chitoglycan is to take advantage of its regenerative capacity in order to reduce inflammation and bleeding of oral tissues.

MOUTH WASH

This mouth wash is prepared by dissolving sodium saccharin in water in the turbo emulsifier; then citrus grandis glycerin and N-carboxymethyl chitosan are individually added and the emulsifier is operated to reach omogeneity (Table 2).

Table 2
Composition of a mouth wash.

N°	INCI NAME	%
1.	AQUA	q.b. 100
2.	SODIUM SACCHARIN	0.10
3.*	CITRUS GRANDIS, GLYCERIN	0.60
4.*	N-CARBOXYMETHYL CHITOSAN	5.00
5.	5-PPG-26-BUTETH26, PEG-40 HYDROGENATED CASTOR OIL	1.00
6.	AROMA	0.10

** Available from Sinerga*

Pre-mixed 5-PPG-26-buteth26, PEG-40 hydrogenated castor oil and aroma are then added and the homomixer is operated to reach homogeneity. The pH value may be adjusted with NaOH.

The final product is a clear and colourless solution with pH 5.20.
The rationale behind the use of Chitoglycan is to take advantage of its regenerative capacity in order to reduce inflammation and bleeding of oral tissues.

ARTIFICIAL SALIVA

The preparation includes the dispersion of hydroxyethyl cellulose in water at 70°C with the aid of the homomixer for 15 min (Table 3).

Table 3
Composition of artificial saliva.

N°	INCI NAME	%
1.	AQUA	q.b.100
2.	HYDROXYETHYL CELLULOSE	1.000
3.	SODIUM CHLORIDE	0.042
4.	POTASSIUM CHLORIDE	0.060
5.	MgCO3.6H2O	0.026
6.	CaCl2.2H2O	0.007
7.	K2HPO4	0.017
8.*	N-CARBOXYMETHYL CHITOSAN, SORBITOL	3.000

* Available from Sinerga

Then, the inorganic salts are dissolved.
Finally freeze-dried NCMC is dissolved at 40°C.
The characteristics of the gel are: clear gel of pale yellow colour, pH 5.34, viscosity at 25°C 950 mPa.s with VT-02.
The gel is made of hydroxyethylcellulose and N-carboxymethyl chitosan. Sorbitol, already present as a plasticizer in the freeze-dried form of N-carboxymethyl chitosan, exerts a moistening action.
The salts are necessary to match the physicochemical and organoleptic characteristics of human saliva.

This artificial saliva is preservative free, to be packed in sterile environment and to be used in monodose applications.
The rationale behind the use of N-carboxymethyl chitosan is to take advantage of its mucoadhesive properties that ensure a long-lasting hydrating effect in the oral cavity.

GINGIVAL GEL

This gel is prepared with the aid of a homomixer by dispersing hydroxyethyl cellulose in water at 65°C for 15 min; then cooling at 40°C and adding the reduced sugars xylitol and maltitol to obtain a clear solution (Table 4).

Table 4
Composition of gingival gel.

N°	INCI NAME	%
1.	AQUA	q.b.100
2.	XYLITOL	10.00
3.	MALTITOL	10.00
4.	HYDROXYETHYLCELLULOSE	2.00
5.*	N-CARBOXYMETHYL CHITOSAN	2.00
6.	POLYSORBATE-20	0.35
7.	AROMA	0.15
8.	CHLOREXIDINE DIGLUCONATE	0.50

** Available from Sinerga*

Pre-mixed polysorbate-20 and aroma are then added.

Finally, the sorbitol plasticized freeze-dried form of N-carboxymethyl chitosan preliminarily dissolved in a minimum quantity of water is added, followed by chlorexidine digluconate.
The gel characteristics are: clear, pale-yellow gel, pH 5.00, viscosity at 25°C 15000 mPa.s with VT-02.
N-carboxymethyl chitosan is here used with the intention of providing relief to oral tissues who-

se functionality has been compromised by infections, or that have undergone surgical operations. Bleeding, inflammation and sour are promptly limited by N-carboxymethyl chitosan, particularly in the gingival pockets. This gel may find ample use at the end of periodical oral hygiene interventions.

EMULSIONS

After-sun body milk

Melt ceteryl alcohol, ceteryl glucoside, glyceryl stearate PEG-100 stearate, octyldodecanol, caprylic/capric triglyceride, ethylhexyl ethylhexanoate, dimethicone at 70°C, then add stearyl glycyrrethinate and bisabolol (Table 5).

In the homomixer warm water at 70°C and disperse guarhydroxypropyltrimonium chloride, add disodium EDTA, aloe barbadensis, glycerin and keep turbo on for 5 min.

Add the lipid phase to the water phase with turbo on for 10 min.

Cool to 50°C, add cyclopentasiloxane, dimethicone/vinyl dimethicone crosspolymer and use the turbo for 5 min and add perfume (~60%).

Cool further to 40°C, add perfume (~40%), and also propylen glycol, sophora japonica, N-carboxymethyl chitosan, hydrolyzed vegetable protein, menthyl lactate (ingredient menthyl lactate should be previously melted).

The characteristics of this white fluid emulsion are pH 4.55, viscosity at 25°C 5000 mPa.s with VT-02.

This emulsion includes a quaternary guar, various plant extracts, and therefore it should help reduce the unfavorable effects of sunshine on the skin thanks to the presence of Aloe barbadensis that protects against UV radiation and together with bisabolol exerts lenitive action.

The purpose of N-carboxymethyl chitosan in this formulation is to exert protection thanks to its filmogenicity against salt and adverse environmental substances, and help re-hydrate the skin.

Table 5
Composition of after-sun body milk.

N°	INCI NAME	%
1.	CETERYL ALCOHOL, CETEARYL GLUCOSIDE	2.50
2.	GLYCERYL STEARATE PEG-100 STEARATE	2.50
3.	OCTYL DODECANOL	5.00
4.	CAPRYLIC/CAPRIC TRIGLYCERIDE	7.50
5.	ETHYLHEXYL ETHYLHEXANOATE	7.50
6.*	DIMETHICONE	0.50
7.	STEARYL GLYCYRRETHINATE	0.10
8.	BISABOLOL	0.25
9.	AQUA	q.b.100
10.	GUAR HYDROXYPROPYLTRIMONIUM CHLORIDE	0.35
11.	DISODIUM EDTA	0.10
12.	ALOE BARBADENSIS	0.20
13.	GLYCERIN	2.00
14.*	PARFUM	1.00
15.*	CYCLOPENTASILOXANE, DIMETHICONE/VINYL	
	DIMETHICONE CROSSPOLYMER	2.50
16.*	PROPYLEN GLYCOL, SOPHORA JAPONICA	5.00
17.*	N-CARBOXYMETHYL CHITOSAN	10.00
18.*	HYDROLYZED VEGETABLE PROTEIN	10.00
19.	MENTHYL LACTATE	0.20

** Available from Sinerga*

CONCLUSIONS

N-Carboxymethyl chitosan is a versatile product that lends itself to a number of formulations. Besides the amply accepted emulsions already present in niche markets since 15 years, some innovative cosmetic formulations have now been prepared in order to take advantage from this functional ingredient. As a further extension of the emulsion range, an after-sun body milk has been presented, but, more important, a line of products suitable for dental/oral applications has been formulated.

The functional characteristics of N-carboxymethyl chitosan include hemostasis, ordered re-

construction of wounded tissues, anti-inflammatory and lenitive action, bactericidal/bacteriostatic action, candidacidal action, buffering capacity at physiological pH values, full biocompatibility, mucoadhesivity and biodegradability, that are definitely superior to those of other polysaccharides.

Being non-toxic, N-carboxymethyl chitosan can be used at any desired percentage in cosmetic and pharmaceutical applications, including percentages higher than those reported here.

Formulations of toothpastes have been developed including traditional alumina- or silica-based toothpastes, as well as advanced toothpastes deprived of inorganic ingredients.

N-Carboxymethyl chitosan is also recommended for mouthwashes, and especially for the treatment of pyorrhea or other gum diseases, where it improves effectively the health of gums and oral mucosae. Formulations undergoing pre-clinical studies include artificial saliva, and freeze-dried materials for the regeneration of gingival tissues.

A series of pre-systematic tests has been carried out with several representative formulations, in order to exploit the capacity of N-carboxymethyl chitosan to stabilize the emulsions. Final formulations of pre- and after-sun care products have been created and their organoleptic and stability characteristics have been found satisfactory.

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ATOPIC DERMATITIS EDITED BY

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Atopic Dermatitis (AD) is an increasingly prevalent chronic pruritic inflammatory skin condition that is thought to have an immune and genetic basis influenced by environmental factors.
AD affects 5-20% of infants and children, two thirds of those are under the age of 16.
Despite the frequency higher in more affluent countries with a westernized lifestyle, it is often viewed by society and the medical community as a minor dermatological condition.
This interesting book is divided into six parts for a total of 30 chapters.
Part I examines the impact of AD addressing the epidermiological (chapter 2) physiological (chapter 3), and socioeconomic effects (chapter 4) of this disease.
In chapter 1, a distinction is also made between allergic extrinsic type IgE-mediated vs intrinsic type non-IgE-mediated dermatitis. Therefore the modern immunological findings of a Th2 cell-related activation pattern of cytokine release in both allergic and non allergic types of bronchial asthma and Atopic Dermatitis, allow a redefinition of the term atopy.
So far, the extrinsic, IgE-mediated and intrinsic non-IgE-mediated types of asthma, rhinitis, and eczema represent an atopic manifestation, according to the results of allergy skin and in vitro tests.
Chapter 2, is focused on Epidemiolology and reviews the way in which the concepts and methods have been applied to the study of AD.
One of the major goal of epidemiological research is, in fact, to identify groups who are at high risk for this disease with the hope of modifying potential risk factors to prevent AD.
In this respect, it is important to distinguish between primary, secondary and tertiary prevention. The real possibility of primary prevention is to identify prenatal or early life factors that may be involved in sensitization and development of AD in the first 5 years of life.
This may be obtained by altering exposures during pregnancy or by the prevention of sensitization in early infancy.
Secondary prevention refers to the identification of those who have already developed the disease with the implication of intervention measures to reduce the associated morbidity.
Finally tertiary prevention involves the treatment of established disease.
Chapter 3 describes all the psychosocial stresses that seem important as significant modulators of AD.
The relationship between stress and this disease is underlined by studies showing that daily hassles could be associated with symptom severity.
As matter of fact, atopy –relevant effector cells, such as mast cells and Langerhans cells, form a close anatomical relationship with nerve fibers capable to secrete neuroactive stress-stimulated substances.
At this purpose, psychotherapy can be performed with individual patients affected by AD, with fami-

lies, or even in groups. An analytically treatment may be indicated, especially in conjunction with chronic skin diseases, since stable and supportive family relationships appear to considerably improve the coping with disease in chronically ill patients.
With chapter 4, focused on the socio-economic impact of AD, ends the 1st part of the book.
Atopic Dermatitis has, in fact, a high effect on the patient's quality of life, disrupting family and social relationships, and interfering with work, school, and recreational activities. Moreover this disease lowers self-image, self-esteem, and confidence in older children just as they are beginning a stage of social interaction. Finally, given its frequency, the treatment of AD is also accompanied by significant costs.
Part II of the book, begins with chapter 5 dedicated to Genetics of Atopic Dermatitis. It provides an overview of the general mechanisms with in-depth discussions on the immunological basis of AD.
No gene can be implicated as the gene responsible for the development of their disease, meanwhile the major hystocompatibility complex (MHC) class II genes, as well as the cluster of interleukins on human chromosome 5, are certainly implicated.
AD is a multifactorial syndrome, and the many components of the disease may be harder to identify if too loose criteria are applied.
For these reasons epidemiology offers the methodological frame work to answer questions relating to the potential environmental and genetic determinants of this disease.
Likewise the finding of migrant studies, the chapter focuses on the importance of environmental risk factors for the expression of the AD, that seems associated with advantages lifestyle.
Conversely the atopic eczema related to food allergy early in life, may represent a subgroup of children in whom nutritional aspects to infant feeding may play a role, particularly the introduction of solid food.
Finally, some aspects of the environment play also a role in either aggravating Atopic eczema, as in the case of water hardness, or in inciting new cases of intrinsic atopic eczema, as in polluted industrial areas.
Chapter 7 is entirely dedicated to the Epidermal barrier as an highly site of lipid synthesis. As matter of fact, in AD a defect in skin barrier function exists.
Compared with normal controls of the same age, Atopic Dermatitis displays a decrease in the contents of total lipids, phospholipids and sterol esters, as well as an increase in free fatty acids and sterols.
Moreover, a marked reduction in the amount of ceramides, especially 1 and 3, has been found also.
The barrier compromise of AD affected patients, leads not only to increased permeability of allergens through the Stratum Corneum (SC), but also to altered immune functions of epidermal dendritic cells that can potentiate T-cell activation.
Such over regulation of immune reactivity, coupled with barrier repair, may be critica ation-induced.
T-cell apoptosis plays therefore a role in the control of circulating skin-homing memory/effector T-cell numbers in peripheral blood.
In contrast, T-cell apoptosis is prevented by citokynes and extracellular matrix components in the eczematous skin to form dermal T-cell infiltrates and mediate effector functions.
The knowledge of the molecular basis of dysregulated apoptosis is pivotal in understanding the pathology in AD and may lead to more focused therapeutic application in future.
With these affermations ends chapter 8.
Because of the high impact on quality of life, most of the patients affected by AD measure the severity of the eczema by the intensity of pruritus. Pruritus is, in fact, regularly intense but intermittent

with greater intensity in the evening and night. Thus itchiness and dry skin lead to scratching and trauma-induced inflammation.
So far, most effective and consistent antipruritics remain systemic immunomodulators such as glucocorticoids, cyclosporin H, tacrolimus (FK506), ascomycines (ASM 981), and ultraviolet light therapy.
Moreover cooling the skin with specific lotions results in relief of itch and application of hydrophilic emollients and bathing with oily baths may combat skin dryness, Pathophysiology of itching is the topic of chapter 10, meanwhile chapter 9 is dedicated to Animal Models of Atopic Dermatitis.
Part III of this book focuses on the individual cell types that contribute to AD for intervention.
In fact in AD, Langerhans cells, monocytes/macrophages, T and B cells, keratinocytes eosinophils, and mast cells are activated with cytokines largely involving T cell Type 2 and Type 1. On chapters 11 to 16 the function of all these cells are reported.
They participate to the pathogenesis of skin inflammatory disease through the production of numerous inflammatory signals which amplify and sustain skin inflammation.
A better understanding of the molecular bases of these phenomena may ultimately afford the identification of novel targets, providing specific and effective therapeutic intervention.
Part IV (chapter 17 to 20) reviews the immunologic triggers such as food, inhalants, bacteria and fungi, that aggravate AD.
In fact some of the evidence suggests that allergen inhaled and absorbed through the respiratory tract can exacerbate this disease and may be particularly important in pruritus. Thus it seems likely that the allergens of dust play two roles: (1) contributing to the inflammation, priming of T cells, and production of IgE by direct contact with the skin; and (2) as a trigger for acute exacerbation and itching either from inhalation or direct contact.
Some studies have also proven that clinical syntomatology of AD may be directly affected by the ingestion or avoidance of certain food antigens.
Moreover colonization and infection with S. aureus, producing bacterial toxins and consequently superantigens, contributes to the severity of AD.
Once attached to the skin, these staphylococcal superantigens can augment allergic skin inflammation and reduce corticosteroid sensitivity.
Finally fungi, such as C.Albicans and Malasseria, containing polysaccharides and proteins as antigenic components, induce Th1 and/or Th2-dependent immune responses, if they penetrate the skin.
The last ten chapters of the book (part V) deal with the therapeutic management of AD.
At this regard, it is necessary, first of all, to evaluate the eczematous skin lesions by the Atopy Patch Test (APT) known to elicit IgE-mediated reactions.
As matter of fact, APT seems to give the most specific results with regard to clinical history as compared to the classical skin prick and radioallergosorbent tests.
Soon after, education of patients and tbeir families is a critical component of successful management of AD.
Patients or parents should demonstrate an appropriate level of understanding adjusted and reviewed on follow-up visits.
The education of the child and the family very often requires, in fact, a lot of time because of preconceived ideas about AD. No management can be effective without this essential step.
Moreover use of effective emollients, especially when combined with hydration therapy, will help restore and preserve the SC barrier. Emollient may also decrease the need for topical corticosteroids, that remain the mainstay of treatment for AD. They are necessary to reduce inflammation and pruritus

and are useful for both the acute and chronic phases of the disease.
To be safe, topical corticosteroids should be used for brief periods on limited areas without occlusion.
Finally wet-wrap dressing therapy may be useful as a barrier from trauma associated with scratching, to reduce pruritus and inflammation by cooling the skin, and improve penetration and activity of topical corticosteroids.
Chapter 24 focuses on the role of cyclicnucleotide phosphodiesterases (PDE) in the phatogenesis of AD.
Besides blocking the abnormal PDE activity, PDE 4 inhibitors may interfere with the most relevant features of AD immunophatogenesis, acute phase, chronic phase, and bacterial superantigen-mediated effects.
Between the immunomodulator agents, topical tacrolimus and pimecrolimus have a high specificity for inhibiting the expression of inflammatory T-cell cytokines, both binding to the FKBP-12protein.
However these drugs may decrease immune surveillance of treated skin, increasing the risk of basal cell or squamous cell carcinoma.
Thus, patients receiving therapy with topical immunomodulator should be educated about adequate measures of sun protection.
At this purpose, a master approach to photo-therapy of AD, appreciated for decades, has to reflect treatment decisions on the background of recent pathogenetic concepts, specially when used in combination with immunosuppressive substances. However, symptomatic photo-therapy of acute, severe exacerbation of AD may be achieved with UVA-1 systemic psoralen plus UVA radiation (PUVA), and extracorporeal photochemo-therapy, whereas conventional UVA/UVB and narrow-band UVB therapy represent phototherapeutic modalities, primarily indicated for treatment of chronic stages of this disease.
Chinese herbal therapy is also an alternative medication used from a minority of patients.
It is based upon the treatment of a number of contributory factors with a combination of herbs containing a multitude of different chemical that may act in concern. As explained in chapter 28.
However the list of recommended substances for systemic treatment of patients suffering from AD is long, ranging from antihistamines, antibiotics, and corticosteroids to immuno-suppressants and from dietary supplements to PUFA and Chinese herbs.
It is to be remembered that the quality of the early cutaneous experience and the touch of loving caregivers the infant received during the early months of life has also a great influence on physical symptoms of AD.
As a matter of fact, the higher than normal levels of anxiety characteristic of atopic individuals are most likely related to this early experience. For these reasons psychotherapeutic treatment procedures for a correct mother-child relationship constitute important therapeutic support strategy for people affected by AD.
Notwithstanding research progress over the years, this multifactorial disease remains an attractive challenge in terms of research and management.
In particular, further investigation is needed into the factors associated with the western lifestyle that seems so strongly associated with atopic eczema expression.
However there is no doubt that the current efforts in understanding the photomechanisms of AD will rapidly lead to the design of new compounds able to specifically target discrete but essential mechanisms contributing to this condition.
This interesting book thanks to the different topics treated and the vast bibliography reported, gives

the reader all the information necessary for understanding the modern management of AD. Atopic Dermatitis written by leading experts in the field of this multifactorial disease, will be surely useful for chemists, pharmacologists, immunologists interested to know more about this pathology. The books will be of help also for medical doctors who constantly have to face all the problems joined to atopy and skin dryness.

P. Morganti
Editor-in-Chief

HYPERHIDROSIS AND BOTULINUM TOXIN IN DERMATOLGY

By O.P. Kreyden, R. Böni and G. Burg
2002. 254 pages Hardcover
CHF. 228.00 - EUR 163.00 - US$ 198.25
ISBN: 3-8055-7306-5
Karger AG, Basel (CH)
Fax: ++41 61 3061234
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Botulinum is the most toxic material known to humanity but, paradoxically, as a result of its effectiveness, it is also the safest medication available.
As matter of fact, it is administered in accurate doses at the required treatment site and side effects are limited only to local spread of the toxin to unwanted muscles, causing ptosis and/or bruising and pain.
Therefore the exotoxin of Botulinum A (BTX-A) has extensively used for the management of facial lines, wrinkles and axillary hyperhidrosis, which is the main topic of this interesting book divided in VII parts for a total of 24 chapters.
The first three chapters give a comprehensive overview on the Anatomy of Sweat Glands, the Pathophysiology of Sweating and the relative and consequent Good and Bad Body Odours.
Sweat glands are distributed over the entire body surface, producing up to 10 liters of sweat per day, responsible of the healthy adult's body odor.
The secretary product of apocrine sweat glands is sterile and odorless, generating potent odours compounds as a consequent of bacterial decomposition.
For these reasons natural human body odours are classified as body odours from westernized societies. Moreover exaggerated local systemic sweating responses result in hyperhidrosis, which is not only unpleasant, but also impairing social and occupational activities.
Causes of symptomatic hyperhidrosis include endocrinological disorders, disorders with elevated catecholamines and neurological disorders. However excessive sweating occurs, also, physiologically during acclimatization and postmenopausal women.
Odours seem to play also a role in families and in mother-offspring interaction. Babies can recognized their mother's odours, and mothers can correctly recognize their own babies by odour.
Traditional treatment of hyperhidrosis and Surgical Intervention of hyperhidrosis are the topics of the second and third part of the book.
The topical pharmacological application of antiperspirants is the mainstay of treating local hyperhidrosis in circumscribed areas of excessive eccrine sweating.
Aluminum salt solutions are the first choice for this topical and localized therapy.
Metallic salt solutions generate, in fact, an obstructive and temporary plug in the acrosyringium, due to the formation of complex between muco-polysaccharides of the sweat duct cuticle and the metal ions. For this reason this obstruction against secreted sweat prevents also from further penetration of metal ions through the skin and from the related systemic effects.
Moreover repair of acrosyringium due to renewal of the epidermis restores the normal function of

sweat glands. Therefore aluminum chloride solution have to be applied on a regular basis.
However in most cases of severe hyperhidrosis, the efficacy of this topical treatment is unsatisfying, and special prescriptions have to be used.
Among the systemic drugs, anticholinergics are the most kindly used even if they carry the risk of many side effects.
They block neuroglandular transmission due to the competitive inhibition of synaptic acetylcholine.
Tap Water Iontophoresis (TWI) is the first line of treatment in palm-plantar hyperhidrosis. It is safe, well tolerated and has been shown to be very efficient.
TWI is less convenient for the axillae since it may cause considerable irritation.
In this case a limited sweat gland excision may represent a relatively simple and high effective treatment for recalcitrant axillary hyperhidrosis as well as bromhidrosis.
Alternatively sympathectomy should be reserved to severe forms of primary (idiopathic) hyperhidrosis by the video-assisted thorascopic technique.
The 4th and the 5th part of the book are entirely dedicated to the Botulinum Neurotoxins.
Botulinum is a form of food poisoning caused by the neurotoxin-producing bacterium Clostridium Botulinum, found ubiquitously in soil and damp environments.
The therapeutic benefits derived from a local injection of a botulinum neurotoxin preparation are based on the site-specific delivery and on its high-affinity uptake by cholinergic neurons.
This results in a temporary chemo-derivation and loss of activity of the target organ, such as muscle, sweat gland, etc.
The combination of the right delivery method, low dose and neural uptake provides the expected local efficacy with minimal systemic adverse effects.
Therefore the clinical use requires precise injections of BTX-A into specific muscles to cause a temporary chemoderivation of the skeletal muscle and the relief of the clinical symptoms.
The 7-botulinum neurotoxins, indicated with letters from A to G, constitute a group of metal proteases very specific for the presynaptic nerve terminals.
These bacterial metalloproteases bind to receptors localized on the presynaptic membrane, exerting their enzymatic action in the cell cytosal on selected proteins.
Recommended dilutions of botulinum toxin have ranged from 10 ml/vial to 1 ml/vial.
In hyperhidrosis, a dilution at 5 ml/vial is widely accepted for clinical use.
Moreover the biological availability of botulinum toxin can be enhanced by lowering its concentration, supplementing with albumin and increasing the injection volume.
However a higher concentration allows for more accurate placement, greater duration of effects and fewer side effects.
The concentration of the toxin would be highest at the point of injection and the concentration gradient decrease rapidly with distance from this point.
With higher dilutions and more volume of solution injected, this area of diffusion would naturally increase and the concentration gradient would be much less steep.
However BTX-A treatment is a new conservative alternative to surgery in the treatment of severe hyperhidrosis. Intracutaneous injections of BTX-A are safe and effective, and offer long-lasting relief of symptoms.
The recommended treatment interval is 3-6 months and the injection of botulinum toxin A into the axillary region is simple and easy.
The respective dose for one axilla is 2 ml divided into 8-12 aliquots, which are injected strictly intra-

dermally by creating a visible wheal on each injection point.
The distance between two injection points should not excelled 2.5 cm.
Final chapters of part 5th and 6th are reserved for rare forms of hyperhidrosis and indications, such as the cosmetic use of BTX-A.
Its major cosmetic indication in the facial area are glabellar frown lines, crow's feet, and horizontal lines of the forehead and to reshaping the brow.
Minor applications are in the lip lines and the corners of the mouth.
Botox on its own is a safe, effective, well-accepted and repeatable treatment for many facial wrinkles, working better in younger female patients (20-45 years old).
It is particularly acknowledged for its effectiveness in the upper face, meanwhile collagen is more effective in the lower face.
Both the treatments are excellent modalities for smoothing and erasing wrinkles in the age face.
Many other indications of BTX-A from Facial Hemispasm To Paralytic Strabismus and Sialorrhea, are reported in this interesting book.
This book of special interest to dermatologists, plastic sungeons and neurologists, will be surely useful for all medical doctors, general practitioners and medical students who wish to have the basic information necessary to work with botulinum toxin.

P. Morganti
Editor-in-Chief

GLICOLYC ACID PEELS

by R.Moy, D. Luftman and L. Kakita
2002. 240pages Hardcover
U$ 125.00
Marcel Dekker Inc.
ISBN: 0-8247-0722-2
250 Madison Avenue New York, NY, 10016
Fax. ++1 - 212-685-4540
http://www.dekker.com

Alpha hydroxy acids (AHAs) are a class of naturally occurring compounds derived from fruit and dairy products. Whether desquamation or epidermolysis occurs is dependent upon the concentration of the acid, its bioavalability, the condition of the influencing delivery, and the absolute amount of acid delivered to the particular skin compartment over a given period of time.

AHAs are chemically characterized by having a hydroxyl group on the alpha carbon, of the first carbon after the carbon containing the carboxyl group.

Glicolyc acid, the smallest of AHAs, is the topic of this book, reporting in 14 chapters the most recent data on its availability, clinical and hystological effects.

Glycolic acid, and all the AHAs, beta hydroxy acids (BHAs) and the more recent poly-hydroxy acids (PHAs) seem capable to bind water, maintain optimal skin hydration, normalize keratinization and desquamation, enhance barrier efficacy, reverse epidermal–dermal atrophy, maintain optimal skin morphology; and decelerate skin aging processes, especially those caused by oxidative damage.

Hystological findings reveal that all detachment provoked by AHAs is at level of stratum compactum. An immediate consequence is that the thickness of the Stratum Corneum is minimal but later is restored to normal thickness, or even slightly thicken.

Whether these sequential stratum corneum/epidermal responses are due to direct influence of the AHAs or whether the response are normal homeostatic events secondary to desquamation is unknown. In other case, the sum consequence of topical AHA applications seems to be of a modulatory nature, wherein abnormal stratum corneum and epidermis are restored toward normal.

However, the topical efficacy of a formulation containing an AHA for cosmetic and dermatological indications depends on two major factors: (1) bioavailable concentration of the AHA, and (2) the vehicle used. The bioavailability is the sum of the number of undissociated molecules of AHA divided by the number of initial concentration in the topical formulation plus the dissociated molecules. Thus partial neutralization of glycolic acid will lower the bioavailability and bioavailable concentration. In fact is to be remembered that at the pka of a given acid, 50% of it is in free acid form, and 50% is in dissociated ionized form; moreover the pka of glycolic acid is 3.38. Therefore identical topical efficacy of AHA may be obtained from two different parameters: higher bioavailability with lower initial concentration or lower bioavailability with higher initial concentration.

Thus a 5% glycolic acid at pH 3.2 (bioavailability 4.1) may have approximately the same efficacy as 10% glycolic acid at pH 4.0 (bioavailability 4.0).

However the 10% glycolic acid at pH 4.0 may have two advantages: (1) less skin irritation with higher pH and (2) a reservoir for potential second phase of percutaneous permeation, if the partial neutralization is made with a weak alkali or with an amphoteric compounds, such as glycine or alanine.

In fact, during the first phase of permeation, free glycolic acid penetrates into the skin and the con-

Bari 28 29 30 novembre 2002

Cari Colleghi,
la Dermatologia é una materia in continua evoluzione e per questo rappresenta un "challenge" costante per tutti noi. La Dermatologia intesa in modo tradizionale probabilmente non rappresenta in pieno la realtà attuale. I dermatologi oggi devono confrontarsi con le nuove tecnologie. La dermatologia "digitale" ed i LASER permettono di affrontare la gestione diagnostica e terapeutica delle malattie cutanee con mezzi più efficaci che rendono più selettivi i risultati clinici e più obiettiva la diagnosi. In campo farmacologico le novità terapeutiche sono un ulteriore fattore di stimolo poiché i prodotti più recenti a nostra disposizione, superando i limiti delle terapie tradizionali, rendono più agevole il nostro compito fornendo armi più sicure ed efficaci. Purtroppo, l'innovazione fa apparentemente lievitare i costi di gestione della malattia, ponendo a noi medici problemi nuovi anche di tipo deontologico. Compito dei Congressi é quello di confrontarsi tra esperti e di educare i giovani. L'educazione medica continua é un obiettivo comune sia per chi é relatore sia per chi é uditore. Personalmente ritengo che insegnando, e soprattutto comunicando, si impara. Da una domanda nasce una discussione e da una discussione un'idea e così via in continuo divenire. Gradirei un'ampia partecipazione a questo Congresso che rappresenta per la Dermatologia dell'Italia meridionale un'occasione unica di apprendimento. Per questo motivo si é voluto anche evitare la quota di iscrizione al Congresso. Il programma scientifico presenta i requisiti necessari per ottenere dalle Autorità competenti i crediti ECM secondo la nuova normativa ed avrà il patrocinio delle maggiori società scientifiche di dermatologia italiane. Ringrazio fin d'ora tutti i partecipanti e tutte le aziende che attraverso la sponsorizzazione disinteressata contribuiranno alla riuscita del Congresso.

Gino Antonio Vena

Presidente del Congresso
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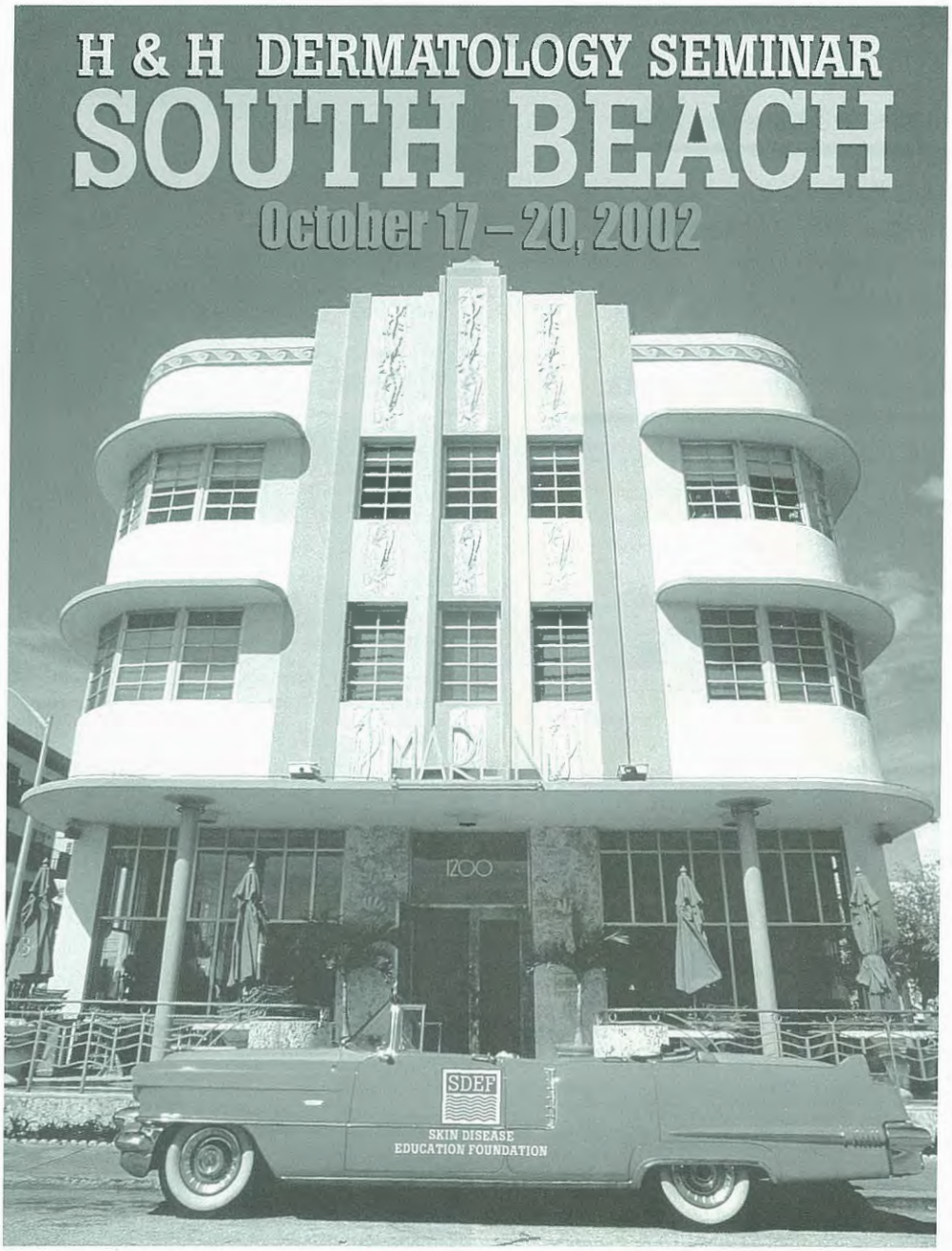

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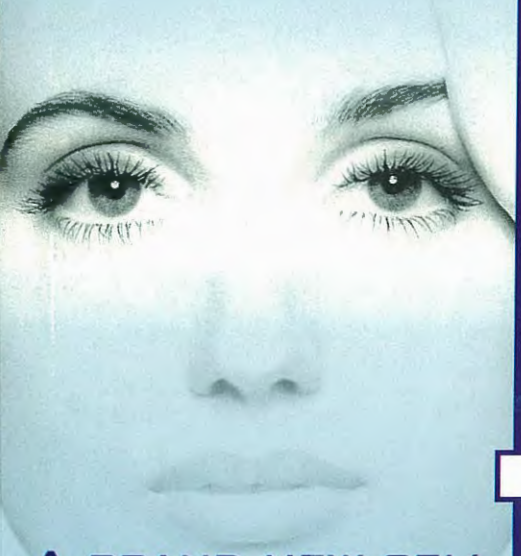

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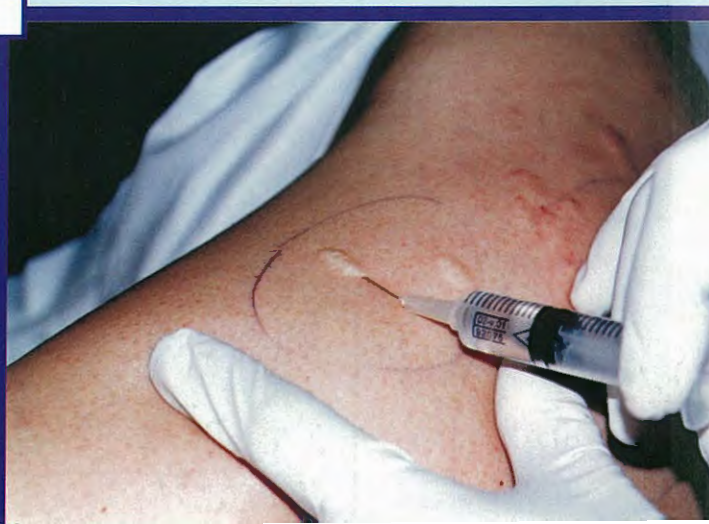

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