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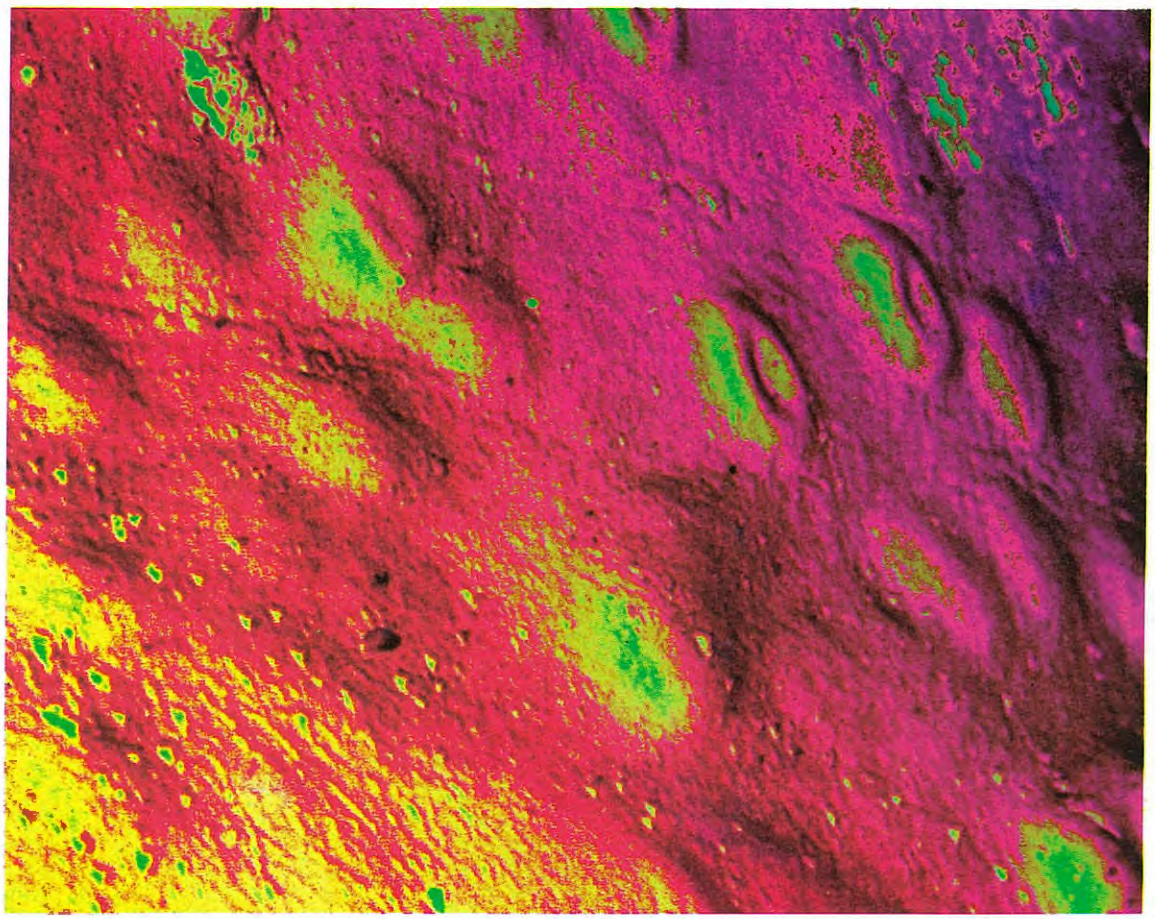

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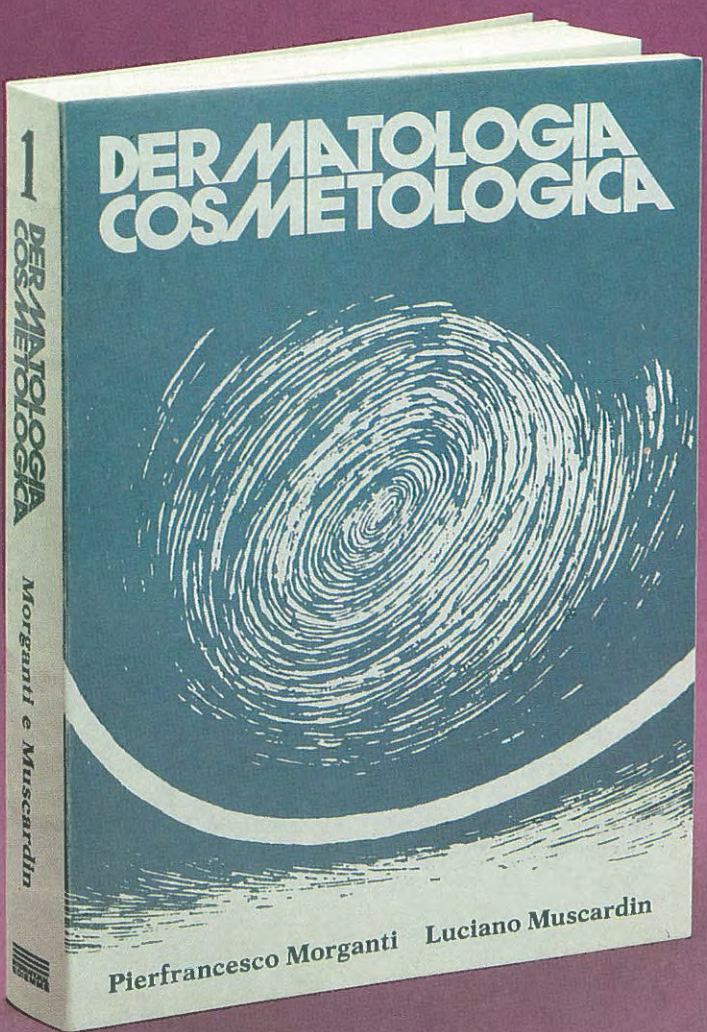

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A cura di P. Morganti e L. Muscardin
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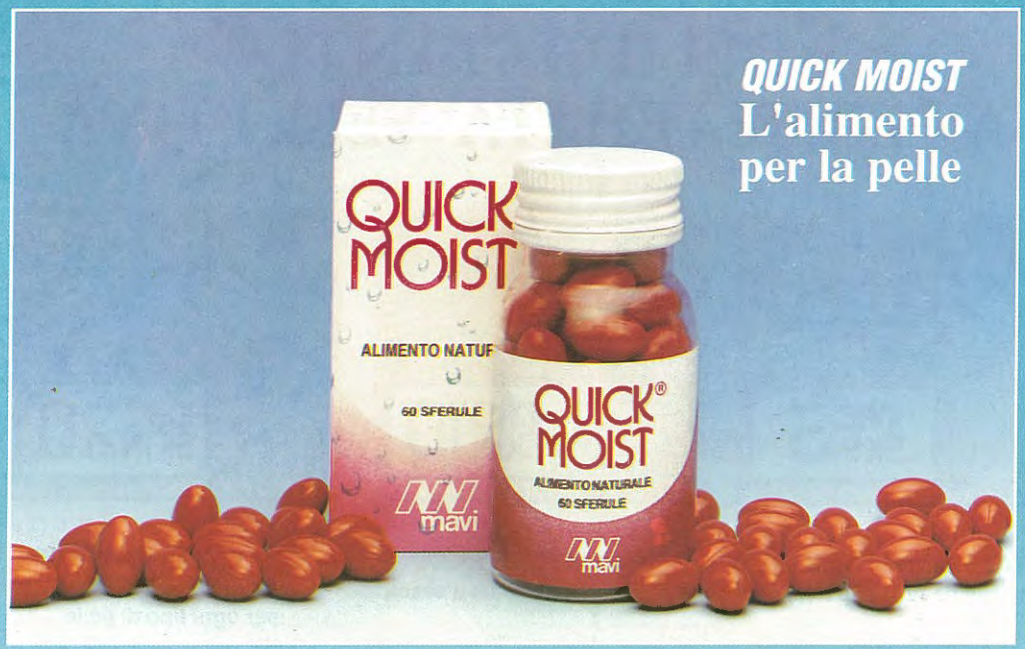

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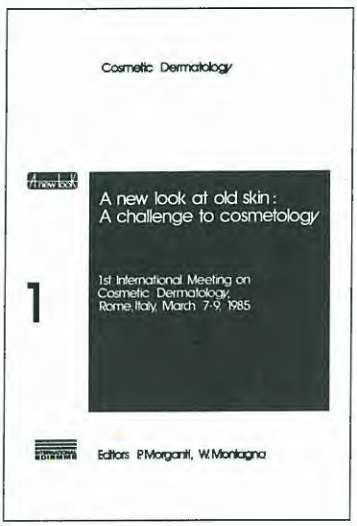
A new look at old skin: A challenge to cosmetology

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

Editors: P. Morganti, W. Montagna



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Contents

The Evolution of Medical Science and Dermatology

From the magical interpretation of disease and the doctrine of humours to experimental research on etiology and immunopathology, the evolution of medical science, including dermatology, was slow until the beginning of the 20th century and then accelerated rapidly (Tilles and Wallach).

The introduction of microscopy in the XVII century boosted investigation of certain diseases.

One may smile at the long labours of medicine and the concepts of disease from the beginning of mankind until the present, but it is easy to understand. From "instinctive medicine", by which the first men healed themselves, as animals still do when they spontaneously look for drugs, medical science progressed with the other cultural, ideological and technological achievements of mankind. It took more than four centuries to discover the agent causing syphilis (1905), whereas in recent times only three years passed from the identification of AIDS to the isolation of the virus, even if the existence of only one factor determining the disease is still under debate.

Technology has considerably developed and accelerated scientific research, but an important contribution must be credited to conceptualists and keen observers of the past, as "anything a man touches has something of the man who touched it before" (Scarna).

The first documents mentioning skin diseases - Ebers's papyrus (2000 B.C.), Sanskrit writings and the Bible (1000-800 B.C.) - are very vague and it is difficult to give them indisputable nosological attributions.

It was the Greek culture that brought about more significant dermatological references. In that period, the first profound observer of matters concerning the skin was Empedocles of Agrigento (Sicily, 500-440 B.C.). He guessed the skin-breathing theory which replaced the lung theory and was demonstrated 24 centuries later by Lazzaro Spallanzani (Bellini).

Hippocrates (born in Cos, in Dodecanese, around 460 B.C.) described dermatoses as idiopathic and symptomatic, and terms like "erythemata, exanthemata, phlyctena, lichen " firstly appeared.

Aulus Cornelius Celsus (25/30 B.C. - 45/50 A.C.) linked sound to the scalp, Pliny the Elder (23-79 A.C.) identified herpes zoster and mentagra (chin sycosis), Avicenna (Abu Alì Al Hussein Abdullah Ebn Sina, 980-1037) described "albarras nigra" (ichthyosis).

The institution of Universities (XIII century), the freedom to engage in anatomical dissection and the invention of the press (XV century) helped the deepening and dissemination of medical science. Present-day dermatology has its roots at the end of the XVIII century and developed in Europe and throughout the world from the XIX century onwards. Vincenzo Chiarugi (1759-1820) started teaching a course on "Sordid skin diseases and mind disorders" in Florence in 1978, and wrote an essay on "Sordid Skin Diseases" in 1799.

In Italy, the first autonomous Chair of Dermatology was assigned to Casimiro Manassei, at the University of Naples, in 1859.

Terminology of Acne and Diseases

The naming of disease was useful to designate the major morphological and subjective features. Many diseases are referred to by the names of the researcher who first identified them or even of illustrious patients (Job's disease for leprosy; Socratic nose for Socrates's saddle-nose, St. Lazarus's disease for the ulcers covering his body), of mythological figures (Syphilus's disease, for syphilis - according to others from the Greek terms "siflos" meaning

filthy; "bacchia", face redness, from Bacchus, of wine) of cities, regions and rivers (Button of Aleppus, Baghdad, Damascus, etc, for skin leishamaniasis; Naples disease or French disease for syphilis, Asturias disease for scabies, Crimean disease for Cossack leprosy), of Saints giving protection from the disease (St. Damian for erysipelas, St. Anthony for herpes zoster), of fruits and legumes with morphological reference (date sickness and fake lupin for skin leishamaniasis) etc. (Cipriani).

Usually, nosological denomination is linked to Greek or Latin. Therefore, the etymological study of the scientific terms suggests the explanation of the reference to the disease. However, the connection between the terms and the disease is not always clear. In fact, it is difficult to trace back to the period when the term was firstly used and the meaning given to it and, furthermore, with the passing of time, the word has been distorted and differs from its original form.

It is not easy to list the terms relating to what is meant by acne today though the disease appears to have been studied since long ago. (Delaberge et al.). The difficulty is due to the unclear definitions of dermatoses given for many centuries and the multiple uses of any single term. In the beginning, each term was used to designate more than one vaguely related pathological form; subsequently authors often used the term to designate single forms. Moreover, the same term may refer to quite different dermatoses because, at the time, it was difficult to make differential diagnoses. On the other hand, the same

Table I

Synonyms of acne

1) Italian and foreign synonymy

ACNE - Italian and Spanish
BOURGEONS, SAPHIR, BOUTON, COUPEROSE, MENTAGRE - French
AXNE, ZENION JONTHOS, - Greek
VARUS - Latin
STONEPOCK MAGGOT, PIMPLE WHELKS - English
FINEN, BOTHGESICT - German
VINEN, STEENPUISTJES - Dutch

2) Chronological synonymy

AXNE - Aezio
VARUS - Sennert, Linneo, Sagar.
BACCHIA, GUTTA ROSEA vel ROSACEA - Linn.
PSYDRACIA ACNE - Sauv.
JONTHUS VARUS ET CORYMBIFER - Young
PHYMAFACIEI, PHYMA WASI - Good.
HERPES PUSTULEUSE - Alibert.
ACNE, MENTAGRE, COUPEROSE - Biett, Cazenave et Schedel, Guibert, Rayer

According to: Delaberge, Monneret e Fleury: Compendium of Practical Medicine, 1954

Willan's authority in 1080. In 1832, Alibert re-instated the Latin term "varus", but to no purpose.
Willan and his follower Bateman identified four kinds of acne: simplex, pointed, hardened and rosacea. In 1842 Wilson made a cleardistinction between acne simplex and acne rosacea.
Other special clinical variants (acne necrotica, conglobata, flemmonosa, cystica, keloid acne) and chemically induced acne-like rashes (e.g. by chloride, bromide, iodide, mineral oils such as grease and tar) have been added to so-called acne vulgaris, connecting each species to its specific causation.

Development of etiological concepts and Acne Treatment

As Bazzi points out, a first period, from the ancient Greek time to the 1850's, is ruled by the Hippocratic humoral doctrine based on the influence of blood, phlegm, yellow bile and black bile or actrabile.
During the second period, from 1842 with Simon up to the earliest 1900's, the parasite theory (Simon's Acarus follicolorum, Wilson's Entozoon folliculorum, Gervais's Simonea folliculorum) prevailed.
In the third period, the XX century, attention has been drawn to genetic factors (race and familial heretability), age and sex, sebum production and acid fat metabolism (lipasis), androgenic hormones, rash media, the lack of vitamins (vitamin A), the influence of complementary (food, environmental, professional, mental) factors, and to the bacteriological and biochemical role of Propionibacterium acnes, Staphylococcus epidermidis and Pityrosporum ovalis.
This led to the classification of several clinical, morphological and pathogenic species, with different therapeutic implications.
1600 years ago Marcellus, Theodore I's (Hecht) physician, suggested a simple care: "Glare at a falling star and, at the very same time the star is still falling from the sky, cover boils with a cloth or anything else to hand. Whilst the star is falling from the sky, boils will fall from your body, yet you must pay special attention not to touch them barehanded or they will pass on your hand".
This is a case of magic and psychological medicine, but it is not to be wondered at since similar suggestions still appear successful for warts and exhaustive explanations of their mechanism are given by neuroendocrine-immunologists.
Buchan suggested that great care must be exercised in the therapy of chronic and refractory forms. He proposed the sole use of palliatives, since "assuming a cure exists, this will surely involve some danger" ensuing from likely internal complications. Copland (cited in Delaberge's dictionary) also warned about curing acne that "can sometimes be placed amongst the diseases that are dangerous to heal. This circumstance caused stomach, intestine, breast and head diseases, which surrendered to the influence of skin diseases. Such distinctive accidents are very frequent after the retropulsion of other eruptive diseases".
Actually, such statements, although seemingly funny, are the basis for some modern psychosomatic theories, specifically related to acne and psoriaris. It is, incidentally, worth considering the popular theory claiming that acne is to be "led out", thus being thought of as "youthful outlet".
Aporti reported that "sometimes acne fades out at once, to extend for sure to internal organs; then the patient's life is more or less endangered."
However, Alibert was rather doubtful. He believed "medical helplessness to have led to the false idea of acne as a natural and healthy depuration, thus being dangerous to fight back."
Researchers claimed that continuing and intense studying moods and fright, wrath, daily

troubles (Aporti), some sad passions, a lively spiritual pain (Delaberge et al.), lively emotional affections, tasks requiring mental concentration and a heavy blood flow to the head (Rayer); unrestrained spiritual toil or pain (Buchan); excessive mental or physical work (Aporti), as well as a sedentary and idle life seem to favour acne (Delaberge et al.). Also arthritis and lymphatic disorder (Bazin), goitre end scurvy (Buchan), pregnancy and menstruation (Chiarugi), cold and wet climates (Aporti) can favour acne.

So can any dissoluteness like sensual pleasures (Buchan), intemperance and youthful addiction to the fatal habit of onanism (Delaberge et al., Besnier and Doyon).

However, Hardy linked acne to sexual abstinence, so that the French called acne in the young who were unaccustomed to the pleasures of love as "wisdom buttons".

Everybody acknowledged the influence of dietary errors: sour and salty foods, pepper, spices, coffee, chocolate, wine, spirits (Buchan) and beer (Chiarugi). yet, Buchan acknowledged that "people exist whose behaviour is blameless and regular even on food and yet are affected".

External causes include cosmetics: "it seems undoubted that creams and red lead that women use to tan or smooth their skin help pimples to rise as they clog pores and suppress transpiration".(Buchan).

Patients are counselled to arm themselves with constancy, to be compliant and not give in to vain hopes, while physicians are recommended to persevere.

The suggested treatments consist of "a diet poor in nutrients: white meat, fresh vegetables, dairy products, vegetable jellies, water-rich and laxative fruit" (Delaberge et al.); soups, young animal meat, sole or wine-hued water during meals (Buchan).

In addition, dry, pure (Migne) and fresh (Rayer) air.

For systemic treatments, absolute preference is given to bleedings and leeches for local effects in proximity of the affected parts "in order to free skin tissues from blood in excess, or on peripheral parts to obtain a local fluxion".

Rayer claimed that foot bleeding and leeches applied behind ears or on temples and nose lobes usually succeed (Ambrogio Pareo suggested broad bleeding ...., from the basilic, front and nose veins; many leeches will be attached to the face at then same time, and cupping glasses sacrified on shoulders).

If related to lack of menstruation and a haemorrhoids, leeches will be posted on vulva and anus correspondingly to the time of such periodical evacuations".

In order to attract blood to the feet, Buchan suggested plunging the legs in hot water over cycles of eight days followed by eight day of rest. Patients were counselled to avoid cold feet, causing blood to flow to the head, and to cover the head with a light hat (Devreaux).

Frequently, the oldest local remedies included turpentine, vinegar, soap and myrrh-based liniments (Rayer). In order to force chronic eruptions of pimples to an acute stage, caustics such as hydrochloric acid and pure silver nitrate (lunar caustic) were used, such that "any misuse caused face skin to be externally and deeply ruined with scars disfiguring the patient's physiognomy more than the disease itself (Aporti).

Ammonium chloride, mercuric sulphide, sulphur, iodide and calcium oxide based ointments were used or "ill parts were covered with a cantharidine powder-based vesicant up to provoking strong pain and deep tegumental injuries whose traces could hardly be destroyed" (Delaberge et al.).

Alibert reported that, "Men of great dignity called many physicians of different worth from Egypt to Rome and paid enormous amounts to be healed. Pamphylus was among them. He gained special distinction and great fame for his vesicant that he used to apply with extraordinary success. History has it that he soon gained considerable fortune; but wrecking scars

resulted from his remedy which could not be deleted".
Correctly, Rayer warned that "less painful, dangerous but equally effective remedies" existed, though he acknowledged that vesicants could lead to brilliant results.
Rayer was surely stricken by the effects noted on one of his patients: After three of four hours using the vesicant she felt her bladder heating, her matrix neck swelling and stinging, and vomited, passed and went restlessly, moving all around as if on fire, seemingly insane and feverish". But, finally, Rayer reported - the lady "back home, was married off, had nice children and lives without anyone realized she had her face scarred."
However chemical peeling with dilute trichloracetic acid and cauterization by carbon dioxide cryotherapy at not very low temperature are still brilliantly successful.
At the end of this presentation on the history of dermatology it can be stated that although scientific investigations have greatly deepened our knowledge at the pathology it is possible to claim that many theories developed in the past are still valid and acne is not yet fully understood.
As several factors participate in the clinical manifestations and there are numerous morphological components of the disease, therapeutic approaches still differ and their results are inconstant.
The mistery of acne remains, and is a source of ever new observations.

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THE NEED FOR TOPICAL TREATMENT OF PHOTOAGED SKIN

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Synopsis

Photoaged skin, a misnomen for photodamaged skin, is seen more often in the offices of the dermatologists. The reasons are clear: people expose themselves to the sun but accept the erythema threshold dose as the only borderline for their almost addictive desire to tan by sun exposure. The repair mechanisms of the epidermal cells are overcharged, mutations occur the sun of which lead to the unpleasant picture of dermatoheliosis. This skin disease is disturbing for the patient due to its senile appearance, and disturbing for the doctor who regognizes the precancerous state. Until recently, not much could be done. But, those last four years brought evidence for the valuable action of tretinoin: may changes of dermatohelioses may be reversed by continuing applications of this retinoid.

Riassunto

La cute fotoinvecchiata o fotodanneggiata viene rilevata sempre più spesso presso gli ambulatori dei dermatologi. Le ragioni sono chiare: la gente si espone al sole accettando l'eritema come una conseguenza necessaria per ottenere la desiderata abbronzatura. I normali meccanismi di riparazione delle cellule epidermiche non sono più sufficienti, il sole provoca così mutazioni a livello del DNA, principale causa delle sgradevoli forme di dermatoeliosi. Queste manifestazioni cutanee non piacciono a maggior ragione al dermatologo che le riconosce come stati precancerosi. Fino a pochi anni fa non venivano proposti rimedi. Da qualche anno viene proposto come rimedio l'uso dell'acido retinoico, che può rendere reversibili alcuni di questi fenomeni.

Introduction

A well-tanned skin is still regarded as a sign of youth and health. So, people continuously expose themselves to the sun. The doses of UV-B rarely exceed the erythema threshold as sunburn is unpleasant and painful, and sun-worshippers have learned to avoid it. But regularly, the dose for irreparable DNA damage is surpassed. Therefore, dermatologists see more and more patients with prematurely aged skin (photoaged skin, heliodermatitis, dermatoheliosis, chronic actinic skin damage).

Skin ageing

In the skin, there are two different forms of ageing: intrinsic (genetic) and extrinsic. Extrinsic ageing is caused by physical influences, mainly by UV-B irradiation.
UV-B irradiations provokes acute and chronic effects. Among the acute effects, sunburn, phototoxic and photoallergic reactions, and photodermatoses have to be mentioned. The chronic effects consist of DNA-damage. Photones of the UV-B range may react with DNA in the cell nuclei of epidermal cells causing dimerization, hydration, chain break or protein-cross linkage. The repair system of the cell takes care of such damage: within 24 h., newly synthetized parts replace the damaged sequences in the DNA strands. However, the capacity for repair is neither unlimited nor adaptive. It is assumed that the threshold dose for irreparable damage lies at about two thirds of the erythema (sunburn) threshold dose. And, as already mentioned, people used to stay out in the sun until the last minute below their sunburn dose. In consequence, an increasing amount of damaged DNA is transferred to the generations of daughter cell and mutations arise, which are clinically seen as photodamaged skin, actinic keratoses and, lastly, non-melanoma skin cancer (1, 5, 6, 7, 8, 9).
Carcinogenesis in the epidermis occurs in three stages (11):
- initiation, i.e. mutation-like genetic changes by irreparable damage to the DNA caused by UV-B,
- promotion of tumour formation by exposing initiated cells to an environment that induces a selective outgrowth of the initiated cell clones, e.g. UV-B radiation,
- conversion of pre-malignant to malignant cells, again by UV-B irradiation (or spontaneously).

Significance of photodamaged skin

Photodamaged skin is of medical and cosmetic concern. The medical aspect is the presence of pre-malignant skin lesions, either visible or subclinical, and the dry, itchy skin which needs continuous care and protection. The cosmetic aspect is prematurely aged skin. However, the symptom of looking old, the decrease in self-esteem cannot be neglected and should not be regarded as a purely cosmetic problem. One can look at photodamaged skin from two viewpoints, but either warrants a medical treatment is.

Measures in photodamaged skin

Genetically aged skin and photodamaged skin needs regular skin care, i.e. a substitution for the lacking hydrolipid emulsion. Furthermore, as alkalineneutralization is weak, slightly acid cleaning bars or lotions with excellent tolerance are recommended (8). Lastly, the skin must be protected against any further irradiation with UV-B to avoid further promotion and conversion (cf. carcinogenesis above).

In the last years, a new treatment has been tried and found to be most successful in photodamaged skin: the topical application of tretinoin (2, 3, 4, 10). In numerous investigations, the beneficial effects of tretinoin (= all-transretinoic acid, = Vitamin-A-acid) have been confirmed. The most prominent features were:
- Skin surface: formation of a shiny, glossy, even, homogeneously pigmented, pink surface. Comedones, hyperkeratoses and actinic keratoses disappear.
- Horny layer: regular arrangement of the layers, broader intercellular spaces, reduced number of layers.
- Rete Malpighi: atypical and dysplastic cells disappear, regular layers are formed, the number of Langerhans cells increases, cells show signs of metabolic activity. Melanosomes are distributed in a homogeneous, fine manner.
- Dermis: formation of new, fine collagen fibres just below the basal membrane, angioneogenesis, improved vascularization.

On the basis of its numerous pharmacological actions, tretinoin has to be considered as a useful drug for topical treatment of photodamaged ("prematurely aged") skin.

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PIGMENTARY CHANGES IN SKIN SENESCENCE

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Synopsis

Numerous pigmentary changes occur during aging, physiological variations as well as changes associated with disease. In sun-protected areas, the number of melanocytes decreases by about 10% per decade. The effect of UV radiation may partially offset the effect of aging on melanocytes and explain why some elderly subjects have few melanocytes although their skin is dark. Sunlight may cause an uneven accumulation of pigment cells and of melanin in keratinocytes, resulting in blotchy appearance of the skin. This is probably due to reactive hyperplasia of melanocytes in some foci adjacent to regions where they have a decreased ability to transfer pigment to adjacent keratinocytes.
It is proposed that other cutaneous disorders associated with pigmentary changes be classified as follows: epidermal hyperpigmentation with keratinocytic hyperplasia; atypical epithelial neoplasms with melanocytic hyperplasia; atypical melanocytes neoplasms; post-inflammatory melanosis and metabolic pigmentation.

Riassunto

Con l'invecchiamento si verificano numerosi cambiamenti a livello del pigmento cutaneo provocati sia da cause fisiologiche che patologiche. Nelle aree protette il numero dei melanociti si riduce di circa il 10% ogni dieci anni. L'azione svolta dagli U.V. può parzialmente compensare gli effetti provocati dall'invecchiamento sui melanociti per cui alcuni soggetti anziani presentano la pelle scura pur possedendo pochi melanociti. La luce del sole può causare un accumulo irregolare di cellule pigmentogene e di melanina nei cheratinociti, dando luogo a formazione di "macchie" cutanee.
Questo fenomeno é probabilmente provocato da una iperplasia dei melanociti presenti in alcune zone adiacenti alle regioni che presentano una ridotta abilità a trasferire il pigmento ai cheratinociti adiacenti. Altri disordini cutanei associati a variazioni della pigmentazione possono essere classificati come segue: iperpigmentazione epidermica con iperplasia dei cheratinotici, neoplasma epiteliale atipico con iperplasia dei melanociti, neoplasma melanocitivo atipico; melanosi e pigmentazione metabolica post-infiammatoria.

INTRODUCTION

Skin colour is normally produced by the pigments which are melanin, carotenoids and oxygenated or reduced hemoglobin. Other pigments may be also involved at variable degrees in some diseases such as icterus, ochronosis, haemochromatosis (15), chromhidrosis, xanthomas, pseudoxanthoma elasticum, solar elastosis, ...

Of these pigments, melanin is responsible for most of the physiological variations in skin colour. The number, size, type, and distribution of melanosomes in keratinocytes are in truth, the major determinants of the normal pigmentation.

Melanocytes are normally sandwiched between tightly packed basal keratinocytes. Each melanocite is associated with about forty keratinocites to which they transfer melanosomes (23, 24). This entity, which has been called the epidermal melanin unit, is responsible for the genetically determined constitutive skin colour.

The facultative inducible skin colour depends on a complex relationship between hormones (1), paraneoplastic influences, nutritional deficiencies, intake of various drugs, light, and other environmental factors such as heat and mechanical stimuli (fig. 1, 2). In these conditions, both the number and the metabolic activity of melanocytes can be altered. In particular, melanocyte division is of importance in amplifying the population of functional melanocytes in UV-irradiated skin (6,8).

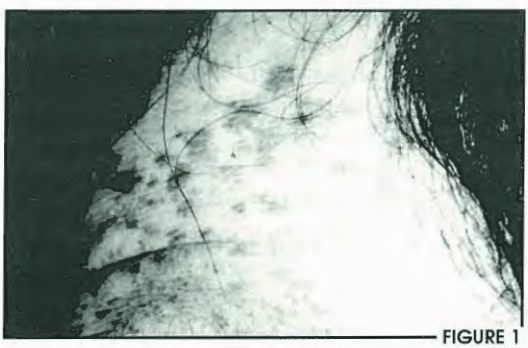

FIGURE 1

Fig. 1: Spotty pigmentation corresponding to lentigines related to photoaging.

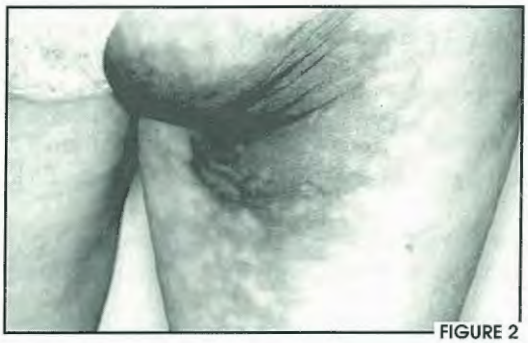

FIGURE 2

Fig. 2: Reticulated pigmentation induced by heat (erythema ab igne). The pattern of pigmentation is different from that seen in fig. 1.

Primary pigmentary changes during aging

Pigmentary changes are numerous during aging (13). The main group of diseases concerns the fate of melanocytes during intrinsic aging and photoaging. In sun-protected areas, the number of melanocytes decreases about 10% per decade after the third decade of life (5, 10, 22). However chronic exposure to sunlight may increase the population of melanocytes as well as their activity (6, 8). The effect of ultraviolet light seems therefore partially to offset the effects of chronologic aging of melanocytes, and this may explain why some elderly individuals have dark skin. These modifications related to photoaging are usually uneven and the clinical presentation is that of spotty hyperpigmentation (fig. 1). A conspicuous feature of these pigmented macules is that their size is limited in relation to the large range that would seem possible (fig. 3).

Most of the largest macules result from confluence of smaller spots. It may be supposed that the skin initially contains a continuous sheet of approximately identical normal

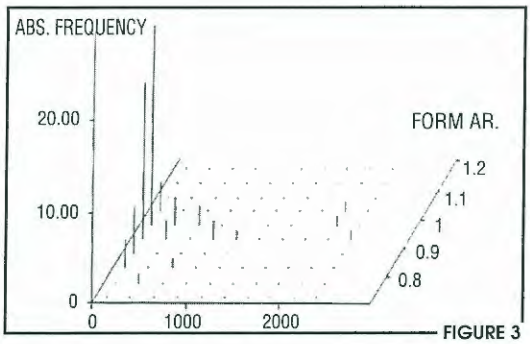

FIGURE 3

Fig. 3. Relationship between the area, the shape (From Ar.) and the number (Abs. frequency) of pigmented macules seen in fig. 1. Form Ar. is close to 1 when the shape is rounded, and its value decreases when the outline is irregular. Most of the macules are small and rounded. Larger lesions are few and result from the confluence of smaller macules

melanocytes. Under the influence of a homogeneous ultraviolet irradiation, some groups or clones of melanocytes are stimulated while others are suppresses. Such features of photoaging recall the eruptions of ephelides in youth, the lentigines occuring during photochemotherapy (12, 14) and genetically induced lentigo macules (26). They depend on the interaction between melanocytes and keratinocytes (17, 18), the rate of melanogenesis in melanocytes, the rate of transfer of melanosomes from melanocytes into keratinocytes, and the fate of melanosomes in keratinocytes (fig. 4 a, b).

FIGURE 4a

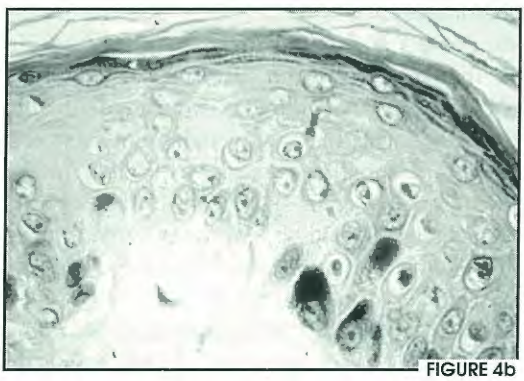

FIGURE 4b

Fig. 4a, b: Variations in the melanin distribution within keratinocytes of lentigines.

Table I

Chromametry of the forehead

Groups			L		a		b	
Origin	N.	Photo type	Novem 88	June 89	Novem 88	June 89	Novem 88	June 89
Belgian	8	II	71,3±3,3	54,1±4,3	11,5±2,3	15,2±2,1	11,8±2,3	13,2±1,2
Belgian	16	III	69,5±2,1	59,5±3,1	9,3±0,9	12,4±0,3	16,3±0,9	17,1±1,1
Arabs	12	IV	61,5±2,3	58,3±4,1	5,6±1,1	12±3,4	17,3±1,8	16,7±2
Vietnamese	8	IV	65,1±3,1	64,5±3,2	5,4±0,8	10,2±0,5	15,4±1,1	15,8±1
S. Americ.	12	IV	63,5±2,6	60,3±2,6	6,8±1,6	11,2±1,1	14,9+1,1	15,6±0,9
Black Africans	8	VI	37,6±1,3	36,7±2,1	6,9±1,4	8,8±2	10,7±2,3	10,6±2,3

Non invasive evaluation of the skin pigmentation

It is possible to measure accurately the skin pigmentation by the technique of chromametry (Chromameter Minolta CR200). Three types of information are gained in the standard CIE L ab, including the luminance (L ranging from 0 for black to 100 for white), the spectrum of green to red (with a value "a" increasing when red predominates) and the spectrum of blue to yellow (with a value "b" incresing when yellow predominates).

We compared 6 groups of volunteers aged 31-49 having different ethnic origins and phototypes. Measurements were made on the forehead during the cloudy autumn of 1988 and during the sunny season of 1989 (table I). We found, as expected, significant changes in the parameters "L" and "a" for the different groups of volunteers. Phototypes, UV-induced redness and tanning influenced the data.

We also evaluated skin pigmentation according to age. This study was conducted in winter in families of outdoor workers with Belgian ancestry and phototype III. Measurements were made on a sun-exposed area of the forearm in 12 young adults aged 18-27 and in one of their grand-parents aged 61-79. With aging, we found a significant reduction of 20% in the "L" value and of 12% in the "a" value. A moderate increase of 5% was found for the "b" value. This could be interpreted as the result of decreased vascularity associated with increased pigmentation in the elderly individuals.

Complex pigmentary changes during aging

One of the main alterations found during intrinsic and photoaging is the loss of the orderly structural and functional association between melanocytes and keratinocytes. This leads to various clinical presentations associating epidermal hyperpigmentation and hyperplasia of keratinocytes. These include among others pigmented seborrheic keratoses (Fig. 5), lichen

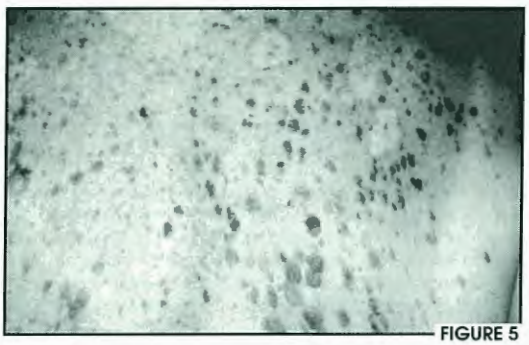

FIGURE 5

Fig. 5: Pigmented seborrheic keratoses of variable size and shape.

planus-like keratosis, melanoacanthomas and pigmented sebaceous hyperplasias (7, 9, 11, 19-21).

An abnormal pigmentation may also be found in atypical epithelial neoplasms such as solar keratosis, basal cell carcinomas, pigmented porocarcinomas (fig. 6) and breast carcinomas abutted to the epidermis (3, 4, 16). These neoplasms have to be distinguished from true atypical melanocytes neoplasms represented by lentigo maligna and lentigo maligna melanoma (fig. 7).

The last group of the melanin related

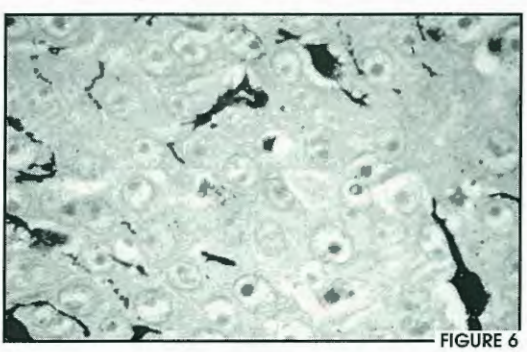

FIGURE 6

Fig. 6: Melanocytes dispersed within a pigmented porocarcinoma.

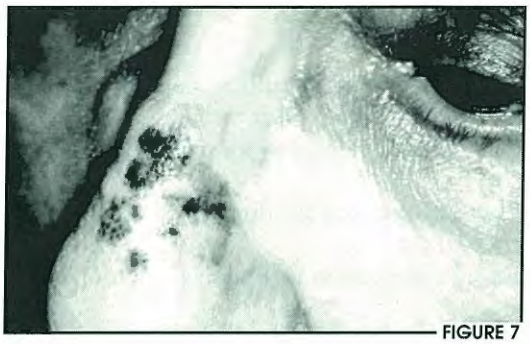
FIGURE 7

Fig. 7: Lentigo maligna melanoma with an irregular pigmentation.

dyschromias, include poikilodermas, Civatte and Riehl's type and inflammatory pigmentations (fig. 8). In these disorders melanin can be

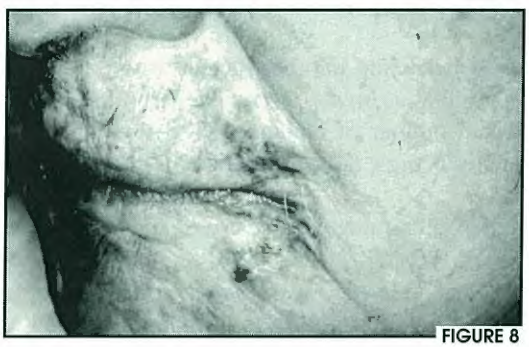
FIGURE 8

Fig. 8: Post-inflammatory pigmentation.

found in Fact XIIIa and OKM 5 positive dendrocytes of the dermis acting as activated phagocytic cells (2, 25). These dendrocytes are more numerous in photoaged skin than in sun-protected areas. Tretinoin increases their number and size in the superficial dermis (fig. 9).

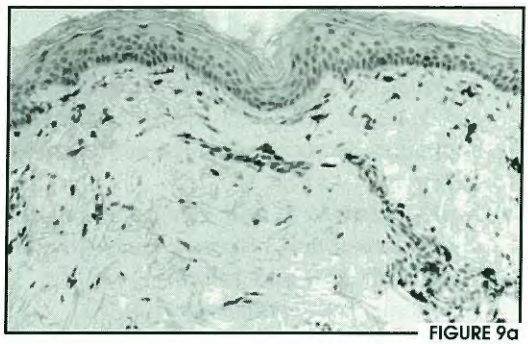
FIGURE 9a

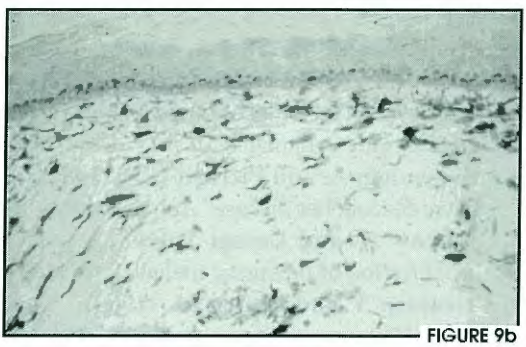
FIGURE 9b

Fig. 9: Fact XIIIa positive dendrocytes in the superficial dermis recruited in large numbers in aged skin treated by tretinoin. a: before, b: after 6 months of treatment.

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AN IN VIVO BIOCHEMICAL SYSTEM TO ASSESS THE ANTIOXIDANT, ANTI-AGING EFFECTS OF COSMETIC PRODUCTS.

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Key words: *Malonaldehyde; Lipid Peroxidation; Skin Aging; Free Radical Scavenger.*

Synopsis

The purpose of this work was to develop an "in vivo" biochemical system capable of assessing the ability of cosmetic products to control free radical induced lipid peroxidation and tissue damage that accompanies the aging process. There is extensive support in the literature regarding the involvement of free radicals in the etiology of the skin aging process. Our system employs both indirect and direct measurement of Fe++EDTA induced lipoperoxidation. The measurement of malonaldehyde (MDA) presence on skin surface is an indirect method of measuring lipoperoxidation, while direct fatty acid analysis is done by using gas liquid chromatographic techniques.
Reduction or inhibition of MDA production, as well as changes in the ratio of unsaturated/saturated skin fatty acids in treated subjects may be an indication of the effectiveness of certain cosmetic products in anti-aging treatment

Riassunto

Lo scopo del nostro lavoro é stato quello di sviluppare un sistema biochimico "in vivo" capace di valutare l'abilità di un cosmetico a controllare la perossidazione lipidica indotta dai radicali liberi e le alterazioni tessutali che accompagnano il processo dell'invecchiamento. Numerosi dati della letteratura indicano il coinvolgimento dei radicali liberi nell'etiologia dell'invecchiamento della pelle. Il sistema da noi adottato utilizza sia la misurazione diretta che indiretta della lipoperossidazione, indotta incubando con Fe-EDTA. La determinazione della malonaldeide presente nel film lipidico superficiale della cute é un metodo indiretto di misura della lipoperossidazione, mentre mediante gas cromatografia é stata effettuata un'analisi diretta degli acidi grassi cutanei.
La riduzione o l'inibizione della produzione di MDA, così come modifiche del rapporto insaturo/saturo degli acidi grassi cutanei, nei soggetti trattati, possono fornire indicazioni sull'efficacia dell'impiego di un cosmetico nel trattamento "anti-aging della pelle.

Introduction

In recent years, free radical generation has been increasingly implicated in a variety of physiological processes in living systems (1), as well as in the etiology of several human diseases (2). Molecular oxygen can maximally accept four electrons to produce two molecules of water. The one, two and three-electron reduction of oxygen results in the production of toxic and reactive intermediates: superoxide anion ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2) and hydroxyl radical ($OH^{\cdot}$) respectively.

The major toxic effects, however are probably due to $OH^{\cdot}$ formation from O_2 and H_2O_2, which generally leads to membrane lipid peroxidation and other cellular lesions (3-4). Lipofuscin accumulates in cells with age and, in general, shows a linear increase over the life span.

This heterogenous polymer, referred to as aging pigment, is apparently the result of an aldehyde, such as malonaldehyde, conjugating with primary amine groups of other lipids, nucleic acids, and proteins, to form Shiff's base type compounds.

This process may be related to the concept that skin aging involves oxidative mechanisms with the participation of oxygen free radicals, subsequent lipid peroxidation of cell membranes, and production of reactive by-products like malonaldehyde.

Polyunsaturated fatty acids, targets of free radical attack, and production of its by-product malonaldehyde, may be viewed as the dynamic parameters in evaluating the rate of age-related changes that occur at tissue levels.

This background information prompted our design of an in vivo biochemical model which could be used to assess the effects of topical treatments (i.e. cosmetics) as antioxidants which protect against lipoperoxidative changes of the skin.

Materials and methods

Treatment and sampling:

The study was limited to adult males, who were required to avoid the use of hair dressing and other sources of lipid contamination.

The surface lipids were preleved from all areas of the forehead according to a standardized procedure which consisted of rolling a cotton flock over the forehead three times horizontally and then three times vertically. The collection site was washed thoroughly with neutral soap 4 hours prior to the removal of surface lipids which began at 12,00 noon.

Treatment with Vitamin E was made by α–pplying a 3 ml solution containing 5% α–tocopherol in 20% ethanol over the total skin surface area of the forehead using the method described above. Samples were taken at different time intervals after treatment.

Specimens were stored in test tubes with teflon-lined screw caps at -20° C, and analysed within a week.

Extraction of skin surface lipids

Specimens were transferred to a mixture of methanol (2.5 ml) and chloroform (lml). The mixture was kept at room temperature for lh. The lipid residues were extracted once more with 1.0 ml of chloroform-methanol (1:1 v/v) for 30 min and then pooled with the first extract. Heneicosanoic acid (10μg) was added to the combined extracts as an internal standard, and 2 ml of 1% NaCl in HCl 0.01 M, was then added to the extract.

Following centrifugation the upper layer was discarded and the lower layer was washed with 3 ml methanol-H_2O (1:1 v/v).

The phases were separated again by centrifuga-

tion and the chloroform phase was evaporated. The lipids were then dissolved in 3 ml chloroform-methanol (2:1 v/v), and the solution was stored at -20°C until analysis.

System for inducing peroxidative stress on skin surface lipids:

Aliquots (1.5 ml) of lipid extract were brought to dryness under a stream of nitrogen.
In order to stimulate peroxidative reactions Fe^{2+}-EDTA (0.2 mM) containing 0.1 M phosphate buffer pH:7.5 was added to the reaction mixture, (final volume of reaction of 0.5 ml) and maintained at 37°C for 1 hr. At the end of the incubation period, MDA was measured.

Assay for MDA

MDA was measured using a micromethod modified from Slater and Sawyer (5): to 0.5 ml of the reaction mixture was added 0.5 ml of 20% (w/v) thrichloroacetic acid; after centrifugation, 0.9 ml of the supernatant fraction was added to 1 ml of 67% thiobarbituric acid (Sigma, St. Louis, MO) dissolved in 0.026 M Tris-HCl buffer (pH:7.0).
The samples were heated in boiling water for 10 min. After cooling, the absorbance was measured at 532 nm, on a Beckman spectrophotometer.
Extraction blanks were prepared and treated in the same way as the experimental samples but an equal volume of buffer was substituted for reaction mixture. MDA was quantified using MDA standard (Aldrich, Milwaukee, WI) and expressed in nanomoles of MDA per nanomole of phosphate.

Assay for phosphate

Phosphate was measured using an ultramicro modification of Bartlett (6). To the aliquots (1.5 ml) of lipid extract was added 0.3 ml of 10 N H_2SO_4 and the mixture was heated to 200°C for 3 hours. Two drops of 30% H_2O_2 were added and the solution was heated for 1.5 hours more at 200°C to complete the reaction by decomposing all the peroxide. 0.65 ml of H_2O, 0.2 ml of 5% ammonium molybdate, and 0.05 ml of the Fiske-Subbarow reagent were then added, and the solution was heated for 7 minutes at 100°C. The optical density was read at 830 nm. Inorganic orthophosphate was used to prepare the standard curve.

Fatty acids analysis

Lipids contained in half of the extract were transesterified in 1 ml of 2 % sulphuric acid in methanol-henzene (1:1 v/v) for 4 hours at 65°C. Methyl esters so obtained were brought to dryness under a gentle stream of nitrogen and resuspended in 2 ml of hexane, plus 1 ml of methanol. The hexane layer was then transferred into 3 ml vials, covered with teflon-lined screw caps, dried, and resuspended in 100ul of hexane. Fatty acid analysis was carried out with a Carlo Erba gas-chromatograph (mod. Fractovap 4200). SE 30 3% on 80/100 mesh Chromosorb WHP was used as the stationary phase in a 2 m x 2 mm ID glass column with nitrogen as carrier gas. The temperature was programmed from 160°C to 260°C at a rate of 8°C/min. The detector linearity was checked using commercially available mixed standards. Peak height measurements were used for quantitation, and expressed as micromoles of fatty acid per nanomole of inorganic phosphate.

Results

Figure 1 illustrates MDA formation per nmole of lipidic material as related to different concentrations of lipoperoxidation inducing material Fe-EDTA. The data show that MDA formation is linearly related to increases in concentration of Fe-EDTA.

Figure 2 illustrates the effects of a topical treatment of Vitamin E (α-tocopherol) on skin surface peroxidation. According to the data, skin lipids incubated in Fe-EDTA mixture exhibit notable resistence to lipoperoxidative damage after treatment with Vitamin E, as noted by the decrease in MDA formation. In relation to time, the protective effect of Vitamin E begins 4 hours after treatment and persists until 24 hours.

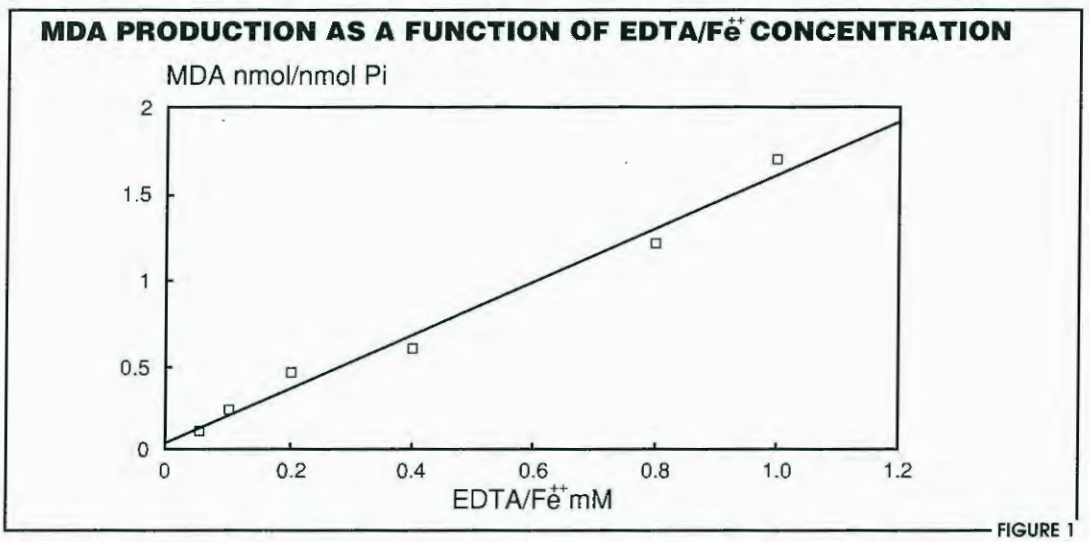

FIGURE 1

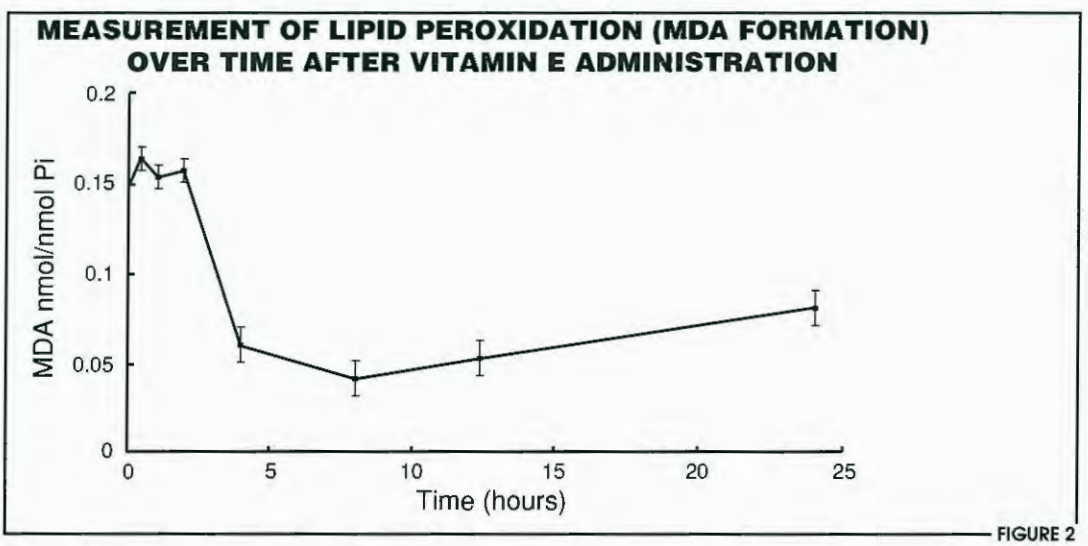

FIGURE 2

Figure 3 illustrates the effects of different concentrations of Fe-EDTA on skin surface fatty acid peroxidation. Lipoperoxidation, directly measured as % decrease in unsaturated/saturated fatty acid ratio is higher after incubation with 1 mM Fe-EDTA as compared to concentrations of 0.5 and 0.2 mM. Furthermore, this decrease is greatest for even-chain-length fatty acids C-14 and C-18 as compared to other even-chain-length fatty acids. Interestingly, odd-number carbon chain C:15 reveals the lowest percentage of unsaturated/saturated fatty acid breakdown at all concentrations of Fe-EDTA mixture.

Figure 4 shows the effects of "in vivo" treatment of skin surface lipids when Vitamin E is topically applied as 3 ml of 5% α-tocopherol, as significantly protective against free radical induced lipoperoxidation. Of the different fatty acids, C:15 appears to be the best protected by Vitamin E treatment, while C:14 is the most susceptible to peroxidative damage.

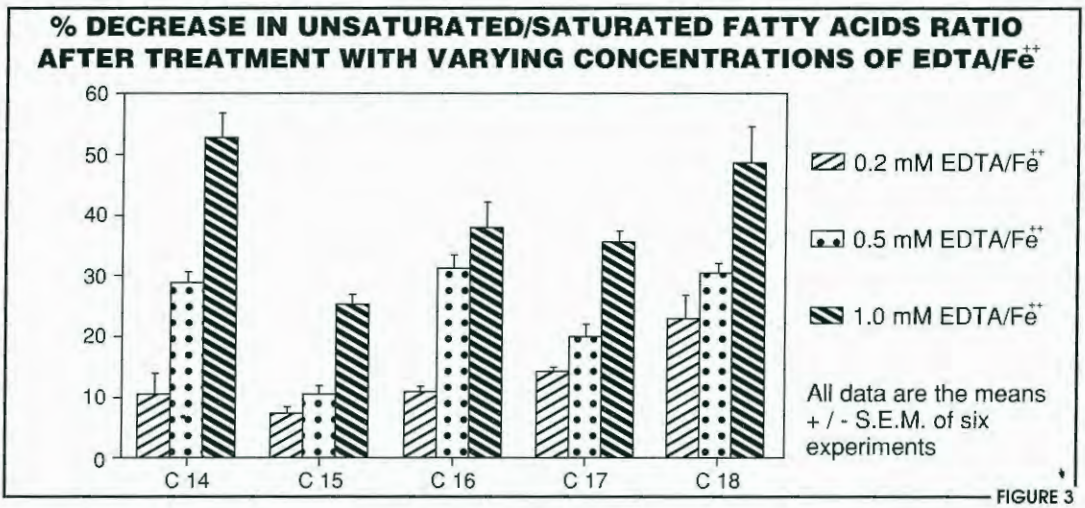

FIGURE 3

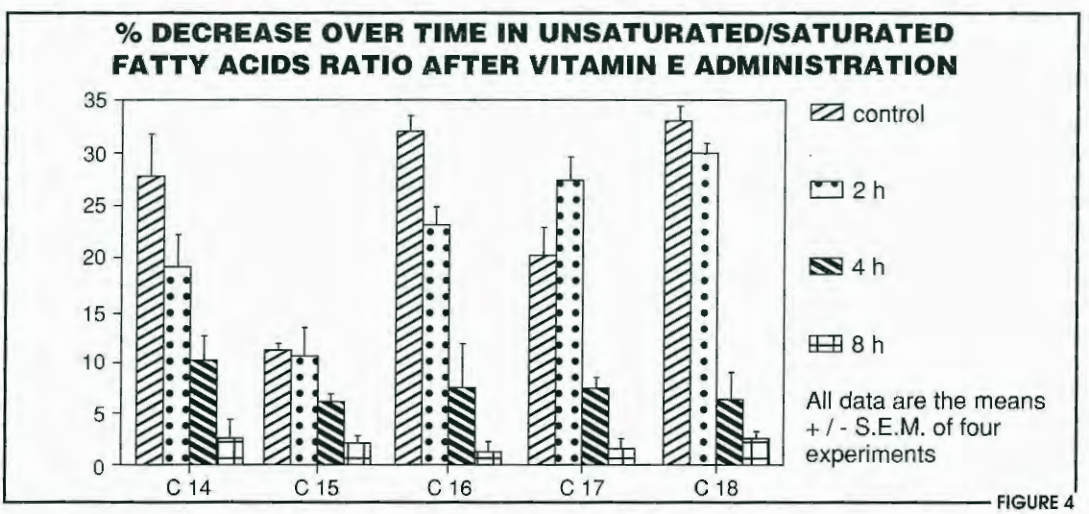

FIGURE 4

Figure 5 plots MDA formation against the percent decrease in the unsaturated/saturated fatty acid ratio obtained over time (8 hours total) for differing chain-length fatty acids.

LIPID PEROXIDATION AFTER VITAMIN E ADMINISTRATION OVER TIME: PLOT OF MDA VS. % DECREASE IN UNSATURATED/SATURATED FATTY ACID RATIO

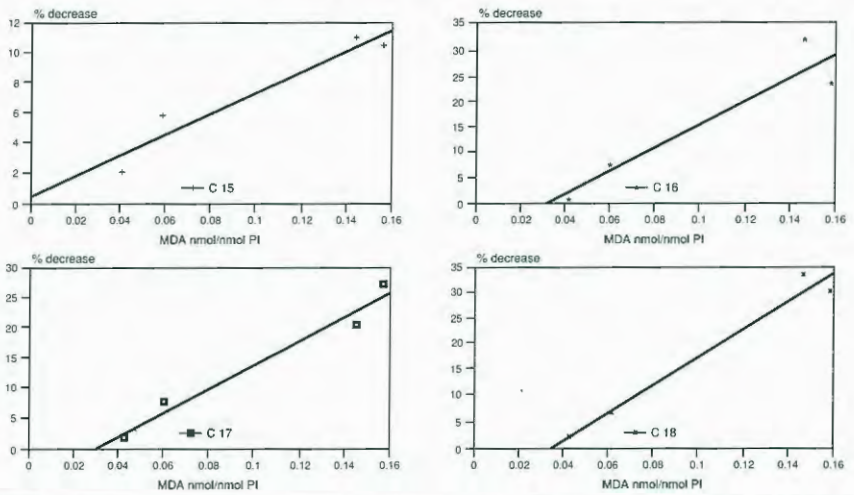

FIGURE 5

Discussion

Skin is an highly differentiated and certainly complex organizational structure. A number of degenerative skin disorders appear late in the life of humans suggesting that, among other factors, aging may act as primer or as an adjuvant factor in the expressivity of the skin pathology. Furthermore, as a result of immulogical changes that come naturally with human aging such as the involution of the thymus and altered differentiation of lymphocytes, aged skin becomes hypersensitive to photocarcinogenesis (8).

Peroxidative damage in cells results from an imbalance between production of free radicals (oxygen singlet, hydroxyl radical, hydrogen peroxide) and their neutralization by the cellular antioxidant defense system (superoxide dismutase, glutathione peroxidase, catalase, glutathione and tocopherol). When the production of superoxide predominates, cells accumulate products of lipid peroxidation. One of the most useful indicators for measuring peroxidative damage or oxidative stress is the presence of malonaldehyde.

Using Fe-EDTA, we created a situation of oxidative stress which was intended to reproduce the pathogenic condition which is believed to underlie the skin aging process and cancerous cutaneous processes. When EDTA-Fe is added to skin surface lipids of normal subjects, MDA production linearly increases. Direct analysis of lipoperoxidation of skin fatty acids, by gas liquid chromatographic techniques, revealed a strong correlation between

decrease in the unsaturated/saturated fatty acids ratio (i.e. peroxidative breakdown of unsaturated fatty acids) and MDA formation.
Treatment with Vitamin E, as an antioxidant, provided significant protection against oxidative stress, as the measured decrease in MDA formation, and as the unsaturared/saturated fatty acids ratio maintained closer to control value, suggests. The above data suggest that our method may be a particularly useful tool for investigating the antioxidant and even antiaging effects of cosmetic products.

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2

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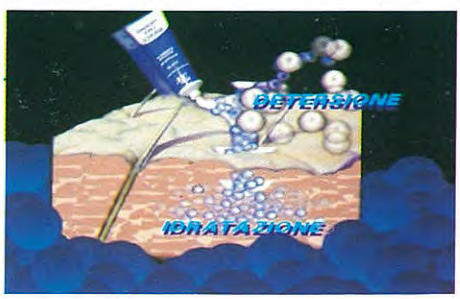

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