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Hypopigmented Macules of Photodamaged Skin and Their Treatment with Topical Tretinoin

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Hypopigmented macules are frequently observed in the photodamaged skin of elderly people. We undertook to study and treat 2 types of hypomelanosis of photoaged skin. These lesions were: 1) idiopathic guttate hypomelanosis; and 2) macular hypomelanosis. Comparative studies included: 1) high-resolution photography using parallel polarized light, ultra-violet (UVA) and epiluminescence; 2) Silflo replicas for microtopography; and 3) suction device (Cutometer®) for elasticity. Macular hypomelanosis was distinguishable from idiopathic guttate hypomelanosis because the macules were less white and less well demarcated. Glyphic markings were essentially absent in macular hypomelanosis, but variably effaced in idiopathic guttate hypomelanosis. Distensibility of the macules was characteristically low in proportion to the loss of glyphic markings. The chief histologic finding was the absence of melanin in basal keratinocytes. Macular hypomelanosis and idiopathic guttate hypomelanosis are probably related disorders along a spectrum of depigmentation. Treatment with tretinoin for 4 months restored the elasticity, the glyphic markings, with a partial restoration of pigmentation. ***Key words: idiopathic guttate hypomelanosis; elasticity; macular hypomelanosis; microtopography.***

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Hypopigmented macules are common on the arms and legs of older people who have had excessive exposure to the sun (1, 2). Apart from stellate spontaneous pseudoscars (3), the most common type of hypomelanosis in elderly people is idiopathic guttate hypomelanosis (IGH), with a reported incidence of over 60% (4–6). IGH consists of multiple asymptomatic, macular, sharply defined, 2–8 mm off-white lesions. These appear on the sun-exposed areas of the legs and forearms, rarely on the trunk (4, 5, 7–10). IGH appears after the third decade; the macules tend to increase in number with time (5, 9, 10). The microtopographic feature (glyphics) was not altered in the only study that examined this (7).

In our extensive studies of photodamaged skin, we have come to recognize a hypopigmented macule which bears similarities to IGH, but which consistently lacks glyphic lines and is less completely depigmented. We call this macular hypomelanosis (MH).

We investigated: 1) the clinical and histologic features of IGH and MH, and 2) their elastic properties and microtopography. Finally, skin bearing hypopigmented macules was treated daily for 4 months with tretinoin.

MATERIALS AND METHODS

Epidemiology

A total of 40 Caucasian women (phototypes 2 and 3), living in the Philadelphia suburban area (40° latitude) were examined. Their age range was evenly distributed, between 31 and 74 years (mean 52 ± 13 years). The dorsal forearms and lower legs were examined. We identified MH as small macules, smooth, typically lacking glyphic markings and paler than the surrounding skin, but never as white as IGH (Fig. 1). IGH, on the other hand, was recognized as small asymptomatic, macular, sharply defined off-white lesions, with or without glyphic markings (Fig. 2A) (4, 5, 7–10). Under Wood's light, whiteness was accentuated (7), more so in IGH.

Non-invasive methodologies

We studied 7 MH and 3 IGH lesions in 7 Caucasian women between 60 and 74 years old. The following tests were performed on selected macules: ultraviolet-A photography; parallel-polarized photography; epiluminescence photography; elasticity; and replicas (Silflo). All the macules were located on the dorsal forearm, except for 1 IGH lesion on the lower leg.

Light photography. The photographic equipment comprised a standardized table-camera unit (Faraghan Studio, Philadelphia, PA, USA). One 1200-watt xenon flash lamp (White Lightening Ultra 1200, Paul C. Buff Inc., Nashville, TN, USA) was mounted in front of the subject at a 30-degree angle from the horizontal plane. The subject placed the arm or leg in a fixed arm/leg-rest.

Black-and-white UVA photographs were used selectively to enhance the visualization of melanin pigment (11). A 315–390 nm UV-transmittance filter (18-A Kodak) was mounted on the 90-mm macro lens (Tamron) of a 35-mm camera body (Minolta X-700). We used T-Max 400 Kodak film. This was processed in a high-speed developer to increase sensitivity to approximately 1000 ASA.

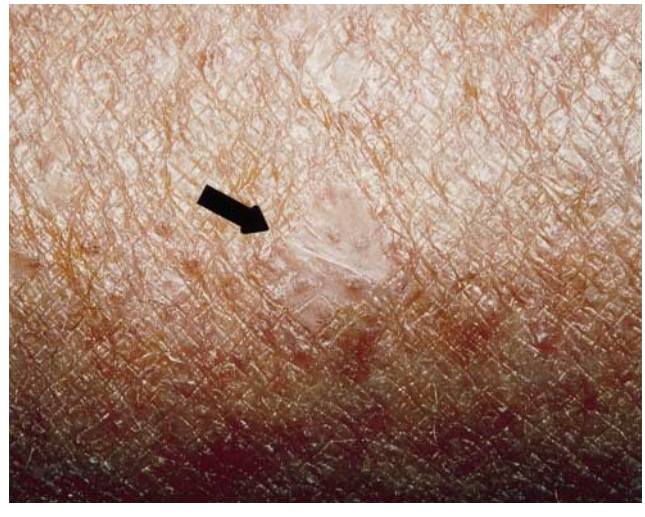

Fig. 1. Macular hypomelanosis (→) is hypopigmented, but not as white as idiopathic guttate hypomelanosis. The macule also shows smoothness and lack of glyphics.

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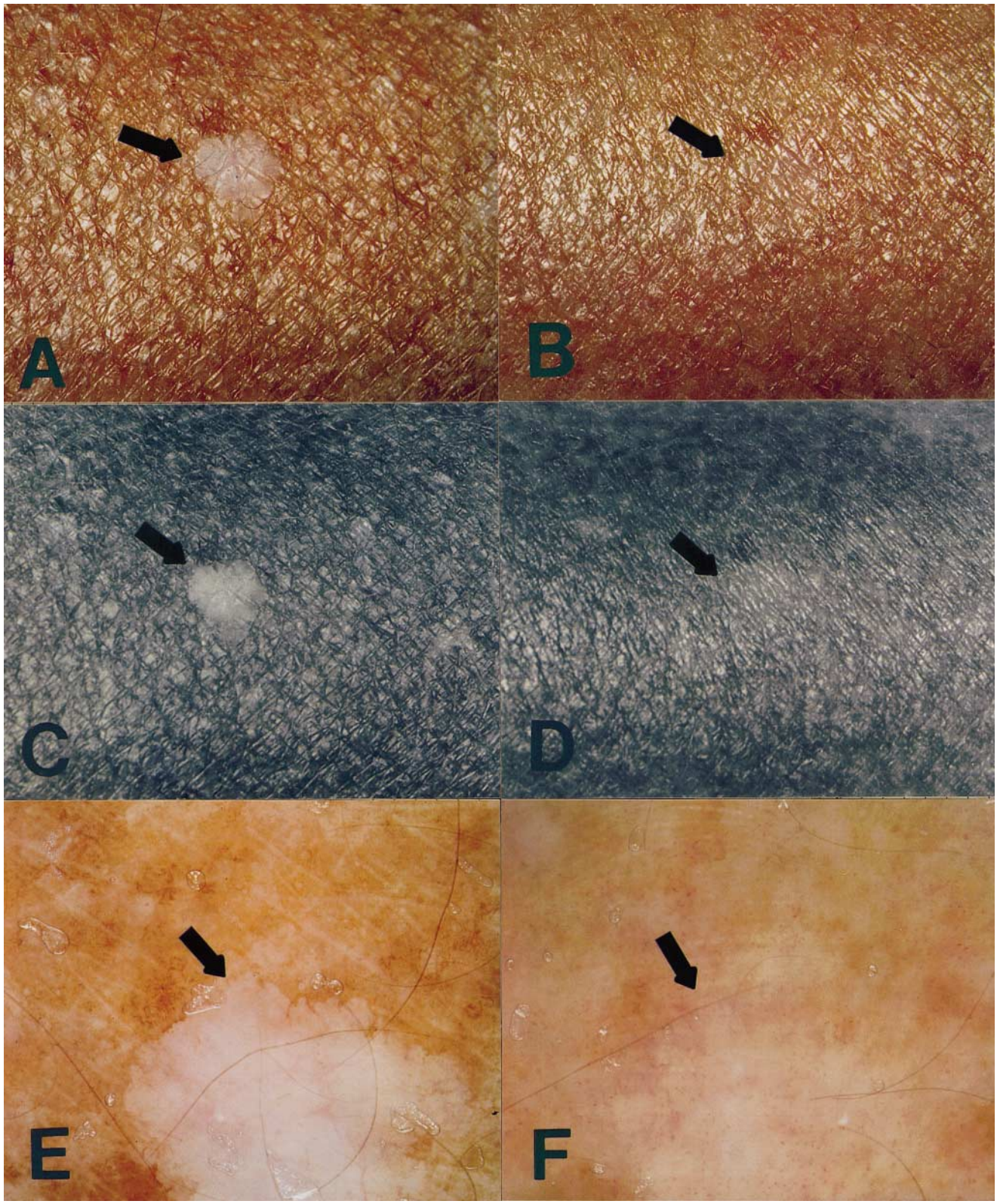

Fig. 2. Idiopathic guttate hypomelanosis (→) (A, C, E) before and (B, D, F) after 4 months of tretinoin applications. (A – B) Flash light photography. (C – D) UVA light photography. (E – F) Epiluminescence photography. After 4 months there was (B, D) a marked rebuilt of glyphics and (B, D, F) recovery of pigmentation. Also, the epiluminescence photos showed a striking decrease in the hyperpigmentation surrounding the macule after treatment.

Parallel polarized light was used to enhance surface details. We attached a linear polarizer filter in front of the flash lamp and a linear polarizer (Tiffen filter) on the camera lens. The planes of polarization of the 2 filters were adjusted in parallel position to enhance the surface structure (12, 13). We used 100 plus Kodak Ektachrome film.

Epiluminescence photography. Hypopigmented macules were also recorded by a hand-held epiluminescence camera (Dermaphot, Heine Optotechnik, Herrsching, Germany), kept in contact with the skin. Peanut oil was first applied to the skin to reduce reflectance and to enhance visualization of sub-surface features (14).

Skin replica. Silicone replicas (Silfo, Flexico Developments LDT, England) were obtained in order to visualize glyphic patterns (15). After polymerization, the film was peeled off and photographed.

Elasticity. Skin distensibility and elasticity were measured using a vacuum device, Cutometer SEM 575 (Courage + Khazaka, Koln, Germany) (16). This consists of a hand-held cylindrical probe with an opening of 2-mm (17 -- 19). An electrically controlled vacuum lifts the skin into the cylinder and an optical system measures the height (in millimeters) of the skin pulled inside the cylinder. For each measurement a suction of 400 mbar was applied for 3 s and then released for 3 s, for 3 cycles. The maximum elevation of the skin during the suction is called "distensibility" (R0), which refers to the capacity of the skin to be stretched. When the vacuum is released, the skin retracts to a point of residual elevation (R1). The ratio of retraction (R0 -- R1) to the maximum extension (R0) defines the biological elasticity or "gross elasticity" (R2).

Four subjects were studied. Six macules were investigated: 3 IGH and 3 MH. All were on the dorsal forearm, except for 1 IGH on the lower leg.

Skin biopsy

A 3-mm punch biopsy was obtained, fixed in formalin and stained with hematoxylin-eosin, Hale, Fontana and Luna stains.

Two typical MH were biopsied from the dorsal forearms of 2 subjects and 2 typical IGH were biopsied, 1 from the lower leg and 1 from the dorsal forearm of another 2 subjects. The nearby photodamaged skin was also biopsied in the first 2 people with MH. The samples were evaluated by image analysis (analySIS, Soft-Imaging Software GmbH, Munster, Germany) for a measure of epidermal thickness.

Tretinoin treatment

Four photodamaged women between 61 and 74 years old completed a 4-month treatment on the dorsal forearms. Three had MH and 1 had IGH. One forearm received tretinoin (Retin-A® cream, Ortho Pharmaceutical Corp., Raritan, NJ, USA) once nightly. We started with 0.025% for 1 week, increased to 0.05% the second week and, finally, to 0.1% until the end of the study. Nivea cream® (Beiersdorf Inc., Norwalk, CT, USA) was applied to both sides each morning to moderate dryness. The study was conducted during fall and winter, when the subjects were wearing long-sleeve clothes. A sunscreen was therefore not applied.

The following tests were performed, before and after treatment, on selected macules of both dorsal forearms: ultraviolet-A photography; parallel-polarized photography; and epiluminescence photography as described above. In 3 subjects, Silflo replicas were obtained and elasticity was determined by suction. In 1 subject a 3-mm punch biopsy was taken from an IGH macule before and after treatment.

Statistical analysis was conducted using the *t*-test.

RESULTS

Epidemiology

On the lower legs, no MH were observed at any age, while IGH were found in 9% of the subjects aged 51 – 60 years, and in 18% in those aged 61 – 74 years. By contrast, on the dorsal forearms MH and IGH were found in all age groups. However, the size of the macules and the prevalence percentage increased proportionally with increasing age. In the group 31 – 40 years old only 2-mm-size macules were observed: these were MH in 30% of the subjects and IGH in 10%. The frequency of 2-mm MH remained the same in the entire population, but these were associated with larger ones starting around 50 years of age. Larger MH lesions were present in 9% of subjects between 51 and 60 years old and in 45% of those between 61 and 74 years old. Over 41 years of age IGH were always larger than 2 mm. These were observed in 13% of people aged 41 – 50 years, 18% in ages 51 – 60 years and 28% in ages 61 – 74 years.

Both types of macules were found in the same subjects in only 10% of women.

Non-invasive methodologies

Clinical photographs showed a marked loss of pigment in both types of lesions, IGH being much whiter and more sharply demarcated than MH (Figs. 1, 2C and 2E).

Parallel-polarized pictures correlated well with the glyphic patterns on Silflo replicas. The replicas, however, reproduced microtopographic details more precisely (Figs. 2A and 3A). Both showed a marked lack or absence of glyphics in both types of macules on the dorsal forearms, compared with adjacent skin. The IGH on the leg, however, had only a slightly diminished glyphic pattern.

The Cutometer readings on both MH and IGH are shown in Table I. The lesions of the dorsal forearms had 37% lower extensibility-R0 than the adjacent skin. R2, a measure of skin

Table I. *Comparison of elastic values (R0: extensibility, R2: gross elasticity) of hypopigmented macules (IGH and MH) and adjacent uninvolved skin on 5 dorsal forearms*

Dorsal forearm	R0 (mm)		R2	
	Uninvolved skin	Macules	Uninvolved skin	Macules
A	0.18	0.07	0.57	0.86
B	0.13	0.06	0.52	0.83
C	0.26	0.19	0.58	0.37
D	0.22	0.20	0.57	0.65
E	0.18	0.09	0.56	0.56
Mean (±SD)	0.19 (±0.05)	0.12 (±0.07)*	0.56 (±0.02)	0.65 (±0.20)

*$p < 0.005$ compared with uninvolved skin (*t*-test: paired 2 sample for means).

elasticity, did not show statistically significant differences. These same macules showed a lack of glyphics. The IGH on the leg, that displayed a more regular glyphic pattern, showed extensibility and gross elasticity similar to that of the nearby skin. The percent change for this IGH, compared with adjacent skin, was as follow: R0 = +7% and R2 = –12%.

Histology

MH and IGH could not be differentiated histologically. Dorsal forearm lesions showed a flat dermo-epidermal junction and variable epidermal thickness. In one sample, the epidermal thickness was 40 μm vs. 70 μm in adjacent skin and, in a second sample, 64 μm vs. 54 μm, as measured by image analysis. The stratum corneum showed variable thickness; thinner in some lesions, thicker than normal in others. Fontana stain revealed much fewer melanin granules in the basal layer compared with adjacent skin and only a few granules in the viable epidermis. Luna stain showed a massive increase in thick, curled, branched elastic fibers (elastosis). Hale stain showed a thicker Grenz' zone and an increased amount of glycosaminoglycans (GAGs) compared with adjacent skin. The IGH specimen from the leg showed similar epidermal findings. However, the elastosis and GAGs were much less prominent.

Treatment

In Nivea-treated forearms, no changes in pigmentation, glyphic pattern, elastic values and histology were observed either in IGH or MH.

By contrast, the tretinoin-treated macules clinically disappeared after 4 months, with an almost complete recovery of glyphics and partial repigmentation (Figs. 2, 3A and 3B). A great improvement was already evident after 2 months of therapy.

Parallel-polarized light photos correlated with the silicon replicas in showing a dramatic reconstitution of the glyphic pattern both in IGH and MH (Figs. 2A, 2B, 3A and 3B). In Silflo replicas microtopographic details were slightly less prominent than on adjacent skin.

UVA and epiluminescence photos showed a partial repigmentation in both IGH and MH (Figs. 2C–F).

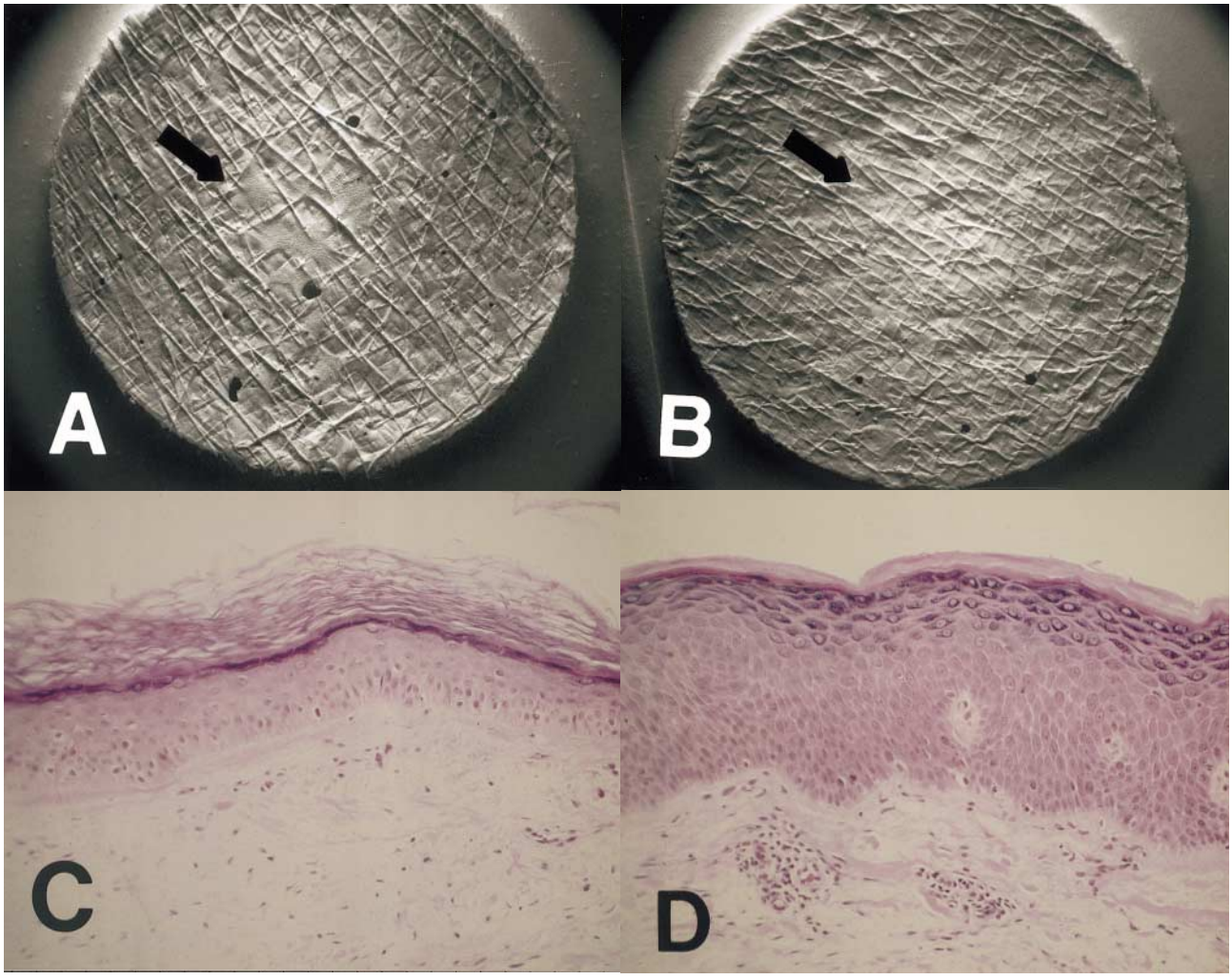

Fig. 3. Idiopathic guttate hypomelanosis (→) (A, C) before and (B, D) after 4 months of tretinoin application. (A–B) Silflo replicas. (C–D) hematoxylin-eosin stain, ×20 magnification. After 4 months there was a marked rebuilt of glyphics, as shown in (B). Tretinoin induced epidermal acanthosis along with correction of atypia (D). A modest redevelopment of rete pegs was observed.

Interestingly, the surrounding skin showed a decrease in pigmentation.

After tretinoin treatment both IGH and MH showed a statistically significant increase ($p < 0.005$) in distensibility-R0 (77%) and gross elasticity-R2 (34%) compared with the pre-treatment values. Also, the values of R0 and R2 for the tretinoin-treated macules were statistically significantly higher ($p < 0.05$) compared with Nivea-treated ones.

Tretinoin induced epidermal acanthosis along with correction of atypia. A modest redevelopment of rete pegs was observed (Figs. 3C – D). Fontana stain showed an increased density of melanin, not only in the basal layer, but throughout the entire epidermis including the stratum corneum. The elastotic tissue and GAGs remained unchanged.

DISCUSSION

From our findings both MH and IGH increase in number and size with increasing age. Sunlight clearly plays an etiologic role in MH. Indeed, MH was observed only on the dorsal forearms, a common photodamaged area, and characteristically showed loss of glyphics and histological changes of photodamage.

Previous histologic studies on IGH reported contradictory findings on stratum corneum thickness (5, 7, 9, 10). Also, the epidermis was either of normal thickness with well-developed rete ridges (4, 5, 7) or flat and atrophic (6, 9, 10). Invariably, the keratinocytes had a decreased amount of melanosomes (4 – 7, 9, 10, 20, 21). The melanocytes were fewer, smaller, with rare dendrites or normal in shape and number, but both types of cells produced immature melanosomes with sparse melanin (4 – 7, 20). The papillary dermis was either normal (4, 5, 7, 10, 20) or thickened (6).

The histologic aspect of IGH and MH on photodamaged dorsal forearms did not allow us to differentiate between the 2 types of lesions. The main epidermal feature in all macules was a lower density of melanin granules compared with the adjacent skin.

From the literature, photodamage is apparently not a prerequisite for the development of IGH (7, 9, 10). The IGH we biopsied from the lower leg did not show histologic signs of photodamage and, clinically, retained a good glyphic pattern. This suggests a pathogenesis different from MH. Additionally, MH and IGH do not frequently occur together in the same individual. Gilhar et al. (22) suggested the presence of a systemic factor in the development of IGH, because IGH epidermis transplanted into mice re-pigmented after 3 weeks. In any case, restoration of pigmentation indicates that melanocytes, though inactive, are present in hypopigmented macules. In this study, the increase in melanin pigmentation after tretinoin, could indicate an improvement in melanin transfer to keratinocytes or a stimulation of melanin synthesis. It is interesting that in photoaged hyperpigmented skin tretinoin has a bleaching effect. These apparently conflicting results could be partially explained by the capacity of tretinoin to "normalize" functions.

The absence of skin glyphics is more critically linked to solar radiation, as observed in the IGH and MH on the dorsal forearms. Indeed in the lesions described by Wilson et al. (7), where glyphics were well developed, there were virtually no actinic changes of the epidermis and dermis.

Our data support the view that the 2-mm probe we used for biomechanical measurements is sensitive to detect variations on the superficial part of the skin (17), possibly epidermis and stratum corneum. On the dorsal forearm, the elastic properties of the macules were quite different from those of the adjacent skin. The loss of skin glyphics could alone account for lower distensibility (R0). It has been shown in cyanoacrylate biopsies that the folding of the stratum corneum into glyphics enables the skin to conform when a force is applied (23). It is noteworthy that the IGH on the leg that had a good glyphic pattern also showed extensibility and elasticity similar to the adjacent skin. Additionally, the increased distensibility of the macules after tretinoin treatment was accompanied by the restoration of glyphics.

The marked amelioration of both types of lesions with topical tretinoin was noteworthy. Since Nivea alone had no effect in any of the parameters studied, simple moisturization is not enough to achieve these improvements. Follow-up of 2 patients with MH a year after stopping tretinoin showed clinical regression of the macules to the original state.

We found that the frequency of IGH was much lower than reported in the literature (4 – 6). This difference can be attributed to the following factors: 1) the literature did not distinguish between MH and IGH, in which case the frequency approaches ours; 2) our subjects were recruited from a "normal" population and not from dermatologic clinic.

We conclude that tretinoin dramatically improves IGH and MH and, although these lesions are mainly cosmetic defects, this treatment can be recommended for those concerned with appearance. In addition, maintenance therapy may be required for durable effects.

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