EXPERIENCES WITH METHOXSALEN IN THE AMERICAN TROPICS

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The dermatologic potentialities of methoxsalen in populations living in the tropics are especially intriguing for several reasons. The nationals of tropical countries tend to be more or less darkly pigmented; in them such physically innocuous processes as vitiligo may have serious social and economic impact. White-skinned residents may be subject to greater actinic dermal injury than would be the case in their normal, temperate climates. Finally, the optimal source of ultraviolet energy (i.e., intense natural sunlight) is readily available.

While the mode of action of the furocoumarins is not entirely clear, it has been shown that systemic administration of appropriate doses of methoxsalen followed by ultraviolet radiation will produce a series of morphologic changes in skin (1, 2). The stratum corneum thickens and a structure resembling stratum lucidum may appear within two weeks of daily exposures; there is a possibility this may be intimately related to the stratum corneum conjunctum of Szakall (3). Although more work remains to be done on the relation of altered structure to altered function, Imbrie et al. (4) have clearly demonstrated that a single ultraviolet exposure of methoxsalen-conditioned skin nearly doubles the amount of energy required to induce a minimal erythema in the treated area five to six weeks later.

Another change has to do with melanin pigmentation, which may become increased (as compared to skin areas exposed to ultraviolet without methoxsalen). Two explanations have been offered. The first, which seems to be the case in normal skin, is that the altered epidermis simply increases retention of melanin formed in ordinary amounts in response to sunlight. The second suggestion, that the melanocytes are somehow stimulated to increased production of melanin, seems to have application in one abnormal condition, vitiligo. This is a disease characterized by failure of pigmentation in areas of skin containing a normal complement of melanocytes, twice the normal amount of sulfhydryl, tyrosinase, and ample substrate, tyrosine (4). The reason for loss of function of the tyrosinase system in these melanocytes is unclear, as is the exact mode of action of methoxsalen-ultraviolet in correcting it.

It is the purpose of this report to present preliminary data bearing on the clinical aspects of these problems.

MATERIAL AND METHOD

Thirty-five individuals, ranging in age from 15 to 39 years of age, resident in or near Puerto Armuelles which is located in Panamá adjacent to the Costa Rican border, were included. Twenty were females, fifteen were males. Only ten were more or less pure Caucasian. The other 25 were mestizos of mixed Spanish, Indian and, uncommonly, Negro ancestry. Twenty-four had some degree of vitiligo. The remainder simply desired a protective suntan. The study was carried out during the dry season when several hours of intense sunshine were available daily.

Each subject was given a bottle of 30 protection coated methoxsalen* tablets containing 10 mg. of active crystalline drug per tablet. Direction sheets and questionnaires were issued in English or Spanish, to the effect that two tablets should be taken daily for 15 days, preferably after a meal or with a glass of milk, and that approximately two hours later the skin should be exposed to sunlight for 20–30 minutes.

RESULTS

Increased solar tolerance. Five individuals reported a suntanning effect on the first or second day of treatment but the remainder were conscious of darkening only on the third day and thereafter. This feature was difficult to quantify, and in the absence of controls, it would be unscientific to report that the effects seen were greater than might have been the case following similar exposures without the drug.

Vitiligo. Several mild cases of vitiligo “disappeared” or became inapparent by the fifteenth day. Marked cases all showed some degree of repigmentation. In several who exposed their skin to sunlight for the maximum of 30 minutes, there was intense erythema, but in no instance

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* The trade name for methoxsalen, Upjohn, is Meloxine®.
did blistering of the skin occur. Subjective discomf
	
t in these reddened areas was distinctly less than an observer might expect. In spite of limited cosmetic improvement in a number of patients with extensive vitiliginous areas, all 24 subjects were pleased.

After an interval of thirty days, five of these vitiligo patients were re-treated with an identical course of methoxsalen. This group included two persons who believed that they had experienced a slight recrudescence of vitiligo. In each of these five, some additional repigmentation was experienced.

**Side effects.** Ten patients reported some degree of nausea, usually within 15 minutes after taking the tablets, but none vomited. All except one, however, were able to complete the 15-day course. The exception, a fair-skinned blond woman of 34 years, developed a persistent nausea on about the eighth day. This lasted for four days after medication was suspended. In spite of this, she was quite satisfied with the treatment because of the tan she acquired easily and quickly and because a dozen or more hypopigmented spots became apparent.

**DISCUSSION**

Aside from the cosmetic features of suntanning, which vary according to whims of fashion the complex of skin changes involved represents Nature's attempt to shield the living parts of the skin from solar insult. The erythema of sunburn reflects actinic injury to the deeper cellular layers of the epidermis, and possibly even the dermis. The normal reaction of protection, "suntanning", depends on the capacity of the skin to undergo changes similar to those described by Becker, Jr. (1). It would seem reasonable to think that measures which would accelerate or augment these self-preservative changes would be desirable, if they are specific and not inherently injurious to other organ systems.

In the dark skinned races there is apparently considerable protection "from the start", and in spite of lifelong exposure to sun, wind, drying, and other factors causing skin weathering, primary carcinoma of that organ, including melanomas (6, 7), is uncommon in them at all ages. The association between sunlight (actinic insult) and skin cancer in light skinned races is well documented (8). From data presently available it seems that methoxsalen plus ultraviolet energy, even single solar exposures (4), or after repeated suberythemal exposures to artificial sources of ultraviolet (1), may so alter the skin that solar tolerance is markedly increased. This is apparent within one week (4) and may persist for months. It is not due entirely to pigmentation. This is in keeping with the fact that increased solar tolerance has been induced in albinos who cannot form melanin. Whatever the mechanisms, these morphologic and functional changes would seem to be desirable, self-protective ones for light complected residents in tropical and other sunny areas.

Reports are conflicting concerning results of methoxsalen in the treatment of vitiligo. It is significant, however, that results seem to be more and more encouraging as one approaches the equator. Intense natural sunlight appears to produce changes which cannot be completely duplicated by presently available artificial sources of photomagnetic energy.

It should also be pointed out that many reports are given in terms of the investigator's evaluation of percentage repigmentation or similar criteria. It is important not to lose sight of the fact that the cardinal objective of treatment is to improve the appearance and social acceptability of the patient, as he evaluates it. The majority of subjects in this study, for example, still have obvious vitiligo, but were pleased and encouraged by the early changes they observed. All of these wished to extend treatment further.

**SUMMARY**

Thirty-five individuals living in a hot, humid Pacific coast area of western Panamá were treated with a 15-day oral regimen of 20 mg. of methoxsalen daily followed by measured exposures to sunlight. Twenty-four had vitiligo of some degree and all were improved. The repigmentation appeared to be complete in a few mild cases but only partial in the majority. A second course in five of the latter induced further repigmentation.

Suntanning was apparent in most of the light skinned patients only on the third day and thereafter. Because controls were not used, it is not possible to compare this effect with the results of similar solar exposures without the drug. Reasons have been given that point up the desirability of these self-protective changes in such residents of tropical areas.
REFERENCES

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