PSORIASIS, PSORALEN AND SUNLIGHT

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Summary

Topical or oral administration of photoactive furocoumarins followed by exposure to Ultraviolet light from artificial sources has been shown previously to clear psoriatic lesions. Sunlight has been chosen as the source of UVL in two separate paired comparison studies using topical and oral 4, 5, 8—trimethylpsoralen. 2 out of 21 on topical therapy and none out of 6 patients on oral paired-comparison study showed faster clearance of the drug treated lesions compared to control sites.

Recently topical psoralen (8-MOP) followed by exposure to longwave ultraviolet light has been shown to improve psoriasis[1]. Clinical trial resulted in regression of the psoriatic lesions[2]. Parrish et al[3] have observed that orally administered 8-MOP followed by exposure to high intensity long wave ultraviolet light clears psoriasis andis superior to conventional ultraviolet light alone.

Stimulated by these studies paired comparison studies using[4,5] 8-trimethylpsoralen (TMP) topically and orally in different groups of patients were done. Sunlight served as the source of ultraviolet light. The purpose of choosing sunlight as the UV source is that in India sophisticated high intensity artificial UV light installations are not available. Even when these become available, these will be only in big institutions and will not be accessible to the country-side patients. If proved effective our regimen using sunlight can be carried out by the patient himself at home.

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Material and Methods

In one paired comparison study 21 patients were treated with topical application of TMP plus sunlight over lesions on one side of the body and the base of TMP lotion and sunlight on the other side of the body. The other paired-comparison study consisted of a group of 6 patients, who were treated with oral TMP plus sunlight on one half of the body and only sunlight on the other half. Another 7 patients were treated with oral TMP and whole body exposure. It was explained in detail to the patients about the procedure in each case, strongly suggesting to them that this new method was the most effective in clearing psoriasis.

The psoriatics selected for the topical therapy had a stable nummular type of lesions which were roughly symmetrical. On their first and second visits they were shown how to apply the medicine

after a soap and water wash followed by a meticulous, gentle, manual removal of scales. After exposure to sunlight for the prescribed length of time the medicine was washed off with soap and water. Psoriasis involving the palms and soles and scalp was not treated as above.

The patients selected for oral therapy had a stable psoriasis involving at least 50% of the body surface. Those who underwent the paired comparison method were hospitalised for a minimum period of 30 days. The other group which was treated as outpatients was advised whole body exposure. Patients with guttate and pustular psoriasis were excluded from the study as were those associated with other systemic illnesses.

It was ascertained that the patients had not taken topical or systemic medicine at least 2 weeks before starting them on this regimen.

The synthetic 4, 5', 8-TMP was employed in this study. A 0.2% concentration of TMP in isopropyl alcohol was used in the topical therapy, the base isopropyl alcohol serving as placebo for control sites. After descaling the lesions the lotions from separate containers inscribed 'Right' and 'Left' were applied accordingly with separate pieces of cotton. About 0.5 cms of normal looking skin around the lesions also received the application. An hour later the lesions were exposed to sunlight.

In the paired comparison study with oral administration, capsules of 40 mg of TMP were given 2 hours prior to sun exposure on alternate days. This was carried out only with the hospitalised patients where a day-to-day observation was possible. No topical medication except for vegetable oil was allowed. In another group of patients treated as out patients the drug administration and exposure to sunlight were carried out on alternate days.

The mid day sunlight between 12 noon and 1 p.m. was chosen for exposure.

The patients on topical therapy started with an exposure of 5 minutes and reached 30 minutes with daily 5 minutes increments and were maintained on 30 minutes exposure for the rest of the course. The treatment period ranged between 30 to 40 days.

After oral administration of 40 mg of the drug at 10 a.m. the patients were taken to the terrace at 12 noon where one half of the body was exposed to sunlight; the other half being covered by a double layer of thick dark green sheet. The front portion of the body received sunlight for the first half an hour and the corresponding back surface the second half an hour. The patients were protected from sunlight after this. The next day no drug was administered and that half of the body which had exposure with the drug the previous day was protected and the other half exposed on front and back. The procedure was followed for at least 30 days before the patient was discharged. If the patients' skin felt dry they were allowed application of vegetable oil which also helped in the removal of scales after bath.

A weekly assessment was made in case of topical therapy, a daily progress recorded on in-patients and a weekly assessment on out-patients taking oral medication. The junior author who was not aware of the side which was treated with the psoralens made an independent observation weekly and this was compared with the progress note made by the senior author who administered the drug. Observations were made with reference to the degree of scaling, thickness and redness of the lesion. Clinical photographs were taken at regular intervals.

Results

Topical therapy: (Fig. 1 to 4). The results of the therapy in the three

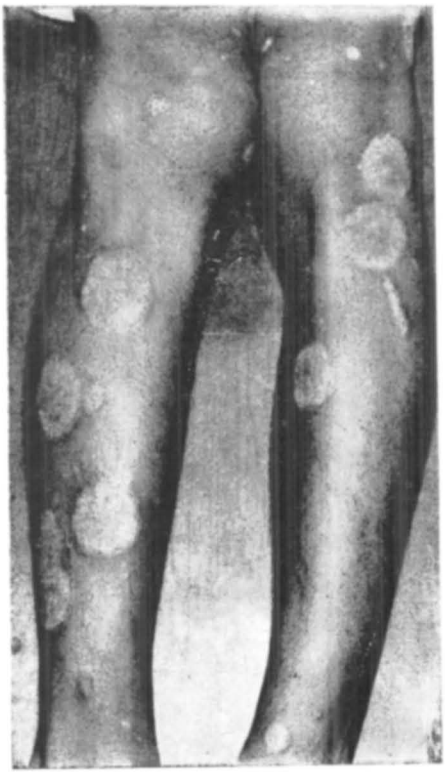

Fig. 1 Lesions on legs before and after 40 days topical therapy. No difference in TMP + sunlight side (Right side) compared to base + sunlight side though there is slight regression on both sides

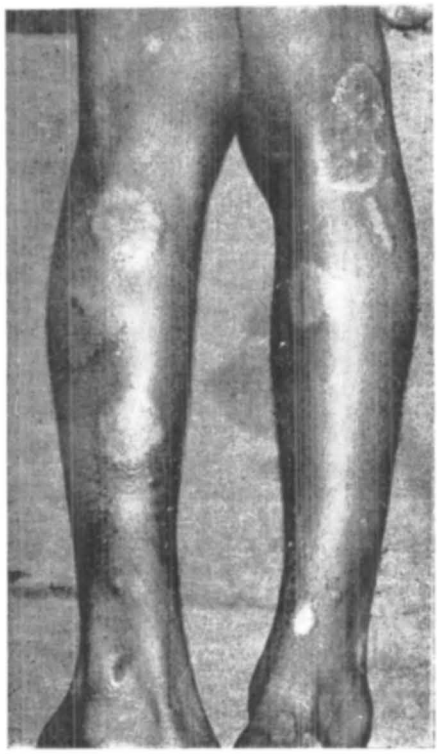

Fig. 2 Lesions on legs before and after 40 days topical therapy. No difference in TMP + sunlight side (Right side) compared to base + sunlight side though there is slight regression on both side

TABLE 1
Results of therapy in the three groups.

No. of Patients	Duration of Therapy	Response			Treatment Discontinued
		Both sides	Faster on TMP Treated side	No Response	
Topical Therapy					
21	30–60 days	6	2	7	6
Oral Therapy—Paired Comparison					
6	30–42 days	3	–	3	–
Oral Therapy—Whole Body Exposure					
7	30–60 days		Complete clearance & lesions 4	3	–

groups are summarized in Table 1. Except for 2 patients who had topical therapy all others showed either general improvement or no improvement on both sides. The side effects of the topical therapy are shown in Table 2.

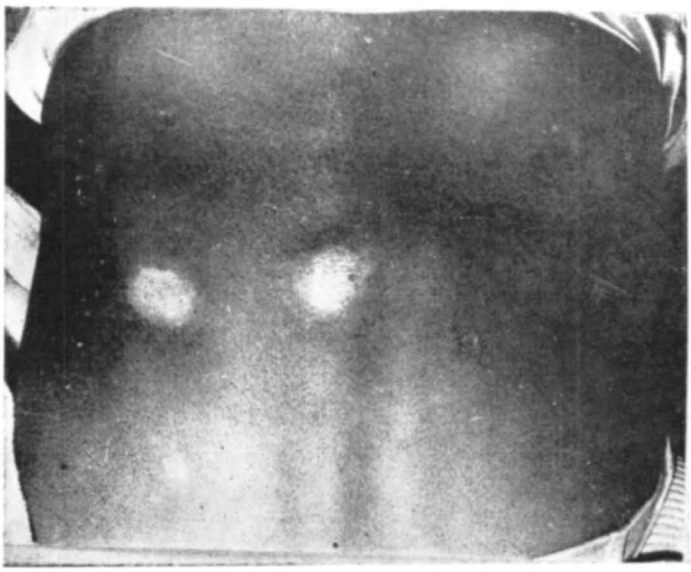

Fig 3
Lesions on back before and after 40 days topical therapy. TMP treated lesion (Right) has cleared faster than the base treated lesion

None of the patients on the oral paired comparison study improved on the TMP plus sunlight side compared to the control side. (Figs. 5 & 6). In the 3 patients who improved on both sides complete clearance of the lesions occurred only after adding topical tar ointment.

Side effects : Dryness and itching were experienced by all the patients and they used to get some relief with vegetable oil application. One patient developed a generalised itchy erythematopapular rash on 12th day of initiation of therapy. Treatment was discontinued and antihistamines were given for

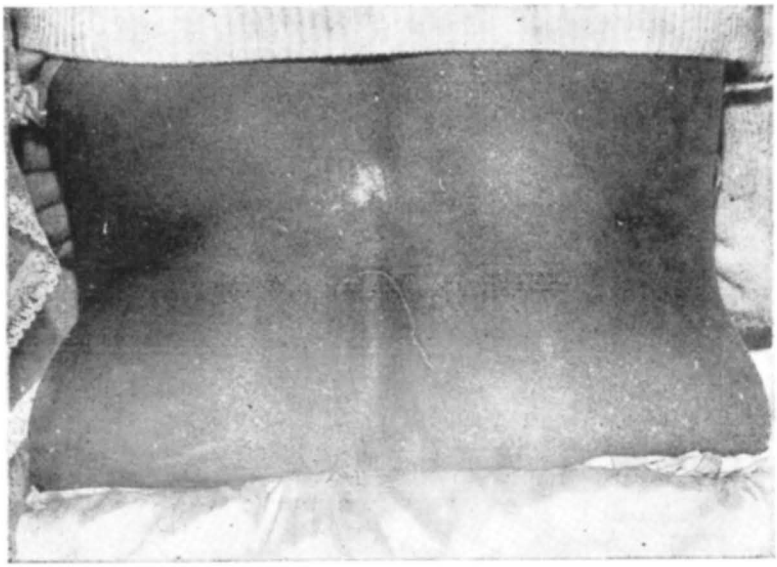

Fig. 4 Lesions on back before and after 40 days topical therapy. TMP treated lesion (Right) has cleared faster than the base treated lesion

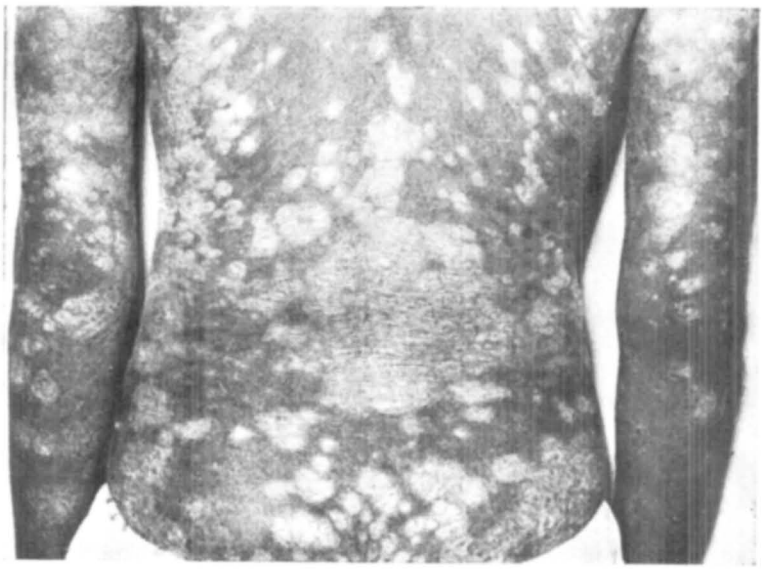

Fig. 5 Lesions on back before and after 26 days oral therapy (13 alternative days with the drug). No difference in the TMP + sunlight treated Right half and only sunlight treated left half seen

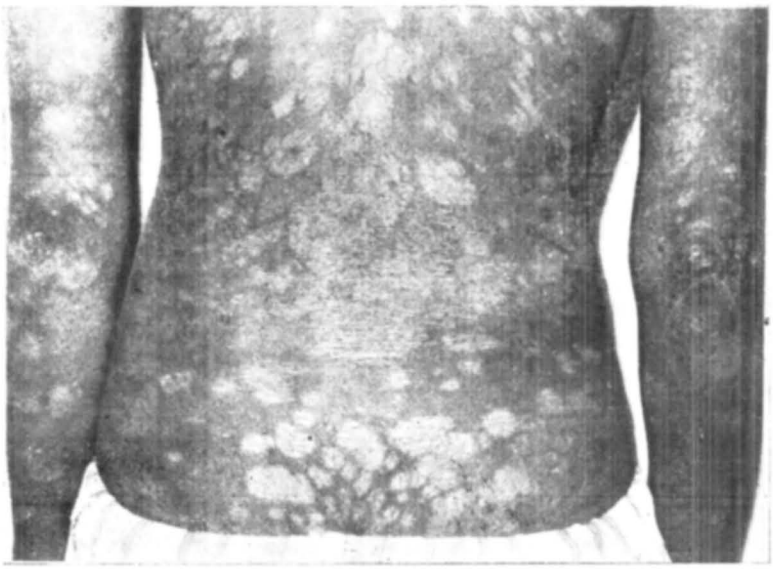

Fig. 6 Lesions on back before and after 26 days oral therapy (13 alternative days wlth the drug). No difference in the TMP + sunlight treated Right half and only sunlight treated left half seen

one week. The rash subsided with desquamation without leaving psoriatic lesion in its place.

Complete clearance of lesions was observed without any topical medication in 4 of the 7 patients in the whole body

exposure group. One patient improved till 12 sittings and then developed papulosquamous lesions all over.

TABLE 2
Side Effects of Topical Therapy

	No. of Patients
Pigmentation around TMP treated lesions	6
Pigmentation around both sides lesions	1
Pain, dryness and fissuring	4
Blistering around the lesions	1

Discussion

In the recent past many workers have reported on the effectiveness of psoralens and UV light in psoriatic lesions. The covalent bonding of psoralen to thymine forming cyclobutane photoadducts and thus inhibiting the DNA synthesis was the basis for the use of these drugs in psoriasis. The earlier belief that the psoralens could harm the liver has been dispelled[4] and the wide usage of these drugs in the treatment of Vitiligo has not been associated with any side effects. Though chromosomal aberrations have been reported with psoralens plus UVA[5] it has not been proved that the doses given clinically can produce such effects.

Walter and Voorhees[1] have observed improvement in 8 of 11 patients treated with topical TMP and black light. In Weber's[2] large series of 74 patients using 0.15% solution of 8 MOP in Isopropyl alcohol the response has been moderate to excellent in a majority of cases. Farrish et al[3] have tried oral 8-MOP and a new high intensity longwave UVL in 16 patients in a paired comparison study and have found it superior to conventional UVL alone.

In all the foregoing studies artificial UVL sources have been used. In the present two paired comparison studies, one using topical and other oral TMP, natural sunlight served as the source of UVL. The results with both the methods have not been very encouraging.

Of the 21 patients put on the topical TMP (0.2%) in isopropyl alcohol only two showed improvement of TMP treated sites compared to base treated sites. The failure in most of the patients might be due to the following reasons :

The concentration of TMP is perhaps low; but the fact that Weber[2] used only 0.15% of 8-MOP appears to exclude the possibility of the TMP concentration being so low as to be ineffective even considering the possible differences in the phototoxic properties of these psoralens. The other component is the UVL energy. It is possible that the longwave UVL energy present in sunlight is not adequate to produce the required beneficial effect. It is also likely that longwave UVL energy required for producing phototoxicity with TMP is many times more than that with 8 – MOP. However since an increase in the length of sunlight exposure produced blistering around the lesions without affecting the psoriatic lesions it did not seem advisable to give it any further trial.

Hyperpigmentation around the psoriatic lesion of TMP treated sites suggests that phototoxic reaction associated with pigmentation has been taking place in the normal looking skin around. Perhaps the melanocytes in the psoriatic skin also respond by producing more melanin but are not able to cater melanosomes to the rapidly dividing and increased number of keratinocytes. Okum's[6] suggestion that the lesions regress if pigmentation is achieved seems fitting.

The dryness and fissuring which the patients experienced are due to the combined effect of isopropyl alcohol and exposure to sunlight.

No explanation can be offered for the improvement noticed in 2 of the 21 patients who had treatment similar to the rest of the patients in the group.

Psoriasis is by no means a rare disease in this part of the country; but it is rather difficult to convince patients to undergo 30 days' inpatient treatment for any paired comparison study. These are never subjected to any embarrassment at home because of the malodourous tar applications. Many expressed that they can not afford to stay away from work for financial reasons. Though the number of the patients is small, since there was not even the slightest indication that response to TMP plus sunlight is any better than to sunlight alone this modality does not appear useful. Exposure time can not be increased with a view to provide more longwave UVL energy as more than one hour's sunlight at mid day would be tedious and intolerable. However it appears that longwave UVL energy in sunlight in this part of the country during October–February when this study was conducted is adequate[7] thus suggesting that TMP is ineffective in psoriasis. This is in agreement with Verbov's[8] and Swanbeck et al's[5] experience with TMP. The gradual general improvement of psoriasis observed might have been due to the beneficial effect of sunlight alone. There is also the possibility that the strong suggestion that this 'new' method offered as the best remedy, contributed to some extent in producing a beneficial effect.

Our experience with 8-MOP and sunlight in this dermatosis is very little but initial observations have shown some encouragement and certainly deserve a more detailed study.

It also needs to be stressed that the psoralens are safe drugs. There are insignificant, if at all any long term side effects, when psoralens are given to otherwise healthy subjects.

Acknowledgements

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INHIBITION OF PSORIATIC SKIN ALKALINE PHOSPHATASE BY LEVAMISOLE

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Summary

The inhibition of psoriatic skin alkaline phosphatase by the anthelmintic drug levamisole was studied. It was shown that "in vitro" levamisole is an extremely effective inhibitor of the enzyme. A possible role of levamisole in the treatment of psoriasis is suggested.

It has been demonstrated that the alkaline phosphatase level of the psoriatic plaque is tremendously elevated as compared to normal skin.[1] Inhibitors of alkaline phosphatase can have therapeutic implications as the physiological role of alkaline phosphatase in the skin may be related to the keratinization of epidermis and in the endothelium of small vessels its function could be that of aiding the transfer of materials to and from the vessels.[2] Biochemical and cytochemical studies have shown that the anthelmintic drug levamisole is a potent, non competitive, organ specific inhibitor of alkaline phosphatase from a variety of organs.[3] It was therefore planned to study the inhibition of psoriatic skin alkaline phosphatase by levamisole.

Material and methods :

Skin biopsies of uniform thickness and 5 mm diameter were taken by a trephine after a subcutaneous injection of 2% xylocaine hydrochloride. These were quickly washed and transferred to a glass mortar precooled to (—20C°). Biopsies from 10 patients were pooled and homogenized by grinding with 5 ml, 0.05 M glycine buffer pH 10.5. The homogenate was centrifuged at 4000 r.p.m. and the clear supernatant used for enzyme assay. Enzyme activity was measured according to the method of Bessey et al[4].

Briefly the reaction mixture (1.1) ml) contained glycine-3 0.05M, $Mgcl_2$ 5×10^{-4} M, p-nitrophenyl phosphate (Sodium salt) 5.5×10^{-3} M, homogenate 0.1 ml and various concentrations of the drug levamisole. Incubation was done at 37°C for 4 hrs. The reaction was stopped by adding 5 ml 0.02 N sodium hydroxide and the O. D. of the solution measured at 400 mu. Appropriate blanks and controls were also run and the percent inhibition of activity at various concentrations of inhibitor calculated.

Results :

Our results are shown in Fig. 1. Measurable inhibition of activity occurs at extremely low concentrations of levamisole (0.0125 M) percent. Inhibition increased with higher concentrations of levamisole and 83% of the activity was inhibited with 0.2 M levamisole.

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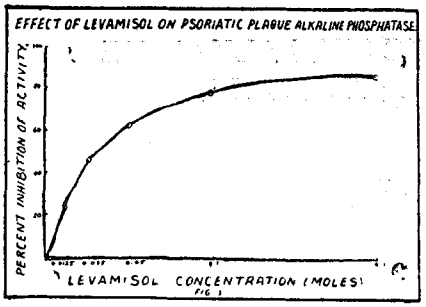

FIG. 1

Discussion :

To date there is no completely satisfactory systemic therapy for control of psoriasis. Drugs currently employed for controlling psoriasis like corticosteriods, methotrexate, azaribine and hydroxyurea have limited use because of their serious side effects. Photochemotherapy has recently been shown to be effective for controlling psoriasis[5] but is inconvenient to the patients who have to come daily to the hospital for exposure to U. V. light. We have previously shown that the alkaline phosphatase level of the psoriatic plaque is nearly 4 times that of normal skin. Mammalian alkaline phosphatase also acts as a pyrophosphatase[6] and may be involved in the polymerization of D.N.A. in the cell. In the endothelium of small vessels alkaline phosphatase could have the function of aiding the transfer of materials to and from the vessels[2]. In view of the above observations inhibition of skin alkaline phosphatase could have therapeutic implications for the treatment of psoriasis. Our studies confirm the effectiveness of levamisole in inhibiting the alkaline phosphatase of the psoriatic plaque in vitro and suggest a possible role of this drug for the treatment of psoriasis.

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