

LETTERS TO THE EDITOR

Treatment of Psoriasis with Oral Psoralens and Longwave Ultraviolet Light

I read with great interest the article by Dr Swanbeck and associates on the treatment of psoriasis with oral psoralens and longwave ultraviolet light. I was especially interested in the cytogenetic study finding that 8-MOP and UVA treatment of lymphocytes in vitro gives rise to chromosomal aberrations.

I treated 4 patients with xeroderma pigmentosum (2 with DeSanctis-Cacchione syndrome and 2 with ordinary xeroderma pigmentosum) after reports of benefits to these patients with this treatment (2, 3). All developed a great number of malignancies of the skin, and one may have developed his lymphatic leukemia after the usage (4).

Dr James German has presented evidence that with increased chromosomal breakage there is an increase in carcinoma, mainly lymphosarcoma: i.e. Bloom's disease, ataxia telangiectasia, Fanconi's anemia (personal communication). However, when I asked about these findings recently from experts on psoralens, they discounted our findings. I know that Dr Swanbeck is a very thorough investigator and if he has different results now, he would report them. I am strongly opposed to the use of psoralens with longwave ultraviolet light, fearing that we will have multiple carcinomas of the skin in these patients after a few years.

Studies by Cleaver, Bootsma & Freidberg (1), state that psoralens are ultraviolet light carcinogens, since we know that after ultraviolet radiation the psoralens attach to the DNA. Any disturbance of DNA and its repair processes deserves a thorough study. Two therapies that I once opposed have now been considerably modified, i.e. corticosteroids with occlusive dressings, and methotrexate, after studies on psoriasis published by me.

Unfortunately, in the U.S. these longwave ultraviolet machines are being sold clandestinely. I hope that Dr Swanbeck, by answering this letter, will give further details on his studies—whether wrong or right.

References

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A reply

We share the concern expressed by Dr William B. Reed regarding possible carcinogenic effects of PUVA-treatment but we also share the enthusiasm expressed by others (2, 6) regarding the positive aspects of this treatment. The purpose of our work (4) has not been to show how wonderful or how dangerous this treatment is. Our purpose has been to collect data that it is of relevance for the optimal use of the PUVA-treatment with regard to both effectiveness and safety. Concerning the relevance of our study of chromosomal aberrations caused by PUVA-treatment, we would like to make the following comments.

Addition of 8-MOP to lymphocyte suspensions, and subsequent irradiation of the suspension with UVA-light gives rise to chromosome aberrations in the cells after the 48-72 hours of culture time. The frequency of aberrations is dose dependent with regard to both the 8-MOP and the UVA-dose, while the two used separately give no effects. Thus the chromosome breaking effect of the combined treatment is clearly established in vitro. Our results are less clear, however, with regard to the in vivo effect of the clinical treatment. Some patients did

present high figures for the frequency of chromosome aberrations after a period of treatment, while others did not. Moreover, we cannot exclude the effects of previous treatment, and/or other factors as a cause of the aberration frequency in the patients investigated so far. It follows from the results of the *in vitro* experiments that a necessary prerequisite for the chromosomal effect of PUVA-treatment on peripheral lymphocytes *in vivo* would be that 8-MOP is present in the circulation in a sufficient concentration at the time of irradiation. We studied this problem by isolating lymphocytes from patients 2 hours after intake of their ordinary 8-MOP dose, irradiated the cells *in vitro* with therapeutic UVA-doses at the same times as the patients, and found a significant increase in the aberration frequency. A similar experiment carried out recently showed that the frequency of sister chromatid exchanges also increases significantly after this combined *in vivo* – *in vitro* treatment (5). It still remains to be shown, however, whether the dose of UVA-light which may eventually reach the dermal lymphocytes during clinical therapy is high enough to produce a significant number of chromosome aberrations. We are therefore at present following a number of patients with chromosome analyses before, during, and after treatment.

With regard to possible cytogenetic effects on the germinal layer of epidermis, we feel that the considerations should be somewhat different, since these cells are actively proliferating. From the beneficial clinical results we infer that the cells receive a PUVA-dose which is large enough to have an inhibiting effect on cell propagation. Autoradiographic experiments carried out in our laboratory show that radiolabelled 8-MOP binds preferentially to the nuclei of UVA-irradiated dermal fibroblasts in tissue culture, although a considerable amount of label was also found in the cytoplasm (5). We know from previous experience that PUVA affects mitochondrial genes (3), but evidently also chromosomal material. Which effect is dominant at the doses given therapeutically is not known. We may assume, however, that part of the inhibiting effect of PUVA on cell propagation is caused by UVA-mediated adduction of 8-MOP to nuclear DNA, giving rise to base substitutions and interstrand cross-links. Such lesions, if not properly repaired, would inactivate DNA replication or could give rise to gene and/or genome mutations, including chromosome aberrations. Thus it seems probable that the DNA-repair

function is of importance for protecting the skin against cytogenetic effects of PUVA-treatment as well as it is for UVB-irradiation. In this context Dr Reed's report of four cases with xeroderma pigmentosum developing multiple malignancies after PUVA-treatment is interesting, since it has been shown that PUVA-treatment induces unscheduled DNA synthesis in normal cells but not in xeroderma pigmentosum fibroblasts (1).

Very little is known about the kinetics and efficiency of human DNA-repair processes *in vivo*. However, UV-induced DNA-repair synthesis *in vitro* has a limited capacity. At lower dose levels eventually all lesions may be repaired provided that the cells are given sufficient time for repair synthesis. One would therefore assume that lower doses would reduce the risk of remaining DNA-lesions when the cells enter the replication phase and thus minimize the risk of cytogenetic effects. These considerations may be of relevance also in the case of PUVA-treatment.

Although we look upon the conceivable cytogenetic effect of PUVA-treatment on peripheral lymphocytes and epidermal cells as a matter of the highest concern, we are not aware of any studies demonstrating firmly carcinogenic effects of therapeutically or inadvertently induced chromosome aberrations.

The experience that some clinics have with regard to the safety of psoralen treatment of vitiligo is not directly applicable to psoriasis treatment. In the normal or in the vitiliginous skin the erythema reaction is a warning signal against overdosage. When psoriasis is treated, the uninvolved skin usually pigments well, while the lesions are fairly free from melanin protection. When the dosage of the PUVA-treatment (usually the UVA-dose) is increased, the unprotected lesion cannot react with an erythema as it already is strongly erythematous. Therefore it is possible that the involved skin receives very high doses of PUVA compared with what has earlier been given to vitiliginous skin.

Such a local overdosage may occur more easily with topical application of psoralens, especially for epidermal cells, as the penetration into the epidermis of psoriatic lesions is much more effective than into uninvolved skin.

We therefore think that for white, not particularly sunburned patients, a safe way to use PUVA is to test out the minimal erythema dose after 8-methoxy-psoralen intake with UVA radiation, and

use this dose 2 to 4 times weekly and not increase the dose during the treatment.

In this way the time it takes to heal patients gets longer and a larger percentage of the patients do not heal completely. Another possibility is to use this scheme for seven weeks and subsequently start increasing the light dose. In this way a large proportion of the patients do not unnecessarily receive a high PUVA-dose daily. Our present impression is that it is not the accumulated dose but the accumulated overdose that is important with regard to possible carcinogenicity.

We feel therefore that PUVA-treatment of psoriatic patients should definitely continue but that unnecessarily high PUVA-doses should not be given. With regard to the risks with PUVA-treatment one must keep in mind that other types of treatment for psoriasis do not seem completely innocent. Coal tar, so frequently used in USA, contains several carcinogens, and coal tar is a potent carcinogen on laboratory animals. UVB or sun therapy for psoriasis may be more or may be less dangerous than PUVA-treatment. We do not know today. More work on cellular genetic effects of different antipsoriatic agents made in as relevant a way as possible, is needed.

References

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An Immunohistochemical Study of the Skin of Healthy Individuals

In a Letter to the Editor (*Acta Dermatovener (Stockholm)* 55: 398, 1975) E. H. Beutner et al. criticized our article: "An immunohistochemical study of the skin of healthy individuals" (*Acta Dermatovener (Stockholm)* 54: 271, 1974) on several points. We should like to deal with each of these points in the following remarks.

On no occasion did we state that the fluorescence of the epidermal basement zone and blood vessel walls was *invariably* "conspicuous". Our micrographs naturally represent sections in which the staining patterns were most clearly observable. Although in the other biopsies the phenomena described were sometimes less distinct, they were always easily detectable to the experienced eye. Our experience in this field also covers a period of 12 years; at present two thousand biopsy specimens per annum are being processed in our laboratory.

The following considerations may help to explain the discrepancies between our observation and those made by Beutner et al.

1. Beutner et al. based their criticism partly on the assumption that the extensor surface of the forearm is not light-exposed, a view with which we do not agree. (Moreover our examination was carried out in the summer months of 1973.) One reason for choosing this particular part of the skin is the fact that this area of the (clinically uninvolved) skin is usually biopsied for diagnostic purposes in systemic lupus erythematosus. In biopsies of the skin of the back, a region generally less exposed to light, the IF staining patterns which are characteristic of this disease are less frequently demonstrable (Baart de la Faille-Kuyper, E. H., *Lupus Erythematosus. An Immunohistochemical and Clinical Study of 485 Patients*, Schotanus & Jens, Utrecht, 1969, pages 40 and 70). In biopsies of the skin of the back of healthy individuals we did not come across a single instance of the patterns mentioned for the skin of the arm with anti-IgG and anti-albumen reagents. The frequency of granular staining for IgM and of vessel wall staining with the anti-complement reagents was considerably lower. The use of anti-C3d and anti-C4,3 (=C4+C3c+C3d), however, revealed staining of the epidermal basement zone in all cases (unpublished observations). The foregoing seems to provide evidence that besides the choice of a particular part of the body