THE JOURNAL OF INVESTIGATIVE DERMATOLOGY, 69:387-391, 1977

Vol. 69, No. 4
*Printed in U.S.A.*

# SISTER CHROMATID EXCHANGES IN PHOTOCHEMOTHERAPY

ELISABETH C. WOLFF-SCHREINER, M.D., D. MARTIN CARTER, M.D., PH.D., HANS GEORG SCHWARZACHER, M.D., AND KLAUS WOLFF, M.D.

*Department of Histology and Embryology (ECWS, HGS), University of Vienna, Austria; Department of Dermatology (DMC), Yale University School of Medicine, New Haven, Connecticut, U. S. A.; Department of Dermatology (KW), University of Innsbruck, Austria*

Sister chromatid exchanges (SCE), presently considered highly sensitive indicators for chromosomal effects of potential mutagens and carcinogens in mammalian cells, were studied in circulating white blood cells from patients with widespread psoriasis who were being treated with 8-methoxy-psoralen and long-wavelength ultraviolet light (UVA) photochemotherapy (PUVA). SCE counts of patients with psoriasis treated with PUVA neither differed from SCE counts of those treated with topical dithranol and corticosteroids, nor from SCE of nonpsoriatic, clinically healthy individuals. The duration of PUVA treatment (up to 2 years) and the total cumulative dose of UVA energy given to the patients also had no effect on the number of SCE of circulating lymphocytes. However, the SCE counts of patients with psoriatic arthropathy were higher than those of patients with psoriasis without joint involvement or normal controls, irrespective of the type of treatment given. There was no difference between SCE counts obtained before and after PUVA treatment sessions, but when white blood cells removed from patients after treatment were reirradiated with UVA in vitro there was a significant increase of SCE.

It is concluded that, whereas the principle of PUVA does induce an increased number of SCE in human lymphocytes in vitro, the same principle, employed as a clinical form of therapy, does not result in similar alterations in circulating lymphocytes in vivo. This study has therefore failed to detect harmful effects of PUVA on the genome of circulating lymphocytes in patients subjected to this treatment.

The interaction of 8-methoxypsoralen (8-MOP) and long-wavelength ultraviolet light (UVA), as employed therapeutically in photochemotherapy (PUVA) of psoriasis [1–3] leads to the formation of monofunctional and bifunctional, i.e., cross-linking, psoralen–DNA photoadducts [4–8] which may result in a decrease of DNA replication and cell division within the epidermis [9–11]. Since approximately 50% of the UVA energy at wavelengths employed in PUVA penetrate into the superficial dermis [12], and since it has been postulated recently [13] that one of the targets of PUVA could be the inflammatory infiltrate in the dermal papillae of psoriatic lesions, the blood cells circulating through the capillaries in the superficial dermis could also be affected by this treatment.

Some concerns have been expressed as to the long-term biologic consequences of PUVA, particularly with regard to cytogenetic alterations or possible oncogenic hazards [3]. 8-MOP and UVA have been shown to be mutagenic in bacteria [15,16] and to induce chromosomal damage in cells in vitro [17,18]; also, in a combined in vivo and in vitro study, lymphocytes collected from patients treated with PUVA were found to exhibit an increased rate of chromosomal aberrations when they were reirradiated in vitro [19].

A more sensitive method to detect chromosomal damage in vivo or in vitro is to count sister chromatid exchanges (SCE) which indicate DNA break and repair events [20,21]. Using this method, Carter et al [22] have shown that 8-MOP plus UVA induce a significant, dose-dependent increase of SCE in cultured human lymphocytes in vitro. The present study was designed to determine whether this holds also for an in vivo situation and, specifically, whether (1) PUVA causes an increase of SCE in circulating human lymphocytes in vivo, suggesting acute DNA damage to these cells; (2) whether long-term PUVA treatment alters the SCE rates of circulating lymphocytes in vivo, suggesting cumulative DNA damage; (3) whether the SCE rates of circulating lymphocytes collected from patients after PUVA treatment in vivo can be altered by additional in vitro

Manuscript received February 15, 1977; accepted for publication March 31, 1977.

This study was supported, in part, by grants from the Fonds zur Förderung der wissenschaftlichen Forschung (No. 3228), Vienna; the Austrian National Bank, Forschungsförderungsfonds der Gewerblichen Wirtschaft, Vienna; and Schering AG, Berlin.

Reprint requests to: Dr. E. C. Wolff-Schreiner, Department of Dermatology, University of Innsbruck, Anichstrasse 35, A-6020 Innsbruck, Austria.

Abbreviations:
8-MOP: 8-methoxypsoralen
SCE: sister chromatid exchanges
UVA: long-wavelength ultraviolet light

irradiation; and (4) whether the SCE of lymphocytes from patients receiving PUVA differ from those of patients subjected to conventional antipsoriatic treatment with dithranol or topical corticosteroids.

## MATERIALS AND METHODS

### *Patients*

Nineteen patients were chosen for the study. Sixteen of them had been treated with PUVA from 1 week to 26 months for severe, generalized psoriasis of the plaque type and 1 for psoriatic erythroderma; 3 patients had psoriatic arthropathy and 1 had ankylosing spondylitis. One patient with generalized lichen planus and 1 with vitiligo were also studied. Patients received 0.6 mg/kg body weight 8-MOP orally; 2 hr later they were irradiated with 0.5 to 8 J/cm$^2$ of UVA (peak 365 nm) according to a treatment schedule, outlined previously [23].

### *Experimental Protocol*

Three 10-ml blood samples were collected from each patient with light-protected syringes which contained a drop of a 5% heparin solution. The A samples were collected exactly 2 hr after the ingestion of 8-MOP and before UVA irradiation, i.e., at the time of the estimated peak concentrations of 8-MOP in the plasma [1,3]. The B and C samples were collected immediately after the completion of UVA irradiation. All samples were delivered into centrifuge tubes containing 0.5 ml of a 1% phytohemagglutinin solution (Welcome) and processed as described previously [22]. C samples were irradiated at a distance of 30 cm with a Westinghouse black light source delivering 2.5 mW/cm$^2$ at 365 nm for 7 min, whereas A and B samples were not irradiated and were kept in the dark. All samples (A, B, C) were cultured at 37°C for 24 hr; after addition of 0.3 ml of a 5-bromodeoxyuridine solution (6 $\mu$g/ml), cultures continued for 48 hr, 5 $\mu$g of colchicine being incorporated into the medium for the last 2 hr of culture time. After hypotonic treatment and fixation with methanol:glacial acetic acid (3:1), chromosome spreads were prepared [24] and stained with Hoechst 33258 and Giemsa [21]. SCE were evaluated in 50 cells of each preparation; exchanges at centromeres were not counted. A statistical analysis of SCE counts was performed by a *t*-test for two means. All preparatory steps had been performed under safe-light conditions or in the dark.

### *Controls*

Seven patients with moderate to severe psoriasis, 2 of whom also had psoriatic arthropathy, served as the control group I. Five of these patients had been treated for more than 1 week, twice daily, with 0.1 to 4% dithranol in petrolatum. Two patients had been treated with topical fluorinated corticosteroids. Twelve clinically healthy volunteers, aged 22 to 56, served as control group II (nonpsoriatic controls). Blood samples of control groups I and II were processed as were the A and B samples of the PUVA patients.

## RESULTS

The results obtained from counting SCE in white blood cells of patients treated with PUVA

TABLE 1. *Sister chromatid exchanges in patients treated with PUVA*

| Patient code | Sex | Age | PUVA months | Total cumulative J/cm$^2$ at time of evaluation | Sister chromatid exchanges[a] | | |
|---|---|---|---|---|---|---|---|
| | | | | | Sample A | Sample B | Sample C |
| FE/36 | M | 36 | 26 | 1147.5 | 14.3 ± 4.6 | 13.8 ± 4.5 | n.d. |
| HA/34 | M | 63 | 17 | 429.2 | 13.2 ± 4.3 | 13.2 ± 4.8 | 22.2 ± 3.8 |
| GM/35 | M | 27 | 17 | 898.0 | 14.1 ± 3.4 | n.d. | n.d. |
| VH/30[b] | M | 32 | 14 | 968.1 | 19.1 ± 5.2 | 17.3 ± 4.5 | 26.7 ± 7.2 |
| HR/19 | F | 36 | 13 | 861.1 | 15.2 ± 5.1 | 15.3 ± 5.7 | 19.7 ± 5.5 |
| RK/31[b,c] | M | 37 | 12 | 986.6 | 17.2 ± 6.5 | 17.8 ± 6.0 | 25.1 ± 7.5 |
| VJ/27 | M | 63 | 8 | 443.4 | 13.2 ± 3.2 | 13.0 ± 3.7 | 21.3 ± 5.3 |
| ZH/28[d] | F | 55 | 4 | 255.0 | 13.5 ± 5.6 | 12.2 ± 5.6 | 19.3 ± 5.1 |
| WH/9 | F | 47 | 4 | 100.7 | n.d. | 11.8 ± 4.4 | 17.0 ± 5.8 |
| MF/10 | M | 27 | 2 | 146.0 | 15.7 ± 5.4 | 14.3 ± 4.3 | 17.1 ± 6.3 |
| HE/11[b,c] | F | 36 | 2 | 76.7 | 17.6 ± 6.6 | 17.0 ± 5.7 | 20.5 ± 5.8 |
| BC/20 | F | 30 | 2 | 127.3 | n.d. | 12.8 ± 4.3 | n.d. |
| KK/21 | F | 28 | 2 | 141.6 | 15.6 ± 4.5 | 13.1 ± 4.8 | 18.9 ± 4.4 |
| WW/6 | M | 25 | 1.5 | 68.6 | n.d. | 13.9 ± 5.4 | 23.2 ± 5.5 |
| FD/7 | F | 35 | 1.3 | 137.9 | 14.6 ± 5.6 | 11.9 ± 4.7 | 19.0 ± 6.0 |
| HJ/17 | F | 28 | 0.5 | 19.0 | n.d. | 15.6 ± 6.0 | 21.3 ± 5.0 |
| MH/29[e] | M | 47 | 0.3 | 13.0 | 18.5 ± 5.5 | 17.5 ± 6.0 | 22.9 ± 5.7 |
| GM/15[f] | F | 41 | 0.25 | 12.0 | n.d. | 18.4 ± 6.3 | 21.9 ± 6.9 |
| WH/16 | F | 32 | 0.25 | 14.8 | n.d. | 11.6 ± 3.6 | n.d. |

[a] Mean frequency per cell ($\bar{x}$ ± SD) (n = 50). Sample A: Before irradiation in vivo. Sample B: After irradiation in vivo. Sample C: After irradiation in vivo and subsequently in vitro. Statistical analysis (*t*-test for two means): A > B, $p < 0.1$ (not significant); A < C, $p < 0.01$ (significant); B < C, $p << 0.01$ (highly significant).

[b] Arthropathic psoriasis.

[c] Patients treated with methotrexate before PUVA therapy.

[d] Vitiligo.

[e] Ankylosing spondylitis.

[f] Generalized lichen planus.

n.d. = Not done.

TABLE II. *SCE[a] in patients with psoriasis treated with conventional therapy (control group I)*

| Patient code | Sex | Age | Total body area treated | Type of treatment | SCE counts |
|---|---|---|---|---|---|
| KM/8 | M | 45 | 75% | Dithranol 2% | 16.2 ± 6.2 |
| HJ/12 | M | 35 | 40% | Dithranol 0.1% | 12.4 ± 4.4 |
| SF/13 | M | 72 | 25% | Dithranol 4% | 16.8 ± 7.5 |
| BF/24[b] | M | 67 | 50% | Dithranol 1% | 17.8 ± 4.6 |
| KJ/25 | M | 62 | 75% | Dithranol 0.5% | 15.8 ± 4.9 |
| SD/32 | M | 12 | 100% | Corticosteroids | 15.0 ± 3.1 |
| SH/33 | M | 34 | 75% | Corticosteroids | 14.2 ± 4.8 |

[a] Mean frequency per cell ($\bar{x}$ ± SD) (n = 50).
[b] Psoriatic arthropathy.

TABLE III. *SCE in healthy control persons (control group II)*

| Patient code | Sex | Age | SCE counts[a] |
|---|---|---|---|
| C1/37 | F | 35 | 14.9 ± 6.2 |
| C2/38 | M | 34 | 14.3 ± 4.9 |
| C3/39 | M | 26 | 11.6 ± 3.6 |
| C4/40 | F | 22 | 13.7 ± 3.7 |
| C5/41 | F | 54 | 14.7 ± 5.2 |
| C6/43 | F | 56 | 13.6 ± 4.4 |
| C7/44 | M | 32 | 13.4 ± 4.8 |
| C8/45 | M | 29 | 10.7 ± 2.4 |
| C9/46 | M | 32 | 11.8 ± 3.5 |
| C10/47 | F | 56 | 12.1 ± 3.4 |
| C11/48 | M | 32 | 14.9 ± 5.2 |
| C12/49 | F | 56 | 11.0 ± 3.3 |

[a] Mean frequency per cell ($\bar{x}$ ± SD) (n = 50).

and in the two control groups are listed in Tables I–III and can be summarized as follows: (1) In the patients treated with PUVA, the SCE counts before (sample A) and after (sample B) the individual treatment sessions were within the same range and, as shown in Table I, there was no statistically significant difference between the two samples (A > B, $p < 0.1$). (2) White blood cells collected immediately after treatment and subsequently reirradiated in vitro demonstrated a highly significant increase of SCE counts as compared to cells not irradiated in vitro (sample B < sample C, $p << 0.01$, Tab. I). The mean increase after in vitro irradiation was 43.6% (± 17.4%), ranging from 19.0 to 68.2% (Tab. I). (3) The overall duration of PUVA treatment and the total doses of energy delivered to the patients during this treatment (Tab. I) did not have any effect on the SCE rates of white blood cells in vivo. Table IV compares the mean SCE counts of patients treated less than 1 year with those of patients treated for more than 1 year. There is no significant difference between the SCE in the two experimental groups. (4) Some variation of the SCE counts was noted in all samples (A, B, C) tested. In comparing patients with widespread though uncomplicated psoriasis and patients with joint involvement (Tab. I), a higher rate of SCE was found in the patients with arthropathy and in the patient with ankylosing spondylitis (see below). A similarly high value was recorded in a patient with severe, generalized lichen planus (Tab. I). (5) Among the patients treated with dithranol and corticosteroids (control group I) the highest SCE counts were again recorded in a patient who had arthropathic psoriasis. A comparison of the mean SCE values of this group of patients (Tab. II) and the patients with psoriasis treated with PUVA (Tab. I) shows no difference of statistical significance (control group I = sample A of PUVA patients; control group I > sample B of PUVA patients, $p > 0.1$ (not significant)). (6) The SCE of nonpsoriatic, clinically healthy individuals (Tab. III) were in the same range as those of the PUVA-treated patients. However, when the arthropathic patients, treated with PUVA or conventional therapy were removed from their respective groups and grouped together, a statistically significant difference emerged between the SCE of this arthropathy group and those of PUVA-treated patients and healthy controls (Tab. V).

## DISCUSSION

This study demonstrates that individual PUVA exposures are not followed by an increase of SCE rates in vivo, but that an increased frequency of SCE is induced by an additional UVA exposure of the same cell population in vitro. The latter experiment supports previous in vitro observations [22] that 8-MOP alone does not increase SCE rates and indicates that, in the experimental set-up of the present study, sufficient amounts of the photosensitizer were present in the blood samples tested to lead to the expected changes when the cells were reexposed to UVA in vitro. This may be taken to suggest that, in vivo, insufficient UVA energy is delivered to circulating white blood cells, either because insufficient quanta of light reach the dermal cappillaries because the cells are not exposed long enough to absorb sufficient light energy, or because an insufficient number of susceptible lymphocytes is hit by UVA quanta to result in a noticeable increase of SCE at the level of detection attainable by the method employed.

Our study also shows that long-term PUVA treatment (up to 26 months) does not result in an increased frequency of SCE. The comparison of SCE counts of patients treated for less than 1 year and of those who had received photochemotherapy

TABLE IV. *Mean SCE counts in relation to duration of PUVA treatment*

| Duration of PUVA therapy | Mean J/cm² ($\bar{x}$ ± SD) | Number of patients | Sample A | SCE counts[a] sample B | Sample C |
|---|---|---|---|---|---|
| Less than 1 year (range 0.25 to 8 months) | 119.7 ± 120.3 | 13 | 15.5 ± 2.0 | 14.1 ± 2.3 | 20.2 ± 2.1 |
| Longer than 1 year (range 12 to 26 months) | 881.8 ± 242.7 | 6 | 15.5 ± 2.2 | 15.4 ± 2.0 | 23.4 ± 3.1 |

[a] Mean frequency of SCE in the number of patients examined. There is no difference of SCE in the two groups of patients compared ($p < 0.01$).

TABLE V. *Mean SCE counts in different patient groups and controls*

Statistical analysis (*t*-test for two means): Z > U, $p < 0.005$; Z > V, $p < 0.025$; Z > W, $p < 0.005$; Z > X, $p < 0.005$; Z > Y, $p < 0.005$.

| Code | Patient groups and controls | Number of patients | SCE counts[a] |
|---|---|---|---|
| U | Normal subjects | 12 | 13.1 ± 1.5 |
| V | Psoriasis, conventional therapy (including patients with arthropathy) | 7 | 15.5 ± 1.8 |
| W | Psoriasis, conventional therapy, (excluding arthropathic patient) | 6 | 15.1 ± 1.6 |
| X | Psoriasis, PUVA (including patients with arthropathy) | 17 | 14.4 ± 2.1[b] |
| Y | Psoriasis, PUVA (excluding arthropathic patients) | 13 | 13.4 ± 1.3[b] |
| Z | Psoriasis with arthropathy (patients on PUVA or conventional therapy | 5 | 17.5 ± 0.3 |

[a] Mean frequency of SCE in patient group examined.
[b] Compiled from data of samples B.

for longer periods of time, fails to suggest a cumulative effect of photochemotherapy on the lymphocyte population.

There was, however, an increase of SCE counts in those patients who had psoriatic arthropathy, and this appears to be in accord with a previous study in which an increased frequency of chromosomal aberrations was reported for patients with severe psoriasis [25]. The SCE rates in the patients with arthropathy were also independent of the overall duration of PUVA therapy, indicating that they were not related to this treatment. Two of our patients (R.K./31 and H.E./11) had received methotrexate, known to cause chromosomal changes, prior to PUVA, but this regimen had been discontinued 12 and 6 months, respectively before SCE were evaluated. Whether the increased SCE counts in patients with psoriatic arthropathy reflect some unknown genetic anomaly, or whether they are due to previous forms of therapy other than PUVA, or whether they are due to statistical scatter cannot be decided from our investigation.

The significance of SCE is, as yet, not fully understood. SCE may be taken to express damage of the genome and are, in fact, employed as a cytologic means for the detection of possible oncogenic potentials of chemical agents [26]. SCE may also represent an expression of DNA repair [17] and, since UVA-induced psoralen–DNA photoadducts and cross links have been shown to be repaired in unicellular organisms [8,16] and mammalian cells [9,27,28], the increased SCE counts observed in white blood cells treated with 8-MOP and UVA in vitro [22] may reflect such an event.

Recent studies of xeroderma pigmentosum cells treated with mutagens in vitro [29] have indicated that SCE may be the result of different lesions than are chromosome aberrations; it was also demonstrated that, at least for these cells, SCE are presently the most sensitive indicator for chromosomal effects of potential mutagens [29]. It is in this context that the results of the present investigation may acquire considerable relevance, particularly with regard to the safety of PUVA as a clinical treatment. Whereas the principle of PUVA is capable of inducing increased SCE rates in lymphocytes in vitro [22], it is shown by our present study that the same principle, applied as a form of clinical therapy, need not necessarily result in similar alterations in circulating lymphocytes in vivo. Within the possible limitations of the technique employed, our experiments have failed to detect harmful effects of PUVA on the genome of circulating lymphocytes, but this, of course, does not exclude such effects on the genome of other target tissues.

We wish to thank Dr. Peter Fritsch for the statistical analysis.

REFERENCES

1. Parrish JA, Fitzpatrick TB, Tanenbaum L, Pathak MA: Photochemotheray of psoriasis with oral methoxsalen and longwave ultraviolet light. N Engl J Med 291:1207–1222, 1974
2. Wolff K, Hönigsmann H, Gschnait F, Konrad K: Photochemotherapie bei Psoriasis. Deutsch Med Wochenschr 100:2471–2477, 1975
3. Wolff K, Fitzpatrick TB, Parrish JA, Gschnait F, Gilchrest B, Hönigsmann H, Pathak M, Tanenbaum L: Photochemotherapy for psoriasis with orally administered methoxsalen. Arch Dermatol

112:943–950, 1976
4. Musajo L, Bordin F, Caporale G, Marciani S, Rigatti G: Photoreactions at 3655 Å between pyrimidine bases and skin-photosensitizing furocoumarins. Photochem Photobiol 6:711–719, 1967
5. Cole RS: Light-induced cross-linking of DNA in the presence of a furocoumarin (psoralen). Biochim Biophys Acta 217:30–39, 1970
6. Carter DM, McMacken MV, Condit ES: Defense of cutaneous cells against UV irradiation. I. Photomediated binding of trimethyl psoralen to DNA of melanoma cells in culture. J Invest Dermatol 60:270–273, 1973
7. Pathak MA, Kramer DM, Fitzpatrick TB: Photobiology and photochemistry of furocoumarins (psoralens), Sunlight and Man: Normal and Abnormal Photobiologic Responses. Edited by MA Pathak, LC Harber, M Seiji, A Kukita; TB Fitzpatrick, consulting editor. Tokyo, University of Tokyo Press, 1974, pp 335–368
8. Cole RS: Repair of DNA containing interstrand crosslinks in *Escherichia coli*: sequential excision and recombination. Proc Natl Acad Sci USA 40:1064–1068, 1973
9. Baden HP, Parrington JM, Delhanty JDA, Pathak MA: DNA synthesis in normal and xeroderma pigmentosum fibroblasts following treatment with 8-methoxypsoralen and long-wave UV light. Biochim Biophys Acta 262:247–255, 1972
10. Walter JF, Voorhees JJ, Kelsey WH, Duell EA: Psoralen plus black light inhibits epidermal DNA synthesis. Arch Dermatol 107:861–865, 1973
11. Epstein JH, Fukuyama K: Effects of 8-methoxypsoralen-induced phototoxic effects on mammalian epidermal macromolecule synthesis in vivo. Photochem Photobiol 21:325–330, 1975
12. Everett MA, Yeargers E, Sayre R, Olson RL: Penetration of epidermis by ultraviolet rays. Photochem Photobiol 5:533–542, 1966
13. Wolff K, Gschnait F, Hönigsmann H, Konrad K, Stingl G, Wolff-Schreiner E, Fritsch P: Oral photochemotherapy–results, follow-up, and pathology. Proceedings 2nd International Symposium on Psoriasis. Stanford, Plenum, (in press)
14. Reed WB: Treatment of psoriasis with oral psoralens and longwave ultraviolet light. Acta Derm Venereol (Stockh) 56:315–318, 1976
15. Ben-Hur E, Elkind MM: Psoralen plus near ultraviolet light inactivation of cultured Chinese hamster cells and its relation of DNA crosslinks. Mutat Res 18:315–324, 1973
16. Igali S, Bridges BA, Ashwood-Smith MJ, Scott BR: Mutagenesis in *Escherichia coli*. IV. Photosensitization to near ultraviolet light by 8-methoxypsoralen. Mutat Res 9:21–30, 1972
17. Latt SA, Stetten G, Juergens LA, Buchanan GR, Gerald PS: Induction by alkylating agents of sister chromatid exchanges and chromatid breaks in Fanconi's anemia. Proc Natl Acad Sci USA 72:4066–4070, 1975
18. Ashwood-Smith MJ, Grant E: Chromosome damage produced by psoralen and ultraviolet light. Br Med J 272, 1976
19. Swanbeck G, Thyresson-Hok M, Bredberg A, Lambert B: Treatment of psoriasis with oral psoralens and longwave ultraviolet light. Acta Derm Venereol (Stockh) 55:367–376, 1975
20. Latt SA: Sister chromatid exchanges, indices of human chromosome damage and repair: detection by fluorescence and induction by mitomycin C. Proc Natl Acad Sci USA 71:3162–3166, 1974
21. Perry P, Wolff S: New Giemsa method for the differential staining of sister chromatids. Nature (Lond) 251:156–158, 1974
22. Carter DM, Wolff K, Schnedl W: 8-Methoxypsoralen and UVA promote sister chromatid exchanges. J Invest Dermatol 67:548–551, 1976
23. Wolff K, Gschnait F, Hönigsmann H, Konrad K, Parrish JA, Fitzpatrick TB: Phototesting and dosimetry for photochemotherapy. Br J Dermatol 96:1–10, 1977
24. Schwarzacher HG: Preparation of metaphase chromosomes, Methods in Human Cytogenetics. Edited by HG Schwarzacher, U Wolf. Berlin/Heidelberg/New York, Springer-Verlag, 1974, pp 78–81
25. Nielsen J, Zachariae H: Chromosome aberrations in severe psoriasis. Acta Derm Venerol (Stockh) 53:192–194, 1973
26. Perry P, Evans HJ: Cytological detection of mutagen-carcinogen exposure by sister chromatid exchange. Nature (Lond) 258:121–125, 1975
27. Carter DM: Biological effects of photomediated binding of trimethyl psoralen to DNA (abstr). J Invest Dermatol 64:288, 1975
28. Day RS, Giuffrida AS, Dingman CW: Repair by human cells of adenovirus 2 damaged by psoralen plus near ultraviolet light treatment. Mutat Res 33:311–320, 1975
29. Wolff S, Rodin B, Cleaver JE: Sister chromatid exchanges induced by mutagenic carcinogens in normal and xeroderma pigmentosum cells. Nature (Lond) 265:347–349, 1977