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ORAL 8-METHOXYPSORALEN PHOTOCHEMOTHERAPY OF PSORIASIS

The European PUVA Study: a Cooperative Study among 18 European Centres*

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Summary In a multicentre study in eighteen European cities 3175 patients were treated with photochemotherapy (PUVA) for severe psoriasis and data obtained during a period of 39 months were analysed. A response better than marked improvement was obtained in 88·8% of patients; twenty exposures and a total cumulative UVA dose of 96 J/cm^2 were required for clearing, the duration of the clearing phase being 5·3 weeks. A comparison of the results of this study with those of a similar multicentre study in the United States on 1300 patients and using a different treatment protocol, revealed that while treatment results and the number of individual treatment sessions were similar the European protocol requires only half the time and less than half the total cumulative UVA dose for clearing of psoriasis. When patients in the European study who received continuous maintenance treatment were compared with patients who received no maintenance treatment the probability that a patient would remain in remission for a period of 80 weeks was the same, irrespective of whether patients received maintenance treatment or not. This study confirms the dramatic efficacy of PUVA in clearing psoriasis and contains two important messages for the reduction of possible long-term hazards of this treatment. Firstly, the total UVA energy requirements for clearing psoriasis strongly depend on the treatment schedule and can be kept low if an individual approach aimed at rapid clearing of psoriasis is used. Secondly, maintenance therapy may not significantly prevent recurrences for prolonged periods of time and may thus not be necessary in most patients.

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Introduction

IN 1974, Parrish et al.[1] introduced systemic photochemotherapy (PUVA) with oral 8-methoxypsoralen followed by irradiation with high-intensity long-wave ultraviolet light (UVA, 320–400 nm) for the treatment of severe psoriasis. Their encouraging results have been confirmed in Europe and in the United States.[2–9] In 1975 a multicentre randomised trial was set up in the United States, and data from the first 18 months of therapy and follow-up have been reported.[10] Also in 1975 a similar study was started in eleven European countries, and the data on 3175 patients in this European PUVA study during a period of 39 months form the basis for this report.

Patients and Methods

Patient selection and treatment were done according to a protocol provided to the participating centres before the study began and results were collected in questionnaires adapted for electronic data processing.

Patients

Data were recorded for a total of 3175 patients. 58·4% were men and 41·6% were women. The mean age was 41·7 years but there were two peaks (at ages 30 and 50–60) in the age distribution curves for both sexes.

Type of Psoriasis and Extent of Skin Involvement

The predominant form of psoriasis (clinical expression) was entered as first order diagnosis; if a patient also had features of a different form of psoriasis this was entered as a second order diagnosis. The first order diagnosis was usually widespread chronic plaque type psoriasis (86·6%) or guttate psoriasis (9·5%); the remaining diagnoses were pustular psoriasis of Zumbusch (1%), psoriatic erythroderma (1·5%), and non-specified psoriasis (1·4%). Second order diagnoses were psoriatic arthritis in 7·1%, guttate psoriasis in 3·8%, and other forms in 1·8%.

In 50% of the patients more than 53% of the skin was involved. Fig. 1 plots skin involvement for all cases and for patients who had persistent, stable psoriatic lesions during the two years before PUVA and patients whose lesions had been variable. 44% of patients had a persistent, stable type of psoriasis and this was more frequent in patients older than 30 years. In patients with remissions

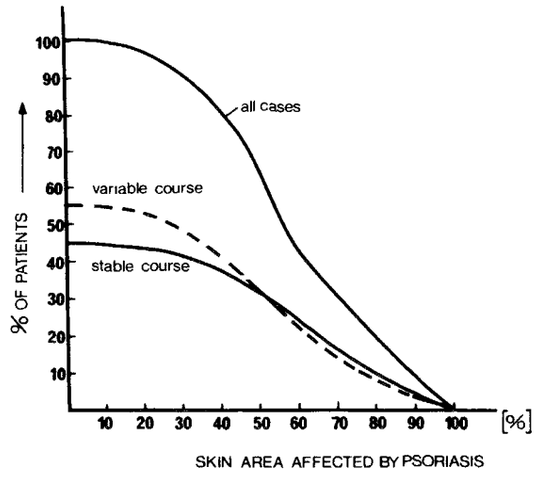

Fig. 1—Plot of number of patients against area of skin involvement.

In 50% of patients more than 53% of skin was affected.

and relapses during the 2 years before PUVA the area of skin involvement was smaller than that in patients with persistent lesions.

Skin Typing

Sensitivity to UV light and ability to tan were estimated[10] (table I). There was a wide variation of skin types, though more than half the patients were type III.

Laboratory Investigations

Laboratory data were recorded before therapy and regularly after the clearing phase. Eye examinations were also done.

Trial Design

PUVA was given by established methods[11] and phototoxicity testing[11] was done before treatment to determine the minimal phototoxicity dose (MPD) of UVA in 1312 patients; in the remainder dosimetry was arbitrarily determined (see below). Treatment was divided into a clearing phase and a maintenance phase.

Clearing phase.—Patients received four treatments per week[11] until clearing was obtained, starting with the MPD, as determined by phototoxicity testing, or at a UVA dose arbitrarily determined as 1·5 J/cm^2 for skin types I and II, 2 J/cm^2 for types III and IV, and 2·5–5 J/cm^2 for types V and VI. During treatment the UVA dose was adjusted[11] on the basis of MPD, skin type, presence or absence of erythema, and response of psoriatic lesions. The endpoint was complete clearing of psoriasis (i.e., more than 95% of the lesions had regressed). If complete clearing was not achieved and the patient discontinued PUVA or switched to other treatment, results were evaluated quantitatively by the estimated percentage of cleared lesions and qualitatively as no change or slight, definite, or marked improvement.

Maintenance phase.—The last effective UVA dose in the clearing phase was used for maintenance treatment, the frequency of treatments ranging from twice weekly to once every 3 weeks. Three groups of patients were compared: (A) patients whose treatment stopped before the maintenance phase, (B) patients on maintenance treatment for only a limited period, the final evaluation being done after a period off maintenance, and (C) patients on continuous maintenance treatment up to the point of evaluation.

Response to therapy expressed as percentage improvement over the initial state of psoriasis, was evaluated weekly. New lesions or reappearance of old lesions which reduced the improvement rate by more than 15% were defined as relapse.

TABLE I—SKIN TYPES

Skin type[10]	Criteria	% of patients
I	Always burn, never tan	3·7
II	Always burn, then slight tan	28·7
III	Sometimes burn, always tan	51·2
IV	Never burn, always tan	14·3
V	Moderately pigmented	1·6
VI	Heavily pigmented	0·5

TABLE II—RESULTS OF INITIAL TREATMENT, AS DETERMINED QUANTITATIVELY (% SKIN CLEARED) AND QUALITATIVELY

Qualitative criterion	% clearing of affected skin	No. of patients
Worse	. .	28 *(0·9%)*
No change	. .	53 *(1·7%)*
Minimal improvement	35·1±16·5	91 *(2·9%)*
Definite improvement	65·6±15·3	179 *(5·7%)*
Marked improvement	87·0± 9·4	741 *(23·6%)*
Complete clearing	97·0± 6·3	2044 *(65·2%)*

Statistical Methods

Non-parametric methods were used and data are recorded as mean ± SD (see below). For most calculations we used the Wilcoxon signed rank test, the U test, or the Kruskal-Wallis test. Significance was defined as $p \leqslant 0{\cdot}05$.

Where possible our findings were compared with the results of the U.S. Cooperative Study (USCCT).[10] Because most of our data were non-symmetrically distributed (though occasionally approaching a gaussian distribution after log-transformation) arithmetic means do not represent absolutely reliable data, but we had to replace medians by means ± SD in table VI to permit a comparison of the two studies. Standard deviations not reported by Melski et al.[10] were calculated from their published data; they were approximately 85% of means and thus of the same order of magnitude as standard deviations in our study.

Results

CLEARING PHASE

The response evaluated by percentage of cleared skin, correlated well with response judged qualitatively ($r^2 = 0{\cdot}920$), as table II shows. Complete data on clearing were available for 3136 patients (table III). The average number of treatments required was twenty, clearing taking 37 days and a cumulative UVA dose of 96 J/cm^2; the average UVA dose increment from the first to the last dose during the clearing phase was 5·5 J/cm^2 (from 2·0 to 7·5 J/cm^2).

Withdrawal of PUVA

PUVA was discontinued in 231 (7·3%) patients during the clearing phase with treatment results worse than marked improvement. This was because of failure to clear (9·7%), side-effects (28·1%), or for reasons (58·4%) unrelated to treatment such as transport problems, holidays, and cost. In 528 patients (16·7%) PUVA was discontinued at the end of the clearing phase, mainly because of reasons unrelated to treatment. These patients were not followed up.

No relationship could be found between the duration of the clearing phase and the age of the patients or the extent of body

TABLE III—SUMMARY OF RESULTS OF INITIAL TREATMENT (3136 PATIENTS)

—	No.
Treatment response better than marked improvement	2785 *(88·8%)*
Exposures required for clearing	20*
Duration of treatment required for clearing	5·3 wk*
Total cumulative dose required for clearing	96·0 J/cm^2*

*Medians.

TABLE IV—SKIN TYPES, TREATMENT MODALITIES, AND RESULTS

Skin type	No. of patients	UVA dose (J/cm²)			No. of treatments	Duration of treatment (days)	% improvement of lesions	PUVA discontinued because of:	
		First	Last	Total				Failure	Side-effects
I	113	1·5	4·6	59	20	36·5	91·6±14·1	5·6%	6·5%
II	875	1·5	7·0	90	20	37	92·5±13·0	2·8%	3·5%
III	1563	2·0	8·0	99	19	36	92·3±14·6	2·5%	1·8%
IV	436	2·0	8·2	114	20	38	92·5±14·2	2·6%	1·7%
V	49	2·5	9·0	126	20	46·5	89·5±13·5	2·0%	..
VI	14	3·0	10·0	207	25	54	98·5±5·6	.	..
	p	<0·001	<0·001	<0·001	NS	<0·05*	NS	<0·05†	<0·01‡

*For (I–IV) *v* (V+VI). †For I *v* III. ‡For (I+II) *v* (III+IV).

involvement, or between the degree of improvement and either cumulative dose of UVA or magnitude of the first and last single UVA dose or duration of clearing phase.

Skin Type

Comparing the initial and last doses of UVA delivered to patients with skin types I–VI reveals that the greater the sensitivity to phototoxic reactions the smaller the initial, final and cumulative UVA doses required for clearing. Although the final UVA dose was 3 or 4 times greater than the initial one in all skin type groups, the total UVA doses of skin types II, III, and IV (which comprised 95% of all patients) were surprisingly close (90–114 J/cm²). Significant differences in total UVA doses were found only for skin types I and V–VI when these were compared with types II—IV (table IV). The numbers of treatments required for clearance was much the same. In most cases the clearing phase lasted about 5 weeks. Treatment failures or dropouts due to side-effects were similar in frequency for all skin types except type I, where they were considerably higher (table IV).

Type of Psoriasis

The degree of improvement did not differ with the type of psoriasis (table V). However, the failure rate of patients with psoriatic erythroderma was significantly higher (14%) than that in patients with other types of psoriasis, where it ranged from 2 to 3%.

Probably as a consequence of the higher sensitivity to phototoxic reactions of the patients with pustular psoriasis and psoriatic erythroderma the first and last single doses of UVA were considerably lower in these patients than in patients with guttate of plaque psoriasis. Table V suggests that pustular psoriasis requires lower UVA doses and fewer treatments than do psoriatic erythroderma, guttate psoriasis, and plaque psoriasis.

Comparison with U.S. Study

The duration of the clearing phase was approximately twice as long in the U.S. study[10] than in the European trial, despite the fact that in both studies a comparable number of treatments had led to the same degree of improvement (table VI. In the U.S. study the total UVA dose required for clearing was more than twice as high and the last single UVA doses differed by about 90%. These differences were especially striking for psoriatic erythroderma.

Chi-square analysis of skin types in the two studies reveals significant differences ($p \leqslant 0{\cdot}001$). However, calculation of the weighted average of the differences of skin type frequencies, using the increase in dose with skin type as

TABLE V—TYPE OF PSORIASIS, TREATMENT MODALITIES, AND IMPROVEMENT

Type	No. of cases	UVA dose (J/cm²)			No. of treatments	Duration of treatment (days)	Patients with marked improvement or complete clearing (%)
		First	Last	Total			
Pustular	30	1·5	3·7	46·0	17·5	30·5	81·3
Erythrodermic	49	1·5	5·0	66·5	18·0	41·0	76·1
Guttate	303	2·0	8·0	85·0	19·0	35·0	90·4
Plaque	2749	2·0	7·8	98·0	20·0	37·0	88·7
p	..	⩽0·05*	⩽0·001*	⩽0·001†	⩽0·001†	NS	NS

*For (pustular + erythrodermic) *v* (guttate + plaque).
†(pustular) v (erythrodermic) *v* (guttate) v (plaque).

TABLE VI—COMPARISON BETWEEN U.S. COOPERATIVE CLINICAL TRIAL (USCCT) AND EUROPEAN STUDY (EPS)*

Type of psoriasis	No. of patients†		Total dose (J/cm²)		No. of treatments		Duration of treatment (wk)		Last single dose (J/cm²)	
	USCCT	EPS	USCCT	EPS	USCCT	EPS	USCCT	EPS	USCCT	EPS
Guttate	122	208	208	91·0±67·9	20·3	17·6±8·2	9·8	5·4±3·9	13·2	7·1±3·7
Plaque	831	1789	251	106·4±88·9	23·6	19·3±8·7	11·8	5·8±3·6	14·3	7·4±3·7
Erythrodermic	25	28	368	94·2±101·1	31·6	19·8±9·1	16·4	6·2±4·2	13·2	5·7±3·1
Pustular	..	32	..	51·8±43·6	..	14·5±6·8	..	3·5±1·9	..	4·9±2·1

*For USCCT standard deviations were not given. In the EPS medians have been replaced, in this table, by arithmetic means with standard deviations in order to provide comparable data.
†Based on patients cleared completely and for whom data for comparison were available.

TABLE VII—MAINTENANCE TREATMENT: CONDITION OF PATIENTS AT TIME OF EVALUATION*

Group†	No. of patients	Duration of treatment (wk)	Duration of follow-up (wk)	Duration of remission (wk)	Remaining % of improvement
Patients without relapse (777):					
A	64	—	49	49	99
B	320	21	34	55	99
C	393	32	—	32	95
Patients with relapse (1056):					
A	164	—	32	32	58
B	133	11	23	34	60
C	759	22	—	22	70

*Only for patients for whom complete data are available. 90 patients failed to clear during initial treatment; in 708 patients initial treatment was discontinued due to side effects (78) and due to personal reasons not related to therapy (630). In 544 patients follow-up data are missing.
†A no maintenance therapy; B limited maintenance therapy; C continuous maintenance therapy.

weight, shows that the differences of UVA doses which may be due to different skin types should be less than 25%. Thus, the dissimilar distribution of skin types in both studies cannot account for the striking discrepancy in the total cumulative doses of UVA in the European and U.S. cooperative studies.

MAINTENANCE PHASE

1152 patients (group C) had received continuous maintenance therapy; after 32 weeks 393 (34%) were still free of a recurrence. No recurrences were noted in 320 (71%) of the 453 patients (group B) who had received limited maintenance therapy for 21 weeks and were evaluated after another 34 weeks. However, in the remaining 66% of group C a relapse was seen at a median of 22 weeks, and in group B the 29% relapse rate was recorded 23 weeks from the end of 11 weeks' (median) treatment (table VII). 228 patients (group A) did not receive maintenance therapy at all and 64 (28%) were still free of disease after 49 weeks, whereas the other 72% had a recurrence, after 32 weeks.

Groups A (no maintenance) and C (continuous maintenance) were compared, and the probability that a patient would remain in remission was calculated by life-table techniques.[12,13] Fig. 2 shows that within a follow-up period of 80 weeks the chance that a patient will remain in remission is

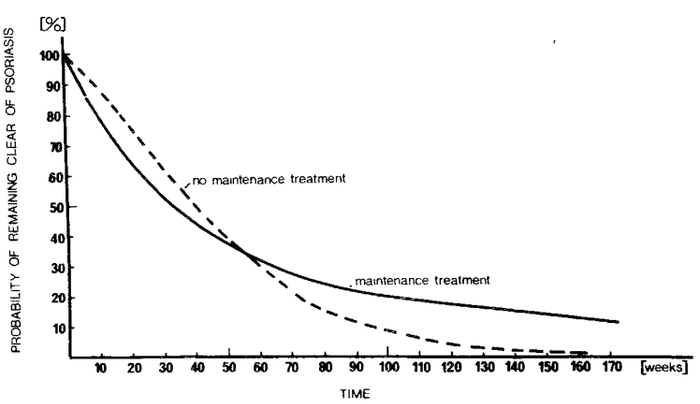

Fig. 2—Actuarial calculation of remission rates in patients without and with continuous maintenance treatment.

almost the same with or without maintenance therapy; however, for longer periods of time patients with continuous maintenance therapy have a greater chance of remaining free of psoriasis than patients without treatment. This, however, was seen only in 20% of the patients.

The severity of recurrences was different in the maintenance groups studied (table VII). In patients of group A the recurrence reduced the degree of improvement achieved by clearing phase treatment to 58%, whereas in group C this reduction was less (30%). These data suggest that whereas maintenance therapy fails to prevent a recurrence it does reduce its severity.

Recurrences were significantly more frequent in those patients who had had chronic persistent psoriasis during the two years before PUVA ($p \leqslant 0 \cdot 001$) as compared to patients with a variable course before initiation of PUVA therapy, and recurrences were significantly more common in those patients who had required longer periods of time to clear ($p \leqslant 0 \cdot 0001$). On the other hand, type of psoriasis and skin type were not related to the frequency of recurrence.

SIDE EFFECTS

Table VIII lists the side effects observed in 3175 patients. The most common were erythema (32%), pruritus (26%), and nausea (13%). As expected, patients with high sensitivity to

TABLE VIII—SIDE-EFFECTS OF PUVA TREATMENT (3175 PATIENTS)

Side-effect	Frequency (%)	Effect of side-effects on treatment (%): Discontinuation*	Interruption in clearing phase	Interruption in maintenance phase
Erythema	32·38	1·68	6·73	0·30
Nausea	13·45	0·59	1·45	0·30
Pruritus	25·58	1·38	2·86	0·36
Headache	1·95	0·10	0·13	0·12
Köbner reaction	1·96	0·16	0·46	0·06

*During clearing and/or maintenance phase.

phototoxic reactions (low MPD) showed a significantly higher incidence of erythema ($p < 0 \cdot 01$) and of pruritus and Koebner reactions than patients with a lower sensitivity. 7 patients acquired acute conjunctivitis due to accidental exposure to sunlight without appropriate eye protection during the hours of photosensitivity; these changes were reversible.

LABORATORY DATA

Complete data were available from seven centres. Since each centre used its own laboratory standards and normal ranges, statistical evaluation was done by sign test on the last and the first results for each patient. No significant changes were found for any of the laboratory tests (table IX).

Discussion

The results of this multicentre trial in 3175 patients with severe widespread psoriasis confirm the impressive response of psoriasis to photochemotherapy. A clearing rate of 88·8% was achieved, requiring twenty treatments and 37 days; the median total UVA dose needed was 96 J/cm^2, for all skin types and psoriasis types combined.

Comparison of the results of the clearing phase with those reported for the U.S. Cooperative Clinical Trial[10] (USCCT)

TABLE IX—LABORATORY DATA:SIGN TEST* FOR LAST MINUS FIRST LABORATORY VALUE

Test	Change		
	Negative	None	Positive
WBC count	169	11	193
RBC count	174	6	176
Blood glucose	200	22	211
SGOT	285	57	256
SGPT	235	105	265
LDH	196	15	221
Alkaline phosphatase	287	29	282
Serum creatinine	187	102	225
Serum uric acid	214	13	186
Urine analysis	83	11	73

*All non-significant ($p>0\cdot05$).

shows that the duration of treatment was twice as long in the U.S. study even though the number of treatments required for clearing was much the same. Total UVA requirements were higher also, means being 249 J/cm^2 in the USCCT and 105 J/cm^2 in our study. The USCCT[10] used a rigid, slower, and more conservative treatment protocol: UVA doses were predetermined for the different skin types, treatments were given only two or three times a week and dose increments also followed a predetermined rigid schedule. By contrast, the European PUVA study used phototoxicity testing to determine the starting dose in nearly half of the patients, and the protocol provided for four treatments per week and rapid dose increments adjusted to the patients' response. The rationale of this approach was to clear the lesions before intense pigmentation raised the tolerance of skin to UV radiation. This approach not only saved time but also reduced the total UVA dose compared with the more rigid dosimetry of the USCCT. Long-term side-effects of photochemotherapy are probably related to total cumulative UVA dose.[15,16] So any treatment schedule which reduces this cumulative radiation load should make for safer PUVA therapy.

The object of maintenance therapy is to keep the patients in remission after clearing, and various regimens have been tested to determine the most effective and economic way of achieving this.[14-16] In one of the earlier studies more than 80% of the patients were kept in remission by continuous maintenance therapy[2] and in the USCCT and in a large single centre study from Europe[16] significantly higher recurrence rates were observed in patients not given maintenance therapy. The best results to date have been achieved by schedule in which the frequency of maintenance treatments is adjusted to the patient's needs,[15,16] but concern has been growing that maintenance treatments given to patients over very long periods of time may result in unjustifiably large cumulative radiation loads.[17,18] Surprisingly, the European multicentre study shows that the probability of a patient remaining in remission over a period of 80 weeks is almost the same whether maintenance treatment is given or not. We cannot explain the discrepancy between this finding and earlier data.[10,15,16] If maintenance therapy does indeed not, in most patients, influence the course of psoriasis after clearing—and our calculations seem to indicate that this is so radical revision of current strategies in the management of severe psoriasis may be necessary. PUVA could be discontinued at the end of the clearing phase to be resumed only if a major recurrence occurs. This will result in a big reduction in total UVA energy load.

PUVA therapy does not harm internal organs,[10,15,16] and our laboratory data confirm this.

Lately, there has been concern over the long-term side effects of prolonged PUVA.[17,18] Premature, UV-induced ageing is one of these concerns and, since psoralens interact with DNA under the influence of light[19] and since psoralen-UVA has proved mutagenic in unicellular organisms,[20,21] the oncogenic potential of PUVA therapy has been raised.[22-24] Although our study provides no data relevant to these questions, it does contain two important messages directed towards the desirable reduction of possible long-term hazards. Firstly, the total UVA energy requirements for clearing psoriasis depend on the treatment schedule used and can be kept low if an individual approach aimed at rapid clearing of psoriatic lesions is used. Secondly maintenance therapy may not prevent recurrences in the long term and may thus not be necessary in most cases.

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REFERENCES

1. Parrish JA, Fitzpatrick TB, Tanenbaum L, Pathak MA. Photochemotherapy of psoriasis with oral methoxsalen and long wave ultraviolet light. *N Engl J Med* 1974; **291:** 1207–11.
2. Wolff K, Hönigsmann H, Gschnait F, Konrad K. Photochemotherapie bei Psoriasis: Klinische Erfahrungen bei 152 Patienten. *Dt Med Wschr* 1975; **100:** 2471–77.
3. Wolff K, Fitzpatrick TB, Parrish JA, Gschnait F, Gilchrest B, Hönigsmann H, Pathak MA, Tanenbaum L, Photochemotherapy with orally administered methoxsalen. *Arch Derm* 1976; **112:** 943–50.
4. Swanbeck G, Thyresson-Hök M, Bredberg A, Lambert B, Treatment of psoriasis with oral psoralens and long-wave ultraviolet light: Therapeutic results and cytogenetic hazards. *Acta Dermatovener* 1975; **55:** 367–76.
5. Hofmann C, Plewig G, Braun-Falco O. Klinische Erfahrungen mit der 8-Methoxypsoralen-UVA-Therapie (Photochemotherapie) bei Psoriasis. *Hautarzt* 1976; **27:** 588–94.
6. Lakshmipathi T, Gould PW, Mackenzie LA, Johnson BE, Fraim-Bell W. Photochemotherapy in the treatment of psoriasis. *Br J Derm* 1977; **96:** 587–94.
7. Weissmann K, Howitz J, Bro-Jørgensen A. Treatment of resistant psoriasis with oral 8-methoxypsoralen and longwave ultraviolet light (PUVA). *Acta Dermatovener* 1977; **57:** 73–76.
8. Roenigk HH, Martin JS. Photochemotherapy for psoriasis. *Arch Derm* 1977; **113:** 1667–70.
9. Thivolet J, Ortonne JP, Chouvet B. La photochimiotherapie du psoriasis: Technique et resultats. *Lyon Méd* 1977; **237:** 87–92.
10. Melski JW, Tanenbaum L, Parrish JA, Fitzpatrick TB, Bleich HL et al. Oral methoxsalen photochemotherapy for the treatment of psoriasis: a cooperative clinical trial. *J Invest Derm* 1977; **68:** 328–35.
11. Wolff K, Gschnait F, Hönigsmann H, Konrad K, Parrish JA, Fitzpatrick TB. Phototesting and dosimetry for photochemotherapy. *Br J Derm* 1977; **96:** 1–10.
12. VICC, ed. Klassifizierung der Malignen Tumore and allgemeine Regeln zur Anwendung des TNM-Systems. Berlin: Springer, 1976.
13. Berkson J, Gage RP. Survival curve for cancer patients following treatment. *J Am Stat Ass* 1952; **47:** 501.
14. Schmoll M, Henseler T, Christophers E. Evaluation of PUVA, topical cortico-steroids and the combination of both in the treatment of psoriasis. *Br J Derm* 1978; **99:** 693–701.
15. Wolff K, Hönigsmann H. Clinical aspects of photochemotherapy. *Pharmacol Ther* (in press).
16. Wolff K. PUVA 1979. In: Braun-Falco O, Wolff HH, ed. Klinik und Praxis, Fortschritte der praktischen Dermatologie und Venerologie: Vol IX. Berlin: Springer, 1979: 129–38.
17. Fitzpatrick TB, Parrish JA, Pathak MA, Tanenbaum L. The risk and benefits of oral PUVA photochemotherapy of psoriasis. In: Farber EM, Cox AJ, eds. Psoriasis. New York: Yorke Medical Books, 1977: 320–27.
18. Farber EM, Abel EA, Schaefer H. PUVA appraisal: Comment. *Br J Derm* 1978; **99:** 715–17.
19. Rodighiero G, Dall'Acqua F. Biochemical and medical aspects of psoralens. *Photochem Photobiol* 1976; **24:** 647–53.
20. Igali S, Bridges BF, Ashwood-Smith MJ, Scott BR. Mutagenesis in *Escherichia coli*. *Mutat Res* 1970; **9:** 21–30.
21. Swanbeck G, Thyresson M. Induction of respiration-deficient mutants in yeasts by psoralen and light. *J Invest Derm* 1974; **63:** 242–44.
22. Stern RS, Thibodeau LA, Kleinerman RA, Parrish JA, Fitzpatrick TB et al. Risk of cutaneous carcinoma in patients treated with oral methoxsalen photochemotherapy for psoriasis. *N Engl J Med* 1979; **300:** 809–13.
23. Halprin KM. Psoriasis, skin cancer and PUVA. *J Am Acad Derm* 1980; **2:** 334–37.
24. Hönigsmann H, Wolff K, Gschnait F, Brenner W, Jaschke E. Keratoses and non-melanoma skin tumors in long-term photochemotherapy (PUVA). *J Am Acad Derm* 1980; **3:** 406–14.