The Time-Course of Psoralen Ultraviolet A (PUVA) Erythema

Sally H. Ibbotson and Peter M. Farr

Department of Dermatology, Royal Victoria Infirmary, Newcastle upon Tyne, U.K.

The time-course for the development of ultraviolet A-induced erythema in psoralen-sensitized skin differs from that caused by ultraviolet B or ultraviolet A but objective data are not available. During psoralen ultraviolet A therapy, the minimal phototoxic dose is determined 72 h after exposure, when psoralen ultraviolet A erythema is assumed to be maximal. This measurement is of fundamental importance in optimizing the therapeutic regimen. We examined a detailed time-course for development of psoralen ultraviolet A erythema in 16 subjects. The erythemal responses to ultraviolet B, ultraviolet A and psoralen ultraviolet A were assessed visually and using a reflectance device. Ultraviolet B erythema was maximal 24 h after exposure compared with subsequent time-points. Psoralen ultraviolet A erythema was evident at 24 h, with reduction in the median ultraviolet A minimal erythema dose from 14 to 5 J per cm^2 in the presence of psoralen ($p < 0.01$; $n = 9$). Peak psoralen ultraviolet A erythema, assessed by minimal phototoxic dose, did not occur until 96 h or later in 75% of subjects. Using individual dose–response curves, we determined that only 67% of mean maximum psoralen ultraviolet A erythemal intensity had developed by 72 h. Furthermore, at the time of maximal erythema, the slope of the psoralen ultraviolet A dose–response curve was approximately 2-fold shallower than that for ultraviolet B-induced erythema. If assessment of psoralen ultraviolet A erythemal sensitivity had been made at 96 h instead of the conventional 72 h time-point, peak erythemal responses would not have been missed in any of the subjects. Based on these findings, it seems appropriate to consider whether psoralen ultraviolet A minimal phototoxic dose measurements should be performed 96 h after exposure. ***Key words: dose-response curve/irradiation monochromator/minimal phototoxic dose/peak erythema/slope. J Invest Dermatol 113:346–349, 1999***

During psoralen and ultraviolet A (PUVA) therapy, for example when treating psoriasis, it is the potential for erythema development in nonlesional skin that limits the dose of UVA that can be given at each treatment. The time-course and dose–response characteristics of PUVA erythema are therefore of fundamental importance when attempting to design an optimal treatment regimen.

The time-course for development of UVA-induced erythema in psoralen-sensitized skin is known to be different from that resulting from exposure to UVB or UVA alone. PUVA erythema is said to appear at 24 h after exposure and peak between 48 and 72 h after irradiation (Fitzpatrick *et al*, 1955; Parrish, 1976; Pathak *et al*, 1976; Frain-Bell, 1985; Gupta and Anderson, 1987), although there are little experimental data to support this. In this study we report the first detailed examination of the time-course for the development of PUVA erythema.

MATERIALS AND METHODS

Subjects We studied 16 healthy adults (12 female; median age 33 y; range 21–74) of skin types I ($n = 2$), II ($n = 11$), and III ($n = 3$). None of the subjects had a history of abnormal sunlight sensitivity, and none were receiving medication or UV therapy. The responses of each subject to UVB, UVA, and PUVA were measured on the untanned normal skin of the mid-back.

Photoirradiation apparatus An irradiation monochromator (Diffey *et al*, 1984a), optically coupled to a liquid-filled light guide, was used to achieve a uniform irradiation field of 1 cm diameter.

UVB phototesting Seven sites on one side of the back were exposed to a geometric series of doses at 300 ± 5 nm (dose range 10–80 mJ per cm^2, increment factor 1.4).

UVA phototesting Nine sites on the opposite side of the back were exposed to a geometric series of doses at 350 ± 30 nm (dose range 1.7–28 J per cm^2, increment factor 1.4).

PUVA phototesting Two hours after ingestion of methoxsalen (Crawford Pharmaceuticals, Milton Keynes, U.K.) at a standard dose of 25 mg per m^2, calculated to the nearest 10 mg (Sakuntabhai *et al*, 1995), 11 sites adjacent to the UVA test sites, were exposed to a geometric series of doses at 350 ± 30 nm (dose range 0.45–14 J per cm^2, increment factor 1.4). Under these conditions, the spectral power distribution of the irradiation monochromator approximates that of a typical PUVA-type UVA fluorescent lamp (e.g., Philips TL-09) (Sakuntabhai *et al*, 1993a). For comparison, 0.28% of the UV energy is less than or equal to 320 nm (UVB) for the monochromator and 1.03% for the TL-09 source. The high irradiance achieved with the irradiation monochromator (≈120 mW per cm^2), however, allowed considerably shorter exposure times than would have been required had a conventional PUVA lamp been used for phototesting.

Erythemal response The minimal erythema dose (MED), or the minimal phototoxic dose (MPD), in the presence of psoralen sensitization,

Manuscript received November 9, 1998; revised February 26, 1999; accepted for publication June 3, 1999.

Reprint requests to: Dr. Sally Ibbotson, Department of Photobiology, Dermatology Department, Ninewells Hospital & Medical School, Dundee, DD1 9SY, U.K. E-mail: S.H.Ibbotson@dundee.ac.uk

Abbreviation: MPD, minimal phototoxic dose.

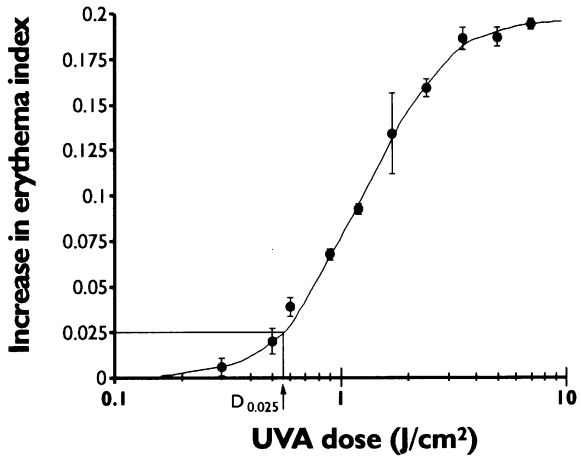

Figure 1. An example of a dose–response curve for PUVA erythema in one subject. Each point represents the mean ± SD increase (ΔE) in erythema index compared with unirradiated sites. The line drawn through the data points is the logit function obtained by regression analysis. The $D_{0.025}$ (as indicated) is the dose of radiation required to cause an increase in erythema index of 0.025.

was defined as the smallest dose of radiation to achieve faint but easily discernible erythema. The MED and MPD values were judged visually at 24, 48, 72, 96, 144, and 168 h (7 d) after irradiation. Any increase in melanin pigmentation was detected by blanching the irradiated skin. At all time-points until increased pigmentation was detected, erythema was also measured objectively using a reflectance instrument (Diffey *et al*, 1984b). Erythema measurements were made in triplicate at each irradiated site, and at adjacent nonirradiated sites. In each subject, for each quality of radiation (UVB, UVA and PUVA), and at each time of measurement (until pigmentation was apparent), the increase (ΔE) in mean erythema index compared with nonirradiated skin was plotted against the logarithm of the UV radiation dose. A logit function was fitted to the data to construct dose–response curves (Diffey and Farr, 1991) for the different wavebands, at each time-point, and in each subject. The dose of radiation required to cause an increase in erythema index of 0.025 ($D_{0.025}$), clinically equivalent to just perceptible erythema (MED/MPD), and also the maximum slope, was calculated for each dose–response curve (**Fig 1**).

Statistical analysis Values are given as median (range). The significance of the data was determined by Wilcoxon-matched-pairs signed-rank test.

RESULTS

Time-course UVB responses were measured in eight subjects. UVB erythema was maximal (lowest MED and $D_{0.025}$ values) in all subjects at the first assessment 24 h after exposure, compared with subsequent time-points, with the intensity of erythema subsequently declining at a variable rate (**Fig 2**). UVA erythemal responses were measured in nine subjects. The MED was recorded at 24 h in all cases, but too few of the irradiated sites were erythematous to allow dose–response curves to be constructed. Pigmentation was apparent at the UVA irradiated sites in the majority of subjects at 72 h and at subsequent time-points. PUVA erythema responses were measured in nine subjects from 24 to 96 h, and in a further seven subjects at 72 and 96 h. Erythema was apparent 24 h after irradiation, with the MPD and $D_{0.025}$ values then decreasing stepwise, reaching a minimum at 96 h (**Fig 3**). Measurements at subsequent time-points of 144 h (n = 6) and 168 h (n = 12) showed no further overall significant increase in erythemal intensity, although the 168 h MPD value in one subject was lower than that at 96 h. Assessment of erythema at 144 h or beyond, however, was interpreted with caution because of the development of pigmentation at PUVA irradiated sites.

Effect of psoralen 24 h after UVA irradiation At 24 h after exposure, in the presence of methoxsalen, the median UVA minimal

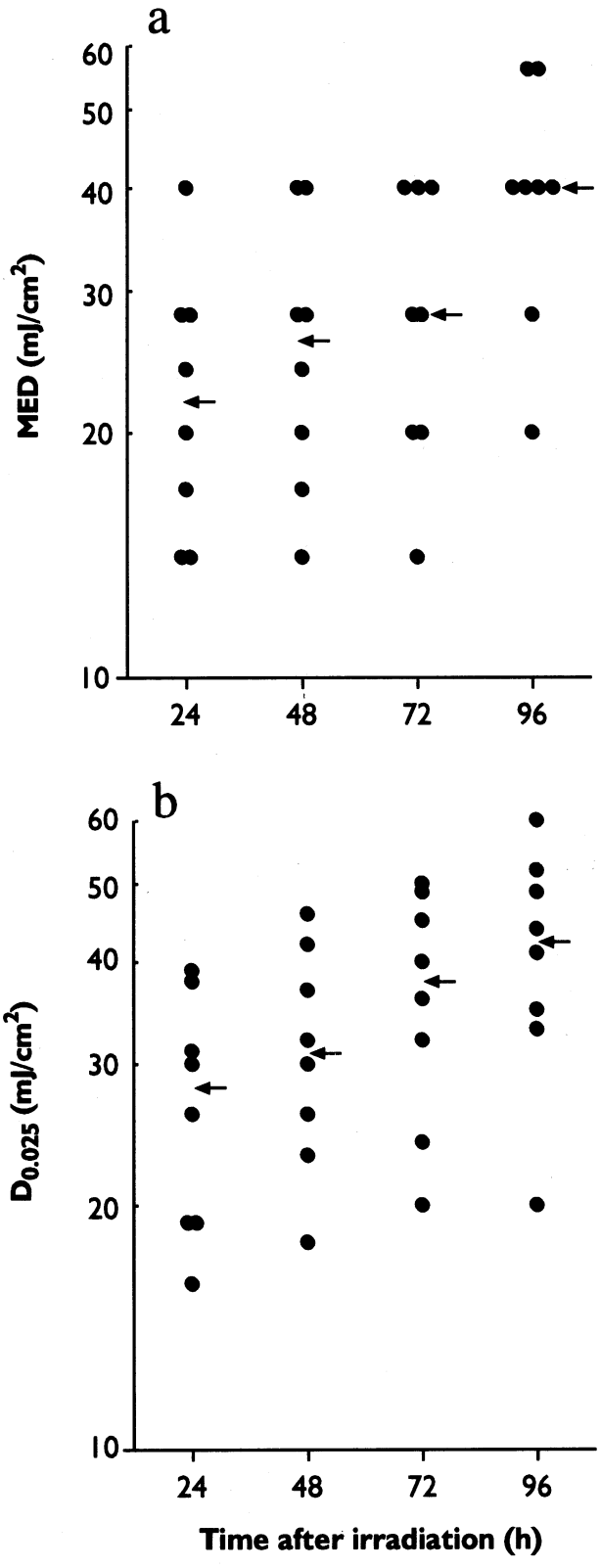

Figure 2. Maximal UVB erythema had been reached 24 h after irradiation. (*a*) The UVB MED was at a minimum 24 h after exposure compared with subsequent time-points (median 22 mJ per cm^2; range 14–40). (*b*) The $D_{0.025}$ was also at a minimum at 24 h [28 (16–39) mJ per cm^2] compared with values at 48 h [31 (18–46) mJ per cm^2] or subsequent time-points (p = 0.01; n = 8). The median values at each time-point are indicated by *arrows*.

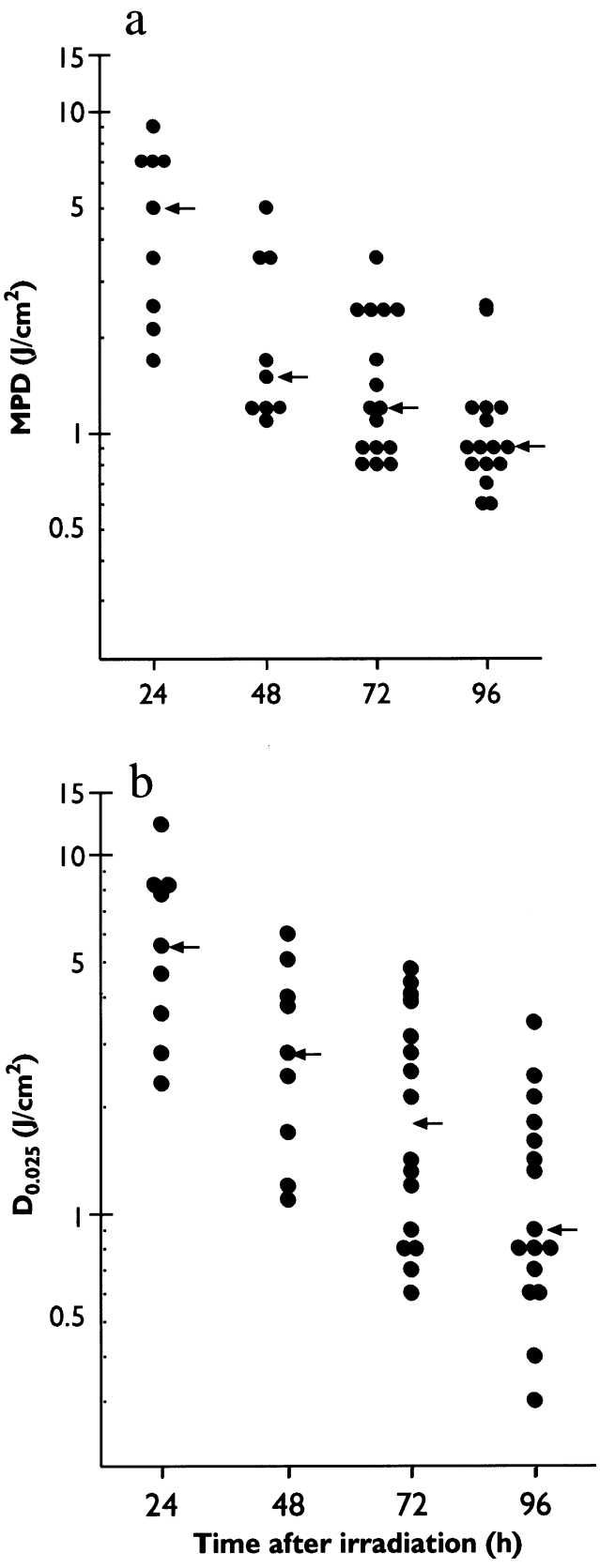

Figure 3. PUVA erythema was maximal 96 h after irradiation. (*a*) The MPD at 96 h [median 0.9 (range 0.6–2.5) J per cm^2] was significantly lower than that at 72 h [1.2 (0.8–3.5) J per cm^2] ($p < 0.01$; $n = 16$). (*b*) The median $D_{0.025}$ was also at a minimum at 96 h [0.9 (0.3–3.4) J per cm^2] and was significantly lower than that at 72 h [1.8 (0.6–4.8) J per cm^2] ($p < 0.01$; $n = 16$). The median values at each time-point are indicated by *arrows*.

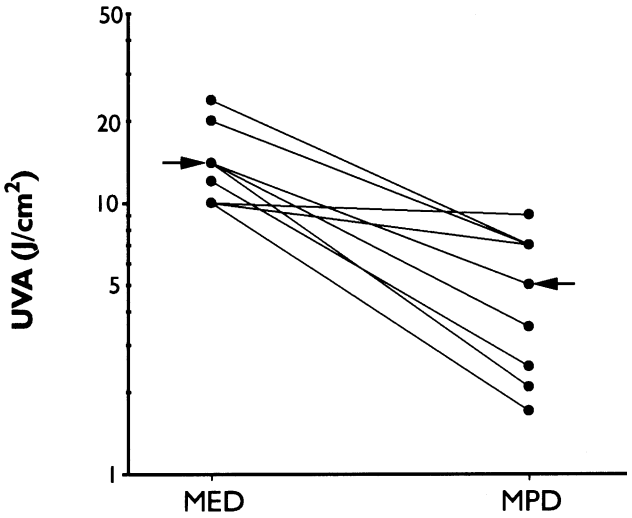

Figure 4. The effect of psoralen was apparent 24 h after irradiation. The median UVA MED (no methoxsalen) was reduced from 14 (range 10–24) J per cm^2 to an MPD of 5 (1.7–9) J per cm^2 in the presence of methoxsalen, 24 h after exposure ($p < 0.01$; $n = 9$). The median UVA MED and PUVA MPD values are indicated by *arrows*.

erythema response was reduced from 14 (range 10–24) J per cm^2 to 5 (1.7–9) J per cm^2 ($p < 0.01$; $n = 9$) (**Fig 4**).

Dose–response curves for UVB and PUVA erythema The maximum slope of the dose–response was significantly steeper for erythema induced by UVB (measured at 24 h) (median slope 411, range 262–826) compared with erythema induced by PUVA measured at 72 h (median 227, range 90–407) or 96 h (median 225, range 76–460) ($p < 0.05$; $n = 8$).

DISCUSSION

Contrary to previous reports (Fitzpatrick *et al*, 1955) we have shown that PUVA erythema is well-established 24 h after exposure, with the UVA dose required to achieve a minimal erythema response reduced, on average, by 64% in the presence of psoralen. UVB erythema was maximal at the first assessment time, 24 h after irradiation, compared with subsequent measurements. This concurs with the findings of previous work in which peak UVB erythema had been reached by 24 h (Farr *et al*, 1988). Similarly, UVA erythema was at a peak at 24 h, with the reaction either fading or being replaced by pigmentation at subsequent time-points. In contrast, the intensity of PUVA erythema increased at each time-point, first reaching a maximum (i.e., lowest minimal phototoxic dose) by 72 h in four of 16 (25%) subjects and by 96 h or later, in the remainder (75%). If the erythema measurements had been made at 96 h, peak erythemal responses, based on MPD measurements, would not have been missed in any of the subjects studied. Observations up to 7 d after exposure showed no further significant increase in sensitivity.

Minimal erythema is widely used as an end-point for the assessment of erythema in both the clinical and research setting; however, it is somewhat subjective, and imprecise. Also, it may be surprisingly difficult to judge which site, in a series exposed to increasing doses of radiation, is the first to show "just detectable erythema". This is even more problematic when small dose increments are used in an attempt to improve the precision of the MED/MPD measurement. In order to overcome these problems we made objective reflectance measurements of the intensity of erythema at each irradiated site, in addition to the visual assessment of minimal erythema. A logit function was computer-fitted to these data (Diffey and Farr, 1991), resulting in an UV-dose erythema–response curve for each patient, at each time of observation, for both PUVA and UVB. From these individual curves we chose to calculate the dose of radiation required to cause an increase in

erythema index of 0.025 ($D_{0.025}$). This degree of erythema is approximately equivalent to that which can be just detected visually (Diffey and Farr, 1991), and therefore the $D_{0.025}$ can be considered as an objective equivalent of the MED or MPD. The low MED, MPD, and $D_{0.025}$ values found in this study reflected the skin type distribution of the volunteers studied (81% were of skin types I and II). The $D_{0.025}$ measurements confirmed the prolonged time-course of PUVA erythema. If the 96 h erythemal response is considered to be 100%, then the mean intensity of PUVA erythema at other time-points would be 31% at 24 h, 59% at 48 h, and 67% at 72 h.

In addition to the $D_{0.025}$, we also calculated the maximum slope for each dose–response curve. This parameter gives an indication of the rate at which the intensity of erythema increases once doses of radiation are used in excess of those required to produce minimal erythema. As might be expected, susceptibility to burning in the clinical setting is related to the steepness of an individual patient's erythema dose–response curve (Sakuntabhai *et al*, 1993b). We have confirmed our previous observation (Cox *et al*, 1989) that PUVA erythema has a shallower dose–response curve than UVB erythema (by a factor of $\approx$ 2) and have shown that this difference is maintained even at the time of maximum erythema determined in this study (24 h for UVB and 96 h for PUVA).

Our results are at variance with previous reports (Fitzpatrick *et al*, 1955; Parrish, 1976; Pathak *et al*, 1976; Morison *et al*, 1977; Wolff *et al*, 1977; Frain-Bell, 1985; Gupta and Anderson, 1987; British Photodermatology Group, 1994) which suggest that PUVA erythema reaches a maximum at about 48–72 h after irradiation. Statements on the time-course of PUVA erythema, however, are usually unreferenced and very little experimental data have been published. Likewise, it is often stated without supporting evidence (Morison *et al*, 1977; Parrish *et al*, 1982; Gupta and Anderson, 1987) that the erythema dose–response curve for PUVA is steep whereas, in fact, our results show that it is considerably shallower than that for UVB erythema.

During PUVA therapy, for example when treating psoriasis, it is the potential for erythema development in nonlesional skin that limits the dose of UVA that can be given at each treatment (Speight and Farr, 1994). The time-course and dose–response characteristics of PUVA erythema are therefore of fundamental importance. It is recommended (British Photodermatology Group, 1994) that the UVA dose given at the start of PUVA therapy should be based on the MPD (for example, 70% of the MPD). The MPD is conventionally measured 72 h after irradiation (Wolff *et al*, 1977; Carabott and Hawk, 1989; Sakuntabhai *et al*, 1993b), at a time when our results show that the response is not maximal. Using the dose–response curves it was possible to model the effect of giving 70% of the MPD measured at different times after irradiation. For example, we could calculate for each subject the intensity of erythema that would have resulted at 48 h and at 96 h from a UVA dose of 70% of the 72 h $D_{0.025}$. If the erythemal response had been assessed at the conventional time, 72 h after first exposure, and 70% of this dose had been given as first treatment, 10 (63%) of the subjects would have developed visible erythema (i.e., $\Delta E > 0.025$) at some time between 48 and 96 h. If the MPD had been assessed at 96 h and 70% of this dose given as first treatment, however, only one subject (6%) would have developed visible erythema at any time between 48 and 96 h. In the light of these findings it seems appropriate to consider whether the PUVA MPD assessment should be performed 96 h after first exposure and the dosage regimen based on this reading.

Our observations indicate that treatment given even as infrequently as twice weekly may incur the risk of development of cumulative erythema as the interval of 72 h will result in the patient being re-treated before maximal erythema from the previous exposure has occurred. Treatment intervals of 96 h or greater would minimize the risk of missed treatments due to the development of erythema, although therapeutic efficacy with this regimen would need to be examined.

Finally, it should be noted that our results apply to erythema induced after sensitization of the skin using methoxsalen given orally. The dose–response characteristics and time-course of erythema induced after topical application of psoralen may be quite different.

The contribution of Dr. Peter Kirkham in the early part of the study is gratefully acknowledged.

REFERENCES

British Photodermatology Group: British Photodermatology Group Guidelines for PUVA. *Br J Dermatol* 130:246–255, 1994

Carabott FM, Hawk JLM: A modified dosage schedule for increased efficiency in PUVA treatment of psoriasis. *Clin Exp Dermatol* 14:337–340, 1989

Cox NH, Farr PM, Diffey BL: Comparison of the dose–response relationship for psoralen-UVA erythema and UVB erythema. *Arch Dermatol* 125:1653–1657, 1989

Diffey BL, Farr PM: Quantitative aspects of ultraviolet erythema. *Clin Physiol Meas* 12:311–325, 1991

Diffey BL, Farr PM, Ive FA: The establishment and clinical value of a dermatological photobiology service in a district general hospital. *Br J Dermatol* 110:187–194, 1984a

Diffey BL, Oliver RJ, Farr PM: A portable instrument for quantifying erythema induced by ultraviolet radiation. *Br J Dermatol* 111:663–672, 1984b

Farr PM, Besag JE, Diffey BL: The time course of UVB and UVC erythema. *J Invest Dermatol* 91:454–457, 1988

Fitzpatrick TB, Hopkins CE, Blickenstaff DD, Swift S: Augmented pigmentation and other responses of normal human skin to solar radiation following oral administration of 8-methoxypsoralen. *J Invest Dermatol* 25:187–190, 1955

Frain-Bell W: Treatment. In: *Cutaneous Photobiology*. Oxford University Press, 1985:pp 170–202

Gupta AK, Anderson TF: Psoralen photochemotherapy. *J Am Acad Dermatol* 17:703–734, 1987

Morison WL, Paul BS, Parrish JA: The effects of indomethacin on long-wave ultraviolet-induced delayed erythema. *J Invest Dermatol* 68:130–133, 1977

Parrish JA: Methoxsalen-UV-A therapy of psoriasis. *J Invest Dermatol* 67:669–671, 1976

Parrish JA, Stern RS, Pathak MA, Fitzpatrick TB. Photochemotherapy of skin diseases. In: Regan JD, Parrish JA (eds). *The Science of Photomedicine*. New York: Plenum Press, 1982, pp 596–623

Pathak MA, Fitzpatrick TB, Parrish JA. Pharmacologic and molecular aspects of psoralen photochemotherapy. In: Farber EM, Cox AJ (eds). *Psoriasis: Proceedings of the Second International Symposium*. New York: Yorke Medical Books, 1976, pp 262–271

Sakuntabhai A, Farr PM, Diffey BL: PUVA erythemal sensitivity depends on plasma psoralen concentration and UVA sensitivity. *Br J Dermatol* 128:561–565, 1993a

Sakuntabhai A, Sharpe GR, Farr PM: Response of psoriasis to twice weekly PUVA. *Br J Dermatol* 128:166–171, 1993b

Sakuntabhai A, Diffey BL, Farr PM: Calculation of 8-methoxypsoralen dose according to body surface area in PUVA treatment. *Br J Dermatol* 133:919–923, 1995

Speight EL, Farr PM: Erythemal and therapeutic response of psoriasis to PUVA using high-dose UVA. *Br J Dermatol* 131:667–672, 1994

Wolff K, Gschnait F, Honigsmann H, Konrad K, Parrish JA, Fitzpatrick TB: Phototesting and dosimetry for photochemotherapy. *Br J Dermatol* 96:1–10, 1977