

INVESTIGATIVE REPORT

Towards Optimal Regimens for the UVB Phototherapy of Psoriasis: A Mathematical Model

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A mathematical model is described that predicts the response of psoriasis to a treatment course of UVB irradiation. The basis of the model is that UVB acts by a direct effect on keratinocytes and that cell cycle arrest is the major mode of action in the phototherapeutic response in psoriasis. Although it is unlikely that UVB causes resolution of psoriatic plaques through a single mechanism, the current model has been based on epidermal cell cycle arrest and entry into the terminal differentiation compartment because this is likely to be a significant rate-limiting factor in determining response to treatment. The model has been validated against results obtained from published clinical studies on narrowband (TL-01) UVB phototherapy for psoriasis. The principal outcomes of the model are that for a given erythema response, the number of exposures required for clearance is almost independent of the frequency with which patients attend for treatment and that the higher the exposure dose per treatment, the more rapidly will clearance result. The model has been used to suggest optimal regimens for the treatment of outpatients and inpatients.

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There have been several clinical studies conducted over many years that have been aimed at identifying efficient ways of treating psoriasis with UVB phototherapy by permuting variables such as treatment lamps, irradiation frequency and exposure increment. Conducting such studies is costly and generally involves recruiting tens of patients and duration of up to 1 year or more.

The purpose of this paper is to describe a mathematical model that predicts current outcomes in clearance time and which can be used to explore whether there might be more effective regimens for UVB phototherapy of psoriasis and so suggest further potentially beneficial clinical studies. Mathematical modelling is the process of constructing mathematical objects, such as a set of equations or a stochastic process, whose behaviour or properties correspond in

some way to a particular real-world system; in this case, the response of psoriasis to UVB irradiation.

UVB has many effects on skin, and these vary depending on whether the skin has been exposed on a single occasion, on multiple occasions over weeks (as in UVB treatment for psoriasis), or repetitively over many years. Whereas many studies have focused on alterations that occur following single doses of UVB to cells *in vitro* or in normal skin, few investigations have examined the consequences, in terms of variation in signalling pathways, of repeated UVB exposures in psoriatic skin *in vivo*. In the case of short-term UVB therapy for psoriasis, the effects that are likely to be beneficial in the treatment of this disorder include keratinocyte cycle arrest, induction of terminal differentiation, down-regulation of pro-inflammatory cytokine expression, and reduction in lymphocyte numbers within the affected skin (1).

It is well recognized that as psoriatic skin returns to normal following treatment by UVB (and other therapeutic modalities), there is a reduction in hyperproliferation and acanthosis seen histologically. Therefore, although it is unlikely that UVB causes resolution of psoriatic plaques through a single mechanism, the current mathematical model has been based on epidermal cell cycle arrest and entry into the terminal differentiation compartment, because this is likely to be a significant rate-limiting factor in determining response to treatment.

METHOD

The epidermis consists of two compartments: a germinative cell compartment and a differentiating cell compartment. Under steady-state conditions cells enter and leave the differentiated compartment at a constant rate, with a delay equal to the epidermal turnover time, which in psoriasis is estimated to be around 7 days (2). Published data on the cell cycle time (i.e. the interval between the mitosis of one germinative cell and the next division of its daughter cell) in psoriasis vary considerably, with values ranging from 28 h to >200 h (3). Probably the most reliable estimate is of the order of 50 h with an appreciable coefficient of variation (3–5).

The germinative keratinocytes are composed of two basic proliferative populations: cells containing the cycling compartment of the stem cell population and cells representing the transit amplifying cell population which has committed to differentiation but is still capable of proliferation (6). Implicit

in the model described below is that these two subpopulations are treated as a single population of proliferating stem cells and that cells are sensitive to UVB irradiation throughout their cell cycle.

The mathematical model described here is based on stochastic techniques, involving the use of random numbers and probability statistics to investigate problems. The use of these methods allows the investigation of complex systems, in this case the number of cells entering the differentiating cell compartment and used here as a surrogate for disease activity, than might otherwise be possible by conventional mathematical techniques.

The following steps summarize the approach to modelling the response of psoriasis to UVB phototherapy.

1. A large number (~100) of germinative cells are generated. Each germinative cell has a cycle time randomly assigned according to a normal distribution where the mean (± 1 SD) of the population of cells is 50 ± 10 h. Each cell is then randomly allocated (with a rectangular probability distribution) to some point within its cell cycle.
2. An iterative process commences whereby the population of germinative cells is examined at hourly intervals throughout 10 weeks of treatment. A germinative cell gives rise to a differentiating cell on passing through mitosis, and continues within its cycle. A differentiating cell is removed if its lifetime exceeds the epidermal turnover time of 7 days.
3. When the iteration time coincides with a treatment time (e.g. two, three or five times per week), a random number between 0 and 1 is generated for each germinative cell. If this number is greater than the 'survival fraction' of cells deemed to remain clonogenic after a single UVB irradiation, that specific germinative cell is inactivated and resorts to the G_0 phase (effectively inhibition of its nuclear DNA synthesis and mitosis). The survival fraction is the principal variable within the model and is estimated according to the chosen UVB exposure per irradiation (see below).
4. Finally, disease activity is taken to be proportional to the number of differentiating cells present at any time.

A computer program that performs these calculations is given in the Appendix.

RESULTS

Comparison with clinical studies

Low dose. While the model is applicable to either broadband or narrowband (311 nm) UVB phototherapy, only those studies in which narrowband lamps (TL-01) have been used will be considered, as they tend to be the more recent studies and are generally well designed. The results from a number of these published studies (7–12) are summarized in Table I. Broadly speaking, the studies indicate that two-thirds of the patients clear in 15–30 treatments over a period of 5–10 weeks with an exposure per treatment of ~1 MED (minimal erythema dose) and a cumulative UV dose of 10–40 J/cm^2 . Here the MED is not used as an 'exposure unit' but rather as an indicator of the biological consequence of UVB exposure. So the actual radiometric exposure, necessary to sustain a minimal erythema response, will increase throughout the course of treatment to compensate for the photoadaptive changes of hyperplasia and tanning that occur. Hence the UVB exposure resulting in just perceptible erythema (i.e. 1 MED) 8–24 h after irradiation will be less in terms of radiant exposure (in J/cm^2) at the start of treatment than the radiant exposure necessary to result in the same degree of erythema (again 1 MED) at some time into the treatment course.

Fig. 1 shows the fraction of differentiating cells remaining (or *disease activity*) following the start of phototherapy for treatment corresponding to five times per week (days 1–5), three times per week (days 1, 3 and 5) and twice per week (days 1 and 4), respectively. In calculating these curves, it was found that a survival fraction of between 0.85 and 0.95 (i.e. 85–95% of germinative cells remain clonogenic after a single UVB irradiation) was needed in order to derive clearance curves compatible with clinical observation. Choosing this fraction to be outside this range yielded clearance

Table I. Studies on TL-01 phototherapy for psoriasis. Median values for clearance or minimal residual activity

Study	No. of patients	Treatments per week	Increment	% clear	Treatments	J/cm^2	Weeks
Wainwright et al. (7)*	20	3	40%	90	20.5	18	7.5
			20%		21	16	7.5
Dawe et al. (8)*	21	3	20%	76	17	9	5.7
		5			23.5	–	5
Hofer et al. (9)*	13	3–5	40→10%	64	12–16	9–14	–
Gordon et al. (10)†	51	2	40→5%	63	25.3	35	–
Leenutaphong et al. (11)†	44	2	40→0%	75	16	14	8
	25	4		60	32	40	8
Cameron et al. (12)*	58	2	20→10%	69	24.4	–	12.6
	55	3		80	23.0	–	8.3

*Only patients who cleared included in investigators' analysis.

†All patients included in investigators' analysis.

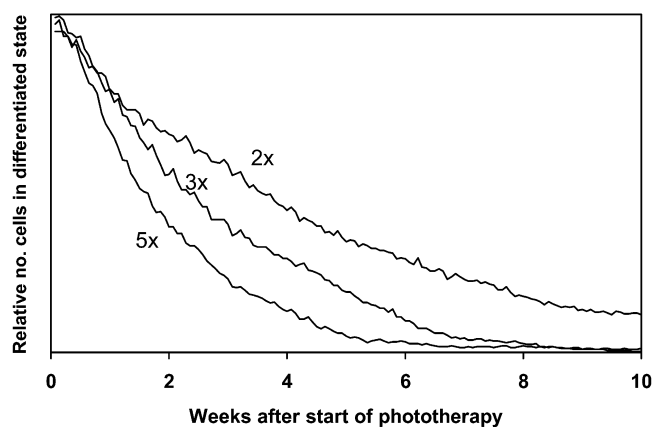


Fig. 1. Disease activity calculated following the start of phototherapy for treatment corresponding to two, three and five times per week.

times that were either too short or too long compared with those found with TL-01 regimens typical of the studies summarized in Table I.

It can be seen that disease activity falls in an approximately exponential fashion and that the time taken for disease activity to fall to 10% and below of that initially (taken to represent minimal residual activity (MRA)/clearance) is around 5–10 weeks. From Fig. 1 the MRA/clearance times for treatment two, three and five times per week are approximately 10 weeks (20 treatments), 6 weeks (18 treatments) and 4.5 weeks (23 treatments), respectively. These summary data are in keeping with clinical observations (see Table I) and indicate that for a consistent acute response following each irradiation, such as minimal redness, treatment frequency has a minor effect on the number of irradiations for clearance.

In a recent study of a standard three-times weekly narrowband TL-01 UVB regimen (13), two similar plaques were allocated randomly to be covered for two of three weekly treatments (i.e. exposed only once per week) and to be exposed to local UVB every treatment. The main outcome measure was the change in scaling, erythema and induration (SEI) score for each selected study plaque. This scoring system is equivalent to disease activity as calculated by the present model. The mean SEI score throughout the 10-week treatment course in the three-times weekly exposed plaques is compared in Fig. 2 with the once-weekly exposed plaques. Also shown in this figure is the predicted response, calculated assuming a survival fraction of 0.92. The agreement is remarkably close, adding support to the robustness of the model.

High dose. A more recent treatment using monochromatic radiation of similar wavelength is the use of a 308-nm excimer laser for psoriasis phototherapy. In this technique the laser beam irradiates only the psoriatic plaque and permits much higher exposures than would

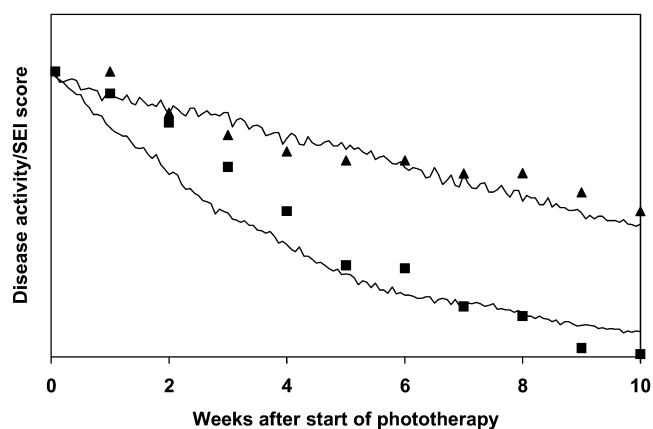


Fig. 2. The mean relative scaling, erythema and induration (SEI) score (13) throughout a 10-week treatment course in plaques exposed three times per week (squares) and once per week (triangles). The continuous lines show the predicted responses based on the model.

be possible with whole-body irradiation, where erythema on uninvolved skin limits the maximum exposure that can be tolerated. It has been observed that a single exposure to several multiples of MED of 308-nm radiation can be effective on localized plaques (14, 15) and that a multicentre study using supra-MED exposures achieved clearing in 75% of patients with a mean of six treatments (16). In the dose-response study reported by Asawanonda et al. (14) an inverse relationship was observed between the number of treatments for achieving a psoriasis severity index of ≤ 1.5 (equivalent to clearance/MRA) and exposure per treatment. For example, it would be expected from their study that four treatments of 6 MED per treatment would be sufficient to clear psoriasis.

In the studies summarized in Table I, exposures per treatment are intended to be around 1 MED, such that little or no erythema is observed on uninvolved skin during the treatment course. The predicted germinative cell survival fraction to a single irradiation of x MED (f_{xMED}), assuming first-order kinetics, can be calculated from the equivalent survival to a single irradiation of 1 MED (f_{1MED}) as: $f_{xMED} = [f_{1MED}]^x$.

Fig. 3 shows the predicted response from twice-weekly treatment as a function of exposure dose per treatment. It can be seen that the model will predict shorter clearance times as the exposure per treatment increases (e.g. five treatments, each of 6 MED, given twice-weekly for 2 weeks will achieve clearance) equally as reliably as clearance times observed with low dose (~ 1 MED per exposure) regimens.

Failure to clear

It is well known that there is a significant range in the number of treatments required for clearance in a population of patients with plaque psoriasis, with a

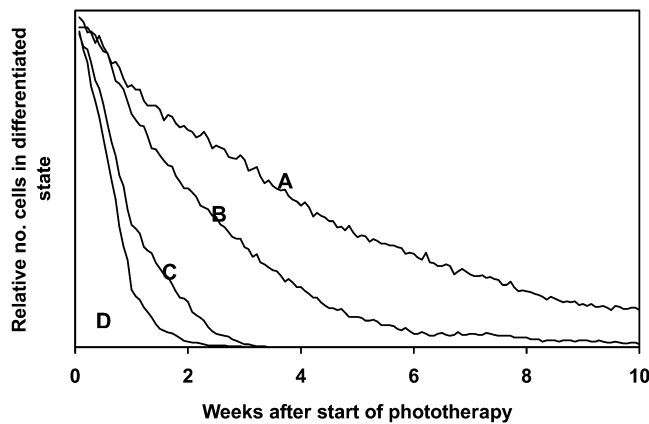


Fig. 3. The predicted response from twice-weekly treatment as a function of exposure dose per treatment (with appropriate allowance for photoadaptation). Curves A, B, C and D: exposure per treatment (MED)=1, 2, 6 and 10, respectively. Survival fraction=0.9, 0.8, 0.5 and 0.3, respectively. Estimated number of treatments for clearance=21, 10, 5 and 3, respectively.

proportion of patients never achieving clearance. Contributory factors to failure to clear may be differences in the percentage of cells surviving a single irradiation and relapse beginning during the phototherapy course.

The effect of the first of these factors is illustrated in Fig. 4, which shows clearance curves calculated for treatment given three times per week and for survival fractions varying between 0.85 and 0.95. The variation in time to clearance is clearly seen and if treatment is terminated after 10 weeks (30 treatments), it is evident that some patients do not achieve clearance. Factors that could account for this variable fraction include variability in cell sensitivity to UVB between individuals and the impact of the optical properties of the overlying epidermis resulting in a variable flux of UVB reaching the germinative cell layer.

Relapse occurs when cells that have resorted to the G₀ phase following UVB are recruited back to active cell cycling. This factor has been incorporated into the

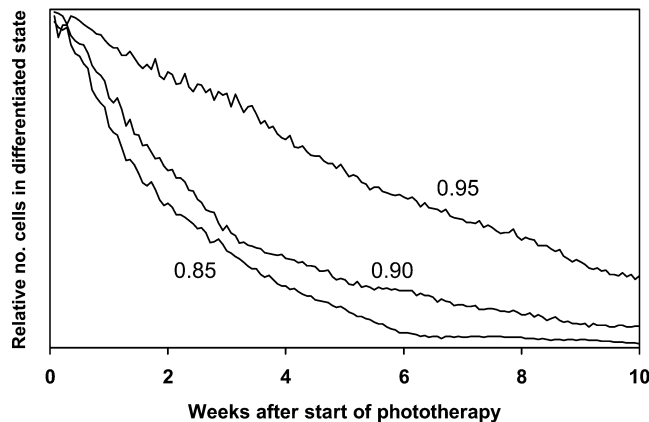


Fig. 4. The predicted response from treatment three times per week for different fractions of cells surviving a single irradiation.

model by permitting a cell that has been 'inactivated' to remain in the G₀ phase for a random time defined by a probability distribution with a mean time before re-entering active cell cycling. Calculated clearance curves are shown in Fig. 5 for mean times before relapse of 3, 6 and 12 weeks. It can be seen that if this mean time is less than the duration of the phototherapy course, patients will not clear.

Optimal regimens

The principal choices facing a phototherapist are how frequently patients should attend for treatment and what is the targeted erythral response following each irradiation, for example, none, barely perceptible or mild redness with no discomfort. Table II shows the results of using the model to predict the number of exposures, or patient attendances, required for 90% clearance as a function of the target erythral response after each visit. It can be seen that for a given erythral response, the number of exposures required for clearance is almost independent of the frequency with which patients attend for treatment. These data can be reduced to the simple equation:

$$\text{No. of exposures for clearance} \times \text{MED per exposure} = 24$$

It is evident, of course, that the less frequent the exposures the longer it will take (in weeks) to clear patients. Furthermore the higher the exposure dose per treatment, the more rapidly will clearance result. Again a simple equation combines these two variables as a rough predictor of time to clearance as:

$$\text{Treatment time (weeks) required for clearance} = \frac{\text{Time between treatments (hours)}}{[7 \times \text{MED}]}$$

These predictions are entirely in line with clinical observation. Cameron et al. (12) found that treating patients either twice or three times per week, with a regimen that aimed to result in equivalent erythral responses in both groups, made no significant difference

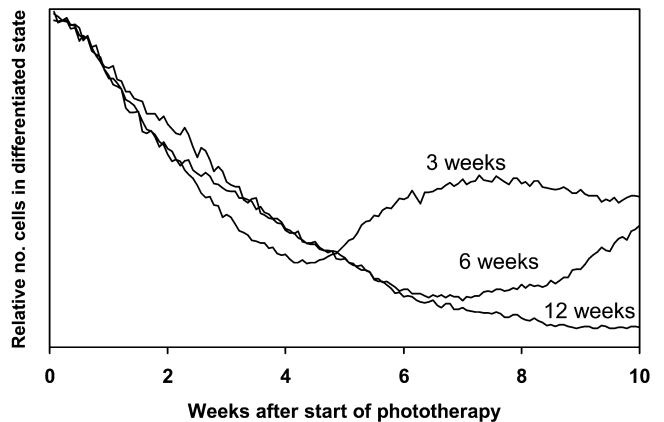


Fig. 5. The predicted response from treatment three times per week for different mean times before re-entering active cell cycling.

Table II. The calculated number of treatments required for 90% clearance in relation to minimal erythema dose (MED)

Response after each exposure		Time between treatments (days)					Mean number of treatments
	MED	1	2	3	4	5	
Erythema							
Subclinical	0.5	53	43	44	42	42	43
Subclinical/possible erythema	0.7	31	32	29	37	37	34
Just perceptible redness	1	*	23	24	21	22	23
Mild, but definite, redness	1.5	*	*	15	15	15	15
Pronounced redness without pain	2	*	*	*	12	11	12

*Unacceptable erythema could result from this combination of exposure and frequency due to the cumulative effects of repeated irradiation.

to the number of attendances required for clearance. In a study comparing near ('high dose') and far ('low dose') erythemogenic doses, Hofer et al. (9) found that the higher dose regimen cleared patients with fewer number of exposures compared with the low dose regimen (Table I).

In terms of maximizing the use of hospital resources and minimizing the disruption to patients attending for treatment on an outpatient basis, a regimen that minimized the number of patient attendances rather than minimized the total time taken for clearance is to be preferred. This is best achieved by maximizing the UVB exposure that an individual patient can comfortably tolerate. To enable the resulting erythema to subside and not be compounded by subsequent irradiations, a regimen is proposed that aims to result in mild but asymptomatic erythema by treating patients twice per week. This should result in around 15–20 exposures requiring 7–10 weeks for clearance. In many cases, patients are currently requiring between 20–30 exposures for clearance and adopting the strategy proposed here should lead to a more efficient use of resources, both time and cost.

For inpatients, adopting a strategy that minimizes overall treatment time is preferred since this keeps hospital stay to a minimum. Here daily treatment is suggested, and with each exposure resulting in little or no erythema clearance would be expected within 1 month. To minimize the risk of cumulative irradiation resulting in excessive delayed erythema during the early days of treatment (17, 18), the erythema response to daily irradiation needs to be carefully monitored and adjusted, as necessary. This prediction excludes the therapeutic benefit of adjunctive agents, such as dithranol or coal tar, which would frequently be a component of inpatient treatment.

DISCUSSION

A mathematical model, based solely on epidermal cell cycle arrest, is described that predicts the response of psoriasis to a treatment course of UVB irradiation. There are two principal motivations for mathematical modelling:

- To predict how a system will behave without the need to undertake expensive, time-consuming, impractical or even impossible experiments.
- To gain an understanding of the mechanisms and behaviour of the system under study.

It is the first motivation that is the basis of the present study, but as the model is shown to predict treatment outcomes reported in clinical trials, it might partially fulfil the second motivation.

Clearly, other UV-induced cellular events contribute to healing, including alteration of cytokine expression and modulation of the immune system (19). UVB has been shown to alter the skin's immune system in a number of important ways, with demonstrable effects on antigen-presenting cells, production of soluble mediators, T-cell apoptosis and expression and function of keratinocyte cell surface receptors. It is possible, for example, that UVB will deplete T cells from the epidermis by apoptosis (20) and this might be regarded as the basis for the clearance of psoriasis by phototherapy. It is tempting to think, however, that since the agreement between model prediction and clinical observation is close, this might suggest that the contribution of effects such as alteration of cytokine expression and UVB-induced lesional T-cell apoptosis may be playing only a minor role in the phototherapeutic response of psoriasis to UVB irradiation. But, of course, this does not exclude an immunological mechanism being the major, or sole, factor in the non-phototherapeutic treatment of psoriasis or in other UVB-responsive diseases such as atopic dermatitis.

Notwithstanding the limitations and assumptions inherent in the mathematical model described here, outcomes from its use are that the frequency of irradiation makes only minor differences to the number of exposure sessions required for clearance in comparison with exposure dose per treatment. With exposure doses per treatment resulting in little or no erythema, the majority (~90%) of germinative cells remain clonogenic after a single irradiation. The model predicts that more effective regimens in terms of reducing the number of treatments required for clearance will require higher UVB doses per irradiation,

and that failure to clear patients may be due, in part, to differences in the fraction of germinative cells surviving a single irradiation and relapse beginning during the phototherapy course.

In conclusion, the approach described here may be helpful as a guide in proposing optimal treatment regimens which can be tested against appropriately designed clinical studies.

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APPENDIX

Computer program in BASIC for calculating the relative number of cells in the differentiated state ('disease activity') for UVB phototherapy given three times per week for 10 weeks and where 90% of cells remain clonogenic after a single UVB irradiation (roughly equivalent to a minimal erythema following each irradiation).

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DIM c(100), d(2500), p(2500), t(100), b(40)
n=100: REM number of germinative cells
t0=50: REM mean cell cycle time (h)
sd=10: REM standard deviation (h) on mean cell cycle time
FOR i=1 TO n
  REM assign cycle time of each cell according to normal
  distribution
  r=0: FOR ri=1 TO 12: r=r+RND: NEXT ri
  t(i)=t0+(r-6) * sd: NEXT i
  REM assign cells to random positions within cell cycle
  FOR i=1 TO n: c(i)=RND * t(i): NEXT i
  et=168: REM epidermal turnover time in hours (7 days)
  f0=0.9: REM fraction cells surviving irradiation
  wk=10: REM weeks of treatment
  tw=3: REM number of times per week treatment is given
  k0=wk * tw: REM total number of treatments
  b(1)=et: b(2)=et+48: b(3)=et+96
  FOR i=4 TO k0: b(i)=b(i-3)+168: NEXT i
  REM iterate through population of germinative cells in hourly
  steps for a time equal to the sum of the number of weeks of UVB
  treatment and the epidermal turnover time. This is to allow
  differentiated cells to reach equilibrium before phototherapy begins.
  m=wk * 168+et: k=1
  FOR t=1 TO m: d(t)=0
    IF t=b(k) THEN f=1: REM test if iteration time coincides
    with a time of irradiation
    FOR i=1 TO n: IF c(i)<0 THEN 30
    c(i)=c(i)+1: REM move cell 1 hour through its cycle
    IF c(i)<t(i) THEN 20
    c(i)=c(i)-t(i): d(t)=d(t)+1: REM create a differentiated cell
    on passing through mitosis
    20 IF f<>1 OR k>k0 OR RND<f0 THEN 30
    c(i)=-1: REM inactivate the germinative cell if it falls into that
    fraction of cells not surviving irradiation
    30 NEXT i
    REM determine the number of differentiated cells, p(t), present
    at time t
    q=t-et: IF q<0 THEN q=0
    d=0: FOR l=q TO t: d=d+d(l): NEXT l
    p(t)=d
    IF f=1 THEN k=k+1
    f=0
  NEXT t
  REM adjust the origin of p(t) for display only following the
  start of phototherapy m=m-et
  FOR t=0 TO m: p(t)=p(t+et): NEXT t
END

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