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Cell Kinetic Basis for Pathophysiology of Psoriasis*

GERALD D. WEINSTEIN, M.D., JERRY L. MCCULLOUGH, PH.D., AND PRISCILLA A. ROSS, M.S.

Department of Dermatology, University of California, Irvine, California College of Medicine, Irvine, California, U.S.A.

Studies on the cell proliferation kinetics of psoriatic epidermal cells are presented and the results compared to similar studies for normal epidermis. The short 36-h duration of the psoriatic cell cycle (T_c) is confirmed with the first double-peaked fraction of labeled mitoses (FLM) curve in human subjects. The growth fraction of psoriasis using two experimental techniques approximates 100% within 36 h, confirming the rapid T_c found by the FLM method.

The cell kinetic basis for the pathophysiology of psoriasis consists of at least 3 proliferative abnormalities in comparison to normal epidermis. By far the largest alteration is the shortening of the T_c from 311 to 36 h. There is also a doubling of the proliferative cell population in psoriasis from 27,000 to 52,000 cells/mm and an increase in the growth fraction from 60% to 100%. As a consequence of these abnormalities the psoriatic epidermis produces 35,000 cells/day from a proliferative compartment of 52,000 cells/mm^2 surface area. This is a 28-fold greater production of cells than the 1,246 cells/day produced in normal epidermis. The biochemical or control factors leading to these kinetic differences continue to remain elusive.

Ever since the concept of psoriasis as a hyperplastic epidermal disease was developed by Van Scott and Ekel [1] many studies have attempted to define and quantitate this process. The hyperplastic component of psoriasis has generally been examined in contrast to the normal epidermis, thereby requiring comparable data for both tissues. The major questions that have been asked are: (1) Do psoriatic and normal epidermal cells proliferate at the same rate, i.e., do they have the same cell cycle parameters? (2) Are the growth fractions similar in the proliferative compartments of the two tissues? (3) Can cell cycle and growth fraction parameters as measures of cell proliferation be related to independent measurements of transit times and cell populations in the two tissues?

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Reprint requests to: Gerald D. Weinstein, M.D., Department of Dermatology, University of California, Irvine, California College of Medicine, Irvine, California 92717.

Abbreviations:

CV: standard deviation expressed as percentage of the mean
FLM: fraction (frequency, percent) of labeled mitoses
GF: growth fraction(s)
LI: labeling index(ices)
SA: epidermal surface area
T_c: duration of germinative cell cycle
t_{g_2}: duration of G_2 phase
t_m: duration of mitotic phase
t_s: duration of DNA synthesis phase

In previous reports from this laboratory the cell cycle time (T_c) of psoriatic epidermal cells was found to be 37.5 h using a partially indirect technique, the stage-duration method, which combines data from the fraction of labeled mitoses (FLM) curve and the labeling index (LI) [2]. Other reports have suggested T_c ranging from 33–114 h [3–6].

The work presented in this report confirms the rapid cell cycle duration of psoriatic cells using the classical direct method of a double-peaked FLM curve and the measurement of the growth fraction in psoriasis. The cell cycle data so derived provide evidence that psoriatic cells proliferate approximately 8-fold faster than do normal epidermal cells [7]. A kinetic model of epidermal cell proliferation is presented for normal and psoriatic epidermis that interrelates these kinetic data with transit time [8] and cell population data.

METHODS

Determination of T_c by the FLM Method

The direct measurement of the T_c by the FLM method requires a double-peaked curve of labeled mitoses (Fig 1). This study extends to 70 h the curve obtained in a prior investigation [2] which utilized biopsy specimens obtained from 8 patients at 3-h intervals from 0–27 h (Fig 2). In the present study 6 patients, over the age of 40 with chronic steady-state plaque psoriasis, were injected intralesionally with 0.1 ml [^{3}H]thymidine (sp act = 1.9–6.0 Ci/mM) in multiple sites. From each patient 4-mm biopsies were obtained sequentially at 3- to 5-h intervals over a period of 27–70 h after injections. The range of 27–70 h was chosen based on the estimated T_c of 37.5 h previously found which would predict that the second peak should occur about 37 h after the first peak which was at 9 h [2]. The specimens were prepared for autoradiography as previously described. A mean of 69 mitoses was counted from each specimen and the values for each time point were averaged. The FLM values from 27- to 70-h samples were combined with the original FLM curve to produce a composite double-peaked FLM curve that is hand drawn and comparable to our previous studies. The distance between the 2 peaks (in hours) is the direct measurement of cell cycle duration and represents the mean time necessary for the labeled cohort of cells to go from mitosis to mitosis (Fig 1).

Growth Fraction in Psoriasis

In 3 patients with psoriasis [^{3}H]thymidine was injected 1–4 times at 12-h intervals into the same sites intralesionally. One hour after the last injection, biopsies of the sites were obtained for autoradiography. In control sites of psoriasis, normal saline was injected intradermally at one or more of the first 3 time points followed by [^{3}H]thymidine for the last injection. One hour after the [^{3}H]thymidine injections the sites were biopsied. LI were counted in the proliferative compartment of psoriatic epidermis as defined previously, i.e., the lower 3–4 rows of the epidermis which contained cells with a higher nuclear/cytoplasmic ratio and mitoses [2].

Age-Distribution Analysis of the Psoriatic Cell Cycle

Duffill et al [4,9] have proposed the incorporation of the age-distribution of an epidermal cell population when determining its cell cycle kinetics. It was suggested that the age-distribution in psoriasis may be exponential resembling a tumor since there are frequently 3 or more rows of proliferative cells in psoriasis. In contrast, the single layer of proliferative cells in small animal skin may have a distribution somewhere between the rectangular and exponential age-distribution depending on the direction of the mitotic axes. The exponential age-distribution equation can be used to determine both the theoretical LI

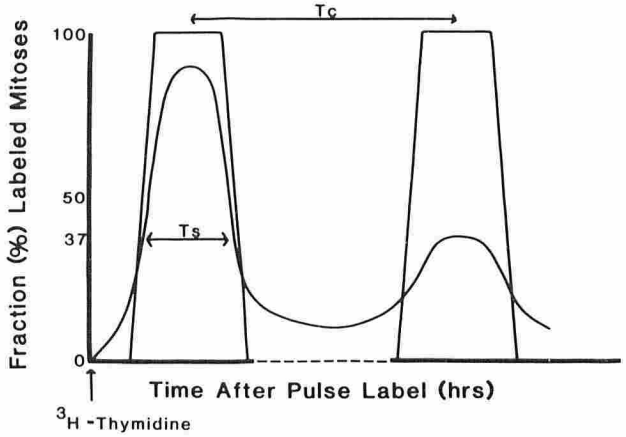

FIG 1. Schematic diagram of hypothetical experimental FLM curve showing 2 waves of labeled mitoses. The first peak of labeled mitosis follows soon after a cohort of cells is labeled in the DNA synthesis phase by [^{3}H]thymidine. The second peak represents the initially labeled cell cohort when it next passes through the mitotic phase. The rectangular forms are the idealized structure of an FLM curve if all cells behaved in absolutely uniform manner without variations in their cell cycle components. Since experimentally the cycles of individual cells vary, there is a damping of the curve, particularly the second peak. The duration of the S phase (T_s) and cell cycle (T_c) are obtained as indicated.

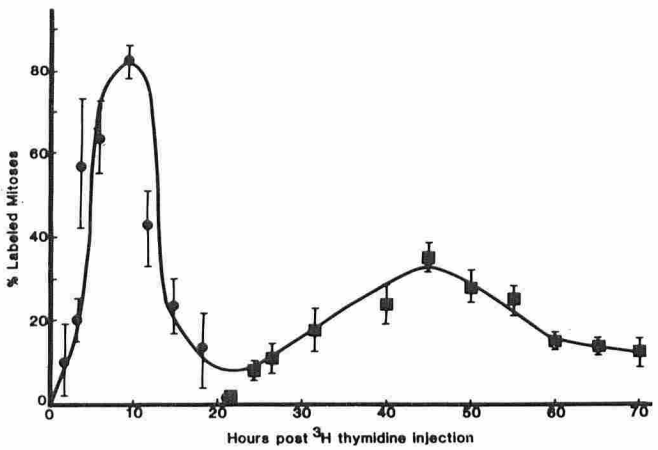

FIG 2. Composite FLM curve derived from data on 2 groups of patients. The first group (●) represents 8 patients studied from 0–27 h [2]. The second group (■) from this study includes 6 patients studied from 27–70 h. T_c measured between the two peaks is 36 h. SEM is indicated for each time point.

and the growth fraction if the T_c is obtained by the FLM method:

$$GF = \frac{LI\ (experimental)}{LI\ (theoretical)} \quad (1)$$

$$LI\ (theor) = \left\{\exp\left[\frac{t_s \ln 2}{T_c}\right] - 1\right\}\left\{\exp\left[\frac{t_{g2} \ln 2}{T_c}\right]\right\} \quad (2)$$

$$LI\ (theor) = \left\{\exp\left[\frac{8.5 \ln 2}{36}\right] - 1\right\}\left\{\exp\left[\frac{4.2 \ln 2}{36}\right]\right\}$$

$$LI\ (theor) = 0.187\ (18.7\%)$$

where t_s equals duration of DNA synthesis phase and t_{g2} equals duration of G_2 phase.

Quantitation of Germinative and Differentiated Cell Compartments in Psoriatic Epidermis

Four-millimeter punch biopsies were obtained from typical chronic steady-state psoriatic plaques in 3 patients. From microphotographs of 6 sections from each patient the proliferative and differentiated cell populations were delineated as previously described for normal epidermis [2]. The nucleated proliferative and differentiated cells were counted and a measurement of the overlying epidermal length was obtained with the results expressed as the mean number of cells/mm surface length.

In order to obtain the total number of cells in each compartment/mm^2 surface area, a three-dimensional measurement of the epidermis is necessary using mean cell diameters. From microphotographs as above 30 vertical columns of cells were measured to obtain the mean cell diameters for each compartment [7]. Based on the average diameter and number of cells in each compartment the total number of cells/compartment/mm^2 epidermal surface area (SA) was calculated.

RESULTS

Determination of Cell Cycle Duration

During the 27- to 70-h period the second peak is obtained with a maximum at 45 h after [^{3}H]thymidine injections. The shape of the second peak, broader and lower, is comparable to most other human and animal studies, indicating some desynchronization of the labeled cohort in each succeeding cycle. The mean T_c of the psoriatic epidermal cell is 36 h as determined by the distance between the 2 peaks (9–45 h) (Fig 2). The components of the cell cycle, t_{g_1}, t_s, t_{g_2}, and t_m, are listed in Table I and were previously determined using the Quastler technique [2].

The FLM results from the 2 sets of psoriasis data were computer analyzed [10] by Dr. M. Mendelsohn (University of California, Livermore). The computer analysis (t_{g_1} = 29.6 h, CV = 0.37; t_s = 7.5, CV = 0.45; t_{g_2} = 4.5, CV = 0.45; t_m = 0.4, CV = 0.45; T_c = 42, CV = 0.28) is similar to the results found with the hand method (Table I) but also provides estimates of the variability of transit rates through the cell cycle or coefficient of variation (CV = standard deviation expressed as percentage of the mean). The relatively small CV for the psoriatic T_c of 28% reflects a small difference in the rates at which cells move around the cell cycle [11]. With a SD of 10 h from the computer analysis, a major proportion of cells will have a T_c that may range from 26–46 h.

Growth Fraction in Psoriasis

With repeated injections of [^{3}H]thymidine at each sequential time point there is an increase in the LI that approximates 90–100% in the 36-h specimens (Figs 3, 4). The increasing LI reflects labeled daughter cells of previously labeled S phase cells that have divided, as well as labeling of new cells that have entered the S phase for the first time during the time periods of additional [^{3}H]thymidine exposure. In addition labeled cells are found throughout the thickness of the differentiated cell compartment and just up to the stratum corneum layer, indicating continuous upward movement of the labeled cells. A transit time of 1.5–2.0 days is confirmed in these specimens [8]. Control specimens with saline injections followed by [^{3}H]thymidine show approximately 20–30% labeling, indicating only a small Koebner-like stimulation of the LI at the latter time points.

Age Distribution Analysis of the Psoriatic Cell Cycle

Using the experimentally determined values of T_c = 36 h, t_s = 8.5 h, and T_{g_2} = 4.2 h (the values t_s and t_{g_2} are obtained from the first FLM peak [2]), Eq 1 and 2 are solved for the theoretical LI and growth fraction (GF). The theoretical LI is 18.7% which is similar to the experimental values obtained by

TABLE I. *Summary of the cell cycle and its components for normal and psoriatic epidermis*

	Duration (h)				
	t_s	t_{g_2}	t_m	t_{g_1}	T_c
Normal	14	10	1	286	311
Psoriatic	8.5	4	0.3	23	36

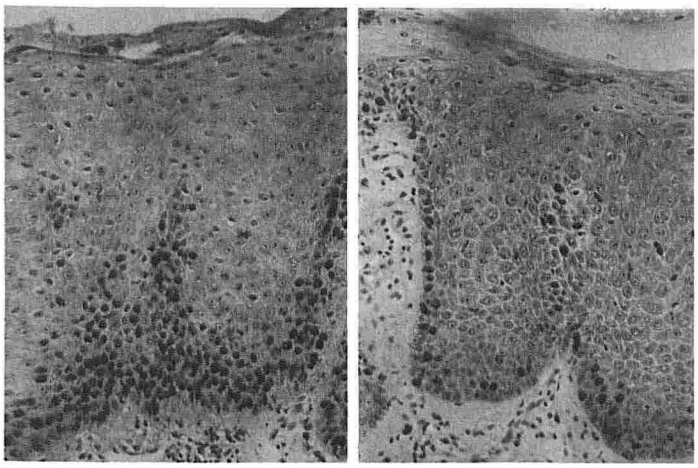

FIG 3. Photomicrographs (× 250) from growth fraction study. *A*, Same site of psoriasis injected with 4 intradermal doses of [^{3}H]thymidine at 12-h intervals with biopsy 1 h after last dose. Approximately 90% of proliferative cells are labeled. *B*, Control site with 3 saline injections at 12-h intervals followed by [^{3}H]thymidine.

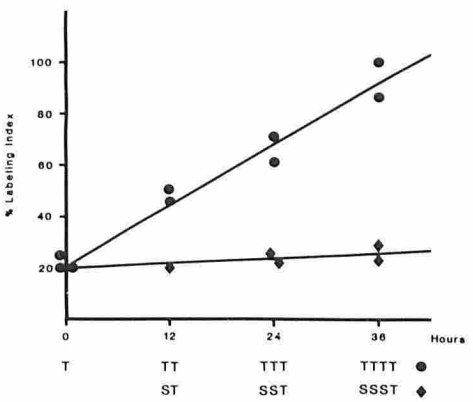

FIG 4. Growth fraction curve using 1–4 intermittent doses of intradermal [^{3}H]thymidine (*T*) at 12-h intervals in same sites. Control (*lower line*) used saline (*S*) injections prior to last injection of [^{3}H]thymidine, i.e., at the 24-h point, 3 injections of [^{3}H]thymidine and/or saline had been given.

Weinstein and Frost [2] of 16.2% (uncorrected) and 22.7% (corrected) and 21.2% by Gelfant [12]. Depending on which experimental LI is used, the GF calculated from Eq 1 ranges from 87–121%, or essentially the same as the experimentally determined GF of 100%.

Quantitation of Germinative and Differentiated Cells

In psoriatic epidermis the number of viable nucleated cells in each section was obtained from 7 sections in each of 3 patients. After extrapolation to 1 mm surface length, the germinative and differentiated cell counts were 608 ± 127 (SD) cells/mm and 870 ± 116 cells/mm, respectively (Fig 5). The mean cell diameters for germinative and differentiated cells were 11.6 ± 1.0 and 18.4 ± 6.1 μm, respectively. To determine the number of germinative cells/mm^2 SA, the number of germinative cells in each 1 mm-long section (608) was multiplied by the number of sections underlying 1 mm^2 of surface area. Since the average germinative cell diameter was 11.6 μm, there would be 86 sections/mm^2 SA (each 11.6 μm thick). The total number of germinative cells in psoriasis calculates to be 52,000 cells/mm^2 SA. In a similar manner the differentiated cell compartment contains 47,000 cells/mm^2 SA (870 cells × 54 sections (18.4 μm thick)). The total viable cell population of the psoriatic epidermis is 99,000 cells/mm^2 SA.

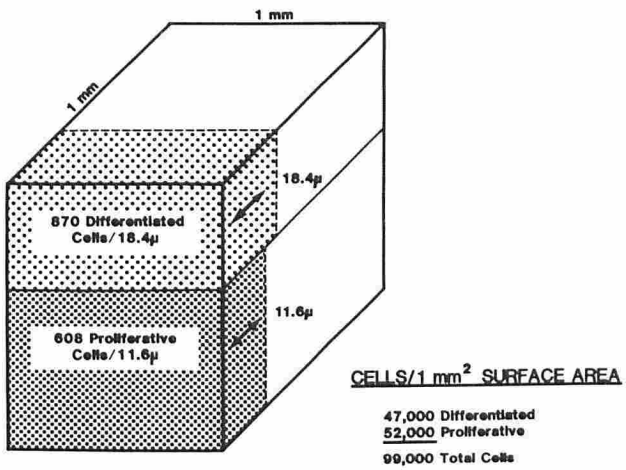

FIG 5. Psoriatic cell populations in proliferative and differentiated compartments under 1 mm surface length and 1 mm^2 surface area. Average width of cells is given in microns.

DISCUSSION

Extensive evidence has accumulated to indicate that the hyperproliferative activity of the epidermal cells is a major pathophysiologic component of psoriasis [1–4,6,8,12–15]. The foundation of cytokinetics today is based on the FLM method [11] which is the most commonly used technique for determining T_c and its components t_s, t_{g_2}, and t_m. If the FLM method is used for a limited time span providing only the first peak, then it must be integrated with other information, i.e., the LI and GF, to obtain the T_c. This is considered an *indirect* technique, generally referred to as the stage-duration method, which has been used in the past by others including ourselves for measuring the kinetics of psoriasis and other tissues. The indirect methods to measure cell proliferation include flash LI, grain counts, and GF determinations. Difficulties with these methods are discussed below and by Wright [11]. If data for the FLM method can be obtained over a long enough span of time to get 2 or more peaks in the FLM curve, then the duration of T_c can be measured *directly*. This is by far the preferred method since it avoids many variables and assumptions inherent in the indirect methods.

The major emphasis in this study is to obtain a second peak in the FLM curve which allows a direct measurement of the time required for a cohort of cells to move through a complete cell cycle from mitosis to mitosis (Fig 1). The T_c of 36 h obtained from the FLM curve confirms the previously calculated value of 37.5 h found by the stage-duration method [2]. The calculation of that value based on the information then available used a "corrected" LI of 22.7%, a t_s of 8.5 h, and assumed a GF of 100%. Each of these values can be examined in retrospect more critically in light of newer information from this and other recent reports. The LI for psoriatic epidermis has varied in several studies from 10–25% [2–4,12,13] depending on different experimental criteria including the definition of the cell population to be counted, in vitro vs in vivo, amounts of isotope used, autoradiographic emulsions, and exposure times [14]. Using techniques similar to ours, except for an autoradiography exposure time 2–3 times longer, Gelfant obtained a LI of 21.2% [12] which is comparable to our "corrected" LI of 22.7%. An absolute LI of approximately 20% is further substantiated by the age-distribution analysis presented above which gives a theoretical LI of 18.7%.

The second value used in our original T_c calculations of psoriasis, a t_s of 8.5 h from the first FLM peak, was subsequently confirmed with FLM derived t_s of 9.8 h and 7.7 h, respectively [3,4], indicating a consistency for this particular cell kinetic parameter.

While the double-peaked FLM curve has been used in many

animal experiments, this is the first study in any human tissue to our knowledge that has been able to obtain a double-peaked curve in vivo. Single-peaked FLM curves in humans have been obtained to a limited extent in hematopoietic tissues, gastrointestinal tract epithelium, skin, and selected tumors. The difficulties in fully utilizing the FLM technique are (1) giving patients, particularly with benign diseases, the large amount of [^{3}H]thymidine i.v. (5–10 mCi) required, and (2) accessibility of the tissue to continued sampling at 3- to 6-h intervals over several days. The skin and lesions therein have permitted relatively easy accessibility at least for the first peak extending over 24–30 h and the intradermal use of small amounts of [^{3}H] thymidine (5 μCi) in each site have minimized isotope exposure. Obtaining a second peak in the same patient would require an excessive number of specimens in a given subject, particularly if there is a prolonged T_c with the second peak several days after the first. The normal epidermis, with a T_c of approximately 13 days [7], would be difficult to study in human subjects [15]. Since previous research on psoriasis had suggested a shortened T_c of 37 h, the second peak could be determined with a limited number of biopsies in each of the subjects. Only one other double-peaked FLM curve has been reported in skin (mouse) which gives a well-defined second peak and a relatively long T_c of about 100 h [16].

The proliferative cell kinetics of normal and psoriatic cells are summarized in Table I. The T_c in normal epidermis of 311 h was obtained by indirect calculations using a t_s from a single-peaked FLM curve, a LI, and a GF from a continuous labeling experiment in vivo [7]. Based on these calculations the normal epidermal T_c is approximately 8-fold longer than the T_c of psoriatic cells (311 vs 36 h).

Two other general approaches to the experimental determination of psoriatic cell cycle kinetics are found in the literature: (a) double-labeling techniques in vitro, and (b) [^{3}H]thymidine grain counts to measure DNA synthesis rates [15]. Both methods suffer for various technical reasons including: (1) loss of physiologic conditions by being in vitro experiments; (2) inadequate quantitative differences experimentally; and (3) in experiments to obtain grain counts there is an unwarranted, if not unlikely, assumption that normal and psoriatic cells are the same physiologically and biochemically. In the latter case it is probable that there are significant differences in precursor nucleotide pool sizes, critical enzyme levels, and certainly local blood flow conditions that can lead to spurious results [7,11]. The direct methods used in the current study avoid the potential errors suggested above.

Much of the controversy surrounding psoriasis proliferation kinetics stems from observations that have suggested a prolongation of t_s in psoriatic cells compared to normal [5,17]. These studies have used indirect methods described above to obtain a t_s in psoriasis of 14–20 h [5,18] which contrasts markedly to the direct FLM-derived much shorter t_s values of 7.7, 8.5, and 9.8 h [2–4]. The *prolonged* t_s for psoriasis found by these investigators [5,17] has led to calculations of longer cell cycle times ranging from 114–200 h and the conclusion that there is little or no difference in the T_c of normal and psoriatic epidermal cells [19,20]. We do not believe that the evidence for a *prolonged* t_s and T_c in psoriasis based on the available information with double-labeling techniques is valid when compared to the weight of evidence for a *shortened* T_c obtained by direct methods using FLM measurements, cell population counts, transit times, and GF information.

Growth Fraction

The problem of obtaining GF in human skin and other tissues is even more difficult than for FLM curves because of the large amount of isotope that must *continually* (or intermittently) be given to the subjects, as well as the number and accessibility of samples. In psoriasis, however, 3 techniques have permitted an approach to estimate that its GF approximates 100%. In an earlier study, methotrexate over 36 h followed by [^{3}H]thymidine intradermally showed that the entire proliferative population of psoriasis was labeled, suggesting a GF of 100% [21].

In the current study the more classical technique using [^{3}H] thymidine in intermittent doses over the putative T_c produces a curve (Fig 4) that reaches 90–100%, indicating that all the cells in the proliferative compartment (the lower 2–4 rows) are in a proliferating mode without significant numbers of G_0 (nonproliferating) cells in that compartment. While it would have been preferable to use i.v. [^{3}H]thymidine for a study like this, the flatness of the control curve using repeated saline injections into psoriatic plaques indicates that the "trauma" of injections does not appreciably affect this cell proliferation parameter. It does suggest that the psoriatic cell is proliferating at its maximum rate and cannot be further stimulated by a Koebner-like insult.

Based on a mathematical approach to the age-distribution of cells in psoriasis [9], the GF ranges from 87–121% which confirms the direct approach values to the GF described above. The GF concept with respect to cancer chemotherapy is concerned with the relative homogeneity of tumor cells in a proliferative phase (rather than in a G_0 resting phase) susceptible to the chemotherapeutic drugs being used. The approximate 100% GF in psoriasis suggests relative cell homogeneity with respect to cell kinetics and that all the cells might therefore be susceptible to an appropriate therapeutic modality such as is seen with methotrexate.

In contrast to psoriasis, the GF in normal epidermis is approximately 60% [7,12] and thus must increase to 100% in the transformation of "normal" (uninvolved epidermis) to psoriatic epidermis. It has previously been hypothesized that there is a small (incorrectly stated as "large" in [7]) GF in normal epidermis and that psoriasis results entirely from an expansion of the GF to 100% without changes in the T_c [19,20]. Since there is an 8-fold difference in the T_c of normal and psoriatic epidermis and less than a 2-fold difference in GF, the above hypothesis cannot be correct.

Kinetic Model for Normal and Psoriatic Epidermis

A kinetic model for psoriasis can be developed for comparison to a similar model of normal epidermis [7]. The model for psoriasis interrelates data from this study and transit time information on psoriasis previously published [8]. In the present study the proliferative and differentiated cell populations of psoriasis were found to contain 52,000 and 47,000 cells/mm^2 SA, respectively (Fig 6). Since the proliferative cell cycle (turnover time) is 1.5 days and the differentiated transit time is 1.75 days (range 1.5–2.0 days), the birth or turnover rate/day of cells in each compartment calculates to be 35,000 (52,000/1.5) and 27,000 (47,000/1.75) cells, respectively. These values are reasonably similar and suggest that a kinetic homeostasis exists between birth and turnover rates of keratinocytes in these two compartments. Although the stratum corneum has a transit

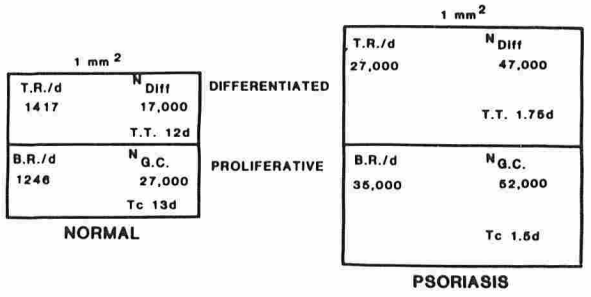

FIG 6. Kinetics model for cell proliferation parameters of normal and psoriatic epidermis. *B.R./d* = birth rate/day; *T.R./d* = turnover (transit) rate/day; $N_{G.C.}$ = number of germinative (proliferative) cells; N_{diff} = number of differentiated (viable) cells.

time of approximately 2 days [8,12] there is no accurate information on the number of corneocytes in psoriasis to get a turnover rate for that compartment. The calculations of kinetic equilibrium seen in the cell turnover rates of each compartment using independently derived cell counts and transit times further confirms the T_c value of 36 h obtained by the FLM method.

The kinetic data for normal epidermal cells [7] can be compared to psoriatic cells in Fig 6. Several proliferative differences are readily apparent in the pathologic transition of "normal" to psoriatic cells. At the cellular level the hyperplasia of psoriasis appears to be mainly the result of an 8-fold shorter T_c which is acting on the second kinetic abnormality, a proliferative cell population that is doubled in the psoriatic epidermis. The third proliferative abberation is an expansion of the normal GF from 60% to 100%. The sum total of these abnormalities causes the psoriatic epidermis to produce 28-fold more cells/day than normal epidermis (birth rate of 35,000 cells/mm^2 vs 1,246 cells/mm^2 in normal). This enormous cellular hyperplasia must be responsible for the clinical presence of hyperkeratosis and extensive continual scaling.

The overall turnover time of the psoriatic epidermis can be considered as the sum of the turnover (cell cycle, transit) times for each of its cell compartments. The mean epidermal turnover time of the psoriatic lesion is approximately 5¼ days, consisting of 1.5 days for the proliferative compartment, 1.75 days for the viable differentiated compartment, and 2 days for the stratum corneum. At this time there is still too little information available to understand the controlling or biochemical influences producing the proliferative differences in normal and psoriatic epidermis. Potentially attractive areas of investigation would be the reasons for the large differences in cell cycle and S phase durations.

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