concordant, progressive, or diverse genetic changes. In tumors in which the differentiation of SCC and BCC is difficult based on histologic examination only and is of clinical or investigative importance, microdissection of different tumor components with subsequent genetic analysis may prove to be a useful diagnostic tool in the future.

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On the Morphogenesis of a Psoriatic Lesion

To the Editor:

In the December issue of the *Journal of Investigative Dermatology*, Iizuka *et al* (1997) made the assumption that the number of total viable epidermal cells is parallel to that of the proliferative compartment in the steady state of cell flow.

This is exact for an established lesion of psoriasis where, effectively, cell loss by desquamation is compensated by an equivalent cell production by the germinative compartment but cannot explain the creation of a psoriatic lesion with its typical morphology (Heenen and Galand, 1984).

What are the minimal kinetic defects needed to generate a psoriatic-like morphology?

1 The increased size of the germinative compartment corresponds to a temporary imbalance between the proportion of germinative cells that repeat the cycle and those that differentiate and migrate into the differentiating compartment. An acceleration of cell production (be it by increasing the growth fraction or by reducing the cell cycle) is insufficient for explaining the growth of the germinative compartment. When the psoriatic lesion is clinically stable, this kinetic perturbation has ceased (Heenen *et al*, 1987).

2 The increased size of the differentiated compartment is determined by the value of the ratio between the transit time (or residence time) in the differentiated compartment and the turnover time of the germinative compartment. Therefore, the morphology of the psoriatic lesion (increase in absolute size and decrease in relative size of the differentiated compartment) reflects the fact that the acceleration of cell transit is more pronounced than that of cell production in the germinative compartment, and the fact that this is accompanied by an increase in germinative compartment size.

In conclusion, two perturbations are needed and suffice to account for the pathogenesis of clinically stable psoriatic lesions: a temporary disturbance of the steady state of the germinative layers, resulting in limited growth of this compartment (this has ceased in developed lesions), and a permanent decrease in the transit time in the differentiated compartment.

How can the extension of the germinative cell pool be achieved? Two alternative explanations (not mutually exclusive) can be proposed. The germinative compartment in human epidermis is probably composed of a small fraction of stem cells with unlimited division potential and a greater proportion of transit amplifying cells already committed to differentiation and with a limited number of divisions remaining (Potten and Morris, 1988). Increased size of the germinative population can be obtained by an increased number of cell divisions in the amplifying compartment. This hypothesis is supported by the observation of involucrin in psoriatic lesions, a terminal differentiation marker, in cells labeled by [^{3}H]thymidine (Dover and Watt, 1987), and by mathematical simulations.[1]

Apoptosis is probably an important regulatory mechanism in epidermal homeostasis. Another possibility is that physiologic apoptosis in the germinative compartment is temporarily decreased.[2] This is consistent with the observation that psoriatic keratinocytes overexpress Bcl-xL, a protein that prevents apoptosis (Wrone-Smith *et al*, 1995).

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Reply:

We are grateful for Dr. Heenen's interest in our paper. As he correctly points out, we assumed that the total number of viable epidermal cells paralleled that of the proliferative compartment in a steady state of cell flow (Iizuka et al, 1997). It should be noted, however, that we did not intend to explain the creation or resolution of the psoriatic lesion, which is apparently Dr. Heenen's point. Rather, we intended to explain psoriatic architecture in a steady state of cell flow, which is determined by our assumption. We would like to point out that this simple assumption is directly related to *in vivo* psoriatic morphology and its typically angulated rete-papilla pattern.

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On the Effect of Estrogen Receptor Agonists and Antagonists on the Mouse Hair Follicle Cycle

To the Editor:

We were quite surprised to read the Letter to the Editor by Stenn *et al* in the *Journal of Investigative Dermatology* (110:95, 1998), stating that the estrogen receptor agonist, 17-β-estradiol, and the estrogen receptor antagonist, ICI 182,780, failed to alter mouse hair cycling. This result is surprising as we have reported that: (i) the topical application of 17-β-estradiol arrests hair follicles in telogen, (ii) the topical application of ICI 182,780 causes telogen follicles to enter anagen, and (iii) the estrogen receptor is expressed in the nuclei of the dermal papilla cells of the telogen follicle in CD-1 mice (Oh and Smart, 1996). In their letter, Stenn *et al* stated that they "made a concentrated attempt in two independent and widely separated laboratories to reproduce the experiments as described." They further indicated that they "treated animals following the Oh/Smart protocol precisely" and both of their studies failed to demonstrate any effect of the agonist or antagonist. It was most unfortunate that we were not afforded an opportunity to read and respond to this letter before its publication because it is obvious that these investigators did not conduct their experiments as we described. The most profound difference we noted was that they used doses of 17-β-estradiol and ICI 182,780 that were 5000-fold lower than the doses we used. Dr. Stenn has confirmed that both his laboratory and Dr. Paus's laboratory used a 10 nM dose, which is 5000-fold lower than the correct dose of 10 nmol per 200 μl of acetone vehicle. This dose is clearly stated in our paper.

In addition, Stenn *et al* did not use the CD-1 strain of mice that was used in our studies, but instead used C3H and C57BL/6 mice because they have "found that careful hair cycle studies using a nonpigmented animal such as the CD-1 mouse, are difficult to interpret." Many high quality, seminal hair follicle cycle studies have been conducted in nonpigmented mice. While it is of interest to determine the efficacy of 17-β-estradiol and ICI 182,780 in other strains of mice, it is regrettable that CD-1 mice were omitted from their experimental design. The inclusion of CD-1 mice as a positive control would have allowed these investigators the chance to detect their dose error, as a 5000-fold lower dose would not be effective in altering the hair follicle cycle in CD-1 mice, thus indicating that something was wrong. The use of the correct dose of 17-β-estradiol and ICI 182,780 would alter the hair follicle cycle in CD-1 mice just as we reported in our studies. Although we do not know if 17-β-estradiol and ICI 182,780 will function in C3H and C57BL/6 mice as they do in CD-1 mice, we do know that other strains of mice such as SENCAR and TG.AC mice respond to 17-β-estradiol in a manner similar to CD-1 mice (unpublished results). Experiments to examine the efficacy of 17-β-estradiol and ICI 182,780 in C57BL/6 and C3H mice are currently underway in our laboratory.

Addendum We have completed the experiments on the effect of 17-β-estradiol and ICI 182,780 on the hair follicle cycle in C3H and C57BL/6 mice. Using the experimental conditions described in our previous publication (Oh and Smart, 1996) we found that in both C3H and C57BL/6 mice, ICI 182,780 caused telogen follicles to enter anagen and 17-β-estradiol arrested the hair follicles in telogen. Thus, if the correct dose (10 nmol per 200 μl acetone vehicle) of estrogen agonist and antagonist are employed, these agents alter the hair follicle cycle in C3H and C57BL/6 mice in a manner similar to that previously described in CD-1 mice.

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REFERENCE

Oh HS, Smart RC: An estrogen receptor pathway regulates the telogen-anagen hair follicle transition and influences epidermal cell proliferation. *Proc Natl Acad Sci USA* 93:12525–125230, 1996

Reply:

The experiments we reported in our letter were described as executed, and the mouse strains investigated were chosen for the reasons stated. The experiments were planned and conducted completely independent of one another but, unfortunately, the same mistake was made in both cases – the concentrations used were not as reported in the original report. Although we take responsibility for this oversight, we also recognize that the dosage listing is not entirely conventional to the field. Before starting the repeat experiments we consulted several independent researchers outside our respective laboratories; in all cases the understood dosage was interpreted exactly as we had.

When we repeated the work using the twice weekly protocol and the concentrations used originally by Oh and Smart (*Proc Natl Acad Sci* 93:12525), β-estradiol did indeed inhibit the normal progression of spontaneous anagen in pigmented mice (C57B16). From additional and subsequent studies that we have since executed, we have learned several important features about the role of estrogen receptor-mediated signaling in murine hair growth control that we did not formerly appreciate. We would hope to share these data in a future report.

We are indebted to Drs. Oh and Smart for calling our attention to this interesting phenomenon and regret the confusion our mistake might have caused.

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Note from the Editor: Due to an editorial office error, Drs. Smart and Oh were not given a chance to reply to the original letter about their paper by Drs. Stenn, Paus, and Filippi (*J Invest Dermatol*, 110:95, 1998). We apologize to all the authors for this mistake.