Objective: To characterize the epidermal permeability barrier function of skin during exposure to ionizing radiation.

Design: A prospective cohort study.

Setting: University hospital medical center.

Patients: Fifteen women receiving local radiation therapy (5000-6000 rad [50-60 Gy]) following breast-conserving surgery for breast cancer.

Main Outcome Measures: Clinical symptoms and transepidermal water loss (TEWL).

Results: Epidermal permeability barrier function is impaired in patients who exhibit clinical signs of radiation dermatitis. The functional damage to the stratum corneum induced by ionizing radiation occurs with a delayed course, starting within a mean period of 11 days and reaching maximal values after a mean period of 27 days (range, 13-75 days). The onset of TEWL increase precedes the onset of radiation dermatitis and the maximal TEWL measurements precede the peak of skin changes. Patients with an early onset of TEWL increase show a longer duration of skin symptoms.

Conclusions: Skin changes caused by radiation dermatitis are associated with an increase in TEWL. The barrier impairment is comparable to the changes observed with UV radiation exposure but exhibits an even more delayed course. Our results suggest that preservation of the epidermal permeability barrier function by topical treatment may ameliorate radiation dermatitis.

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The skin is a protective barrier against a variety of physical and chemical insults from the environment, including mechanical forces, natural and man-made toxins, extreme temperatures, low-voltage electric current, and electromagnetic radiation such as UV and ionizing radiation. The epidermal response to external injury has been well documented and is aimed at the maintenance of epithelial homeostasis.1,2 The latter is accomplished by a tightly regulated process of epidermal keratinization and differentiation.1'4 The end product of this process is the outermost sheath of the skin, the stratum corneum, consisting of protein-rich corneocytes embedded in a continuous, lipid-rich, intercellular matrix.2 This layer mediates the barrier properties of the skin, allowing for control of body fluid loss in an arid terrestrial environment and protection from physical and chemical external assault.

Cutaneous barrier function can be assessed quantitatively using bioengineering techniques, such as measurement of transepidermal water loss (TEWL), which has been proven valuable for the quantitation of external assaults to the skin.5-7 With this technique, impairment of the permeability barrier function in consequence of mechanical (ie, tape stripping) or chemical (ie, acetone, detergents) assault to the stratum corneum can be directly monitored.8 Recently, UV-B irradiation of murine skin has been shown to disrupt barrier homeostasis with a delayed course.9 In this study, we assessed TEWL in patients undergoing radiation therapy, because ionizing radiation is known to directly interfere with differentiation in the epidermis10 and the clinical appearance of irradiated skin bears similarities to a number of other skin conditions with impaired epidermal permeability barrier function (Table 1).11

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PATIENTS AND METHODS

INCLUSION CRITERIA
Female patients receiving radiation therapy for breast cancer were eligible for the study after completing routine staging procedures and giving informed consent. The study was approved by the local ethics committee. The Karnofsky index as measure of the patient’s overall neurological condition had to be greater than 70 in all patients to exclude bias due to general health deterioration. Further exclusion criteria were previous radiation therapy or radiation dermatitis; preexisting skin conditions, including atopic dermatitis, psoriasis, or ichthyosis; diabetes; as well as topical and/or systemic corticosteroid use during the 2 weeks before initiation of radiation therapy. Of the 26 patients who were initially approached, 9 refused to participate, and 15 of the 17 enrolled patients completed the study. Their median age was 57 years (mean, 55.4 years; range, 29-75 years), and their cancer stages were T1-3 N0-2 M0-1. Three patients demonstrated metastases to the axillary lymph nodes and/or to the sternal or supraclavicular region. Seven patients received adjuvant chemotherapy either before or after radiation therapy but none during radiation therapy or TEWL measurements. Patient characteristics are summarized in Table 2.

IRRADIATION
Twelve patients (T1-2 N0 M0) received tangential field irradiation to the breast and chest wall following breast-conserving surgery by external beam using photons (8 MV). One of these patients received an additional boost to the tumor bed using electrons (14 MeV). The 3 patients with metastases (T1-3 N1-2 M1) underwent mastectomy and received a combined radiotherapy of photons and electrons, including the sternal and/or supraclavicular region, respectively. The radiation was generated by a linear accelerator (Philips SL 20; Philips Electronics UK Limited, Crawley, England). Total doses ranged from 5000 to 6000 rad (50-60 Gy), which were applied in single fractions of 20 rad (2 Gy) 5 times a week.

ASSESSMENT OF RADIATION DERMATITIS
Clinical symptoms were assessed qualitatively according to the following parameters: erythema, desquamation, erosion, hyperpigmentation, and induration. Transepidermal water loss was measured for 4 test areas (1.3 cm² each) within the radiation field of the breast (1 site per quadrant) and on a control area of the nonirradiated, volar aspect of the forearm. Transepidermal water loss was recorded in grams per square meter per hour using a Servomed Evaporimeter (Stockholm, Sweden). The probe was handled with a clamp to avoid heating and applied parallel to the skin surface under a closed box with an open top to protect the measurement zone from excess air convection. Transepidermal water loss values were registered after equilibration of the probe on the skin (>60 seconds). Relative humidity, atmospheric pressure, and room and skin surface temperature were monitored along with the TEWL data recorded to ensure comparability of the environmental conditions. Measurements were taken before radiation therapy and biweekly during therapy (total time, 3-6 weeks). In 11 of 15 patients, additional follow-up measurements were taken every 2 weeks for 4 to 8 weeks after completion of radiation therapy. To calculate deviations of measurements from pretreatment baseline values, expressed as percentages, the following formula was used:

\[ \frac{\text{TEWL}_{\text{irradiation area before irradiation}}}{\text{TEWL}_{\text{control area before irradiation}}} - 1 \] \times 100%.

The maximal TEWL value from 4 test sites was used for each time point. In cases of severe cutaneous reactions, routine topical regimens for radiation dermatitis were used, including topical emollients, corticosteroids, and wound dressings. However, no topical treatment was allowed for at least 8 hours before TEWL measurements. When skin erosions occurred (6 patients), permeability barrier function was not quantitated because of exceptionally high TEWL values (up to 25-fold increase).

STATISTICAL ANALYSIS
Pretreatment and posttreatment measurements of TEWL were compared using the t test for paired measurements; \( P \leq .05 \) was considered statistically significant.

RESULTS

CLINICAL ASSESSMENT OF RADIATION DERMATITIS
Clinically, human skin is known to exhibit erythematous changes after exposure to ionizing radiation. A distinction between immediate and typical erythema (after several weeks of repeated exposure) has been made. Four of our 15 patients exhibited an immediate erythema (24-hour erythema), which arose within a few hours after irradiation and subsided within 3 to 4 days. Fourteen of 15 patients developed a typical radiation erythema, which set in after a mean interval of 23 days (median, 22 days; range, 6-37 days) and lasted for an average of 22 days (median, 20 days; range, 6-45 days). In 1 patient, an immediate and a typical erythema were followed by an additional late erythema (onset at day 38, duration of 10 days). Six patients developed skin erosions, which started after a mean period of 37 days after onset of irradiation (median, 43 days; range, 27-68 days). Desquamation was observed in 3 patients after a mean period of 61 days (median, 49 days; range, 21-65 days) and hyperpigmentation in 8 patients after a mean period of 57 days (median, 60 days; range, 46-91 days). Figure 1 illustrates the sequential onset of skin findings in our group of patients. Most patients had 2 or more types of these reactions, but 1 patient did not develop any signs of radiation dermatitis. Clinical signs of radiation dermatitis were limited to the irradiation field. All patients exhibited subcutaneous induration of the irradiated skin of variable degree, beginning approximately 3 weeks after initiation of radiation therapy. Associated symptoms included transient pruritus or burning sensations. Six patients required topical therapy because of the severity of skin symptoms after 4 to 5 weeks, which
Twelve of 15 patients showed an increase of TEWL during radiation therapy. Changes in TEWL started within a mean period of 11 days (median, 8 days; range, 4-26 days). Transepidermal water loss values increased to a mean maximum of 2-fold over pretreatment measurements (mean, 11.8 g/m² per hour). Pretreatment values compared with the maximum TEWL readings during irradiation are shown for each individual patient in Figure 2. Maximal measurements were reached within a mean period of 27 days (median, 25 days; range, 13-75 days) after the onset of radiation therapy. Readings were significantly increased compared with pretreatment values (P = .04, Figure 2). Follow-up measurements were performed in 11 patients after completion of radiation therapy. In this group, TEWL decreased to baseline values within a mean of 66 days (median, 62 days; range, 34-86 days) after onset of therapy.

Increases of TEWL were associated with the occurrence of clinical symptoms (ie, erythema, desquamation, erosions). They did not correspond, however, to the biphasic course of erythema. The onset of TEWL increase (after a mean period of 11 days) preceded the onset of radiation dermatitis (mean, 22 days). Patients with an early increase in TEWL (<11 days after initiation of radiation therapy) reached higher maximal TEWL readings during radiation dermatitis; this difference, however, was not statistically significant (data not shown). The duration of skin symptoms was longer in the group of patients with an early TEWL increase (Figure 3).

Maximal TEWL increases were observed only when clinical signs of radiation dermatitis were present, but maximal TEWL (mean, 27 days) preceded the peak of the skin changes (mean, 35 days; P < .05). Increases in TEWL were most accentuated in the lower medial quadrant of the breast and the intertriginous areas, including the submammary and axillary folds.

Radiation dermatitis is a common and dose-limiting adverse effect of radiation therapy.15,16 Its course and severity are known to depend on both total dosage and fractionation.17,18 Today, conservative surgical strategies for breast cancer, breast-conserving combined with postoperative irradiation, when correctly performed, can provide results as effective as the more invasive surgical
strategies used in the past. Although the skin is not the primary target of ionizing radiation in most cases, exposure of the skin is inevitable. During radiation therapy for breast cancer, the skin is exposed to significant doses of radiation to treat a maximum number of potential, subclinical tumor remnants.

We evaluated the effect of ionizing radiation on epidermal permeability barrier function in a clinical setting by monitoring TEWL values during radiation therapy for breast cancer. Our data demonstrate that radiation therapy for breast cancer is associated with impaired epidermal barrier function. The barrier abnormality induced by ionizing radiation displays inherent differences from other models of barrier abrogation. Mechanical or chemical disruption of the barrier is associated with an immediate barrier defect due to removal of extracellular lipids from the stratum corneum. In contrast, the barrier abnormality induced by ionizing radiation is delayed as has earlier been reported for UV-exposed skin.9 The delay in barrier impairment caused by ionizing radiation (mean onset, 11 days after irradiation; maximum after a mean of 27 days as opposed to 72 hours after UV exposure) may be explained by the facts that the biological tissue reaction to ionizing radiation in general occurs more slowly and that in radiation therapy for breast cancer a considerable amount of ionizing radiation is aimed at deeper, subcutaneous anatomical structures. For ethical reasons, skin biopsy specimens were not obtained from the cancer patients enrolled in the present study. However, the published histological data on radiation dermatitis describe perivascular inflammatory infiltrates around dilated blood vessels with swollen endothelial cells14,15 and degenerative changes of the epidermis with epithelial cell death and hypoplasia.10 Data from the mouse model indicate that ionizing radiation inhibits proliferation and mediates apoptosis in the epidermis by inducing damage to the DNA.10 Moreover, for UV-exposed skin, ultrastructural observations are available, showing the outward migration of a band of lamellar body-deficient keratinocytes, which is associated with abnormal extracellular bilayer formation and a delayed increase in epidermal lipid production.20

The inflammatory reaction, which can be observed clinically and histologically, may be a direct effect of the ionizing radiation on the dermis. The involved inflammatory mediators may reach the epidermis by diffusion, causing additional impairment of epidermal differentiation and barrier function. However, recent work by Trott et al10 in the mouse model has questioned a causal relationship between dermal inflammation and epidermal proliferation or differentiation in radiation dermatitis, because prior treatment with indomethacin did not suppress and prior UV-B exposure did not accelerate (by inducing inflammation) epidermal repopulation. On the other hand, the inflammatory reaction may be secondary to the barrier defect, which itself is known to induce cytokine secretion and may in turn cause fibrosis within the underlying dermal tissue21 (explaining the very common fibrosis after irradiation).

Although the functional assessment presented herein does not allow distinguishing whether the barrier impairment associated with radiation dermatitis is of primary or secondary nature (Table 1), it seems likely that our observation has clinical implications. In fact, this can be tested by the application of topical formulations to radiation dermatitis, since lipid mixtures have been shown to accelerate barrier repair.22 Clinically, radiation dermatitis is assessed by visual inspection and palpation. Noninvasive bioengineering techniques have been used for more accurate evaluation. Most of these techniques have been designed to quantitate erythema using colorimetry, spectrophotometry, or laser Doppler imaging.23,24 Stromal reactions that are not visible to the eye primarily have been assessed using 20-MHz ultrasonic imaging or dielectric methods.25,26 In contrast, our data obtained by evaporimetry provide evidence for damage to the most superficial layer of the skin, the stratum corneum, which can be easily assessed for therapeutic intervention. Thus, application of topical therapeutic agents to the skin might be useful for prophylaxis or therapy of radiation dermatitis and might be monitored by the experimental setting used in this study.

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REFERENCES