Radiation therapy is an effective treatment for various types of cancer. Overall estimates of the worldwide incidence (absolute number of cases per year) of 26 types of cancers in 2002 include 10.9 million new cases, 6.7 million deaths, and 24.6 million people living with the disease within 5 years of diagnosis. Although geographical variations exist, a fair estimate for both the United States and the European Union is that 50% of long-term cancer survivors will have had radiotherapy as a primary treatment or in combination with surgery and/or chemotherapy.

Radiotherapy is used to limit the growth of neoplastic cells. Because radiotherapy exposes healthy cells within the vicinity of tumors and between the tumor site and the radiation source to radiation, undesirable sequelae are unavoidable. Damage is usually most prominent in tissues with rapid rates of proliferation, such as skin, mucosa, and bone marrow. Often, multiple adverse cellular effects are induced by radiotherapy because free radicals and peroxides are generated in tissues, which cause changes in DNA, proteins, and cellular membranes. Although cells possess scavenging
mechanisms to remove potentially destructive free radicals, these protective mechanisms are overcome by episodes of extensive or repeated radiation. Where repair is successful, normal cell function resumes but incomplete repair can lead to mutations that cause cellular dysfunction, altered proliferation, or carcinogenesis.3

Radiation Injury

Nineteenth century scientists who pioneered development of radiation for medical use recognized its adverse effects. Complex changes normally manifest in patients as either immediate (short-term or early) side effects or delayed
A recent review\textsuperscript{11} of normal tissue response to radiotherapeutic injury provides valuable insight into reactions in epithelial surfaces. These reactions account for immediate effects that include changes in endothelial cells, mast cells, fibroblasts, and myofibroblasts, leading to delayed injury. Because the mechanisms of these changes are not yet fully explained, developing effective clinical interventions is difficult.\textsuperscript{12,13} Also, the absence of an assessment tool to grade irradiated skin reactions may have limited the development of clinical guidelines.\textsuperscript{14}

**Management of Radiation-damaged Skin**

Critical analysis of the evidence of clinical interventions available for the prevention and treatment of acute radiation injury demonstrate the lack of objective data; however, skin cleanliness, hydration, and the use of moist healing principles seem appropriate.\textsuperscript{11,14,15} Historically, management has focused on symptoms,\textsuperscript{11} using emollients such as chamomile cream, almond oil, aloe vera, and aqueous cream to prevent skin reaction.\textsuperscript{12,16-18} To date, only one evidence-based practice guideline for management has been developed\textsuperscript{14}; universally accepted guidelines for the management of radiotherapy-induced skin injuries do not exist. Different methods are used in different countries and nurses often base decisions on local knowledge and personal experience.

**Treating chronic wounds with honey.** Honey is an ancient wound remedy. Licensed wound care products containing honey are now available in developed countries, increasing use for the treatment of chronic wounds. Clinical evidence for the efficacy of honey has been reviewed and its potential value within oncology care identified.\textsuperscript{19} The ability to expedite healing and reduce pain, together with antimicrobial and anti-inflammatory properties, were considered relevant to patient management. The authors’ experience using honey on chronic wounds\textsuperscript{20-22} suggested that using honey may facilitate healing and reduce pain in wounds in patients with radiation-induced skin damage. To evaluate outcomes, a prospective series of four patients who had undergone radiotherapy and experienced subsequent wound breakdown or tissue damage were
treated with active *Leptospermum* (manuka) honey. All patients were switched from conventional dressings to honey due to slow healing rates or because patients were experiencing pain at dressing changes. Endpoints were progress toward healing and/or less painful dressing changes.

**Procedure**

The patients were referred to the tissue viability service within the hospital when healing failed to progress. The cases reported here involved patients who experienced the same problems and were treated by the nurse specialist during a 2-year period. Patients 1, 2, and 4 had long-term effects from radiotherapy treatment received several years or months earlier. Patient 3 experienced short-term effects from radiotherapy treatment received immediately before referral to the tissue viability service.

Patients or their next of kin provided written consent for study participation. Patients 1, 2, and 3 were treated during their...
inpatient episode of care and patient 4 was treated by community nursing staff according to a regimen prescribed by one of the authors. Dressings to suit the condition of the wound had been applied before referral. The study product, Medihoney™ Antibacterial Honey (Medihoney Pty, Ltd, Australia), is a mix of Australian and New Zealand Leptospermum honeys (derived from jellybush and manuka nectar, respectively). The gamma-irradiated (sterile) honey, available in 10- and 20-g tubes, is licensed in the UK and indicated for use in chronic wound care.

**Patient 1.** In November 2003, 63-year-old Mr. G was diagnosed with vocal cord carcinoma and underwent a course of radiotherapy that was completed in February 2004. His past medical history included chronic obstructive pulmonary disease. As a result of radiotherapy, the skin around Mr. G’s neck and upper chest atrophied and was extremely fragile. He was admitted to hospital in January 2005 with increased hoarseness, weight loss, and dysphagia. A direct laryngoscopy showed an irregular area on the midline/right supraglottic area, which proved to be poorly differentiated invasive squamous cell carcinoma. In early February, Mr. G developed left lower lobe pneumonia. A tracheostomy was performed before total laryngectomy, thyroidectomy, bilateral selective neck dissection IIa, III, IV, and Povox valve insertion. At 15 days post-op, the wound began to break down from the right side of the stoma (see Figure 1a). An area to the left of the stoma broke down 19 days postoperatively (see Figure 1b.)

Although dressings were changed daily, the skin’s fragility and the copious amount of exudate contributed to maceration of the surrounding skin. The wound base to the left of the stoma had a layer of thick slough. The wound to the right of the stoma contained small areas of granulation tissue. During the first week, the wounds were treated with daily applications of hydrofiber rope to manage the exudate but Mr. G found this painful and uncomfortable. To reduce pain associated with the dressing and to assist healing, a hydrofiber rope dressing (Aquacel™, Convatec Ltd, a division of E.R. Squibb & Sons, princeton, NJ) was soaked with honey before application. This method kept the honey in contact with the wound bed even though this type of wound produces copious amounts of exudate. Daily dressing changes continued due to the amount of wound exudate and honey also was applied directly to the periwound area to reduce and prevent maceration. An absorbent pad was used as the secondary dressing. Because of the tenderness and fragility of the surrounding skin, a paper adhesive tape was used to secure the dressing. After 5 weeks of treatment, the wound to the right of the stoma healed (see Figure 1c) and the wound to the left of the stoma had de-sloughed and was granulating well (see Figure 1d). Dressing change frequency decreased as healing progressed. After 8 weeks, the wound to the right of the stoma remained healed (see Figure 1e). Unfortunately, Mr. G died.
before the second wound had healed completely; the wound was 80% healed and the remaining area had de-sloughed and was granulating well (see Figure 1f).

It is difficult to know whether the patient’s wound would have gone on to heal with the application of hydrofiber dressings alone. Although no recognized pain scale was employed, Mr. G reported that applying honey lessened trauma to the wound during dressing changes.

**Patient 2.** In 1988, 93-year-old Ms. H had a squamous cell carcinoma of the left inner canthus of her left eye removed. Subsequent radiotherapy was completed in November 1989. The eye was later removed for recurrence of the tumor of the left orbit in 1990. In 2007, Ms. H developed a second tumor on her left cheek; she declined further surgical treatment.

Community nursing staff dressed the cheek wound regularly using appropriate dressings to suit the condition of the wound until early July 2007 when the wound deteriorated and became difficult to manage. To forestall further deterioration, Ms. H underwent 2 weeks of radiotherapy to her left cheek; she subsequently developed cellulitis secondary to the treatment. She was admitted to hospital in early July 2007 when the wound deteriorated and became difficult to manage. The area was painful, swollen, and erythematous, bled easily, and was discharging pus. The surrounding area was fragile and tender to the touch (see Figure 2a). A wound swab confirmed the presence of *Staphylococcus aureus* for which the patient was prescribed amoxicillin (500 mg TDS) and flucloxacillin (500 mg QDS).
Honey was applied to the area using a nonadhesive foam dressing secured with tape. Initially, the dressing was changed daily; change frequency was reduced as the wound improved. The area around the wound became less inflamed but an area of slough developed within the wound. The same honey and nonadhesive foam dressing was applied, successfully debriding the area (see Figure 2b,c,d). Exudate amount lessened as the wound improved.

Ms. H complained of pain from the area, especially at dressing change. She could not differentiate whether the pain had increased following honey use; acetaminophen (1 g) at dressing change provided relief.

Ms. H was discharged from the hospital before complete healing had taken place but a markedly improved rate of healing over a 6-week period was observed. The inflammation had reduced, the area of the wound was approximately 90% smaller, and the remaining 10% contained soft slough.

Patient 3. In April 2007, 76-year-old Ms. J, who had type 2 diabetes treated with metformin, presented at the accident and emergency department with a large bleeding vulval mass. She was transferred to a gynecologist and underwent 24 doses of radiotherapy. She was transferred to Intermediate Care for rehabilitation in early June 2007; at that time, she had extensive painful tissue breakdown in the irradiated area. She had been prescribed ‘Tri-Adcortyl cream™’ (Bristol-Myers Squibb, Princeton, NJ), which is indicated for severe inflammatory disorders and contains neomycin and mystatin; and Geliperm hydrogel dressing (Geistlich Medical, Wolhusen, Germany) applied to the area three times per day. She complained that the area was very painful and uncomfortable and that dressing application was traumatic.

Ms. J was assessed by the tissue viability nurse in June 2007. The wound area was erythematous with painful superficial skin loss and included the groin, vulva, and periurethral area extending to the buttocks (see Figure 3a,b). Staff was advised to bathe her daily and apply honey mixed with a small amount of white soft paraffin for ease of application three times per day. After 6 days of this therapy, the area greatly improved and Ms. J was pain-free. She continued to bathe daily and was able to apply the honey herself, improving her independence. The area healed after 2½ weeks (see Figure 3c–f). Despite her diabetes, daily honey application of 10 to 20 g had no adverse effect on her blood sugar levels.

Patient 4. Seventy-six-year-old Ms. K was diagnosed with a grade III ductal carcinoma of the left breast with lymphovascular invasion in April 2004. Two weeks later, she underwent a left mastectomy and axillary clearance. Between May and August 2004 following her operation, she underwent chest wall radiotherapy. By August 2004, Ms. K’s mastectomy wound failed to heal at the lateral end of the scar. Visiting district nurses redressed the wound with alginate packing. In December 2004, the lateral part of Ms. K’s wound was excised to debride the wound and encourage healing.

At her January 2005 outpatient appointment, Ms. K’s wound still had failed to heal. The area exhibited localized redness and maceration caused by the wound exudate. A small cavity approximately 3 cm in depth was noted along with two smaller superficial broken areas along the original suture line (see Figure 4a). A honey-soaked hydrofiber rope was loosely packed into the wound and honey applied along the suture line. A no-sting barrier film was applied to the periwound area and an adhesive foam dressing was applied to the wound. Initially, Ms. K was advised to remove the dressing and shower daily. As the wound improved, dressing change frequency was reduced.

After 2 weeks, Ms. K’s wound was substantially smaller (see Figure 4b). After 4 weeks of honey treatment, the cavity was almost closed (see Figure 4c) and, after a little more than 6 weeks of treatment the wound healed and localized redness subsided (Figure 4d). Table 1 summarizes patient treatment information.

Discussion

Four patients with radiotherapy-impaired wounds and compromised skin received care that included medical grade honey. In all cases, a change from conventional dressings to the topical application of honey was followed by a noticeable improvement in healing. It is not possible to report complete healing in all examples because Patient 1 (Mr. G) died and Patient 2 (Ms. H) was lost to follow-up but the latter reported a noticeable reduction in pain once honey was introduced. No adverse events were observed and even though Patient 3 (Ms. J) had type 2 diabetes, daily honey applications to her wound had no adverse effect on her blood sugar levels. All patients readily accepted honey as a dressing for their wounds.

Radiation damage to healthy tissue begins immediately after radiation exposure but clinical and histological features may not be apparent for weeks, months, or years after treatment. In head and neck cancer patients, radiotherapy has been shown to affect not only skin, but also mucosa, subcutaneous tissues, bone, and salivary glands. Skin and oral mucosal reactions are not uncommon but because the extent of the damage is related to the radiation regimen implemented, as well as genetic and personal factors, they are not easily predictable. A prospective, descriptive, correlational study with repeated measures of 126 women undergoing radiotherapy for breast cancer noted that predictive factors for developing severe skin reactions included smoking, poor lymphatic drainage, weight and/or large breast size, and a history of breast cancer; however, as age increased, the risk of severe skin reaction decreased.

The importance of choosing suitable dressings and topical treatments for wounds in patients undergoing radiation therapy is recognized, despite the absence of empirical evidence. Currently, the chronic irradiated wound is cared for in a manner similar to other chronic wounds because the exact microenvironment of the irradiated wound remains undefined.
According to a review, adequate debridement followed by a use of a dressing that promotes granulation tissue formation have been recommended; adhesive dressings are avoided to prevent epithelial injury. Porock and Kristjanson concluded that dressings promote healing where skin loss has occurred but that empirical evidence was scant to support the use of any specific type of dressing. In a non-comparative study of 20 patients (18 of whom completed the study) in a university-based radiation department, hydrocolloids were used in the management of radiation-induced moist skin desquamation in 18 patients but the small study size and failure to use another dressings for comparison did not facilitate accurate clinical assessment.

In a single case study, a patient with a radiation-induced ulcer of the left breast following partial mastectomy was treated successfully with hyperbaric oxygen. The study demonstrated that the breast ulcer showed a positive response to hyperbaric oxygen after 7 to 8 days of treatment with signs of early healing and re-epithelialization. It reduced from 8 cm x 4 cm in maximum diameter to 4 cm x 3 cm following 30 daily treatments and healed 4 weeks after hyperbaric oxygen treatment was stopped. However, the authors acknowledged that role of hyperbaric oxygen treatment in the management of nonhealing radiation ulcer in breast cancer is poorly documented. A retrospective study of 27 patients with gynecological malignancies showed an overall reduction of 96% in the median size of wound defects. However, of the 27 patients included in the study, only three had wound failures occurring in the radiation field. Because evidence to support these adjunctive treatments is limited by small numbers of patients, the need for specific equipment or facilities, and pain at dressing changes, investigation of additional strategies to manage the complexities of radiation-damaged skin is justified.

Table 1. Patient treatment data and results

<table>
<thead>
<tr>
<th>Patient</th>
<th>Received radiotherapy (duration)</th>
<th>Wound treatment history (duration)</th>
<th>Length of time treated with honey</th>
<th>Result</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>November 2003</td>
<td>Postoperative wound present for 1 week</td>
<td>8 weeks</td>
<td>Right side wound healed week 5; Left side: 80% healed week 8; patient died before full healing</td>
<td>Application of honey and hydrofiber rope less painful than hydrofiber alone.</td>
</tr>
<tr>
<td>Patient 2</td>
<td>November 1989 and July 2007</td>
<td>7 months</td>
<td>6 weeks</td>
<td>75% reduction in size of wound</td>
<td>Patient lost to follow-up</td>
</tr>
<tr>
<td>Patient 3</td>
<td>April 2007</td>
<td>Post radiotherapy tissue breakdown 2 weeks</td>
<td>2 weeks</td>
<td>Complete healing</td>
<td>Achieved pain-free dressing changes</td>
</tr>
<tr>
<td>Patient 4</td>
<td>August 2004</td>
<td>9 months</td>
<td>6 weeks</td>
<td>Complete healing</td>
<td>Local redness resolved as wound healed</td>
</tr>
</tbody>
</table>

Radiation had a negative impact on wound healing in the four patients reported in this case report. The use of conventional dressings did not facilitate healing and three patients reported that dressing changes were traumatic and painful. Although this was a small cohort study without a control arm, the observed improvement in healing when conventional treatments were changed to honey is similar to another case report describing the use of honey to facilitate healing of a chronic wound that had developed on tissue damaged by radiotherapy 30 years earlier.

Other case studies have reported on the use of medical honey to treat diverse wounds in pediatric oncology patients and to eradicate methicillin-resistant *Staphylococcus aureus* from their wounds. In a prospective, controlled randomized study involving 24 skin reactions in 21 breast cancer patients, honey demonstrated a trend toward faster healing and reduced discomfort in radiation-induced skin toxicity when compared to paraffin, but the study sample size was insufficient for statistical analysis.

Results of two preliminary studies suggest that honey may protect oral mucosa from radiation damage. In Malaysia, 40 patients were divided into two equal arms and received either radiation or radiation plus topical honey; a significant reduction in symptomatic grade 3/4 mucositis was seen in honey-treated patients compared to the control group. In Iran, a similar study found significantly reduced mucositis in the honey-treated patients. Animal studies suggest other treatments for the amelioration of radiation-induced impaired wound healing such as platelet-derived growth factor-BB, transforming growth factor beta-1, interleukin-1, curcumin (an extract of turmeric), and aloe vera. Their clinical efficacy has yet to be tested.
HONEY AND RADIOTHERAPY-IMPARED WOUNDS

Conclusion
The results of this case study suggest that recalcitrant wounds resulting from, as well as wounds exacerbated by, radiation therapy may benefit from the topical application of honey. Controlled clinical studies with larger numbers of patients are needed to establish honey’s healing potential and to determine optimum treatment protocols.

References