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Sweat gland function as a measure of radiation change

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Abstract

Background: Radiotherapy may result in dryness of the skin even when no other change can be detected. We describe a system for recording the electrical conductance of skin as a measure of sweat gland function.

Patients and methods: In 22 normal volunteers close agreement was obtained between measurements obtained from comparable sites on both sides of the chest. Measurements were subsequently made in 38 patients treated by radiotherapy to one side of the chest for tumours of the breast or lung using one of five different fractionation schedules. Simultaneous readings were obtained from both sides of the chest with the non irradiated side acting as a control.

Results: A dose response relationship was demonstrated: five patients who received the equivalent total dose of 15 Gy in 2-Gy fractions showed no change in conductance. Sixteen out of 23 who received an equivalent total dose of 42–46 Gy in 2-Gy fractions had a greater than 22% reduction in mean skin conductance compared with that of the control areas despite the skin appearing normal in the large majority. Marked changes in skin conductance were seen after higher total doses. In a prospective study 18 women receiving breast irradiation underwent weekly readings during treatment. A mean reduction of 40% in skin conductance was noted by the end of the second week of treatment prior to any clinical evidence of radiation change. Skin conductance returned to normal in 44% of patients by 6 months. In the remainder, those patients who showed the greatest reduction in skin conductance during treatment demonstrated the least recovery.

Conclusions: Changes in sweat gland function can be detected and quantified in skin which may otherwise appear normal. Differences may so be demonstrated between areas treated using different fractionation schedules and the method may be applied to the detection during radiotherapy of unusually sensitive patient

Keywords: Sweat glands; Radiotherapy; Skin conductance; Dose relationship; Radiosensitivity; Radiation morbidity

1. Introduction

The skin reaction seen during and after radiotherapy has commonly been recorded using arbitrary scales for the clinical findings. Objective methods have been employed to quantitate radiation change in the skin and these have included instrumental measurement of erythema, pigmentation and hair diameter [7,9,32].

An early observation following the introduction of therapeutic radiation was that it caused dryness of the skin and this led to its use in the treatment of hyperhidrosis in the early part of this century [4]. Because 'Roentgen rays could reduce the activity of the sweat gland without causing any visible alteration of the skin', it was suggested that in terms of function they are relatively radiosensitive but provided that there are no anatomic changes in the sweat gland, are able to recover within a few months [5]. This temporary cessation in sweating was demonstrated by Price [26] following electron treatment for mycosis fungoides when patients received a dose of 3600 rads over 10 weeks using 2.5-MeV electrons. The reduction in sweat gland function which followed fully recovered over 3–6 months. When, as in the use of radiotherapy for the cure of a carcinoma, higher doses are given, a permanent dryness of the skin is commonly observed.

Techniques which have been employed for the study of the sweat glands in patients fall essentially into two groups; those that visualise the glands, and those which determine their function [2,10]. In the first group sweat produced by a gland can be visualised by the iodine–starch reaction or by reaction with other substances such as bromphenol blue powder [27,29]. The silicon elastomer mould allows a three dimensional negative impression of the skin to be obtained with emerging sweat droplets visualised as small holes corresponding to the sweat pores [18]. The second group of methods quantitate the secretion of sweat and include the water vapour analyser [25], filter paper absorption [23], and the use of an anaerobic bag [6]. The electrical

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resistance of skin can be used to measure changes in the water content [11,14]. This, as an approach to the measuring of sweat gland flinction, has been recorded [10,23] but is not described in recent reviews of non-invasive methods which may currently be employed [2,10].

The development of a practical method for the quantitative study of sweat gland function after radiotherapy has long been an interest of our group. The number of flinctioning sweat glands surviving after radiotherapy has been successfully measured using the silicon elastomer mould [21]. Since the electrical conductance of the skin surface depends on the concentration of ionic species in the water upon the surface, and that contained within it, a system was designed to record the electrical conductance of the skin as a measure of sweat gland function after radiotherapy.

2. Material and methods

2.1. Skin conductance measurement system

There are two applicators, each having five metal electrodes embedded 20 mm apart on a silicon rubber sheet. The adjacent pairs of electrodes monitor the surface conductance of the skin, with each applicator thus providing simultaneous measurement from four adjacent fields (Fig. 1). The silicon rubber prevents liquid evaporation, therefore an increase in conductance is to be expected with time: the kinetics of this increase provides a measure of the activity of the sweat glands in the region between the electrodes. An amplifier/converter applies a constant, 1-V amplitude, 1 kHz a.c. square wave across the selected pair of electrodes and measures the resulting current, which is proportional to the conductance. The measured current square wave is synchronously rectified so that a d.c. voltage is produced, which is recorded. At the low frequency used, the reactive current component (due to capacitance between the electrodes) is relatively small and the resulting d.c. is thus primarily a measure of the real, i.e. resistive, component of the current. A computer graphically records all eight traces simultaneously, with time along the *x*-axis (min) and conductance along the *y*-axis (microSiemens). The data is stored on EXCEL, and curve fits applied to each graph.

2.2. Method

Patients were requested not to apply any skin preparation such as moisturising creams and talc for 24 h prior to testing as they can influence the capacitance of the skin [20]. Hairy skin gives poor electrical contact, but this was overcome, when necessary, by shaving. Measurements were undertaken in a quiet shaded room kept at stable temperature with the patient lying on a bed having rested for 15 min. Prior to use the electrodes were cleaned with isopropyl alcohol and dried with gauze. Data was accumulated before the applicators were applied to the skin to obtain a baseline reading. It was important to ensure that the electrodes made good

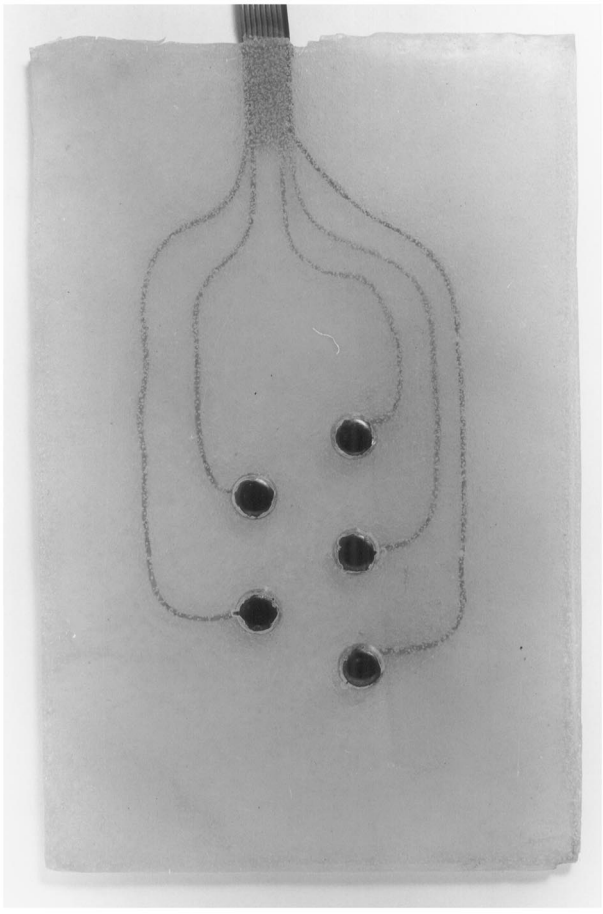

Fig. 1. Apparatus employed to record skin conductance.

electrical contact with the skin during the period of 6 min of data acquisition. The initial vertical rise in skin conductance reflected the moisture of the skin at the time of applying the applicators. There was then a fairly steep rise in conductance as moisture collected under the silicone sheet before giving way to a more gradual rise which, in a number of cases ended in a plateau reflecting maximal conductance (Fig. 2).

The area under the curve was calculated for the first 2 min after the applicators had been applied to the skin, as this corresponded to the time when the greatest change was seen. The average value for the area under the curve over the first 2 min was calculated for each applicator.

Observable changes following radiotherapy were scored using the ‘element system’ [8].

3. Patients

3.1. Normal volunteers

Sweat gland distribution varies between individuals and from one area of the body to another [18,28]. The distribution and number of sweat glands in an area on the one side of

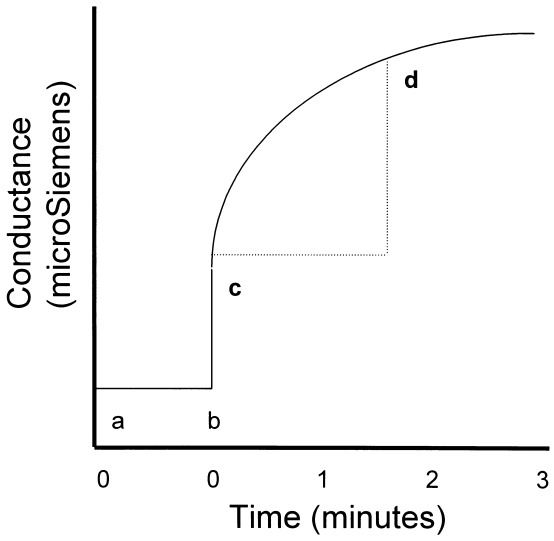

Fig. 2. The analysis of skin conductance changes: a–b initial baseline, b–c vertical rise on contact, c–d rise in conductance over 2 min. The area under the curve during the first 2 min of measurement is contained within the dotted lines.

the body has been found to be closely similar to that on the other side [18,28]. Conductance readings over 6 min were obtained simultaneously from identical areas on both sides of the chest in 13 females and nine males in order to assess the variability within individuals (Fig. 3).

3.2. Retrospective study

Conductance measurements were carried out in a group of patients who had been treated with radiotherapy two or more years previously for a malignancy in one side of the thorax. An irradiated area was tested with an identical area on the untreated side acting as a control.

Five patients presenting inoperable locally advanced non small cell carcinoma of the lung had received radical radiotherapy with 6-MV photons using either the CHART or CHARTWEL (CHART-Weekend less) regime [31]; these had received the lowest dose to the skin. The remaining patients received post operative radiotherapy following either a biopsy or a local excision of a primary breast cancer. A cobalt unit had been employed using two tangential 'wedged' fields and one of four different dose/fractionation schedules used. Measurements were made away from the site of surgery in order to avoid the area which had received an electron boost.

3.3. Prospective group

Patients with carcinoma of the breast who had undergone wide local excision and were attending for post operative radiotherapy entered this study. All were treated by a 6-MeV linear accelerator, and received 40 Gy prescribed as a minimum tumour dose in 15 fractions over 3 weeks to the breast, using tangential fields. The site of the primary tumour then received a boost of 10 Gy in five fractions using 8–10-MeV electrons. Conductance readings were obtained prior to radiotherapy and then were repeated once or twice weekly during treatment. The applicators were placed over identical areas of each breast, with the non-treated breast being used as a control. The area of the boost was avoided as in the previous group. The initial reading was normalised as 100% and subsequent readings expressed as a percentage of the control reading. Once treatment was completed, skin conductance readings were repeated at routine outpatient follow-up attendance.

3.4. Calculated dose at the sweat glands

The sweat glands were considered to be at a depth of 1 mm and the radiation dose was determined at that position. Measurements were made using a thin windowed NACP parallel plate ionisation chamber. The graphite front window was 0.6-mm thick, which is equivalent to a water thickness of 1 mm. Readings obtained were repeatable within the range of $\pm 5\%$. For the breast cases, the sweat glands were calculated to have received approximately 94% of the minimum tumour dose.

For each fractionation schedule employed, the biological effective dose (BED) and the equivalent total dose given in 2-Gy fractions was calculated using an α/β ratio of 3 [12]. Changes in sweat gland function were then related to the BED and equivalent total dose in 2-Gy fractions.

3.5. Statistical analysis of results

Control readings were assessed using method comparison studies [3]. For the different fractionation schedules employed, paired *t*-tests were performed to determine whether there was a significant difference in skin flinction of the irradiated area compared to the control area [22]. Simple linear regression was used to assess whether a dose response effect existed.

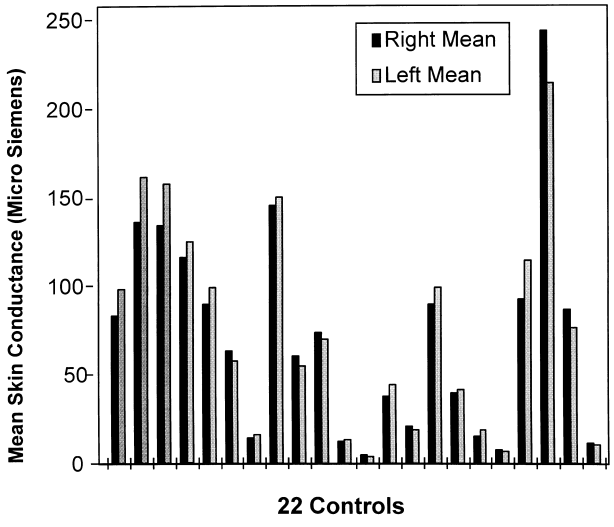

Fig. 3. Mean skin conductance (rise first 2 min) for both sides of the chest in 22 controls.

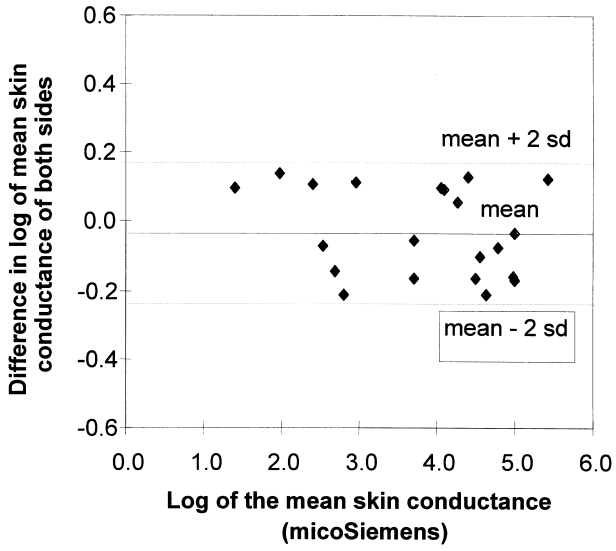

Fig. 4. Difference in the log of the mean skin conductance for both sides plotted against the log of the mean skin conductance. Method comparison study [3]: mean difference is 0.03; 95% limits of agreement are −0.21–0.18 on the log scale. Antilogs of limits 0.78 to 1.19.

4. Results

4.1. Normal volunteers

Twenty-two patients, nine males and 13 females with a mean age of 67 years (range 32–79 years), acted as controls. As expected, a large range of values was obtained (Fig. 3), with mean skin conductance varying between individuals from 3.9 to 214 μS (microSiemens). However, good agreement was observed between mean skin conductance readings obtained from comparable areas on both sides of the chest within the same individual (Fig. 4). For 95% of the cases the measurement from one side differed from the other side by 22% or less (Fig. 5).

4.2. Retrospective group

Measurements were obtained from 38 patients, 34 females and four males with a mean age of 59 years (range 39–74 years). No difference in skin conductance was observed in the irradiated area compared to the non irradiated in five patients who received the equivalent total dose of 15 Gy in 2-Gy fractions. However, patients receiving the intermediate doses (total equivalent dose of 42–46 Gy given in 2 Gy per fraction, BED 70–76) showed a significant reduction in skin conductance ($P = 0.05$) despite no discernible skin changes being present in the tested area in 78%. Of these, a greater than 22% reduction in skin conductance occurred in seven (58%) of 12 patients receiving an equivalent total dose of 42 Gy given in 2-Gy fractions and in nine (82%) of 11 patients receiving an equivalent total dose of 46 Gy given in 2 Gy fractions (Fig. 6).

With the higher doses the changes in skin conductance of the treated breast were more marked. All of the patients treated with an equivalent total dose of 50 Gy given in 2-Gy fractions had a greater than 36% reduction in skin conductance, with four out of eight showing a greater than 50% decrease. The two patients treated with the highest total equivalent dose of 59 Gy given in 2-Gy fractions showed the greatest reduction (Fig. 6). The number of patients treated to this dose was small as this regime was used in patients with advanced local disease and consequently few patients survived long term.

4.3. Prospective group

Eighteen women with a mean age of 59 years (range 35–81 years) were entered into this study. During treatment a continued reduction in skin conductance was noted, so that

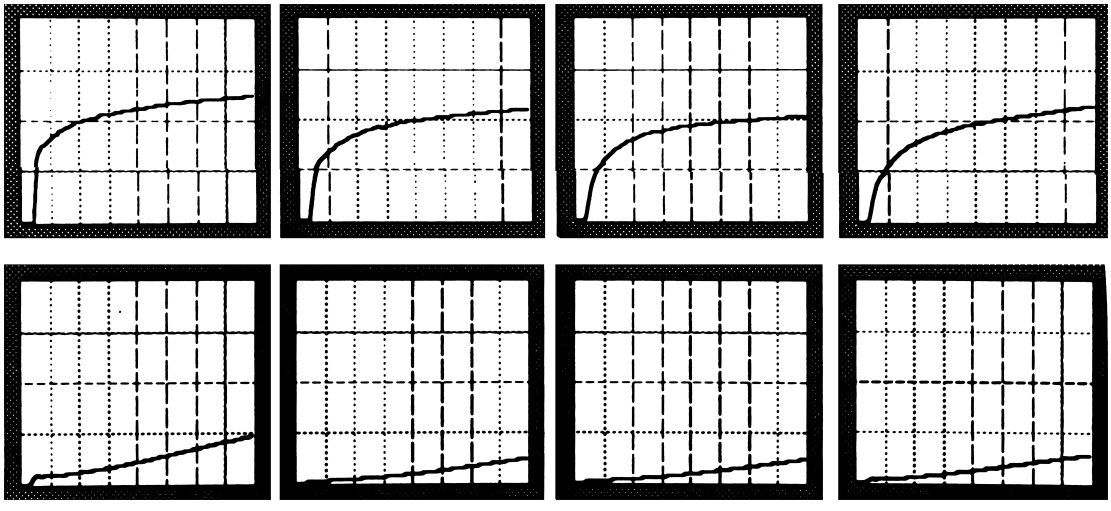

Fig. 5. Skin conductance measurements of a patient whose left breast was treated with 60 Gy/25 fractions/35 days in 1987. *y*-axis 2 μSv/division, *x*-axis 60-s/division. Upper four tracings, right breast (control); lower four tracings, left breast (treated).

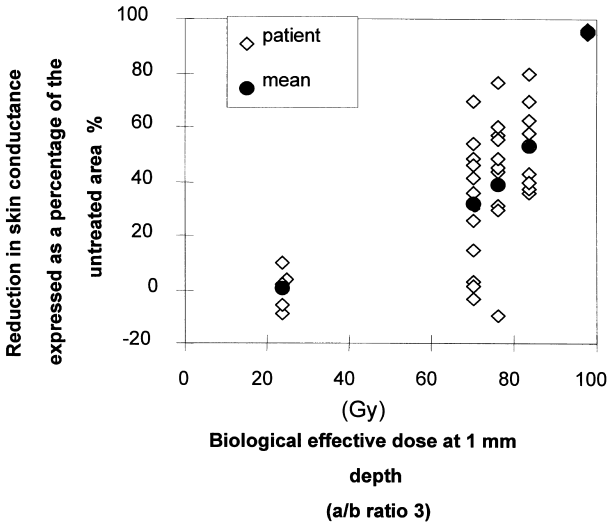

Fig. 6. Percentage reduction in skin conductance of the 38 patients in the retrospective group related to the biological effective dose at a depth of 1 mm ($\alpha/\beta = 3$). Simple linear regression $R^2 = 0.39$, $t = -4.7$, $P < 0.0001$.

by the end of treatment the average skin conductance of the irradiated area was 43% (range 32–68%) of that of the control (Fig. 7).

Changes in skin conductance of the irradiated area occurred prior to any clinical evidence of radiation change in the skin, with a mean reduction of 40% occurring by the end of the second week. A slight erythema of the skin was detected in the majority of patients during the third week of treatment, progressing in some cases to moderate erythema in the fourth week. One patient developed a marked acute radiation reaction greater than that seen in the others, with a moderate erythema of the whole breast visible during the third week which progressed to moist desquamation around the nipple at the start of the fourth week. This patient had a marked reduction in skin conductance on day 10 of treatment with the value for the irradiated area falling to 33% that of the control. Readings then rose slightly during the rest of the treatment but this seemed to reflect the increased surface moisture of the skin due to breakdown of the epidermis. This patient still had a low conductance reading when seen 3 months after treatment.

Patients who demonstrated recovery of skin conductance usually showed improvement within the first 3 months, but in a few there was a delayed recovery up to 6 months. In eight out of 18 patients the skin conductance recovered to within 70–100% of that of the control side. Five patients however showed little recovery over a period of observation up to 9 months. All five had a greater than 50% reduction in skin conductance of the irradiated area during treatment (Fig. 8).

5. Discussion

Skin conductance was measured in just 10 min, the measurement is non-invasive and painless and the apparatus is robust. Epidermal capacitance has been employed to measure the water content of the skin [1,19]. By covering the area of measurement we have determined the accumulation of sweat and so our approach is different from that of those who have previously employed electrical conductance in the investigation of the skin. As the recordings obtained in the area of interest were always compared with similar but untreated areas, the results are unlikely to have been influenced by minor physiological fluctuations.

The range of results, in absolute terms, between individuals was broad and three factors may be responsible. Firstly the room conditions were not rigidly standardised and observations were made throughout the year with inevitably some small differences in room temperature and humidity. Secondly differences exist between individuals in sweat gland function, the maximal sweating rate may range from 2 to 20 μl/min per gland, with the value falling with age [15,30]. Thirdly the actual number of functioning glands is known to vary between individuals. However, good agreement existed between readings obtained from comparable areas on both sides of the body within the indi-

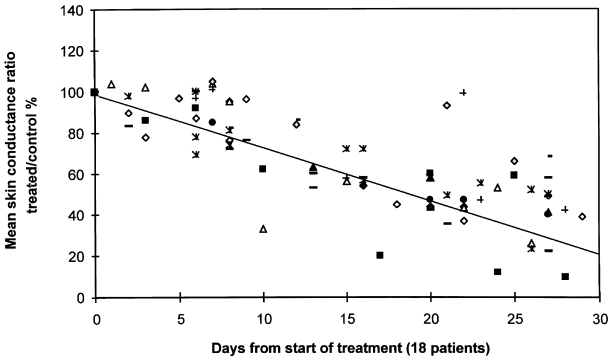

Fig. 7. Change in skin conductance of the treated breast during the first 30 days compared to the control in 18 patients receiving postoperative radiotherapy for carcinoma of the breast.

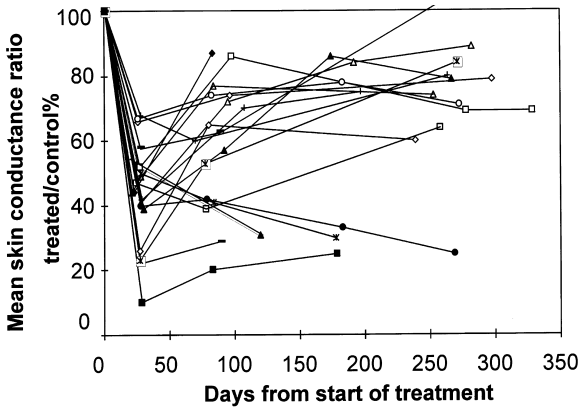

Fig. 8. Change over time of mean skin conductance of treated breast during the first year compared to control in 18 patients receiving postoperative radiotherapy for carcinoma of the breast.

viduals. It was observed, in the control cases, on warm humid days when the conductance readings were higher, that the good agreement between readings was unaffected.

A radiation dose response relationship was seen and these results demonstrate that functional changes can be detected in visually normal looking skin. These changes can be quantified, allowing differences to be demonstrated between different fractionation schedules.

In the 18 patients who received post operative radiotherapy for carcinoma of the breast, a reduction in skin conductance was seen as early as the second week of treatment, despite there being no clinical evidence of an acute radiation reaction at this time. Readings continued to fall throughout treatment. This reduction in skin conductance coincided with a clinical observation of progressive dryness of the skin.

The patient who had the earliest and most marked drop in skin conductance during treatment was the one who clinically had the greatest acute skin reaction, developing moist desquamation at the start of the fourth week of treatment. This patient showed no recovery of skin conductance at 3 months and had moderate subcutaneous oedema of the breast. By detecting an early reduction in skin conductance during treatment, this technique may be able to single out patients who are unusually sensitive to radiation at a time in their course of their treatment when amendment is possible.

Until recently little data was available on the effects of ionising radiation on the eccrine sweat glands in the animal model. Johns and colleagues, measured sweat gland function in the hind feet of mice following irradiation using the silicon elastomer technique [16]. Mice were irradiated with either a single fraction (5.0–13.0 Gy) or a two fraction regime of X-rays (total dose 5.8–16.4 Gy). Loss of sweat gland function occurred rapidly within 2 weeks of irradiation and progressed, resulting in a dose dependent nadir of flinction at 8 weeks. This was then followed by a gradual recovery that was maximal by about 30 weeks after irradiation, leaving a dose dependent residual functional deficit [17]. This pattern matches well the results we have seen with the skin conductance in humans following irradiation. Our five patients who showed the least recovery tended to be those having the lowest values for skin conductance at the time of completion of treatment.

We have compared four different techniques which can be employed to detect changes after radiotherapy [24]. In addition to the electrical conductance of the skin, we have employed the silicon elastomer moulding to determine the number of functioning sweat glands, laser Doppler flowmetry with a heating element to measure the vascular response to heat, and visco-elasticity analysis to determine changes in sub-epidermal connective tissue [13].

Changes in cutaneous blood flow using laser Doppler were only demonstrated in patients who had obvious clinical evidence of late radiation damage following high doses to the skin. The remaining three techniques all proved valuable in demonstrating post radiation change and with all radiation dose response relationships were demonstrated. The silicon elastomer imprint proved a laborious one taking at least 30 min to perform. Although acceptable to patients it did leave an erythema of the skin which in some cases took over an hour to settle. Skin conductance was measured in just 10 min, was non-invasive and painless. The apparatus proved robust and consistent readings were obtained. The visco-elasticity skin analyser also proved effective in measuring late change in the connective tissue beneath the epidermis. This proved to be the simplest of all four procedures to perform. Skin conductance, measuring the function of sweat glands and visco-elasticity, the changes in connective tissue, are directed to different endpoints in late radiation change and so complement each other.

Skin conductance is a reliable and easy method of measuring sweat gland function providing a means of measuring human radiosensitivity during a course of radiotherapy. It is sensitive to changes which may occur at modest levels of radiation dose where no obvious change may be detected clinically. It can be used to compare late changes induced by different dose fractionation schedules.

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