THE QUANTITATIVE ASSESSMENT OF RADIATION CHANGE IN SKIN

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ABSTRACT

In a study of irradiated skin which appeared normal to visual examination functional changes were sought and quantified.

Four different techniques were employed. 1) The electrical conductance of the skin in order to measure the production of surface moisture. 2) Silicone elastomer moulding of the skin to determine the number of functioning sweat glands. 3) Laser doppler flowmetry with a heating element to measure the vascular response to heat. 4) Viscoelasticity analysis.

In unirradiated controls, using these techniques similar readings were obtained from comparable areas on both sides of the body. Consequently patients acted as their own controls: an irradiated site being compared with a similar non irradiated site. Skin function was assessed in 38 patients, treated with one of five different radiotherapy schedules more than five years prior.

Changes in skin function were detected in apparently normal skin and a radiation dose response relationship observed using skin conductance, silicone elastomer moulding and visco-elasticity analysis. These methods have measured functional change in irradiated skin and have allowed precise comparison of different schedules of radiotherapy.

Skin conductance was also measured in 18 patients during and in the first years following radiation for breast cancer. Patients who had the greatest reduction in skin conductance at the end of treatment showed little recovery with time. Furthermore the severest acute radiation reaction occurred in the patient, who had a marked drop in skin conductance on day 10 of treatment. The degree of early change in skin conductance may therefore predict the severity of the late changes and provide a means for detecting the unusually radiosensitive patient.
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CHAPTER 1

1.1. The Effectiveness of radiation in the treatment of cancer

1.1.1 Background and Historical Aspects

Parallel to the discovery of X-rays by Wilheim Roentgen in 1885, was Marie Curie's discovery of radioactivity reported by Becquerel in 1898. Almost immediately, the biological effects of ionising radiation were recognised, with the first report of their use therapeutically, when Prof. Fruend irradiated a “hairy mole”. The first radiobiological observation of an affect on normal tissue was made by Becquerel three years later, when he noted the effect on his skin caused by accidentally leaving a vial containing radium in his breast pocket.

Radiation quickly expanded to the treatment of cancer, and it became apparent that while it had therapeutic benefits, it was not without side effects, often leading to unacceptable damage to normal tissue. This was particularly so from the turn of the century until 1920 when patients were treated with very poorly penetrating X-rays produced at 100-120 kV. The radiation skin reaction limited the dose to the tumour. Furthermore, since dosimeters were not available the skin reaction was often the only available guide to the amount of ionising radiation given.

Claudius Regaud with Nogier in 1911 showed that it was possible to sterilise a ram's testis without damaging the skin if the treatment was given in three fractions rather than one, spacing them two weeks apart (Dische, 1993). This demonstrated the benefit of fractionated radiotherapy. Coutard applied this to clinical practice and in 1932 presented a paper demonstrating that by using repeated smaller doses of irradiation it was possible to cure laryngeal tumours with healing of surrounding normal tissue, and thus great strides were made in the field of clinical radiation therapy (Coutard, 1932). By 1934 Coutard (1934) had extended his period of fractionation to six weeks and reported five year survival figures of 28% in 77 patients treated for advanced laryngeal tumours. Radical treatment schedules today, are still commonly based on this overall treatment time.
Advances in physics and in biomedical engineering have led to better treatment planning and delivery. The introduction of megavoltage radiation and its skin sparing effect increased the clinical indications for radiation treatment. In the field of radiation biology it became apparent that the biological effect of radiation on both normal tissue and tumour was dependent on the scheduling of dose as a function of time and fractionation. This resulted in formulae being derived to relate these parameters to the total dose, with Strandquist (1944) proposing the first mathematical formulae to relate dose and overall treatment time to skin tolerance. Ellis (1969) subsequently introduced the NSD model which separated the effects of fraction number and overall treatment time. However, it became evident that when less than 10 fractions were given there were greater late normal tissue effects than predicted by the Ellis formulae. During the 1980’s the linear quadratic formula was introduced to relate dose to effect (appendix, 7). At clinically relevant doses, early reacting tissues or tumours demonstrate predominantly a linear relationship (α component) between dose and effect. However, with late reacting tissue a large part of the effect is related to the square of the dose (β component). Thus the giving of small doses per fraction should spare late reacting tissue. The linear quadratic equation is now favoured as the best method of predicting the relationship between radiation dose and effect (Fowler, 1989).

In recent years a great effort in radiation research has concentrated on the use of different fractionation schedules both in the laboratory and in the clinical setting, to try and optimise radiation therapy. The aim of radiation treatment being to deliver a precisely measured dose of radiation to a defined tumour target volume, so as to eradicate tumour with minimal damage to surrounding healthy tissue, leaving the patient with a high quality of life.

1.1.2 Normal Tissue Damage

In the treatment of any tumour the surrounding normal tissues will receive part of the radiation dose, resulting in radiation damage. The time of expression of this radiation damage is largely dependent on the interval between irradiation and subsequent cell division since the effects of radiation on most cells do not become apparent until the
cells attempt to divide (Withers, 1982). Clinically, normal tissue damage is divided into early radiation damage which occurs within the first six months and late radiation damage which develops beyond six months. Early radiation damage is seen in tissues which undergo several cell divisions soon after irradiation such as skin and mucosa. The result is erythema and desquamation in the skin and erythema and membrane formation in the mucosa. Both of these reactions resolve within two months provided too high a dose has not been delivered. Late radiation damage without an obvious acute reaction occurs in tissues whose cells normally divide intermittently, for example liver and thyroid. Damage may take the form of tissue necrosis and fibrosis, and it may show a specific clinical pattern, such as in the spinal cord. Late radiation damage does not resolve with time and may be progressive. Thus it is the late radiation effects in normal tissue which are the dose limiting factors.

All normal tissues are affected by ionising radiation therapy. However the skin has been extensively studied, because of the ease with which observations can be made, and because all radiation treatment, excluding intraoperative radiotherapy, involves some exposure of the skin.

1.1.3. Therapeutic Ratio

Goodman and Gilman defined the therapeutic index as the relationship between desired and undesired effects of therapy: tumour cure and complications in the context of radiotherapy and oncology.

As the total dose rises, so does the chance of eliminating the last tumour cell. However the risk of normal tissue damage also increases with dose. The curves relating tumour control and normal tissue complications have a similar shape, and are generally displaced from each other on the dose axis. The relative position of these curves in any given circumstance determines the therapeutic ratio (fig. 1). The further the curve for tumour control is displaced from that of normal tissue complications, the higher the therapeutic ratio. As the dose is raised to increase the probability of cure so the probability of normal tissue damage occurring increases. It is up to the patient and radiotherapist to decide what level of normal tissue damage to accept in return for
improved tumour cure, and this is obviously dependent on the patient’s diagnosis, prognosis, the type of normal tissue and the importance of its damage.

Figure 1. The dose response curve for tumour versus the critical normal tissue. Increasing the dose from A to B results in a marked increase in normal tissue complications.

The level of risk of morbidity depends on the situation. Certain complications are totally unacceptable such as spinal cord necrosis following radical treatment for head and neck cancer. However a small risk of necrosis may be acceptable if there is no alternative way of achieving a good probability of tumour control.
1.1.4 Manipulation of the therapeutic index

The main variables in a course of external beam radiotherapy are the total dose, dose per fraction and overall treatment time. Early and late reacting tissues respond differently to dose per fraction and overall treatment time, with tumours behaving similarly to early reacting tissue.

When radiotherapy is extended over several weeks, regeneration of surviving stem cells during the course of treatment is the most important factor contributing to the differential sparing of early reacting tissues, relative to both late reacting tissues and most tumours. The onset of this process is dependent upon the rate of development of the injury, which in turn, depends upon the cell kinetics of the tissue and to a lesser extent the dose to which the tissue is exposed (Withers, 1985). Regeneration in human skin commences one to two weeks after the start of treatment and quickly reaches a maximum rate. Thus extending the overall treatment time preferentially spares early reacting tissue.

When human tumours are observed their volumes increase slowly, with volume doubling times ranging from 25-100 days (Charbit, 1971). However, it is now possible to measure the doubling time of human tumours at the cellular level using in vivo labelling with bromodeoxyuridine and the use of a flow cytometer (Begg, 1985). With this technique doubling times have been shown to range from 2-12 days, with the majority of patients with squamous cell carcinoma of the head and neck having potential doubling times of less than five days (Dische, 1989). This difference between volume doubling time and cellular doubling time is due to spontaneous cell loss. The concern is that during a course of radiotherapy the high spontaneous cell loss that occurs in the tumour may be greatly reduced and that tumours may realise their full potential. Thus reducing the overall treatment time should result in a reduction in the time when tumour cell proliferation may occur.

The dose response curves for early and late reacting tissue differ, the curve for late reacting tissue being more curved. In terms of the linear quadratic equation this translates into a smaller α/β ratio for late than for early effects. Thus the giving of small doses per fraction should preferentially spare late reacting tissue (Fowler, 1989).
It is possible to alter the therapeutic ratio by the choice of fractionation and overall treatment time, by improvements in the accuracy of treatment, and by the use of interstitial irradiation, radiosensitiser, radioprotectors and chemotherapy.

If the outcome of a new treatment is either an increase in tumour response with no change in normal tissue damage or a reduction, or a decrease in normal tissue damage with no change in tumour response then an increase in the therapeutic ratio has been achieved. It is therefore essential when assessing a new treatment that both normal tissue morbidity and tumour response are recorded. Whilst curing the tumour must be our primary goal, the morbidity of the treatment must be kept to a minimum. Patients expect to be cured of their tumour, but also to be left without side effects.

1.2 RADIATION EFFECTS IN SKIN

1.2.1 Background

Skin lies in the primary radiotherapy field more frequently than any other normal tissue. As it is readily observable, the early and late reaction following radiotherapy have been well-documented. An interesting example of an early skin reaction following exposure to radiation was that observed by Becquerel in 1901. He developed skin erythema and ulceration of his chest after carrying radium in his top pocket.

In the first half of this century orthovoltage radiation therapy was used, with 100% of the radiation dose being delivered to the skin. Consequently, radiation dermatitis was commonly seen following treatment, with the skin reaction often being the dose limiting factor. Radiation dosimeters were not available until the 1920’s, and the skin erythema dose was used as a quantitative measure of the physical dose. This was based on the maximum dose that could be tolerated by the skin without irreversible skin breakdown and was known as the skin erythema dose (SED).
Megavoltage radiation was introduced in the 1930’s, and became more widely available in clinical practice by the 1950’s. With it came a skin sparing effect, such that the dose to the surface of the skin was approximately 20% (Cobalt), with build-up of dose occurring in the subcutaneous tissues. Consequently, the pattern of radiation damage changed, with dermal and subcutaneous damage occurring more frequently in relative terms compared to epithelial radiation damage and ulceration seen with orthovoltage.

1.2.2 Clinical radiation change

The sequence of radiation change in the skin following a course of radiation therapy, using 2 Gy per fraction given over four to six weeks, is well documented.

1.2.2.1 Early radiation change

A “transient erythema” which is not limited to the treatment area, may occur in a minority of patients a few hours after the first treatment, and reaches a peak at 24 hours. Its severity increases with doses of 2-8 Gy (Hopewell, 1990)

Progressive dryness of the skin occurs over the next two weeks due to loss of function of the sebaceous glands and sweat glands, with epilation starting in the third week. The definitive erythema, which is limited to the treatment volume, commences in the third week. The skin becomes red, warm, and oedematous, and patients often complain of a burning sensation and tenderness. Depending on the total dose, during the fourth and fifth week of radiotherapy, radiodermatitis may progress from a phase of dry desquamation to moist desquamation. When the skin becomes denuded and there is a marked inflammatory response with oozing of serum. Patients may experience considerable discomfort during this phase. Recovery starts a week after the end of treatment and re-epithelialisation begins with islands appearing in the centre of the denuded area as well as peripherally. Three weeks from the end of treatment the early reaction has usually settled, leaving in some cases an area of depigmentation.
With the present radiotherapy techniques employed, moist desquamation is rare, if it
does occur it tends to be in areas which have been subject to irritation or to a higher
dose, such as skin folds, or areas which have received full skin bolus. The commonest
reaction seen is that of dry desquamation, which takes the form of scaling and
increased pigmentation, with patients often complain of itching and tenderness which
last two weeks.

Rarely (approximately 1:10,000 people) a generalised skin reaction can occur any time
after the beginning of radiotherapy. It is attributed to the effects of circulating
breakdown products following radiation and manifests itself as a non specific pruritis
as well as a erythematus rash (Rubin, 1968). Constitutional symptoms such as fever,
nausea and joint pain may also occur.

1.2.2.2 Intermediate radiation change

During this phase, between the end of treatment and six months, the acute radiation
skin changes settle. Increased skin pigmentation usually apparent at the end of a
course of radiotherapy, in areas which have not progressed beyond dry desquamation,
disappears over the following months. The function of skin appendages may recover
depending on the dose received, with hair growth beginning towards the end of the
second month along with recovery of sweat and sebaceous gland function.
Subcutaneous oedema due to impairment of lymphatic clearance may occur and
depending on the dose received this either settles or over 12 to 18 months progresses
into subcutaneous fibrosis (Rubin, 1968).

1.2.2.3 Late radiation change

Late radiation change of the skin, by definition, commences after six months. These
changes include atrophy, telangiectasia, altered pigmentation, fibrosis, ulceration,
necrosis and carcinogenesis.
In heavily irradiated skin, epidermal atrophy occurs which may be fairly uniform or irregular, with thin atrophic regions alternating with hyperkeratotic regions. Disturbance of pigmentation occurs due to damage to melanocytes, with hypopigmentation in heavily irradiated areas and hyperpigmentation occasionally occurring at the junction of irradiated and unirradiated skin.

Radiation damage to the skin appendages leads to loss of sebaceous and sweat gland activity with little or no hair growth, resulting in dry, smooth skin. Telangiectasia (dilated, thin walled capillaries, venules, and arterioles in the upper dermis) may appear as red, torturous vessels visible in the treated area.

In the dermis subcutaneous fibrosis can develop and may range from just detectable to a dense band attached to skin and underlying tissue resulting in limited movement. Following high doses of radiation or trauma, ulceration and necrosis of tissue can occur. These lesions are painful, tender and slow to heal. Finally, malignant tumours may arise in irradiated skin, usually after a long latent period of 20-40 years.

The amount of late radiation change that occurs is related to the biological dose. Once developed it persists and may with time become progressively more marked. The mildest of changes however may not progress.

1.2.3 The pathogenesis of the radiation skin reaction

1.2.3.1 Introduction

The skin acts as a barrier for the body protecting it against the environment. It further plays a major role in thermoregulation, conserving the temperature by the insulation provided by fat, temperature dissipation through its peripheral blood vessels and the cooling effect of water evaporation from sweat excreted onto its surface. Other functions it provides include synthesis of vitamin D, detection of sensory stimuli and a role in the body's immune system.
The thickness of skin varies according to the site: from less than 1 mm over the eyelid to in excess of 4 mm on the back. The skin can be divided into two main structures: an outer layer the epidermis; and an inner layer the dermis. The epidermis is the thinnest layer with an average thickness of 0.04 -0.05 mm. The thickest areas are found on the hand and feet, with the greatest being at the fingertips with a range of 0.16-0.56 mm. Age and sex do not influence epidermal thickness (Whitton, 1973).

<table>
<thead>
<tr>
<th>Body site</th>
<th>Mean epidermal thickness (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Face</td>
<td>0.049</td>
</tr>
<tr>
<td>trunk</td>
<td>0.042</td>
</tr>
<tr>
<td>Arms and legs</td>
<td>0.060</td>
</tr>
<tr>
<td>Back of hand</td>
<td>0.085</td>
</tr>
<tr>
<td>Wrist</td>
<td>0.081</td>
</tr>
<tr>
<td>Finger</td>
<td>0.222</td>
</tr>
</tbody>
</table>

Table 1. Mean skin thickness for different sites of the body.
Data taken from Whitton, 1973.

The dermis contributes to most of the skin's thickness and depending on the site can range from 1-3 mm with the trunk being the thickest site. Men have a thicker dermis than females but with age its thickness decreases (Southwood, 1953).

At the junction of the two layers the epidermis can be seen to be undulating over the dermis resulting in interdigitation giving the so called “rete pegs”. Infiltrated throughout the dermis are the skin appendages, which are formed from infolding of the epidermis, these include the hair follicle, eccrine and apocrine glands. Considerable regional variation exists both in the structure and function of the skin with no area being identical in all respects with any other, except importantly the corresponding area on the other side of the body. For example the number of sweat glands varies from over 600/cm\(^2\) in the palms of the hand to 64/cm\(^2\) over the back.
1.2.3.2 Epidermis

The epidermis is a keratinising stratified squamous epithelium from which arise the cutaneous appendages. It is made up of four sub-layers, none of which are sharply defined as the cell types gradually change as they migrate through the layers, maturing and differentiating (Potten, 1985).

The cell kinetic organisation of the epidermis fits that of a steady state self-renewing tissue with hierarchical organisation (type H tissue) of stem cells, transit cells and functional end cells (Wheldon, 1982). The stem cells are found in the basal layer of the epidermis. This layer is separated from the dermis by the basement membrane and within it are found keratinocytes as well as specialised cells such as the Langerhans cells and the pigment producing melanocytes. It is assumed that about 10% of the cells found in the basal layer are stem cells, with a cell cycle time of 180 hours (Hopewell, 1990). These cells have the capacity for maintaining their own number and an unlimited capacity to divide and replace all other epidermal cells. They are very radioresponsive and produce less radioresponsive transit cells, which divide one to three times before migrating out of the basal layer into the stratum spinous layer, and then through the stratum granulosum to the outer layer of the epidermis, the stratum corneum. As the cells pass through these successive layers of the epidermis they undergo differentiation to become functional end cells. This results in loss of their nuclei, synthesis of an insoluble protein keratin and flattening of the keratinocytes to form the plates of the keratin layer. The cells are then lost from the skin surface due to "wear and tear" and their number is maintained by a continual influx of stem cells into the differentiation pathway. The total transit time (time taken for a cell in the basal layer to move through the layers and be shed from the skin surface) ranges from 21-45 days, the variation relating to different locations (Potten, 1985 and Awward, 1990).

Following radiation there is a dose-dependent reduction in stem cells, which results in a decrease in the influx of cells into the transit cell compartment. As the life span of the pre-existing differentiated cells is not altered following irradiation, there is a progressive reduction in the number of epidermal cells, resulting in thinning of the epidermis with flattening of its papillae. If the entire differentiated population of epidermal cells is lost before a new transit cell compartment is re-established from a
sufficient number of surviving stem cells then loss of the skin surface will occur (Awward, 1990).

The time to the appearance of the early reaction and its rate of increase are both dose independent as they are related to cell loss which continues at the pre-irradiated rate. The peak reaction and regeneration are related to the dose as they relate to the proportion of surviving stem cells (Awward, 1990).

![Cross section of the skin](image)

**Figure 2.** Cross section of the skin

Regeneration is initiated two to four weeks after irradiation, this is related to mitotic delay and the need for cellular depletion as a trigger to stimulate the regenerative response. Regeneration occurs from surviving stem cells within the irradiated volume, from cells at the periphery of the irradiated volume, and from the epithelium of the hair follicles and sebaceous glands (Awward, 1990 and Potten, 1985).
1.2.3.3. *Derma*

The dermis supports the epidermis and is composed of fibrous connective tissue components (collagen and elastic fibres) in intimate association with ground substance. Contained within the dermis are the epidermal appendages, blood vessels, nerves and cellular components. The dermis is divided into two layers, papillary and reticular. The papillary dermis is bounded superiorly by the epidermis and the reticular dermis lies between it and the subcutaneous tissue.

Fibroblasts synthesize both collagen and elastin fibres. Collagen fibres are responsible for the tensile strength of the dermis and are laid down in a parallel direction in the reticular dermis thus accounting for the lines of skin cleavage (Langer’s lines). The elastic fibres are responsible for the retractile properties of the skin. In the papillary dermis they are laid down perpendicularly to the skin, while in the reticular dermis they are thicker and orientated parallel to the skin surface.

The dermis receives a rich vascular blood supply through the subcutaneous fat. Most of these blood vessels are directed towards the metabolically active constituents of the skin, namely the epidermis and adnexal structures.
Two vascular plexuses linked by intercommunicating vessels are present in the dermis. A deep vascular plexus lies in the interface between the reticular dermis and subcutaneous tissue; it is composed of small muscular arteries from which arise arterioles that supply the superficial plexus in the superficial aspect of the reticular dermis. The superficial plexus consist of a candelabra-like capillary loop system which supplies the papillary dermis (60-75 capillary loops/mm²). Each loop consist of an ascending arterial limb and a descending venous limb. The amount of blood flowing through the superficial plexus can be controlled by arteriovenous anastomosis which
act as a shunt to short circuit the flow. The cutaneous vasculature not only supplies nutrition but also plays a major role in thermoregulation.

Following irradiation with doses in the range of 12-20 Gy a rapid increase in capillary permeability occurs, which develops within two hours and last 24 hours. This coincides with the transient erythema sometimes observed and is due to the activation of proteolytic enzymes (Jolles, 1966). During the acute radiation reaction the blood flow in the dermis is increased as vessels dilate. This phase coincides with a period of epidermal cell death and is probably a secondary consequence (Moustafa, 1979).

After recovery from the acute radiation damage, depending on the biological dose delivered, the histopathological picture of chronic atrophic skin may develop. The epidermis is reduced to the thickness of two to three cells with flattening of the papillary protrusions. Hair follicles disappear, sebaceous glands atrophy, but the sweat glands appear normal. With time telangiectasia develops as well as progressive dermal and subcutaneous fibrosis. The loose stroma and regular arrangement of fibres in the dermis is replaced by dense irregular fibrous tissue.

Although the mechanisms underlying the acute effects of radiation are understood, the pathophysiological changes involved in the development of late radiation damage is not clear. Pathological changes in blood vessels have been observed in patients developing late radiation sequelae, and this has resulted in the hypothesis that vascular damage is the predominant feature leading to late radiation damage.

Pig skin closely resembles human skin and extensive studies have been carried out on it by Hopewell (1990) to determine the effects of irradiation. He noted that there were two phases of dermal thinning, both associated with a fall in the number of fibroblasts in the reticular dermis (Hamlet, 1988). The first phase occurred between 12-18 weeks and was preceded by a reduction in the density of blood vessels in the dermis and also, by a reduction in endothelial cells lining the blood vessels (Moustafa, 1979). The second phase of dermal thinning occurred after 60 weeks and was associated with diffuse degeneration of the blood vessels’ walls. The tunica media of the arterioles became vacuolated and replaced by hyaline. Changes occurred in the organisation of the collagen fibre bundles resulting in a marked increase in stiffness of the skin (Baker,
1988). In the reticular dermis, the interbundle spacing was less regular, the fibres were thinner and there was loss of ground substance (Hamlet, 1986). The remaining major fibres were also orientated more horizontally.

At the same time telangiectasia developed, an explanation for this being that the loss in smooth muscle cells in the arterioles resulted in a reduction in control of the capillary pressure, the consequence of which is the appearance of grossly dilated telangiectatic capillaries (Hopewell, 1990, 1989). Telangiectasia are a recognised late reaction seen in human skin following fractionated radiotherapy. They are rarely seen earlier than a year after completion of therapy, but they increase in incidence and severity with time up to at least 10 years (Turesson, 1986).

Figure 4  Histological changes in irradiated skin
Hyalinisation of the blood vessels, loss of skin appendages and dermal fibrosis.
1.2.3.4 Skin appendages

1.2.3.4.1 Eccrine sweat gland

The principal function of eccrine sweat glands is thermoregulation during exposure to hot environments or during physical exercise. Failure to regulate body temperature under these circumstances results in hyperthermia.

Over the entire body surface there are 1.6 to 4.0 million eccrine glands. The average density of the glands varies between individuals, and is also dependent on anatomical site: palms and soles 600 to 700 glands/cm²; the back 64/cm²; the forearm 108/cm² (Knip, 1969 and Sato, 1989). The regional variation in sweating is due to the density of sweat gland while the great variation in sweating seen between individuals is related to differing overall sweat gland function (Sato, 1970). The maximal rate of sweating ranges from 2 to 20 nl/min/gland and is correlated with the size of the sweat gland, which can vary five fold (Sato, 1983). Age effects the capacity to sweat and is related to a reduction in sweat gland function (Inoue, 1991).

Sweat glands are characterised by a highly coiled secretory portion, which lies in the lower dermis, a relatively straight duct and a terminal duct which forms a spiral in the epidermis and opens directly onto the skin surface. The function of the secretory coil is to produce from plasma a watery isotonic secretion which can be modified by the duct. Three cell types are found in the secretory coil; dark, clear and myoepithelial. The secretory cell is the clear cell, with the myoepithelial cells providing mechanical support for the secretory coil against the increase in luminal hydrostatic pressure rather than simply pumping preformed sweat. The role of the dark cells is unknown. Sweat formed from these glands has a basic similarity to the plasma from which it is derived. It is a clear hypotonic solution with a pH within the range of 4 to 6.8. In addition to water it contains sodium, potassium, chloride, urea and lactate.

A prerequisite for normal function of the sweat gland is an intact sympathetic cholinergic nerve supply. This efferent pathway is influenced by thermal, gustatory and mental stimuli. The hypothalamic temperature regulating centre, controls thermal sweating and is activated by changes in the temperature of blood perfusing it and by
afferent stimuli from the skin. This temperature centre is set to a specific core temperature; at and above this temperature sweating occurs in order to maintain the body temperature.

One of the earliest observations following the therapeutic introduction of radiation was that it caused dryness of the skin. This led in the early part of this century to its use in the treatment of hyperhidrosis (Borak, 1949). Borak (1936) reported that human sweat glands were much less radiosensitive than sebaceous glands. The lethal dose for a single exposure being 2,400 roentgens for sweat glands as opposed to 1,200 roentgens for sebaceous glands. The lethal dose representing the dose that resulted in the complete destruction of the tissue rather than permanent loss of function (table 2).

<table>
<thead>
<tr>
<th>Skin</th>
<th>Approximate lethal dose roentgens</th>
</tr>
</thead>
<tbody>
<tr>
<td>sweat glands</td>
<td>2,500</td>
</tr>
<tr>
<td>epidermis</td>
<td>2,000</td>
</tr>
<tr>
<td>hair follicles</td>
<td>1,600</td>
</tr>
<tr>
<td>sebaceous gland</td>
<td>1,200</td>
</tr>
</tbody>
</table>

Table 2. Approximate lethal dose (roentgens) for different skin appendages.
(Data from Borak, 1936)

He did however state that 'roentgen rays could reduce the activity of the sweat gland without causing any visible alteration of the skin' suggesting in terms of function they are relatively radiosensitive. Furthermore provided there were no anatomic changes in the sweat gland, sweating resumed within a few months. This temporary cessation in sweating has also been demonstrated by Price (1979) following electron treatment for mycosis fungoides. Patients received a dose of 3,600 rads over 10 weeks using 2.5 MeV electrons. This resulted in a drop in sweat gland function which recovered over three to six months.
Depending on the biological dose received by the glands following irradiation there is a
loss in function of the sweat glands, which is temporary or permanent. A dose effect
relationship has been assumed, however this awaits confirmation.

1.2.3.4.2 Sebaceous glands

Sebaceous glands are most abundant in face, forehead and scalp with up to 900/cm²,
while over the rest of the body they number 100/cm². The glands consist of a duct
arising from an alveolus made up of basement membrane and epithelial cells. The
central alveolar epithelial cells degenerate and the breakdown products constitute the
sebaceous secretion (holocrine gland). The loss of these mature cells is compensated
by cells dividing within the basal layer, with a total transit time in humans of 7-14 days.
Sebaceous glands are more radiosensitive than the eccrine glands but have a
considerable regeneration capacity. Strauss (1959) irradiated the cheek of patients
with acne raising single fraction doses from 300 roentgens to 1500 roentgens using
superficial X-rays and then biopsied the area and the contralateral cheek at varying
times after treatment. The predominant effect of the radiation was a reduction in the
size of the gland which was dose related. Regeneration occurred at doses below 800
roentgens within six weeks but at a dose of 1500 roentgens there was only patchy
redevelopment with restoration of small glands by one year.

1.2.3.4.3 Hair Follicles

Hair follicles are found throughout the skin and are formed from tube like infoldings of
the epidermis, which pass down into the dermis. Their size and number vary according
to the body site: 40-50/cm² over the trunk compared to 800-1000/cm² in the scalp.
The length of hair produced and its growth rate are also dependent on site, with the
average growth rate being 0.35 mm/day.

Hair growth occurs from the hair bulb, which contains the germinal region of the hair
follicle. Beneath the hair bulb and almost enclosed by it is a dermal papilla. This
contains capillaries, which serve to nourish the hair bulb. Cells produced in the
germinal region pass up into the hair root where they differentiate, becoming elongated
and keratinized. These cells then go to form the medulla or the cortex of the hair. Among the cells of the hair bulb are melanocytes which deposit melanin into the hair's cells. Associated with the hair follicles are one or two sebaceous glands the ducts of which open into the hair follicle near the skin surface.

Hair production does not continue within a follicle without interruption. Periodically when full length mature hair has formed the cell proliferation activity ceases for a period of time, and the follicle actually shrinks in size. This stage is referred to as the telogen phase as opposed to the anagen phase when there is hair growth. Due to the proliferative activity of the anagen follicle this is 2-3 times more radioresponsive than the dormant telogen hair follicle (Malkinsom, 1968). In the mouse, hair growth is reasonably well synchronised i.e., all the hair follicles are either in the anagen or telogen phase, while in the human hair follicles are asynchronous. However any dormant telogen follicle can be triggered into hair growth (anagen) by plucking of the mature hair.

Microscopic evidence of radiation damage may be detected early in hair follicles following exposure. This reflects the short cell cycle time of the cells in the germinal region with mice having a cell cycle time of 12 hours and humans 39 hours. Apoptotic cell death has been reported as occurring in mice hair follicles at doses greater than 0.2 Gy, though the target cell susceptible to this process is unknown. The apoptotic cell fragment, and these fragments can be seen a few hours after exposure reaching a maximum level at 12 hours (Potten, 1985 and Geng, 1990).

The reduction in the number of cells in the germinal region following radiation, results in shrinkage of the hair bulb and a decline in the number of cells influxing into the cortex and medulla of the hair. Consequently there is a dose dependent reduction in the diameter and length of hair produced (Potten, 1985, Geng, 1990 and Malkinsom, 1966). These changes can be seen microscopically within 1-2 days in the mouse and by the second week in man.

Epilation will occur in man above 400 cGy given in a single dose using 100 kV. Epilation is associated with the hair shaft becoming loose within the hair follicle as a result of its reduction in diameter and because of shrinkage of the germinal region. In
man it is commonly seen during the third week if daily fractionated radiotherapy is given and provided there are still some surviving cells within the germinal region hair, regrowth will occur over the next three months.

1.2.3.4.4 Melanocytes

Melanocytes are large cells with a number of long projections (dendrites). They are located in the basal layer of the epidermis and in the hair follicles and produce the pigment - melanin which is responsible for the colour of the skin and hair. Each melanocyte forms a functional unit with a group of keratinocytes “the epidermal melanin unit”. Melanin is synthesised within small cytoplasmic granules, the melanosome, which pass down the dendrites. Here they are phagocytosed by the keratinocytes, and the melanin granules form a perinuclear cap to shield the nuclear DNA.

Radiation can result in two completely opposite effects: hypopigmentation associated with the destruction of melanocytes or hyperpigmentation. The latter occurs as a result of increased melanocyte activity, initiation of activity in dormant amelanotic melanocytes and the stimulation of processor melanoblasts to produce melanocytes. Hyperpigmentation occurs at lower doses than hypopigmentation, hence in an irradiated field where melanocytes have been killed (hypopigmentation) the borders of the field may show hyperpigmentation.

1.3 RADIATION INDUCED SKIN MALIGNANCY

Ionising radiation is a recognised cause of skin cancer, resulting in the development of basal cell and squamous cell carcinomas. These occur within the irradiated field or close to it, and can develop in areas which show no evidence of chronic radiodermatitis (Fragu, 1991). The latent period following exposure to radiation before the appearance of radiation induced skin cancer is nearly always greater than 25 years.
For low energy radiation the malignant transformation of the cell appears proportional to the total dose squared, until cell kill significantly reduces the number of cells at risk. Furthermore the cancer incidence following exposure to the same dose is lower with fractionated radiotherapy (Burns, 1989). Quantitative risk estimates per unit of radiation dose are difficult for skin because of the potential confounding effect of Ultra Violet Radiation (UVR) in sunlight which is also carcinogenic. UVR increases the expression of skin cancer following ionising radiation among UVR susceptible people. This was demonstrated by Shore (1990) in a study of 2180 children treated to 3-6 Gy with 120 kV for tinea capitis. They found that twice as many BCC occurred on non-scalp areas i.e. skin with greater potential sunlight exposure and this suggested the involvement of UVR as a promoter of ionising radiation initiated BCC. Furthermore none of the black population developed BCC, probably because they were not susceptible to UVR (Burns, 1989).

Shore (1990) has used 12 studies of the incidence of skin cancer among irradiated populations with known skin doses, to estimate the risk of radiation induced skin cancer. For UVR exposed skin the actual risk was 57.9%/Sv and for UVR shielded skin 0.5%/Sv. He could find no evidence for a threshold dose. In practice the actual incidence of radiation induced cancer is less than that predicted, as the latent period prior to the onset of the radiation induced cancer is often longer than the patient’s life expectancy. Furthermore radiation induced skin cancers rarely pose a risk to life as they are usually cured by further treatment (Parker, 1990).

1.4 SKIN CARE

1.4.1 General Care

There is no standard approach to skin care in this country with practice varying greatly from one department to another (Barkham, 1993). Current practice at Mount Vernon Hospital is to give a simple explanation of the likely effects of radiation on the skin prior to treatment. Instructions are then given during and following treatment on skin care, and on ways to minimise trauma to the treatment area (such as avoiding wet
shaving, sun exposure and scratching). This information is also available in a pamphlet which patients receive prior to treatment.

The no wash policy, during and following radiation treatment, dates back to the era of orthovoltage when the skin received the full dose of radiation. Campbell (1992) compared no washing with washing, plus or minus soap, in a group of patients treated with megavoltage radiotherapy for breast cancer. He demonstrated that the acute reaction was less in the groups randomised to washing, with or without soap.

1.4.2 Managing specific skin problems

**Erythema /dry desquamation**

A barrier cream for example E 45 or aqueous cream is often sufficient to ease the skin irritation that patients experience. Another popular preparation used is 1% hydrocortisone. Preparations which contain alcohol or phenol should be avoided as these will cause irritation (Sitton, 1992).

**Moist desquamation**

Nursing care of moist desquamation focuses on minimising trauma and discomfort, preventing infection and promoting healing. Several different approaches exist from exposing the area to air whenever possible to the application of gentian violet or the use of wet dressings.

Gentian violet has been used extensively because of its antifungal and antiseptic effects. However it is extremely messy, dries the dermis and may interfere with wound healing. Wet dressings or soaks with an astringent such as aluminium acetate have the advantage that they do not stain and are soothing. They cleanse the skin helping to prevent bacterial and candida overgrowth and dry and seal the exudative surfaces (Sitton, 1992).

**Wound healing**

Occlusive dressings are recommended as wound healing proceeds more rapidly in a moist environment promoting reepithelialisation. The presence of an infection often
delays healing and should be treated with local or systemic antibiotics. If conservative treatment fails then plastic surgery using a skin graft after excision of the necrotic area should be performed (Sitton, 1992).

Irradiated skin often results in long term localised xerosis. Lubricant may be added to the bath or applied directly to keep the skin pliable. In addition the skin may be thinner and more susceptible to trauma, which can result in delayed healing. It is therefore important to protect treated skin from excessive sun exposure and other trauma.

1.4.3 Modification of late radiation damage

Sclerosing agent (tetradecyl sulfate sodium)

Gordon (1987) injected a sclerosing agent tetradecyl sulfate sodium into telangiectatic vessels in five patients. Two of the patients experienced complete irradication of telangiectatic vessels following four treatments with improvement in the remaining case.

Pentoxifylline

Pentoxifylline is a haemorrhheologic agent which improves blood flow through narrowed microvasculature by increasing red blood cell deformability and by stimulating prostacyclin release. It has been shown in a study, to aid healing of radiation induced soft tissue necrosis of the skin, oral mucosa and genital mucosa: complete healing was seen in 87% (13 of 15) of the cases. Furthermore the time to healing with pentoxifylline was significantly less than the duration of non-healing prior to pentoxifylline (Dion, 1990).

L-Triiodothyronine.

Glicksman (1959) demonstrated that the use of L-Triiodothyronine at doses of 100 µg. twice a day resulted in an improvement in late radiation damage in the form of fibrosis or ulceration in over half (40 of the 75 cases) of the patients.
<table>
<thead>
<tr>
<th>Process and Agents</th>
<th>Target Tissue</th>
<th>Response affected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Early</td>
</tr>
<tr>
<td><strong>By stimulating cellular proliferation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silver nitrate</td>
<td>Oral mucosa</td>
<td>x</td>
</tr>
<tr>
<td><strong>Growth factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haematopoietic</td>
<td>Bone marrow</td>
<td>x</td>
</tr>
<tr>
<td>Epidermal</td>
<td>Skin &amp; mucosa</td>
<td>x</td>
</tr>
<tr>
<td>Glial</td>
<td>Brain &amp; spinal cord</td>
<td></td>
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<tr>
<td>Endothelial</td>
<td>Vascular connective tissue</td>
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<tr>
<td>Retinoids</td>
<td>Skin &amp; gastro-intestinal</td>
<td>x</td>
</tr>
<tr>
<td><strong>By moderating metabolic responses</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin, indomethacin (non-steroidal anti-inflammatory agents)</td>
<td>Mucosa &amp; bowel</td>
<td>x</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Mucosa &amp; gastro-intestinal</td>
<td>x</td>
</tr>
<tr>
<td>Gamma-linolenic acid (GLA)</td>
<td>Skin</td>
<td>x</td>
</tr>
<tr>
<td>Eicosanoid-pentoneic acid (EPA)</td>
<td>Skin</td>
<td>x</td>
</tr>
<tr>
<td><strong>Alter endocrine function</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroxine</td>
<td>Connective tissue</td>
<td></td>
</tr>
<tr>
<td><strong>By improving Vascularity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE Inhibitors-Captopril</td>
<td>All tissues</td>
<td></td>
</tr>
<tr>
<td>Reduce leucocyte adhesion-antibodies</td>
<td>All tissues</td>
<td></td>
</tr>
<tr>
<td>Haemorrhheological agent-pentoxyfylline</td>
<td>All tissues</td>
<td></td>
</tr>
<tr>
<td><strong>Reduction of chronic re-perfusion injury</strong></td>
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<td>Desferrioxamine-an iron chelator</td>
<td>Spinal cord</td>
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<td><strong>Surface protection</strong></td>
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<tr>
<td>Sucrafalate</td>
<td>Gastro-intestinal tract</td>
<td>x</td>
</tr>
</tbody>
</table>

Table 3. The moderation of early and late reactions in normal tissues - possible mechanisms. (Dische, 1993)
1.5 FACTORS AFFECTING THE SKIN REACTION

1.5.1 Fractionation

Total dose
All other factors unchanged, the intensity of the skin reaction increases with total dose.

Dose per fraction
Late skin reactions are influenced by the fraction size to a greater extent than early reactions. Turessson and Notter (1984) compared the normal tissue reactions of two different fractionation schedules used to treat patients postoperatively for breast cancer. Bilateral parasternal fields were treated with 200 kV, each side receiving a different fractionation schedule: either 5× 2.16 Gy or 1× 6.2 Gy per week over 22 days. The acute reactions were comparable between the two fractionation schedules. However the hypofractionated schedule produced more marked late radiation damage. Bates (1988) similarly showed that in patients with breast cancer treated with mastectomy and post operative radiotherapy that the late skin changes were more marked when 6 fractions were given instead of twelve.

Overall treatment time
During a course of radiotherapy repopulation commences in the epidermis 1-2 weeks after the start of treatment, other factors being constant. Therefore prolongation of treatment beyond this time will result in a reduction in the severity of the early radiation reaction. Kaanders (1992) in the treatment of laryngeal carcinoma compared conventional fractionation (2 Gy per fraction given over 47 days to a total dose of 70 Gy) to an accelerated fractionation schedule where the same total dose and dose per fraction was given but the treatment time was reduced to 37 days. He reported an increased incidence of moist desquamation in patients treated with the accelerated regime.

Dose rate
External beam radiotherapy usually involves high dose rates with each radiation fraction being delivered within a few minutes. Within the range employed clinically there is no difference in the skin reaction. However in the field of brachytherapy
(placement of a radioactive source at the site of the tumour) a low dose rate 0.5-2.0 cGy/min maybe used. This results in prolongation of the time it takes to deliver the dose and thus allows more time for recovery with a consequent reduction in the radiation effect. The magnitude of this reduction is dependent on the tissue’s capacity to recover from radiation damage.

1.5.2 Radiation technique

**Machine**

The depth that an X-ray will travel in tissue before being absorbed is directly related to its energy. The higher the beam energy, the more penetrating the beam in tissue. The radiation reaction in the skin is greater with superficial and orthovoltage X-rays as they give the highest dose at the surface of the skin, while the dose with megavoltage radiation builds up with depth and therefore provides skin sparing (Khan, 1984).

**Bolus**

Bolus is a tissue equivalent material, which raises the dose to the skin when placed over it, thus resulting in an increase in the radiation reaction (Khan, 1984).

**Obliquity**

As the angle of incidence of a megavoltage beam increases so the skin dose rises. This is because of an increase in the contribution of dose from secondary electrons and because the build up of dose occurs in a more superficial area (appendix 8).

**Electron contamination**

Electron contamination from any scattering material in the path of the X-ray beam will raise the skin dose and thus the radiation reaction.

**Field size**

The severity of the skin reactions vary as the field size is altered. Joyet (1955) carried out an extensive study in humans looking at the dependence of the acute skin tolerance on the field size, using moist desquamation that healed within 2-4 weeks as the response criterion on which basis isoeffective doses were determined. Each individual
had five different square fields on their back irradiated using the same fractionation schedule of 18 fractions in 22-28 days but giving different total doses. The tolerance doses increased as the field size decreased.

<table>
<thead>
<tr>
<th>Skin area (cm)</th>
<th>Tolerance dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>50 +/- 4</td>
</tr>
<tr>
<td>16</td>
<td>58 +/- 6</td>
</tr>
<tr>
<td>4</td>
<td>84 +/- 7</td>
</tr>
<tr>
<td>1.7</td>
<td>200 +/- 3</td>
</tr>
<tr>
<td>1</td>
<td>392 +/-100</td>
</tr>
</tbody>
</table>

Table 4. Dependence of acute skin tolerance in man upon field size.
(Joyet, 1955)

An objective field size effect is seen if the field size is smaller than 16 cm², due to the contribution to reepithelialisation by cells migrating from the edge of the treatment field. The migration rate of epithelial cells during healing amounts to 1 mm/week and therefore only plays a significant role in epithelialization following irradiation of small areas.

A field size effect is also important to patients overall tolerance. For example if moist desquamation occurred over 70% of the treated area, this would cause significant discomfort if the area treated was 15 × 15 cm, whereas it would probably be acceptable if the area treated measured 4 × 4 cm.

Skin folds

Skin folds such as those found in the axilla and inframammary area show increased skin reaction. This occurs because the skin folds act as bolus and raise the dose to the skin. Furthermore these areas tend to be warm and moist and are subject to friction all of which contribute to an increased skin reaction (Sitton, 1992).
Temperature

When hyperthermia is given in close association with radiotherapy to the skin there is an increase in the early skin reaction (Overgaard, 1989).

1.5.3 Radioprotectors

A clinically useful radioprotector is a substance which is absorbed by normal tissue cells and reduces their response to radiation but does not affect tumour cells. WR-1721 is the radioprotector which has been most extensively studied. In humans there is no evidence to date that it protects the skin against radiation (Phillips, 1989).

1.5.4 Radiosensitisers

Hypoxic cell sensitisers

Tumour cell hypoxia is a recognised factor contributing to failure to achieve local tumour control following radiation treatment. This is because hypoxic cells are radioresistant requiring up to three times the dose of radiation compared to aerated cells. While hypoxic cells are known to exist in normal tissue their number is small compared to tumours. Research undertaken in the past to overcome hypoxia has focused on the use of hyperbaric oxygen and chemical sensitizers.

In mice hyperbaric oxygen and carbogen has been shown to result in an increase in the skin reaction (Rojas, 1992). This was also demonstrated by Van den Brenk (1965) in humans using hyperbaric oxygen, but this may have occurred because of secondary electron contamination from the hyperbaric oxygen chamber. Certainly most studies report no increase in skin reaction. Misonidazole, a chemical sensitiser has been shown to result in an increase in the skin reaction of mice but this has not been demonstrated in man (Stone, 1974 and Wasserman, 1981). This is probably a reflection of the lower dose used in man due to toxicity.
1.5.5 Heterogeneity of the response.

The degree of radiation response of the skin during and after radiotherapy varies between different individuals and between different sites in the same patients:

*Individual*

We commonly observe variations in the degree of the skin reaction among individuals. This variation was more apparent during the era of orthovoltage radiotherapy when the skin received the full dose.

*Nutritional status*

Normal tissue injuries following irradiation will heal more slowly in a malnourished patient (Sitton, 1992).

*Trauma*

Trauma to the skin during treatment such as the use of adhesive tape results in increased skin reaction, as does exposure of the treated area to sunlight. The use of a variety of creams containing metals should be avoided, as the metal causes increased electron scatter, so raising the skin dose.

*Skin pigmentation*

A generally held belief by Clinical Oncologists is that light skinned patients tolerate radiation less well than dark skinned patients. However Glicksman (1960) and Chu (1960) could find no correlation between the colour of a patient’s skin and the intensity of the skin reaction.

*Site*

The radiosensitivity of different sites of the body with regards to the acute skin reaction was classified by (Kalz, 1941). He found that the most radiosensitive regions were the anterior aspect of the neck and the anticubital and popliteal spaces, with the palms and soles being the less radiosensitive region. He provided no data on late skin changes.
**Age**
Glicksman (1960) demonstrated a marked age dependence of the acute radiosensitivity of the skin. Children appeared to be less radiosensitive than adults; old people were more radioresistant again.

**Metabolic disorders**
It has been suggested that thyrotoxicosis results in an increase in the early radiation reaction seen in skin (Trott, 1991)

**Genetic factors**
A severe reaction to radiotherapy has been noted in patients with the rare genetic disorder ataxia telangetasias (AT). It has been estimated that 1% of the population are carriers for the AT gene (Taylor, 1975). These heterozygotes may be more sensitive to radiation and are more likely to develop cancer than the normal population. Swift (1987) suggested that as many as 18% of all patients with breast cancer may carry the AT gene, so there may be selection of this gene in the irradiated population.

1.5.6 Chemotherapy

The simultaneous administration of chemotherapy and radiotherapy can result in an increase in acute skin reaction. Actinomycin D, Adriamycin, bleomycin, fluorouracil and methotrexate when given simultaneously result in an increased acute skin reaction. Additionally with actinomycin D the increased tendency to develop an enhanced skin reaction may persist many months after its administration. It may also recall the acute radiation dermatitis, when given months or weeks after the radiation (Muggia, 1978). With regard to the late skin reaction the picture is not so clear.

1.5.7 Skin graft

Differences occur in the reaction to radiation between normal and grafted skin. In the first three months after grafting, the skin reaction to ionising irradiation occurs earlier and is more severe, with recovery taking longer (Rubin, 1960). This increase in
reaction is due to vascularisation which is taking place in the grafted skin. Three months to a year after grafting, the tolerance of normal and grafted skin is similar. Grafts older than one year show a reduced skin reaction.

1.6 REVIEW OF MEASUREMENTS OF EARLY AND LATE RADIATION DAMAGE

1.6.1. Early radiation reaction

Subjective measurement
A number of different systems have been introduced to measure both early and late radiation damage to the skin. However none have become universally accepted as standard. Most schemes are based upon scoring the different elements of the reaction and are subject to observer bias (Dische, 1989). This is demonstrated in the study performed by Glicksman (1960), which reported only 38% agreement amongst three physicians in the scoring of the early skin reaction of 85 patients.

Skin erythema is correlated with dose and until about the 1930’s it was used as a biological dosimeter (skin erythema dose). It was fairly reliable when used by one observer under a particular set of irradiation conditions, with dose differences of 15% being detected. However when standardised conditions did not exist the variability in the SED was reported as being between 20-40% (Trott, 1991).

Skin pigmentation using visual ranking has also been shown to correlate with dose. Dische (1976) irradiated different areas of the thigh with strontium-90 plaques to doses of 800, 900, 1000 and 1100 rads. These areas were then ranked with regards to erythema and pigmentation. Good correlation with dose was observed with pigmentation but not erythema over this dose range: increments of 100 rads being distinguishable.
Reflectance spectrophotometer

Skin colour is determined by several factors: oxyhaemoglobin, reduced haemoglobin and melanin. Light of wavelength 578 nm is absorbed by oxyhaemoglobin and may be used to measure the degree of erythema. Pigmentation is registered by the absorption of light of wavelength 660 nm. The reflectance curves of the skin after irradiation mirror the early radiation reaction seen in the skin, with an increase in absorption in the oxyhaemoglobin band in the first 24 hours coinciding with the transient erythema. This is followed by a stable second period and then a marked increase in both bands coinciding with the main erythema reaction (Chu, 1960). This technique has been used in a number of studies and has an advantage over visually scoring as it provides an objective measure of radiation induced erythema and pigmentation with dose differences of 20% being distinguishable (Glicksman, 1960, Chu, 1960, Turesson, 1974 and Nias, 1963). In other hands visual scoring was found to give more consistent results than spectrophotometry (Dische, 1976).

Laser Doppler

Erythema was measured by Simonen (1990) using a laser Doppler flowmetry (LDF) and spectrophotometry as a reference. Good correlation was seen between the two methods. The variation from patient to patient was greater with the LDF with the maximal reaction occurring six days earlier suggesting that LDF might be a more sensitive method.

1.6.2 Radiation damage in the dermis

Dermal fibrosis is often described as a side effect of radiation. Both Potten (1985) and Hopewell (1990) have suggested that this is not a good term as it implies the formation of fibrous tissue. Potten suggested that the term atrophic contraction better described it. Clinically it appears as an increase in the density of the dermis, and it has been suggested that factors of importance may be: organisation of fibrinous exudates resulting from leakage from capillaries; a disturbance of the normal balance between the formation of new collagen and absorption of old collagen resulting from radiation damage to the fibroblasts. Histologically there is dermal atrophy, collagen fibres become hyalinised and may fuse with other collagen fibres. The fibroblasts are reduced
in number over time, with those surviving sometimes appearing markedly enlarged and demonstrating nuclear hyperchromatism (giant fibroblasts). Little, if any, new elastic tissue is formed. Large blood vessels demonstrate fibrous thickening of their walls, which may be obliterated by thrombosis, while the capillaries may be reduced in number with surviving ones often being dilated. The changes in the dermis are therefore dermal atrophy, skin contraction and loss of elasticity, each of which can be quantitatively measured.

Visco-elastic properties - Extensometer
The capacity of the skin to be deformed depends on the viscoelastic properties of its individual components (collagen, elastin, ground substance) and of the relative quantity of each (Leveque, 1980). There is a decrease in flexibility (extensibility) of the skin from 40 years of age due to: a reduction in skin thickness and a change in the elastic properties of collagen fibres due to biochemical transformation.

Many different instruments are available to measure the visco-elastic properties of skin, one example is the extensometer. They work by measuring the force required to stretch the skin by a fixed distance (Leveque, 1980 and Gunner, 1979). The direction of extension in testing is very important, since the skin is anisotropic: it is stiffer in some direction than in others. The stiffest and least stiff axes are always perpendicular to each other, which relates to the natural lines of tension in the skin, termed Langer’s lines (Baker, 1988).

The extensometer has been used clinically in humans to demonstrate the loss of stiffness in steroid atrophied skin (Gunner, 1979). Baker (1989) used it to study the time related changes in the mechanical properties of pig skin following irradiation.

Measurements of skin thickness
Ultrasound offers a non-invasive technique for measuring the atrophy that occurs in skin and subcutaneous tissue following irradiation. Hamlet at al used ultrasound to measure the thickness of the dermis and subcutaneous fat layer in pigs one year after irradiation. The reduction in the thickness of the dermis and fat was dose dependent (Hamlet, 1986).
Skin contraction

Skin contraction can be recorded by measuring the change in the distance between two tattooed points following irradiation. Hopewell (1979) used measurements of skin contraction in the pig as a model to study the late effects of different fractionation schedules.

Serial photographs have been used to assess late tissue morbidity in patients treated for breast cancer. This forms part of a prospective randomised trial of different fractionation schedules being carried out in the radiotherapy department of Sutton and Cheltenham. A photograph is taken prior to radiotherapy and then annually, and scored by three independent observers. Changes noted in the photographs chiefly relate to breast size and shape, with breast shrinkage being the commonest observation sometimes accompanied by a change in shape. A clear dose response for change in breast appearance has been found between 39 Gy in 13 fractions and 42.9 Gy in 13 fractions (Moody, 1994).

1.6.3. Cutaneous blood flow

Many techniques are available for the assessment of regional blood flow these include: arteriography, electromagnetic flow probes, radioactive microspheres deposition, quantitative fluorometry and washout techniques using xenon 133 (Corbally, 1990). Many of these methods are cumbersome, invasive, or expensive to use routinely. Most are not specific for the microcirculation. Laser Doppler flowmetry is a non-invasive technique which can directly measure cutaneous blood flow (CBF) over a small discrete area of the skin continuously and with repetitive accuracy (Corbally, 1990 and Schabauer, 1994).

Cutaneous laser Doppler

Since its introduction into clinical use in 1977 this non-invasive method for measuring CBF has steadily increased in popularity. A change in CBF is a non-specific common feature of many different clinical conditions, and can thus be used as a parameter in the study of a wide range of situations. It has proved to be useful for assessing patients with Raynauds disease and “fixed” arterial obstructive disease, typically atherosclerotic.
Many different variables are known to affect cutaneous blood flow:

**Regional difference:** There is regional variation in CBF. For example, the CBF in the finger and palm may be 6-7 times greater than that of the chest (Schabauer, 1994). However, Huether (1986) demonstrated good correlation between readings of cutaneous blood flow from comparable areas on both sides of the body.

**Temperature:** Ambient temperature and local heating and cooling of the skin affect CBF. Song (1989) in humans demonstrated a 10-15 fold increase in blood flow on heating the forearm from 32° C to 40° C.

**Reflexes and haemodynamics:** Phasic variations in skin blood flow occur with respiration and arterial pulsations.

**Rhythmic vasomotion:** Regular periodic fluctuations in CBF are seen with LDF. The mechanism behind it is uncertain but it is thought to be due to rhythmic contractions of arterioles and precapillary sphincters. The frequency of these rhythmic vasomotions vary from 2 to 17 times a minute depending on the individual and the site. Furthermore, the frequency is decreased by heating and is altered by peripheral vascular disease.

**Patient characteristics:** Women have a lower resting CBF. While the response to thermal stimulus is decreased in the elderly (Evans, 1993).

Since many factors strongly influence blood flow in the microcirculation, it is likely that the most useful clinical information will be derived from stimulus-response measurements, where the effect of the selected stimulus outweighs all other factors influencing blood flow in the selected region (Cochrane, 1986). One way to approach this is to thermally stress the skin and measure the changes in CBF. Rayman (1986) studied the response of diabetic skin microvasculature to minor thermal injury by heating the skin to 44 degree centigrade. A significant reduction in maximum skin blood flow was seen in the diabetic group compared to the controls.

In the field of radiotherapy LDF has been limited to studying the changes in CBF during the early radiation skin reaction, without stressing the skin with heat. Amols
(1988) monitored CBF using LDF in 14 patients undergoing radiotherapy using a comparable side on the untreated side as a control. The author did not specify the fractionation schedules employed. In all patients, alterations in blood flow was detected before skin reactions were observed. A rapid increase in blood flow at doses above 20 Gy was noted with a rapid decrease in flow once treatment ceased. Levels on the irradiated side remained higher than the control a year out from treatment. However whether acute changes in perfusion correlate with chronic changes in perfusion, and whether either correlate with long term cosmesis has not yet been demonstrated.

Telangiectasia

Telangiectasia do not develop until at least a year after irradiation and progress with time. Counting the number of telangiectasia in the treatment field has become a method of assessing late radiation change.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Telangiectasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>&lt; 1/cm²</td>
</tr>
<tr>
<td>2</td>
<td>1-4/cm²</td>
</tr>
<tr>
<td>3</td>
<td>&gt; 4/cm²</td>
</tr>
</tbody>
</table>


Turesson (1986) has extensively studied telangiectasia, as a measure of late tissue damage, in patients treated with different fractionation schedules for carcinoma of the breast. She demonstrated a dose response curve and found that the higher the dose, the shorter the lag period was for detectable change and the higher the progression rate. Additionally she suggested taking the rate of progression, rather than the telangiectasia density at a given time as a meaningful endpoint.
1.6.4 Hair and Hair follicle

The hair or hair follicle makes a useful biological dosimeter for several reasons: (1) the cells of the hair follicle are sensitive to small doses of radiation; (2) hair covers most of the body surface and could be used to measure surface doses; (3) hair and its follicle are readily accessible.

Hair follicle

Potten (1985) demonstrated in mice anagen hair follicles a dose-dependent increase in the number of apoptotic fragments following irradiation. He showed that the maximal number of fragments occurred 12 hours after treatment and were linearly related to the dose, at a rate of 2.92 fragments per follicle section per Gy. The technique was sensitive detecting the effect of doses as low as 0.2 Gy with an upper limit of 10 Gy, due to distortion of the hair follicle. However the disadvantages of using this system as a biological dosimeter are the need for skin biopsies and the transitory nature of the peak effect. Furthermore the application of this technique to human follicles would be further hampered by the fact that many of the hair follicles would be in the resting rather than growing phase of the cell cycle, and would therefore be less radioresponsive.

Actual biopsy may be avoided by plucking the hair 24 hours after irradiation. This may result in sufficient cells bearing apoptotic bodies being extracted with the hair to enable a dose response relationship.

Hair

The advantage of using hair as a biological dosimeter is that it provides a semipermanent record of radiation damage and can be sampled 1-4 weeks following exposure. Furthermore it is non-invasive, requiring plucking of the hair some time after irradiation.

Hair length and diameter have been measured in mice following irradiation, and shows a dose dependent reduction in size (Malkinsom, 1966, 1981). However the dose range over which changes are detected is small, with mouse hair diameter reduced by 7% per Gy over a range of 1 Gy to 6 Gy. Above this dose the hair is so thin that it breaks.
A few studies have been undertaken in man looking at the effects of radiation on hair. Van Scott (1957) in the 1950’s looked at the morphological alterations occurring in the hair root of the scalp of man after epilating or sub-epilating doses of radiation. The earliest sign of radiation effect was a reduction in the diameter of the hair bulb on the fourth day confined to anagen hair with a reduction in hair diameter occurring in the second week. He concluded that the number of anagen hairs showing dysplastic alteration was proportionate to the radiation dose.

Sieber (1992) studied the effect of radiation on the diameter of actively growing human hairs. Patients received either single dose or fractionated radiation with an interfraction interval of greater than four days. In order to identify actively growing hairs the area to be irradiated was shaved, thus any visible hairs following irradiation were assumed to have occurred from new growth. Hairs were plucked from the irradiated area, either prior to the second fraction or on day five to seven, and their diameters measured with the use of a microscope. Owing to the variation in diameter of individual hairs each hair was used as its own control. The diameter of the hair at the cut end was the “control diameter” and this was compared with the minimum diameter which was approximately half way between the hair bulb and the cut end. A reduction in diameter of 2.4% per Gy was observed in the dose range of 2.9 -14 Gy.

In conclusion significant dose dependent changes occur in the hair following irradiation. However the use of this system as a biological dosimeter is limited by the small range over which it is effective, due to hair loss.

1.6.5 Sweat glands and skin moisture

The perpetual loss of water from the human body as vapour from exposed surfaces of apparently dry skin to ambient air, is termed insensible perspiration. The average loss per day is 300-400 ml and the contributions of sweat and transepidermal water loss from the stratum corneum to insensible perspiration is unresolved. However in hot conditions sweating predominates.
The water content of the stratum corneum influences various physical characteristics, such as the brittleness, elasticity and tensile strength of the skin. It also plays an important part in the appearance of the skin with dry rough skin having a low water content. The stratum corneum receives water from within the body by diffusion from underlying tissues and from water taken up from the sweat glands, but water may also be taken up from the environment (Blank, 1984).

The water content of the inner layer of the stratum corneum is in equilibrium with the granular layer and the outer layer with the environment, thus there is a concentration gradient across the stratum corneum which results in continuous diffusion of water from within the body through the skin and into the environment—transepidermal water loss (TEWL). The wetter the surface of the skin the smaller the concentration gradient and the smaller the TEWL.

**Techniques for studying sweat gland function and skin hydration**

1. *Collection of sweat in bags or pads*

   Sweat glands in a defined area are stimulated to secrete either by an intradermal injection of methylcholine or by heat. A pre weighed bag or pad is placed over the area and sweat is collected over a period of time. The quantity of sweat can then be determined by the increase in weight and the sweat itself can be analysed (Parkkinen, 1991 and Boysen, 1984)).

2. *Microcannulae*

   This technique is only carried out on biopsied skin, microcannulae are passed into the duct and sweat analysed (Sato, 1990).

3. *Electrical measurements*

   The skin consists of a series of heterogeneous laminar structures perforated by sweat ducts that are filled to varying degrees. Electrical measurements are difficult to interpret because of the contribution of these different components of the skin. In tissue electrical conductance depends on the ion-permeability of the tissue. The sweat ducts are in parallel with the stratum corneum and offer a very accessible route for electrical conductance. However dry corneum does not as it is almost impermeable but wet corneum, by virtue of its aqueous channels between the keratin plates, is freely
conductive. Thus the conductance of dry corneum is a function of the fullness of the sweat ducts. In contrast, measurements taken when the electrodes are moist reflect conductance of both the sweat duct and stratum corneum (Edelberg, 1977). The interpretation of skin conductance therefore depends on the conditions under which it is measured.

The cosmetic industry is responsible for much of the work undertaken to look at different methods for measuring the properties of the skin. Electrical measurements have been used by them to study changes in skin hydration following the application of different products. Two of the most commonly used non-invasive electrical devices for assessing the hydration of the stratum corneum are the skin surface hygrometer which measures the conductance of the stratum corneum and the corneometer which measures capacitance. The latter is considered able to depict changes of hydration much deeper in the skin than the former (Hashimoto-Kumasaka, 1993).

**Psychogalvanic reflex**

The palmar eccrine glands are innervated by sympathetic fibres and in normal ambient temperatures the glands respond to psychological rather than thermoregulatory stimuli. If an electrode is placed on the palm and one on a reference site, changes in electrodermal indices occur following a sensory stimulus - this is the psychogalvanic reflex. It has been extensively used in the field of psychiatry, where changes in electrodermal indices have been used to study the effects of different treatments for conditions such as anxiety and schizophrenia (Christie, 1981).

This reflex has also been used to relate the number of active sweat glands as measured by the palmar sweat index to measures of skin conductance using a polygraph. Freedman (1994) looked at the number of open (actively functioning) and closed (non-functioning) sweat glands using the palmar sweat index. He found that palmar sweat index and skin conductance correlated best when using open sweat gland counts.

**4. Visualisation of the individual sweat droplets**

Sweat water is easily visualised by reaction with iodine-starch reaction (Minor's Method, one step visualisation method) or by reaction with bromophenol blue powder, pyrogallol, ferric hydroxide and quinazarin (Sato, 1990). There are several methods
using the iodine starch reaction and these are mainly used as the other dyes are toxic, irritating, staining or expensive. The original Minor’s technique required 3% iodine in alcohol to be painted on the skin before applying starch in castor oil and starch powder, respectively. Sweat was visualised by a change in colour of the iodine to deep purple. The main disadvantage of this test was that it did not visualise sweat pores individually. This was overcome by the one-step iodine starch method in which iodinated starch powder was sprayed directly onto the area (Sato, 1988). A semipermanent record can be achieved with the iodinated starch imprint method, although the test is limited to use over flat areas.

The plastic impression method obtains a three dimensional negative impression of the skin with emerging sweat droplets visualised as small holes corresponding to the sweat pores (Sarkany, 1968). This technique provides a numerical count of functioning sweat glands. Kennedy (1984) also used this method to calculate the volume of each sweat droplet by approximating the droplet shape to a sphere (\(V=\frac{4}{3}\pi r^3\)). The effects of radiation on sweat gland function have also been studied with this method. Price (1979) demonstrated that sweat gland function was significantly reduced following electron beam therapy for mycosis fungoides (3,600 rads over 10 weeks 2.5 MeV), but was restored to normal within six months. Morris (1992) working in our department looked at late changes in the skin and demonstrated that this technique provided a quantitative assay for permanent change.

5 Transepidermal water loss

TEWL provides an estimate of skin barrier integrity. Techniques to measure TEWL fall into two categories (Potts, 1982):

Ventilated
A continuous flow of carrier gas passes though a chamber attached to the surface of the skin and changes in water content of the gas are monitored.

Unventilated
An open chamber is placed on the skin. Water loss through the skin alters the relative humidity of the chamber and, thus, measurements of change in moisture within the
chamber provides a measure of TEWL. An Evaporimeter, a commercially available
device is now widely available.

6 Viscoelastic properties.
Viscoelastic techniques measure the time-dependent response of the skin to mechanical
def ormation. There are several non-invasive techniques available. Potts (1982)
described a technique where small amplitude vibrations propagating in the skin surface
were analysed over a broad frequency range from about 20 to 1000 Hz. The depth of
skin probed was dependent on the frequency of the wave propagated. The higher the
frequency the greater the depth probed. Experimental results show that viscoelastic
properties at low frequencies varied dramatically, with water content of the sample
reflecting the hydration of the stratum comeum. These techniques have been used in
the cosmetic industry to assess the efficacy of skin moisturisers.

7 Infrared spectroscopy.
Water is an intense absorber of infrared radiation. Infrared spectroscopy holds promise
for measurement of the water content in the stratum comeum, since the water
absorbance spectrum can, in theory, be uniquely identified and the water concentration
quantitatively measured from the absorbance intensity (Potts, 1982).

1.6.6. Choice of techniques used in the study

A number of methods for measuring changes in the skin following irradiation were
considered, among those discarded were:

1. Measurement of dermal thickness using ultrasound. This system looked promising
but unfortunately the ultrasound machine was unreliable, repeatedly breaking down.

2. Measurement of skin contraction was not possible as many of the patients, entered
into the study, had not had their treatment fields tattooed, making determination of
skin contraction since treatment impossible.
3. Techniques for measuring radiation change in hair was not employed because of the limited range over which a dose effect is seen due to alopecia. Furthermore we were particularly interested in patients treated for breast cancer and the hairs in this area are very fine.

The techniques adopted were:

1. A clinical scoring system for skin morbidity.
   The scoring system employed was one which has been used extensively at Mount Vernon Hospital to record radiation morbidity (appendix 3).

2. Skin conductance
   Irradiated skin is often found to be drier than comparable areas of non irradiated skin. For several years we had been interested in developing a technique for measuring this difference in moisture. Since the electrical conductance of the skin surface depends on its moisture, a novel system was designed in collaboration with B. Vojnovic of the Gray laboratory to record the electrical conductance of the skin surface.

3. Silicone elastomer imprint
   The silicone elastomer imprint technique was chosen as it provides the most sensitive method for determining the numerical density of actively secreting sweat glands. Furthermore we were familiar with this method as Morris (1992) working within the department had modified the technique. Usually the sweat glands in the area of interest are stimulated to secrete by injecting the skin with a cholinergic stimulant prior to applying the silicone elastomer. Morris developed a non-invasive method using pilocarpine iontophoresis to stimulate the glands.

4. Visco-elasticity skin analyser
   This is a new system to measure skin elasticity. Work undertaken in the design and development of this equipment was performed by Raphael Gorodetsky (Head of the Radiobiology Laboratory) and his group at the Sharett Institute of Oncology, Hadassah University Hospital, Jerusalem. We collaborated with them in assessing its use in clinical practice.
5. Laser Doppler flowmetry
This method was chosen as it provides the only direct non-invasive technique for measuring cutaneous blood flow. It has been commonly used to assess cutaneous blood flow in patients with peripheral vascular disease or to monitor the perfusion of tissue flaps postoperatively. In a number of these studies the vascular response to the thermal stress was measured, as impairment of tissue function is often not apparent unless the tissue is stressed.

In the field of radiotherapy the use of laser Doppler flowmetry has been limited to one study, which looked at the changes in blood flow (without stressing the tissue) during the acute reaction (Amols, 1988). No study has used laser Doppler flowmetry to assess late radiation change in skin vasculature, or has measured the vascular response of irradiated skin to heating. We therefore collaborated with Dr. D Chaplin, and B Vojnovic of the Gray laboratory and A. Obied of Oxford Optronics, to design a laser Doppler probe with an in-built heating device, so we could measure real time changes in skin blood flow, while altering the surface temperature of the skin.
OBJECTIVES, METHODS AND MATERIAL

2.1 Objectives:

The objectives of this project are:

1) To assess new and established methods for quantitatively measuring changes in irradiated skin.

2) To determine if functional changes can be detected in irradiated skin which appears apparently normal.

3) To compare results using different fractionation schedules.

2.2 Methods and materials:

2.2.1 Skin conductance

This is a new system which was designed in the Gray laboratory by B. Vojnovic in collaboration with Prof. S. Dische.

The system consists of the following components: (fig. 5)

1. A range of sensing electrode applicators.
2. A signal conditioning-module (conductance-to-voltage converter) into which the applicator and a thermometer probe are connected.
3. A National Instruments input-output card which is housed in the Macintosh computer and forms an interface with the signal-conditioning module.
4. LabVIEW software which runs the application programme, records data and recalls it.
This system consists of two applicators, each having five metal electrodes held at a fixed distance apart embedded into a silicone rubber sheet; the electrodes are in electrical contact with the skin and are arranged to monitor the surface conductance of a defined area of skin. The edge of the silicone rubber sheet makes a seal with the skin, so preventing the loss of liquid by evaporation. There is therefore an accumulation of moisture resulting in an increase in conductance between the electrodes with time. The kinetics of this increase provide a measure of transepidermal water loss and sweat production in the region between the electrodes.

An amplifier/converter applies a constant amplitude AC 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 DC voltage is produced, which is recorded by the computer. Eight traces are graphically recorded simultaneously on the computer, with the time along the x axis and conductance along the y axis (microSiemens) (fig. 7a). Different curve fits can be
applied to the graphs (fig. 7b) and the data stored on a database program such as EXCEL.

Method
The application of skin products for example moisturising creams and talc can influence the capacitance of the skin. Consequently patients were requested not to apply any of these products 24 hours prior to testing. Hairy skin resulted in poor electrical contact, but this could be overcome by shaving. Measurements were undertaken in a quiet room with the patient lying on a bed.

Two identical applicators were used, so that simultaneous measurements could be achieved from comparable areas, each applicator provided four graphic readings of the change in conductance with time. Prior to use the electrodes were cleaned with isopropyl alcohol and dried with gauze. Data was accumulated, to obtain a base line reading, before the applicators were applied to the skin. It was important to ensure that the electrodes made good electrical contact with the skin during the period of data acquisition, which was from two to eight minutes. A proforma was designed to identify the patient and to record the radiotherapy given. To this proforma was added information concerning the area studied and the number of the file in which the conductance data was stored. (appendix 1)
Analysis

**Figure 6.** An example of a conductance reading obtained between a pair of electrodes.

- **a-b** = initial base line
- **b** = vertical rise on contact
- **c-d** = rise in conductance over 2 minutes
- **- -** = area under curve during first 2 minutes of measurement

The initial vertical rise in skin conductance reflects the moisture of the skin at the time of applying the applicators. There is then a steep rise in conductance as moisture collects under the silicone sheet. This is then followed by a gradual rise, which in a number of cases almost plateaus, presumably reflecting saturation of the process.

The area under the curve was calculated for the first two minutes after the applicators had been applied to the skin, as this corresponded to the time when the greatest change was seen. Graph 1-4 represented the readings from one applicator and 5-8 from the other. The average value for the area under the curve was calculated for each applicator.
Figure 7a. Skin conductance results from a normal chest carried out over eight minutes. y axis - 1 μSievert/division, x axis - 60 sec/division
Curves 1-4 = right side, Curves 5-8 = left side

Figure 7b. Figure 7a with the area under the curve for the two minutes following the initial rise calculated.
2.2.2 Eccrine pore imprint: silicone imprint

Silicone elastomer moulds of the skin provide a sensitive method of determining the numerical density of actively secreting eccrine glands. This technique has already been established at Mount Vernon (Morris, 1992). The glands are stimulated using pilocarpine iontophoresis. Following this a low viscosity silicone monomer containing a catalyst is applied to the skin and allowed to harden to form a robust negative imprint of the skin. Sweat droplets emerging from eccrine sweat glands during the hardening process cause the hydrophobic silicone suspension to withdraw from the droplet leaving a characteristic imprint in the surface of the silicone monomer. These imprints can be easily identified under low power microscopy, so that a count of the number of glands per unit area can be obtained (fig 8).

![Silicone elastomer impression of functioning eccrine sweat glands from skin over the chest.](image)

**Figure 8.** Silicone elastomer impression of functioning eccrine sweat glands from skin over the chest.

Scale 1 mm
Method

Eccrine sweat gland stimulation

The skin in the area to be measured was first cleaned with isoprophyl alcohol and dried with gauze. Following this it was lightly abraded for approximately 30 seconds with extra fine sand paper, to reduce skin resistance. A 3 cm by 5 cm piece of blotting paper soaked in 4% w/v pilocarpine nitrate was then applied to the test area. Two pieces of gauze measuring 2 cm by 3 cm were soaked in normal saline, one piece was placed in the middle of the blotting paper and the second was placed on a nearby piece of skin. The positive electrode was connected to the gauze in the test area and the negative electrode to the other piece of gauze. A current of 0.04 mA per cm² was then applied for 5 minutes. The area of skin being inotrophoresed was marked out with a pen, the blotting paper removed and the skin dried. The silicone elastomer was then thinly applied to the area and allowed to set. This took five to ten minutes, after which the elastomer was peeled off the skin and allowed to cure for twenty-four hours. Some patients complained of mild transient irritation in the tested area, and slight erythema was noted in a few, which settled within two hours.

Silicone Elastomer

Medical quality silicone elastomer (McGhan NuSil MED-6382) was used. This was diluted into a liquid by adding naptha at a ratio of five parts of silicone to four parts of naptha. Prior to applying this to the skin a catalyst was added to the elastomer to set it. The catalyst was drawn up into a syringe using a 19 gauge needle and one drop of catalyst was added to each gram of silicone elastomer and quickly mixed before applying to the skin.

Measurement of the number of sweat glands

The silicone impression was mounted in a glass photographic slide and the number of sweat glands in a 2 cm² area was counted using a low power microscope.
2.2.3. Mechanical properties of skin: Visco-elasticity skin analyzer (VESA)

Our work undertaken with the Visco-elasticity skin analyser (VESA) is done in collaboration with Raphael Gorodetsky at the Sharett Institute of Oncology, Hadassah University Hospital, Jerusalem. The VESA prototype was designed at their institution and we are working with them to evaluate its use in clinical practice.

The VESA measures the speed of propagation of a mechanical surface wave in biological tissues. The device consists of a mechanical unit (probe) and electronic hardware (fig 9). The probe houses two piezoelectric transducers covered with plastic tips: one acts as a transmitter and the other as a receiver. The transmitter is connected to a pulse generator and produces tangential oscillatory deformation (pulse)-mechanical wave on the surface of the tissue. The wave that reaches the receiver induces a signal that is amplified. The speed of wave propagation along the vector is measured and presented on a display.

A specially designed highly sensitive force-sensing resistor is built into the VESA to ensure that the piezoelectric elements make optimal contact with the skin surface. In vitro examination has shown that the depth of measurement in human skin is down to 2-3 mm and that any material below this depth cannot affect the readings. The VESA records a speed of wave propagation over a range of 20-200 m/sec. This covers the range seen in human skin.

Method

The machine was calibrated before use, by taking repeated readings of the speed of wave propagation across the surface of a silicone rubber cube. The VESA had been calibrated to give readings of 44-46 m/sec.

Measurements were carried out on skin which was dry and hairless. The area to be tested was mapped out and divided into a number of squares, where readings were taken. The skin is anisotropic, and VESA measurements were therefore taken in two directions at right angles to each other: horizontal and vertical. The probe was placed perpendicularly to the skin and pressure gently increased until an optimal pressure on
the skin was achieved. At that point a wave was propagated through the skin and its speed displayed. Three readings in each area were taken, and the results collected on a proforma (appendix 2).

**Analysis**
The average reading of each area in both directions was calculated and the data stored on a data base program (EXCEL) on the computer.

![Visco-elasticity skin analyzer](image)

**Figure 9.** Visco-elasticity skin analyzer
2.2.4 Dermal vascular perfusion: Laser Doppler flowmetry

Since its introduction in 1977 a wide variety of clinical applications have been developed for laser Doppler flowmetry (LDF), most for assessing cutaneous blood flow. The largest body of work done with LDF has been in assessing vasospasm in particular in relationship to Raynaud's phenomenon. It has also been used to assess patients with arterial obstructive disease, and is used postoperatively to monitor capillary flow in free tissue flaps (Schabauer, 1994). Little data is available about its application in measuring cutaneous blood flow in irradiated skin. Simonenn (1990) used LDF in the measurement of radiotherapy induced erythema and showed that the results correlated well with those obtained with spectroscopy.

Dual channel temperature-controlled blood flow measurements using LabVIEW 2

B. Vojnovic of the Gray Laboratory in collaboration with Andrew Obied of Oxford Optronic designed this system for measuring cutaneous blood flow. Since many factors influence blood flow in the microcirculation, we were more likely to gain useful clinical information from stimulus-response measurements, where the effect of the selected stimulus outweighs all other factors influencing blood flow in the region to be measured. We chose as our stimulus heat, and therefore incorporated a heating device into the laser Doppler probe.

The system developed for the recording of temperature and blood flow data consists of the following (fig 10a, b).

1. Two laser Doppler blood flow perfusion monitors (Oxford Optronix model MPM 35).
2. Each laser Doppler has a heating/cooling device attached to it, with a thermocouple sensor.
3. An interface unit which drives the heater/cooler system and which conditions the thermocouple signals. This unit also incorporates two simple pressure sensors which monitor applicator pressure on the skin. The interface unit is used with a data acquisition card.
4. A Macintosh II cx computer which houses the data acquisition card.
A software system (LabVIEW) which provides facilities for controlling the temperature of the heater/cooler devices, for acquiring temperature and flow data and selectively storing it, and for recalling data.

Figure 10a. Laser Doppler probe with in built heating device
The theory of LDF is that the emitted laser light penetrates tissue to a depth dependent on the light frequency. The light is reflected after it strikes either immobile or moving tissues; the portion of this light reflected from moving blood cells undergoes a Doppler shift. By sampling all reflected light, the device can calculate flux of erythrocytes within the sample volume. Flux is calculated by multiplying the percentage of reflected light returning from the moving blood cells by the mean velocity of movement (Haumschild).
Laser Doppler flowmeters produce an output signal that is proportional to the blood cell perfusion (or flux).

\[
\text{PERFUSION} = \text{number of blood cells moving} \times \text{mean velocity of}
\]
\[
in \text{the measured volume these cells}
\]

Perfusion represents the transport of blood cells through the microvascular network as opposed to just a discreet blood vessel. In the MPM 3S, the measurement area is approximately 16 mm\(^3\) whilst the depth is hemispherical with a radius of 1 mm. Incorporated with the laser Doppler probe is a heating element and thermocouple. This enables the skin temperature to be raised, stressing the underlying dermal vasculature and leading to an increase in perfusion.

The LabVIEW software records the temperature and blood flow data onto four graphs, one for each blood flow probe and one for each thermocouple, with time on the x-axis. This data is stored and can later be analysed (fig. 11a, b).

**Method.**

Readings were carried out in a quiet room, with patients resting supine on a couch for 10 minutes prior to testing. The laser probes were placed over the areas of interest and held in place by the use of a specially designed gig. The pressure applied to the skin by the probe was adjusted using the gig so that a low reading was obtained. Baseline perfusion readings were then recorded at a temperature of 32°C, and, once stable, the skin temperature was raised immediately to 40°C and maintained at this level for the required time. During testing both the vascular perfusion and temperature changes for both probes were recorded graphically.
Analysis
The laser Doppler does not record an absolute measure of vascular perfusion. Consequently the data was analysed in terms of relative changes in vascular perfusion following thermal stress.

Increase in dermal vascular perfusion = peak perfusion at 40 °C
initial perfusion at 32°C

Figure 11a. Laser Doppler control reading from one side of the chest. 60 minutes of heating at 40°C
Figure 11b. Laser Doppler control recording from both sides of the chest. 8 minutes of heating at 40°C

2.2.5 Clinical observation of patients:

All patients who underwent both retrospective and prospective skin measurements were scored clinically for radiation skin damage (appendix 3).

2.2.6 Assessment of area treated in retrospective breast study

The treatment plan of each patient was reviewed. Using the outline through the central axis of the treatment volume, the area encompassed by the minimum tumour dose and the area within the edge of the treatment fields were calculated.
2.3 Controls and Patients

Ethical committee approval was obtained for this study. All patients were given an information sheet regarding the skin test and all freely gave their informed consent for the study (appendix 4).

2.3.1 Controls

The structure and function of the skin varies from site to site, with the only identical area being the corresponding site on the other side of the body. Skin conductance, laser Doppler and visco-elasticity skin analyser measurements were carried out in a number of normal volunteers of both sex. Identical areas of each side of the anterior chest in men and breasts in women were tested to assess the variation in readings between the two sides and amongst individuals. No age limit was imposed, but volunteers who had undergone surgery or radiotherapy to the chest or breast were excluded.

Controls for the skin conductance: (TABLE 6)

Volunteers were excluded if they were on medication which affected sweat gland function or if the area to be measured was hairy, as this resulted in poor skin conductance readings. Measurements were carried out on 22 normal volunteers; in eight the readings were repeated over the same area on four separate occasions (table 6).
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**Table 6.** Controls for skin conductance measurements
Controls for VESA: (Table 7)

Readings were undertaken in 12 normal volunteers. Two identical 9 cm square areas on each side of the chest were mapped out and each was divided into nine areas. Three readings in each direction were obtained from each area and the average calculated (appendix 2).

<table>
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Table 7. Visco-elasticity skin analyser control
Control for Laser Doppler Flowmetry: (Table 8a, b)

Readings of dermal perfusion were obtained initially over the chest area in 6 normal volunteers. Measurements were obtained with the probe at a temperature of 32°C. Once a steady blood flow reading was achieved, the skin temperature was raised to 40°C and maintained at this temperature for 60 minutes with changes in blood flow recorded during this time (fig 11a). All six patients showed an initial peak in the first 6 minutes of heating, followed by a gradual increase in flow over time (table 8a). We decided for our future studies that we would measure blood flow changes over the first 8 minutes of heating, as this would include the peak. Recordings over a longer period would be practically difficult as patients need to remain still.

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<tr>
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Table 8a. Laser Doppler control (60 minutes 40°C)
Simultaneous readings from an identical area on each side of the chest were obtained in ten normal volunteers (table 8b). Blood flow readings at a skin temperature of 32°C were acquired until a stable baseline was achieved. The temperature was then raised to 40°C for 8 minutes and flow readings obtained.

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Table 8b. Controls for laser Doppler readings (heating period 8 minutes)
2.3.2 Retrospective study.

Skin tests were carried out on a group of patients who had been treated two or more years ago with radiotherapy for malignancy confined to one side of the chest. Identical areas on each side of the chest were tested, the untreated side acting as a control.

Breast group: (Table 9)

Patients had undergone either a biopsy or local excision of their primary breast cancer. This was followed by a course of radical radiotherapy to the breast. Patients were treated with two tangential wedged fields on a Cobalt machine.

When measurements were obtained the lumpectomy site was avoided.

The following tests were performed on each patient:

- Skin conductance
- Silicone elastomer impression
- Visco-elasticity skin analyser
- Laser Doppler flowmetry
- Clinical assessment of radiation change of the skin

Four groups of breast patients were studied: (table 9)

Group 1: 12 patients received 40 Gy prescribed to the min.t.d. in 15 fractions treating daily over three weeks.

Group 2: 11 patients received 50 Gy prescribed to the min.t.d. in 25 fractions daily over five weeks.

Group 3: 8 patients received 50 Gy prescribed to the min.t.d in 20 fractions treating daily over four weeks.

Group 4: 2 patients received 60 Gy prescribed to the min.t.d in 30 fractions treating daily over six weeks.
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<th>Radiotherapy (Gy/fractions/days)</th>
<th>Boost (Gy/fraction/days 'electron energy')</th>
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<td>40/15/21</td>
<td>10.5/3/3 (10 Mev)</td>
<td>5.3</td>
</tr>
<tr>
<td>27</td>
<td>70</td>
<td>Left</td>
<td>Lumpectomy</td>
<td>40/15/21</td>
<td>10.5/3/3 (8 Mev)</td>
<td>5.3</td>
</tr>
<tr>
<td>28</td>
<td>64</td>
<td>Left</td>
<td>Lumpectomy</td>
<td>40/15/21</td>
<td>15/5/7 (8 Mev)</td>
<td>5.0</td>
</tr>
<tr>
<td>29</td>
<td>56</td>
<td>Right</td>
<td>Lumpectomy</td>
<td>40/15/21</td>
<td>10.5/3/3 (8 Mev)</td>
<td>6.3</td>
</tr>
<tr>
<td>30</td>
<td>61</td>
<td>Left</td>
<td>Lumpectomy</td>
<td>40/15/21</td>
<td>10.5/3/3 (8 Mev)</td>
<td>5.2</td>
</tr>
<tr>
<td>31</td>
<td>63</td>
<td>Right</td>
<td>Lumpectomy</td>
<td>40/15/21</td>
<td>10.5/3/3 (10 Mev)</td>
<td>5.0</td>
</tr>
<tr>
<td>32</td>
<td>69</td>
<td>Left</td>
<td>Lumpectomy</td>
<td>40/15/21</td>
<td>15/5/5 (10 Mev)</td>
<td>5.2</td>
</tr>
<tr>
<td>33</td>
<td>65</td>
<td>Right</td>
<td>Lumpectomy</td>
<td>40/15/21</td>
<td>10.5/3/3 (8 Mev)</td>
<td>5.0</td>
</tr>
</tbody>
</table>

**Table 9.** Summary of breast cancer patients details: retrospective study.
Tests carried out: - Skin conductance/ Silicone elastomer moulds/ Visco-elasticity skin analyser/Laser Doppler flowmetry/Clinical observations
Electron boost

An electron boost was given to the site of the primary tumour in patients in group one to three. The energy of electrons chosen was dependent on the size of the breast and the site of the tumour. The total dose ranged between 10 to 20 Gy, with the higher doses being given when the resection margins of the tumour were not clear.

Carcinoma of the bronchus group: (Table 10)

All patients had inoperable locally advanced non small cell carcinoma of the lung, and received radical radiotherapy treatment using either the CHART or CHARTWEL (CHART-Weekend less) regime (Saunders, 1993). Patients were treated with a two phase technique: an initial large volume which included the tumour, with a margin, together with the mediastinum from the suprasternal notch to 5 cm below the carina. This was followed by a small volume to encompass the known tumour only with a margin. The standard plan utilised a four field “box” with a weighting of 2:1 between the anterior-posterior and lateral fields. Treatment was carried out on a 6 Mv linear accelerator.

<table>
<thead>
<tr>
<th>No</th>
<th>Age</th>
<th>Sex</th>
<th>Regime</th>
<th>Radiotherapy (Gy/fractions/days)</th>
<th>Time till testing (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65</td>
<td>Male</td>
<td>CHART</td>
<td>54/36/12</td>
<td>1.0</td>
</tr>
<tr>
<td>2</td>
<td>71</td>
<td>Female</td>
<td>CHARTWEL</td>
<td>57/38/17</td>
<td>1.3</td>
</tr>
<tr>
<td>3</td>
<td>67</td>
<td>Male</td>
<td>CHART</td>
<td>54/36/12</td>
<td>2.2</td>
</tr>
<tr>
<td>4</td>
<td>53</td>
<td>Male</td>
<td>CHART</td>
<td>54/36/12</td>
<td>2.5</td>
</tr>
<tr>
<td>5</td>
<td>63</td>
<td>Male</td>
<td>CHARTWEL</td>
<td>54/36/16</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Table 10. Summary of lung cancer patients details: retrospective study.
Tests carried out: Skin conductance/ Silicone elastomer moulds/ Clinical observations

CHART = Continuous, hyperfractionated, accelerated radiotherapy

CHARTWEL = Continuous, hyperfractionated, accelerated radiotherapy weekend less
Tests undertaken:

Skin conductance
Silicone elastomer imprint
Clinical assessment of skin radiation morbidity

Mixed group of patients: (Table 11)

All patients in this group were treated for carcinoma located on one side of the body, with the untreated site on the opposite side acting as a control.

<table>
<thead>
<tr>
<th>No</th>
<th>Age</th>
<th>Sex</th>
<th>Site</th>
<th>Machine</th>
<th>Radiotherapy</th>
<th>Build</th>
<th>Boost</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>83</td>
<td>M</td>
<td>Neck</td>
<td>6 MV</td>
<td>54/36/12</td>
<td></td>
<td></td>
<td>3.3</td>
</tr>
<tr>
<td>2</td>
<td>71</td>
<td>F</td>
<td>Neck</td>
<td>10 Mev</td>
<td>47.5/19/27</td>
<td>yes</td>
<td></td>
<td>3.5</td>
</tr>
<tr>
<td>3</td>
<td>71</td>
<td>F</td>
<td>Neck</td>
<td>6 MV</td>
<td>50/20/28</td>
<td></td>
<td></td>
<td>6.2</td>
</tr>
<tr>
<td>4</td>
<td>64</td>
<td>M</td>
<td>Neck</td>
<td>6 MV</td>
<td>54/36/12</td>
<td>yes</td>
<td>9.4/6/8 (12 Mev)</td>
<td>2.5</td>
</tr>
<tr>
<td>5</td>
<td>79</td>
<td>M</td>
<td>Leg</td>
<td>100 kV</td>
<td>35/5/5</td>
<td></td>
<td></td>
<td>3.0</td>
</tr>
<tr>
<td>6</td>
<td>70</td>
<td>M</td>
<td>Temple</td>
<td>100 kV</td>
<td>35/5/5</td>
<td></td>
<td></td>
<td>4.0</td>
</tr>
<tr>
<td>7</td>
<td>33</td>
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<td>Neck</td>
<td>100 kV</td>
<td>35/5/5</td>
<td></td>
<td></td>
<td>12.1</td>
</tr>
</tbody>
</table>

Table 11 Summary of patients details: retrospective

Test undertaken:

Laser Doppler flowmetry
Clinical assessment of skin radiation morbidity
2.3.3. Prospective study: (Table 12)

Patients

Patients with carcinoma of the breast who had undergone wide local excision and were attending for post operative radiotherapy were entered into this study. All patients were treated on a 6 Mev linear accelerator, and received 40 Gy prescribed to the minimum tumour dose in 15 fractions over three 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 throughout the four weeks of treatment. The applicators were placed over identical areas of each breast, with the non-treated breast being used as a control. Readings were acquired over eight minutes, and repeated once or twice a week over the same area. Once treatment was completed skin conductance readings and silicone elastomer impressions were done at their routine outpatient follow up. Each time a reading was obtained the presence or absence of any radiation change in the skin was noted.
<table>
<thead>
<tr>
<th>No</th>
<th>Age</th>
<th>Breast</th>
<th>Surgery</th>
<th>Dose</th>
<th>Boost</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(Gy/fraction/days)</td>
<td>(Gy/fraction/days)</td>
</tr>
<tr>
<td>1</td>
<td>59</td>
<td>Right</td>
<td>WLE+AC</td>
<td>40/15/21</td>
<td>10/5/5</td>
</tr>
<tr>
<td>2</td>
<td>69</td>
<td>Right</td>
<td>Lumpectomy</td>
<td>40/15/21</td>
<td>10/5/5</td>
</tr>
<tr>
<td>3</td>
<td>53</td>
<td>Right</td>
<td>WLE+AC</td>
<td>40/15/21</td>
<td>10/5/5</td>
</tr>
<tr>
<td>4</td>
<td>57</td>
<td>Right</td>
<td>WLE+AC</td>
<td>40/15/21</td>
<td>20/10/14</td>
</tr>
<tr>
<td>5</td>
<td>78</td>
<td>Right</td>
<td>Lumpectomy</td>
<td>40/15/21</td>
<td>10/5/5</td>
</tr>
<tr>
<td>6</td>
<td>56</td>
<td>Right</td>
<td>WLE+AC</td>
<td>40/15/21</td>
<td>10/5/5</td>
</tr>
<tr>
<td>7</td>
<td>35</td>
<td>Right</td>
<td>WLE+AC</td>
<td>40/15/21</td>
<td>10/5/5</td>
</tr>
<tr>
<td>8</td>
<td>64</td>
<td>Right</td>
<td>WLE+AC</td>
<td>40/15/21</td>
<td>10/5/5</td>
</tr>
<tr>
<td>9</td>
<td>81</td>
<td>Left</td>
<td>Lumpectomy</td>
<td>40/15/21</td>
<td>10/5/7</td>
</tr>
<tr>
<td>10</td>
<td>54</td>
<td>Right</td>
<td>Lumpectomy</td>
<td>40/15/21</td>
<td>10/5/7</td>
</tr>
<tr>
<td>11</td>
<td>54</td>
<td>Right</td>
<td>WLE+AC</td>
<td>40/15/21</td>
<td>10/5/7</td>
</tr>
<tr>
<td>12</td>
<td>64</td>
<td>Left</td>
<td>WLE+AC</td>
<td>40/15/21</td>
<td>10/5/7</td>
</tr>
<tr>
<td>13</td>
<td>56</td>
<td>Right</td>
<td>Lumpectomy</td>
<td>40/15/21</td>
<td>10/5/7</td>
</tr>
<tr>
<td>14</td>
<td>56</td>
<td>Right</td>
<td>WLE+AC</td>
<td>40/15/21</td>
<td>10/5/7</td>
</tr>
<tr>
<td>15</td>
<td>45</td>
<td>Left</td>
<td>WLE+AC</td>
<td>40/15/21</td>
<td>10/5/7</td>
</tr>
<tr>
<td>16</td>
<td>65</td>
<td>Left</td>
<td>WLE+AC</td>
<td>40/15/21</td>
<td>10/5/7</td>
</tr>
<tr>
<td>17</td>
<td>59</td>
<td>Right</td>
<td>WLE+AC</td>
<td>40/15/21</td>
<td>10/5/7</td>
</tr>
<tr>
<td>18</td>
<td>52</td>
<td>Left</td>
<td>WLE+AC</td>
<td>40/15/21</td>
<td>10/5/7</td>
</tr>
</tbody>
</table>

**Table 12.** Summary of breast cancer patients details: prospective study.

Tests carried out: Skin conductance/Silicone elastomer moulds/Clinical observations

**Legend:**

WLE = Wide local excision

AC = Axillary clearance
2.4 Calculation of the radiation dose to the dermal structures

A depth of 1 mm was chosen to present the average position of the sweat glands and dermal capillaries. Furthermore at this depth skin elasticity was measured.

An estimation of the dose at 1 mm was calculated for each of the radiation schedules employed. Factors such as the size and shape of the treatment volume as well as the variables associated with the delivery of the radiation affect the dose delivered at 1 mm below the skin surface. (appendix 8)

Retrospective study

Lung

The standard plan for a lung tumour utilised a four field “box” with a weighting of 2:1 between the anterior-posterior and lateral fields. Patients were treated isocentrically using a 6 MV linear accelerator. A total tumour dose of 54-57 Gy was prescribed to the intersection point, with treatment being given three times a day using a dose per fraction of 1.5 Gy.

Observations of radiation change were made in the skin of the anterior chest wall. The dose to this area was dependent on the incident beam from the anterior field and the exit beam from the posterior field. The dose delivered by the anterior and posterior fields gave two thirds of the total dose to the tumour. Therefore when a tumour dose of 54 Gy was prescribed 36 Gy was given using the anterior and posterior pair of fields, with a tumour dose of 57 Gy, 38 Gy was given with the anterior and posterior pair of fields.

For the calculation of the dose at a depth of 1 mm we assumed an average field size of 10 x 10 cm and a separation of 20 cm. Allowances were made for the build up of dose due to the anterior applied field and for the ‘emerging’ dose from the posterior field. Another factor taken into account when estimating the dose was the use of a lead tray and the isocentric set up. The maximum average dose 1 mm below the skin surface was 20 Gy for patients treated with 54 Gy in 36 fractions and 21 Gy for those receiving a total tumour dose of 57 Gy in 38 fractions.
Breast
All patients were treated on one of a pair of identical Cobalt 60 machine, which did not have a filter. The doses used in the different fractionation schedules were prescribed to the minimum tumour dose, with a dose gradient of 10% across the tumour being acceptable.

Figure 12. Breast contour through the central axis of the treatment volume.
Patient treated with two tangential wedged fields.

The dose at sample Points A and B will differ because of the variation in the obliquity of the incident beam at these two points and because of the variation in the amount of tissue through which the beam passes.

For the calculation of the dose at a depth of 1 mm we assumed an average field size of 10 x 10 cm and a separation of 20 cm. Allowances were made for the build up of dose due to the applied tangential field and for the 'emerging' dose from the opposed tangential field. There was no reason to suggest a difference between the groups in the factors affecting the skin dose.
The average dose 1 mm below the skin surface at Point A was 94% of the minimum tumour dose, with the highest dose being delivered to a small area around Point B (nipple) where the dose was greater than the minimum tumor dose.

<table>
<thead>
<tr>
<th>Fractionation Schedule</th>
<th>Dose 1 mm below skin surface</th>
<th>BED a/b of 3 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>54/36/12</td>
<td>20 Gy</td>
<td>24</td>
</tr>
<tr>
<td>57/38/16</td>
<td>21 Gy</td>
<td>25</td>
</tr>
<tr>
<td>40/15/21</td>
<td>38 Gy</td>
<td>70</td>
</tr>
<tr>
<td>50/25/35</td>
<td>47 Gy</td>
<td>76</td>
</tr>
<tr>
<td>50/20/28</td>
<td>47 Gy</td>
<td>84</td>
</tr>
<tr>
<td>60/25/35</td>
<td>56 Gy</td>
<td>98</td>
</tr>
</tbody>
</table>

Table 13. Estimation of the biological effective dose 1 mm below the skin surface

2.5 Statistical analysis of results

Statistical analysis of the data was undertaken with the help of Christopher Foy, statistician to the department of Research and Development at Mount Vernon Hospital. The software package employed was SPSS for windows.

Control readings were assessed using method comparison studies as described by Altman (1991). This compares differences against means for each pair of readings and provides information on the degree of agreement of the two readings from each side.

Simple linear regression was used to determine whether a dose response effect existed for the different techniques used for measuring radiation change in skin.

To determine whether there was a significant difference in skin function of the irradiated area compared to the control area, for the different fractionation schedules employed, paired T tests were performed (Mould, 1989).
In the prospective study the change in skin conductance observed during treatment was analysed using the analysis of covariance (Altman, 1991). This is a means of comparing the mean response in two or more groups, while taking account of a covariate which may have an affect on response.

p-Values of <0.05 were considered significant.
CHAPTER 3
RESULTS OF THE STUDY

The different techniques used in this study to measure skin function were introduced into clinical practice over a ten month period. Since the apparatus to measure skin conductance and blood perfusion was designed on site, some alterations were made in the early days after problems became apparent during clinical use. For example, a pressure sensing device was added to the Doppler probe when it was noted that blood flow measurement was influenced by the pressure of the Doppler probe on the skin.

3.1 CONTROLS

3.1.1 Skin conductance

This technique was simple to perform taking approximately 15 minutes and causing no discomfort to the patients. Twenty-two patients, with a mean age of 67 years (range 32 to 79 years), acted as controls; nine males and thirteen females. As expected a large range in values was observed as shown in figure 13, with mean skin conductance varying between individuals from 3.9 to 214 microSiemens.

![Figure 13. Mean skin conductance (rise first 2 minutes) for both sides of the chest in 22 controls.](image-url)
Figure 14. Log of the difference between the mean skin conductance for both sides plotted against the log of the average.

Method comparison study (Bland, 1986):
Mean difference is = -0.03  95% limits of agreement are: -0.21 to 0.18 on the log scale.
Antilogs of limits = 0.78 to 1.19

In the twenty two controls good agreement was observed between mean skin conductance readings obtained from comparable areas on both sides of the chest within the same individual. For 95% of the cases the measurement from one side will differ from the other side by 20% or less.
Repeat skin conductance readings

Figure 15. Repeat skin conductance readings on four occasions in 8 controls.

Repeat readings performed in eight of the controls over a period of four days demonstrated that the individual’s skin conductance whilst varying did so within a limited range; patients with low skin conductance had repeatable low readings, while those with high readings had repeatable high readings (fig. 15). There was always good agreement between the paired readings.

Conclusion
The technique for measuring skin conductance is simple and painless, and the apparatus robust. All control readings were undertaken over a period of 4 months. Patients lay on a bed in a quiet room for 10 minutes prior to testing and readings were then obtained over an eight minute period. Despite the fact that the room’s conditions
were not standardised in terms of temperature and humidity, there was good agreement between readings taken from comparable sites within an individual.

In order to achieve good results it was important to ensure that the electrodes were in contact with the skin. Patients with hairy skin made poor electrical contact, and they were therefore either excluded or their skin shaved. Furthermore, talc and moisturising creams alter the electrodermal properties of skin and must be avoided prior to measuring skin conductance.

3.1.2. Silicone elastomer imprint

Variation amongst controls and between comparable sites within the same individual have previously been studied by Morris (1993) using this technique within the department. Exactly the same technique was used in this study.

3.1.3. Visco-elasticity skin analyser (VESA)

This proved to be a very simple technique which could be easily carried out in an outpatient setting. The instrument was readily portable and robust. Measurements could be obtained within 10 minutes and caused no discomfort to the patient. Care had to be taken to ensure that the probe was placed perpendicular to the skin surface in order to obtain accurate readings.

Twelve patients with a median age of 64 years (range 32 to 86 years) acted as controls; nine females and three males. There was always a significant difference in the data obtained in the horizontal direction (fig. 16a) versus the vertical (fig. 16b) with the median reading in the horizontal direction being 73 m/sec range 46-93 m/sec compared to a median of 35 m/sec range 24-62 m/sec in the vertical direction. This variation can readily be explained by the anisotropy of the skin (72).
Figure 16a. 12 controls: nine readings from each in the horizontal direction from an area measuring 8 cm by 8 cm.

Figure 16b. 12 controls: nine readings from each in the vertical direction from an area measuring 8 cm by 8 cm.
For each control the mean and standard error of the mean were calculated for measurements obtained in both the horizontal and vertical direction, for each side of the chest (fig. 17). The mean value within the same individual for the speed of wave propagation in the horizontal and vertical direction were similar.

![Graph showing mean and standard error of the nine readings obtained in the horizontal and vertical direction on both sides in each of the 12 control cases.](image)

**Figure 17.** Mean and standard error of the nine readings obtained in the horizontal and vertical direction on both sides in each of the 12 control cases.
**Figure 18.** Log of the difference between the mean VESA for both sides plotted against the log of the average.

Method comparison study (Bland, 1986):
Mean difference is = 0.0061
95% limits of agreement are: -0.057 to 0.069 on the log scale.
Antilogs of limits = 0.95 to 1.07

Good agreement existed between VESA measurement obtained from comparable areas within the same individual. For 95% of the cases the measurement from one side will differ from the other side by 7% or less.

**Conclusion**
This was a very simple well accepted technique for measuring the elasticity of the skin, with readings being obtained over 10 minutes. As the visco-elasticity skin analyser is small and easily portable readings can easily be carried out in clinics. Good agreement existed between measurements obtained over comparable areas within the same individual.
3.1.4 Laser Doppler

Controls: Measurements over 60 Minutes

The response of cutaneous blood flow by warming the skin from 32°C to 40°C was monitored, the skin temperature being maintained at this level subsequently for one hour. Measurements of blood flow from the anterior chest of six controls were undertaken: four males and two females with a median age of 32 years (range 30-33 years). A steady baseline flow rate was achieved at 32°C before the skin temperature was raised.

![Figure 19](image)

**Figure 19.** Average skin blood flow of the chest in 6 controls at various times before and during heating at 40°C for 1 hr. The bars are 1 standard error.

The blood flow rose to a peak within two-three minutes of heating the skin. This was followed by a fall, and then a gradual rise over the 60 minutes of heating. A similar pattern was seen in all six control with the blood flow rising by a factor of 2.1 to 3.2 during the peak rise (fig. 19). Rhythmic variation in flow was seen which increased in amplitude on heating. Furthermore there were large fluctuations in blood flow during heating. Examining the pattern in blood flow on heating over an hour, we decided that we would confine further measurements to the first eight minutes of heating.
Control: heating over 8 minutes

The procedure for measuring changes in skin perfusion following thermal stress took twenty minutes to complete and proved technically difficult. Care had to be taken to ensure that a consistent pressure was applied to the skin by the applicator as this influenced readings. The subjects needed to remain perfectly still as movement resulted in fluctuations in the Doppler readings. Furthermore the heating element warmed up quickly and consequently felt quite hot for a short period. Although it caused no pain to the patient it was important to inform them, otherwise it came as a surprise and resulted in movement.

<table>
<thead>
<tr>
<th>Control</th>
<th>Sex</th>
<th>Age</th>
<th>32°C * Right</th>
<th>40°C * Right</th>
<th>32°C * Left</th>
<th>40°C * Left</th>
<th>Right relative increase</th>
<th>Left relative increase</th>
</tr>
</thead>
<tbody>
<tr>
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<td>F</td>
<td>100</td>
<td>220</td>
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<td>265</td>
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<td>F</td>
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</tr>
<tr>
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<td>M</td>
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<td>180</td>
<td>140</td>
<td>185</td>
<td>1.29</td>
<td>1.32</td>
</tr>
</tbody>
</table>

Table 14. Increase in cutaneous blood flow in 10 controls on heating similar sites on both sides of the chest. * arbitrary units of skin perfusion

Method comparison study (Bland, 1986):
Mean difference = -0.05  Standard deviation of the differences = 0.14.
The 95% limits of agreement -0.33 to + 0.23
Once again there was a large variation between the individual controls in the increase in perfusion on heating, which ranged from a 1.17 to 3.08 fold increase (table 13, fig. 20). However, as with the other tests, the results from comparable areas in each individual were very similar with the mean difference in the fold increase in blood flow on heating from each side being 0.05, with the 95% limits of agreement ranging from -0.33 to + 0.23.

**Figure 20.** Increase in cutaneous blood flow on heating similar sites on both sides of the chest

**Conclusion**

The equipment for measuring skin perfusion was fragile, not easily transportable and required repair on several occasions. Obtaining readings over an hour of heating was difficult as the patient needed to stay still. It was therefore decided to limit blood flow readings to eight minutes of heating as this ensured that the peak rise in blood flow was obtained.
Readings still took twenty minutes because of the time it took to obtain a steady baseline prior to heating; the problems being movement and achieving a constant applied pressure with each Doppler. As with the other techniques, good agreement was seen within individuals between readings taken from comparable areas of each side of the body.

3.2 RETROSPECTIVE STUDY

3.2.1. Skin conductance

The dose delivered to a depth of 1 mm was calculated for the different fractionation schedules employed. This depth was chosen as it represented the position of the sweat glands. Furthermore it is the depth at which skin elasticity and cutaneous blood flow were measured.

For each fractionation schedule employed the biological effective dose (BED) at a depth of 1 mm was calculated. Changes in skin function were then related to this BED (table 15).

<table>
<thead>
<tr>
<th>Total dose Gy</th>
<th>Number of fractions</th>
<th>Dose per fraction</th>
<th>Overall treatment time</th>
<th>Biological effective tumour dose Gy (a/b=3)</th>
<th>Biological effective dose Gy at a depth of 1 mm (a/b=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>54</td>
<td>36</td>
<td>1.5</td>
<td>12</td>
<td>81</td>
<td>24</td>
</tr>
<tr>
<td>57</td>
<td>38</td>
<td>1.5</td>
<td>17</td>
<td>85.5</td>
<td>25</td>
</tr>
<tr>
<td>40</td>
<td>15</td>
<td>2.6</td>
<td>21</td>
<td>75</td>
<td>70</td>
</tr>
<tr>
<td>50</td>
<td>25</td>
<td>2.0</td>
<td>35</td>
<td>83</td>
<td>76</td>
</tr>
<tr>
<td>50</td>
<td>20</td>
<td>2.5</td>
<td>28</td>
<td>92</td>
<td>84</td>
</tr>
<tr>
<td>60</td>
<td>25</td>
<td>2.4</td>
<td>35</td>
<td>108</td>
<td>98</td>
</tr>
</tbody>
</table>

Table 15. Biological effective dose for the different fractionation schedules
No difference in skin conductance was observed in the irradiated area compared to the non-irradiated in patients treated with the lowest radiation dose (p = 0.742). However, patients receiving the intermediate doses (BED 70-76) showed a significant reduction in skin conductance (p < 0.05) despite the fact that clinically the large majority had no discernible skin changes. A greater than 20% reduction in skin conductance occurred in 7 out of 12 patients receiving 40 Gy in 15 fraction over 3 weeks and in 9 out of 11 patients receiving 50 Gy in 25 fractions over five weeks. With the higher doses the changes in skin conductance of the treated breast were more marked. All of the patients treated with 50 Gy in 20 fractions over four weeks had a reduction in skin conductance, with 4 out of 8 showing a greater than 50% decrease. The two patients treated with the highest dose 60 Gy in 25 fractions showed the greatest reduction (fig. 21). The number of patients treated to the highest dose was small as this regime was used in patients with advanced local disease and consequently few patients survived long term.

**Figure 21.** Mean skin conductance in 10 patients who received post-operative radiotherapy for carcinoma of the breast.

-- 8 treated with 50 Gy/20 fractions/28 days
-- 2 treated with 60 Gy/25 fractions/35 days
Figure 22. Mean skin conductance of the 38 patients related to the biological effective dose at a depth of 1 mm.

Simple linear regression $R^2 = 0.39$, $T = -4.7$, $P = 0.001$. (Altman, 1991)

(Simple linear regression $R^2 = 0.28$, $T = -3.4$, $P = 0.02$. Excluding the patients receiving the lower doses (BED 24-25 Gy))

As the biological dose increased so the mean skin conductance of the treated side relative to the control decreased. Using simple linear regression a dose response effect was seen ($P < 0.0001$).
Figure 23a. Skin conductance measurements of a patient whose left breast was treated with 60Gy/25 fractions/35 days in 1987.
Channel 1-4 = right breast (control), Channel 5-8 = left breast (treated)

Figure 23b. Skin conductance measurements of a patient whose left breast was treated with 50Gy/20 fractions/28 days in 1987.
Channel 1-4 = right breast (control), Channel 5-8 = left breast (treated)
3.2.2 Silicone elastomer imprint

The procedure was painless but left the patients with an area of erythema over the test site, which settled over a couple of hours. It took 30 minutes to obtain both impressions.

Patients who at 1 mm below the skin surface received the lowest biological effective dose 24 - 25 Gy demonstrated no significant reduction in the number or size of the sweat pores seen on the silicone elastomer impression. However at doses above this a reduction in number and size was seen (appendix 5), with a significant reduction in number being seen at biological effective doses greater than 70 Gy. Once the BED to the no sweat glands exceeded 98 Gy no sweat gland function was observed.

<table>
<thead>
<tr>
<th>Dose to the tumour (dose/fraction/days)</th>
<th>BED Gy at 1 mm below the skin surface</th>
<th>reduction in sweat gland count</th>
</tr>
</thead>
<tbody>
<tr>
<td>54/36/12</td>
<td>24</td>
<td>0%</td>
</tr>
<tr>
<td>57/38/15</td>
<td>25</td>
<td>-21%</td>
</tr>
<tr>
<td>40/15/21</td>
<td>70</td>
<td>-36%</td>
</tr>
<tr>
<td>50/25/35</td>
<td>76</td>
<td>-50%</td>
</tr>
<tr>
<td>50/20/28</td>
<td>84</td>
<td>-66%</td>
</tr>
<tr>
<td>60/25/35</td>
<td>98</td>
<td>-100%</td>
</tr>
</tbody>
</table>

Table 16. Percentage change in the sweat gland count of irradiated skin relative to the control for the different fractionation schedules.

Simple linear regression $R^2 = 0.26$, $T = -3.4$, $p = <0.003$ (Altman, 1991)

The mean percentage difference in sweat gland count between the normal and treated side increased with dose ($p<0.003$), with patients who received the highest dose (60 Gy/25/35) having no sweat pore imprint present in their impressions (table 16). Furthermore with the higher doses the holes in the imprint which represent functioning sweat glands were smaller on the treated side compared with the control side.
For each fractionation schedule the range of values for the difference between the treated and control was wide (appendix 5). If it had been possible to measure the area of each sweat pore as a measure of its function, then the spread of results may have been less and a better dose response effect obtained. Due to the number of sweat glands per cm² it would be extremely time consuming to undertake measuring the area of the sweat pore by hand. However if a Magi-scanner is used the process could be automated provided suitable software for the computer is available. Unfortunately while the Gray Laboratory had a Magi-scanner the computer software was not available and would have needed to be designed. This was not feasible in the time provided.

Figure 24. Correlation between mean skin conductance and silicone elastomer imprint.

Coefficient of correlation = 0.68 (Altman, 1991)

A positive correlation was seen between a reduction in mean skin conductance of the treated area compared to the control and a similar reduction in the number of functioning sweat glands /cm².
**Figure 25a.** Silicone elastomer imprint of the non treated breast

**Figure 25b.** Silicone elastomer imprint of an irradiated breast treated 5 years ago with 50 Gy in 25 fractions over 35 days. The surface area of the sweat pores are smaller than the non treated side (fig. 25a)
3.2.3 Visco-elasticity skin analyser

The data from all the patients was pooled together for each of the directions measured. The speed of mechanical wave propagation for each point measured in the treated breast was normalised as a ratio (%) of its contra-lateral control point in the untreated breast (fig 26 a, b). These figures give an impression of the distribution of points with the different treatment regimes, and demonstrate that the effects of radiation are more clearly seen in the horizontal direction. The ratio (treated/untreated) of speed of wave propagation was higher in patients with low initial control readings and thus greater elasticity of the skin. The additional effect of radiation was small in patients who began with less elastic normal skin. (initial high control readings).

![Graph showing the ratio of speed of wave propagation treated/control in the horizontal direction in 33 patients treated with different fractionation schedules for carcinoma of the breast.](image-url)
Figure 26b. Ratio of speed of wave propagation treated/control in the vertical direction in 33 patients treated with different fractionation schedules for carcinoma of the breast.

For each patient the mean and standard error of the mean in both the horizontal and vertical direction for the treated and control breast was plotted. In the treated breast a significant increase in the speed of wave propagation in both the horizontal (p<0.005) and vertical direction (p<0.007) was seen in patients treated with 60 Gy in 25 fractions (2.4 Gy/ fraction) and 50 Gy in 20 fractions (2.5 Gy/ fraction). These fractionation schedules therefore resulted in a reduction in skin elasticity measured in both directions (fig. 27a).
Figure 27 a, b, c. Mean speed of wave propagation and standard error of the mean for 33 patients treated for carcinoma of the breast using different fractionation schedules.

☐ - Mean in the vertical direction  ■ - Mean in the horizontal direction
The change is less marked with the other treatment schedule 40 Gy in 15 fractions (2.6 Gy/fraction) and 50 Gy in 25 fractions (2 Gy/fraction). In the horizontal direction both schedules demonstrate a significant change but this was not seen in the vertical direction. Thus the reduction seen in elasticity of the skin following these fractionation schedules is not as marked (fig. 27 b, c).

A dose response effect was seen with skin elasticity decreasing as the biological effective dose delivered at a depth of 1 mm below the skin surface increased (fig 28). (p<0.0001),

![Figure 28](image-url)  
**Figure 28.** Change in speed of wave propagation relative to the biological effective dose at a depth of 1 mm.

Simple linear regression $R^2 = 0.39$, $T = 4.38$, $p < 0.0001$. (Altman, 1991)
To determine if there was any correlation between the reduction in skin elasticity following treatment and the size of the patient's breast, VESA measurements were related to the area of breast irradiated in the central axis of the treatment field, (fig. 29).

**Figure 29.** Change in speed of wave propagation in the horizontal direction relative to the area of breast in the central axis of the treatment field. 10 patients (2 = 60 Gy/25Fx/25 days, 8 = 50 Gy/20Fx/28 days)

Correlation coefficient = 0.8 (Altman, 1991)

As the area irradiated increased, so the speed of wave propagation of the treated breast relative to the control increased reflecting a reduction in elasticity. This change was greatest in the horizontal direction and more marked in patients treated with the higher doses 50 Gy in 20 fractions or 60 Gy in 25 fractions.
All patients’ skin was clinically scored for subcutaneous fibrosis using a graded score system (appendix 3). The clinical scoring was compared with the VESA measurements obtained from the 33 patients treated with the different fractionation schedules for breast cancer (fig. 30).

![Figure 30: Comparison of clinical scoring system for fibrosis compared to VESA measurement. Thirty three patients treated with radiotherapy for carcinoma of the breast](image)

Patient who had severe/moderate fibrosis showed the greatest increase in speed of wave propagation in both directions. However when there was no or slight fibrosis clinically, there was overlap with the quantitative readings obtained from the VESA. This suggests a superiority of VESA measurement over the clinical scoring, which is influenced by a subjective element especially at low levels of morbidity.
3.2.4. Laser Doppler flowmeter

Laser Doppler flowmetry was performed in the retrospective breast group (table 9) and in the patients listed in table 11. Readings were obtained away from any surgical scar. In a number of breast patients whose boost area was large, it was also possible to obtain measurement at this site and avoid the scar.

Breast patients

Patients who received the higher doses 60 Gy in 25 fractions or 50 Gy in 20 fractions (BED 84-98 Gy), demonstrated an average reduction in the increase in perfusion on heating of greater than 20% when compared to the control result (table 17). However no alteration in skin perfusion was noted in patients receiving 50 Gy in 25 fractions and 40 Gy in 15 fractions (BED 70-76 Gy). (appendix 6)

<table>
<thead>
<tr>
<th>Dose (Gy/fraction No)</th>
<th>No of cases</th>
<th>BED (Gy) at a depth of 1 mm</th>
<th>Average reduction in blood flow on heating</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 Gy/25</td>
<td>2</td>
<td>98</td>
<td>25%</td>
</tr>
<tr>
<td>50 Gy/20</td>
<td>8</td>
<td>84</td>
<td>21%</td>
</tr>
<tr>
<td>50 Gy/25</td>
<td>11</td>
<td>76</td>
<td>3%</td>
</tr>
<tr>
<td>40 Gy/15</td>
<td>12</td>
<td>70</td>
<td>3%</td>
</tr>
</tbody>
</table>

Table 17. Reduction in cutaneous blood flow of the irradiated area in 33 breast patients.

Breast boost

Nine out of the ten patients whose boost area was measured had telangiectasia at this site: six with moderate telangiectasia and three with slight. At a skin temperature of 32°C cutaneous blood flow was higher over areas of skin with telangiectasia compared to comparable sites of normal skin (table 18). Furthermore the greater the number of telangiectasia per square centimeter, the greater the blood flow compared to the
control site. Patients with slight telangiectasia having approximately a 25% increase in baseline perfusion compared to a 30-128% increase seen in patients with moderate telangiectasia.

The percentage fold increase in skin perfusion at sites of telangiectasia was lower compared to the control site but the initial baseline blood flow is higher over sites of telangiectasia. This would suggest that the vessels there were still capable of responding.

<table>
<thead>
<tr>
<th>Case No</th>
<th>Telangiectasia</th>
<th>Control 32°C</th>
<th>Control 40°C</th>
<th>Treated 32°C</th>
<th>Treated 40°C</th>
<th>Control relative increase</th>
<th>Treated relative increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>72</td>
<td>182</td>
<td>75</td>
<td>161</td>
<td>2.5</td>
<td>2.1</td>
</tr>
<tr>
<td>2</td>
<td>slight</td>
<td>75</td>
<td>155</td>
<td>95</td>
<td>170</td>
<td>2.1</td>
<td>1.8</td>
</tr>
<tr>
<td>3</td>
<td>slight</td>
<td>95</td>
<td>145</td>
<td>120</td>
<td>160</td>
<td>1.53</td>
<td>1.3</td>
</tr>
<tr>
<td>4</td>
<td>moderate</td>
<td>50</td>
<td>136</td>
<td>114</td>
<td>157</td>
<td>2.72</td>
<td>1.3</td>
</tr>
<tr>
<td>5</td>
<td>moderate</td>
<td>74</td>
<td>222</td>
<td>126</td>
<td>215</td>
<td>3.0</td>
<td>1.7</td>
</tr>
<tr>
<td>6</td>
<td>moderate</td>
<td>58</td>
<td>244</td>
<td>111</td>
<td>193</td>
<td>4.2</td>
<td>1.7</td>
</tr>
<tr>
<td>7</td>
<td>moderate</td>
<td>87</td>
<td>223</td>
<td>113</td>
<td>148</td>
<td>2.55</td>
<td>1.3</td>
</tr>
<tr>
<td>8</td>
<td>moderate</td>
<td>77</td>
<td>200</td>
<td>125</td>
<td>204</td>
<td>2.6</td>
<td>1.6</td>
</tr>
<tr>
<td>9</td>
<td>moderate</td>
<td>88</td>
<td>179</td>
<td>147</td>
<td>336</td>
<td>1.93</td>
<td>2.3</td>
</tr>
<tr>
<td>10</td>
<td>moderate</td>
<td>80</td>
<td>120</td>
<td>130</td>
<td>150</td>
<td>1.5</td>
<td>1.2</td>
</tr>
</tbody>
</table>

**Table 18.** Laser Doppler flowmetry over breast boost sites correlated with telangiectasia. * arbitrary unit of blood flow.
Other patients

All seven patients were treated either with full skin bolus or superficial X-rays, and all clinically showed evidence of late radiation change such as fibrosis and pallor in the area treated (table 19). A 21-43% reduction in the increase in cutaneous blood flow seen by heat stimulation was noted over the irradiated skin compared to the control.

<table>
<thead>
<tr>
<th>Case No</th>
<th>BED (Gy)</th>
<th>Dose/Fx</th>
<th>Site</th>
<th>Control fold increase</th>
<th>Treated fold increase</th>
<th>Reduction in increase in blood flow on heating</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>81</td>
<td>54/36/12</td>
<td>neck</td>
<td>3.5</td>
<td>2.2</td>
<td>37%</td>
</tr>
<tr>
<td>2</td>
<td>87</td>
<td>47.5/19/27</td>
<td>neck</td>
<td>3.2</td>
<td>2.5</td>
<td>21%</td>
</tr>
<tr>
<td>3</td>
<td>92</td>
<td>50/20/28</td>
<td>neck</td>
<td>3.4</td>
<td>2.6</td>
<td>24%</td>
</tr>
<tr>
<td>4</td>
<td>95</td>
<td>63.5/42/20</td>
<td>neck</td>
<td>3.2</td>
<td>1.8</td>
<td>43%</td>
</tr>
<tr>
<td>5</td>
<td>117</td>
<td>35/5/5</td>
<td>lower leg</td>
<td>1.6</td>
<td>1.2</td>
<td>25%</td>
</tr>
<tr>
<td>6</td>
<td>117</td>
<td>35/5/5</td>
<td>temple</td>
<td>3.6</td>
<td>2.2</td>
<td>39%</td>
</tr>
<tr>
<td>7</td>
<td>117</td>
<td>35/5/5</td>
<td>preauricular</td>
<td>2.6</td>
<td>1.6</td>
<td>39%</td>
</tr>
</tbody>
</table>

Table 19. Cutaneous blood flow measurements in seven patients treated with radiotherapy to different sites.
3.2.5 Clinical Data

In all patients late radiation morbidity of the skin was recorded, with patients treated for carcinoma of the breast having the breast (low dose area) and boost site scored separately.

<table>
<thead>
<tr>
<th>BED (Gy) at a depth of 1 mm</th>
<th>Clinical grade of fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>0</td>
</tr>
<tr>
<td>76</td>
<td>9</td>
</tr>
<tr>
<td>84</td>
<td>1</td>
</tr>
<tr>
<td>98</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
</tr>
</tbody>
</table>

Table 20. Clinical scoring of late radiation skin morbidity

Patients treated for carcinoma of the lung showed no clinical evidence of late radiation change of the skin. Similarly 58% of the breast cancer patients, mainly those receiving the lower biological effect dose, demonstrated no discernible radiation change of the skin in the low dose area. The remaining 42% had some degree of radiation fibrosis of the skin. Except for slight telangiectasia in the low dose area in two patients receiving the higher BED, telangiectasia, pallor and thinning of the epidermis was limited to the boost site.
3.3 PROSPECTIVE STUDY

3.3.1 Skin conductance

Eighteen women with a mean age of 59 years (range 35-81 years) were entered into this study. All were treated with post operative radiotherapy for carcinoma of the breast receiving 40 Gy in 15 fractions over three weeks to the breast followed by a boost to the site of the primary. Skin conductance readings were performed prior to and during treatment, with further readings obtained at out-patient follow up.

Measurements were taken from comparable areas on each side of the chest, with the non-treated side acting as the control. The same site was used for repeat readings. The initial reading was normalised to 100% and any subsequent reduction in skin conductance over the treated area was expressed as a percentage of the control reading.

During treatment a gradual reduction in skin conductance over the treated area was noted, such that by the end of treatment the average skin conductance of the irradiated area was 43% (range 32-68%) of that of the control. Changes in skin conductance of the irradiated area occurred prior to any clinical evidence of radiation change in the skin, with a 20% or greater reduction in skin conductance occurring by the second week (fig. 31).
Figure 31. Change in skin conductance of the treated breast compared to the control in 18 patients receiving postoperative radiotherapy for carcinoma of the breast.

Analysis of covariance: The slope of the regression line of conductance against days having allowed for the effect of differences in individual patient means is -2.23%.
$T = -15.5, \ p < 0.0001$. 

Clinical evidence of radiation change occurred during the third week of treatment with the development of slight erythema of the skin in the majority of patients, progressing in some cases to moderate erythema in the fourth week. A few however, three patients, showed no evidence of skin erythema during their treatment. One patient developed a more marked radiation reaction than the others, with moderate erythema of the whole breast occurring during the third week and progressing to moist desquamation around the nipple at the start of the fourth week. This patient had a
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 reflecting the increased surface moisture of the skin due to breakdown of the epidermis. This patient still had a low conductance reading when seen three months after treatment.

Figure 32. Change over time of mean skin conductance of treated breast compared to control

Patients who demonstrated recovery of skin conductance did so within the first three months, with a few patients showing further improvement up to 6 months (fig. 32). In 8 out of 18 patients the skin conductance recovered to within 70-100% of that of the control side. While five patients showed little recovery, with time, all having had a greater than 50% reduction in skin conductance of the irradiated area during treatment.
CHAPTER 4

DISCUSSION

4.1 CONTROLS

4.1.1 Skin conductance

On applying the electrodes to the skin there was an initial rise in skin conductance reflecting the conductance of the different constituents of the skin. Following this, there was a gradual rise with time as moisture collected under the applicator due to water loss from sweat glands and the stratum corneum. The area under the curve for the first two minutes following the initial rise, was calculated and used as a measure of the change in moisture of the skin. Good agreement existed between readings obtained from comparable areas on both sides of the body within the individual. However the range of results between individuals was broad. This variations may be due to several factors. Firstly the room conditions were not standardised. Since readings were undertaken throughout the year differences in room temperature (range 21-23°C) and humidity occurred between readings. Secondly differences exist between individuals in sweat gland function, the maximal sweating rate ranging from 2 to 20 nl/min/gland, with the value falling with age. Finally the actual number of functioning glands is known to vary between individuals (Sato, 1970, 1983 and Inoue, 1991).

4.1.2 Visco-elasticity skin analyser

The VESA was used to measure the elasticity of the dermis, with the speed of wave propagation increasing with loss of elasticity. The skin is anisotropic, in that it is stiffer in some directions than in others (Baker, 1988). The stiffest and least stiff axes being perpendicular to each other, with the stiffest axis relating to the natural lines of tension in the skin (Langer’s lines). Thus the actual direction of testing is important. VESA readings were obtained in two directions at right angles, the speed of wave propagation being fastest in the stiffest axis, which was in the horizontal direction over
the chest. The median reading was 73 m/sec compared to a median of 35 m/sec in the vertical direction.

Similar results were obtained from comparable sites on both sides of the individual, with good agreement between sides in both the horizontal and vertical direction. Variation existed between individuals; with the mean speed of wave propagation ranging between 46-93 m/sec in the horizontal direction compared to 24-62 m/sec in the vertical direction.

4.1.3 Laser Doppler flowmetry

Blood flow measurements over the chest in six individuals demonstrated that on heating the skin from 32°C to 40°C degrees there was an initial abrupt rise in blood flow over the first few minutes, and then an abrupt decrease followed by a further gradual rise over the hour. At the peak, the flow was 2.1-3.2 times larger than the baseline blood flow prior to heating. The pattern and magnitude of the change in flow varied between individuals. Similar results were demonstrated by Song (1989) when studying the effect of local heat on cutaneous blood flow (CBF) in the forearm. He attributed the initial rise in blood flow on heating to dilation of the arterioles, recruitment of capillaries and opening of arteriovenous anastomoses. However skin over the chest is devoid of arteriovenous anastomoses. One suggestion for the drop in blood flow is that an autoregulating mechanism is evoked following the vasodilation, which results in vasoconstriction and a reduction in blood flow. With time the continuous heating overcomes this mechanism resulting in a gradual increase.

Rhythmic variation in flow is seen with LDF and is thought to be due to contraction and relaxation of the smooth muscle cells of the arteriolar vessel walls. These fluctuations occur at a rate of 2-17 times a minute depending on the area. On heating the skin we found that the amplitude of these increased markedly. In addition to the spontaneous vasomotion, there were large fluctuations in blood flow during heating. The cause of these are not known.

Measurement of the change in blood flow after heating were therefore carried out over a period of eight minutes to ensure that the peak rise in blood flow was recorded.
Again results from comparable sites on both sides of the same individual agreed well with each other, with the variation between individuals ranging from 1.17 to 3.08 relative increase in blood flow on heating.

4.1.4. Summary

Skin structure and function varies between individuals and between different areas in the same individual. Since good agreement was seen between readings obtained from comparable sites in the same individual using all three techniques, it seemed reasonable when looking at changes in skin function following irradiation to use the patients as their own control by using a comparable site on the non treated side.

4.2 Retrospective study

Since late radiation damage can progress over time, we carried out measurements in breast cancer patients who had been treated over the same time (1986-1989).

For each fractionation schedule employed the biological effective dose (BED) delivered to the dermal structures was calculated, so that it could be related to changes in skin function (chapter 2.4).

4.2.1 Skin conductance

A dose response effect was seen: patients receiving the lowest BED 24 Gy (54 Gy/36Fx/12 days) demonstrated no change in conductance. Of those receiving a BED of 70-76 Gy (40 Gy/15Fx/21 days, 50 Gy/25 Fx/35 days) 7 out of 23 showed no change the remainder having a 30-40% reduction in skin conductance over the treated area, despite the fact that in the majority the skin appeared entirely normal. Marked changes in skin conductance were seen at higher doses, with a mean reduction of 50% over the irradiated area in all patients treated with a BED of 84 Gy (50 Gy/20Fx/28 days). The two patients treated with the highest BED 98 Gy (60 Gy/25Fx/35 days) had a reduction of 96%.
For each fractionation schedule employed the biological effective dose (BED) at a depth of 1 mm was calculated. The results were plotted against biological effective dose using an $\alpha/\beta$ ratio of 3, 5, 10 Gy and infinity and appeared to fit an $\alpha/\beta$ ratio of 3 Gy best (appendix 9).

Skin conductance measures the build up of moisture on the skin surface with time. The two processes contributing to this are sweating from the eccrine sweat glands and transepidermal water loss from the stratum corneum. It is difficult to separate the contribution of these two processes. Since the stratum corneum forms the outer layer of the epidermis the dose of radiation delivered to it using megavoltage is small compared to the dose received by the sweat glands (appendix 8). One may then conclude that radiation is more likely to affect the sweat glands rather than the integrity of the stratum corneum, thus resulting in a change in the loss of water through sweating rather than transepidermally.

4.2.2 Silicone elastomer imprint.

This technique has been used to study sweat gland function in the β-pad of the mouse foot after irradiation. Analysis of the mouse data has resulted in an estimate of the $\alpha/\beta$ ratio: eight weeks after treatment the $\alpha/\beta$ ratio for X-rays is -2.3 to 2.7 Gy and 0.2 to 6.7 Gy for later assay times (Judas).

In view of these results an $\alpha/\beta$ ratio of 3 Gy was chosen to calculate the biological effective dose of each of the fractionation schedules used in our study. No reduction in the number of functioning sweat glands in the treated area was seen with the lowest biological effective dose of 24 Gy. However a dose response effect was observed with fractionation schedules delivering a BED of between 70 Gy and 98 Gy. Patients receiving the highest doses 60 Gy in 25 fractions (BED 98 Gy) showed a complete absence of functioning sweat glands.

Similarly a dose response effect was seen in the mouse experimental model using the same technique for measuring sweat gland function. A single dose of 6.8 Gy resulted in normal sweat gland function when measured 45 weeks after treatment, while 13 Gy (single fraction) resulted in little or no recovery of sweat gland function. For
intermediate doses partial recovery of sweat gland function was seen. It is unlikely any further recovery would occur with time, as a plateau in the number of functioning sweat glands was seen between 20-45 weeks (Johns).

Morris (1992) using the same technique had similar results, noting a complete loss of function of sweat glands in skin showing late radiation change such as the boost area in patients treated for carcinoma of the breast. In contrast, where the dose to the skin at 0.7 mm-2 mm ranged from 20-35 Gy given at less than 1.5 Gy per fraction a normal number of sweat glands functioned. His data from patients treated to intermediate doses between 28-50 Gy in 1.9-2.7 Gy per fraction suggested a useful dose-response relationship could be derived, which has been confirmed with the present study.

As well as a reduction in the number of functioning sweat glands following irradiation, we also noted a reduction in the size of the individual sweat pores suggesting that some of the glands that had survived had impaired function. This was not seen in the mouse (direct correspondence M.Joiner). However the timing of the measurements was different, with animal measurements being obtained 45 weeks after radiation therapy compared to 5-8 years after treatment in the humans. There may therefore be other processes resulting from late radiation damage which are contributing to this reduction in individual sweat gland function: for example, fibrosis or a reduction in blood supply. Measuring the area of each individual sweat pore imprint and then using it to provide a measure of sweat gland function, may result in an even tighter dose response relationship (Kennedy, 1979).

A positive correlation was seen between skin conductance and sweat imprint measurements. This would be expected as sweat gland function contributes to skin hydration, although it is not the only factor as transepidermal water loss from the stratum corneum also contributes. The correlation may have been greater if one had taken into account not only the number of functioning sweat glands but also the area of the pores as a measure of function. Certainly Freedman (1994) demonstrated better correlation between the palmar sweat index and skin conductance when he looked at the number of open (actively functioning) sweat glands as, opposed to closed non functioning glands. Furthermore, if conductance readings had been obtained after
maximally stimulating the glands with pilocarpine, the correlation between the readings would have been greater.

4.2.3 Visco-elasticity skin analyser.

The visco-elasticity skin analyser measures the elasticity of the skin. Four groups of patients treated with different fractionation schedules for carcinoma of the breast were studied and a dose response effect observed. Measurements obtained in both the horizontal and vertical directions were significantly elevated in patients treated with the higher doses (60 Gy in 25 fractions or 50 Gy in 20 fractions) with all but one of these patients having slight to severe fibrosis clinically. Patients receiving the lower doses, demonstrated changes, mainly in the horizontal direction, with many (14 out of 23) having no discernible clinical changes. No difference both in terms of clinical scoring of fibrosis and in the readings obtained by VESA, were detectable between the two groups treated with the lower doses: 50 Gy in 25 fractions or 40 Gy in 15 fractions.

When clinical scoring of fibrosis was compared to the results obtained with the VESA good correlation was seen. Patients who were clinically scored as having no or slight fibrosis demonstrated slight overlap in their VESA measurement. This probably reflects the subjective nature of the clinical score. It is quite easy to score moderate or severe fibrosis, but determining whether slight fibrosis exists can be very subjective.

A measure of breast size was derived from the central axis. The area within the edge of the treatment fields were calculated and compared to the results obtained from the VESA. As the area irradiated increased so the speed of wave propagation increased in the treated breast relative to the control, reflecting a reduction in elasticity. This was most marked in the patients treated with the higher dose fractionation schedules. Several reports have noted an association between breast size and poor cosmetic outcome after conserving surgery and radiotherapy. Many of these studies have used subjective measurements relying on patients or doctors assessment of cosmesis (Harris, 1979 and Gray, 1991). Few studies have scored an endpoint which is directly related to a quantifiable radiation effect. Brierley (1991) used subcutaneous fibrosis as his endpoint employing a three point scale (normal consistency, moderate fibrosis and severe fibrosis). He correlated this with bra cup size (A-D). Patients with large
breasts (cup size C-D) had a higher incidence of moderate fibrosis 36% compared to 9% for patients with small breasts.

Moody (1994) looked at why breast cosmesis was worse in large chested patients. He reviewed 37 patients who had had CT simulator scans taken through the centre of the target volume and 10 mm inside the superior and inferior borders prior to treatment. Patients had been treated with dosimetry based on the central slice without lung correction. Retrospectively a measure of breast size was derived from the central axis and the dosimetry was calculated for the other two slices. An association was found between breast size and dose inhomogeneity, suggesting that poor cosmesis in large chested women was related to poor dosimetry, and presumably areas of high dose.

4.2.4 Laser Doppler

Very few studies have documented the effect of ionising radiation on the skin vasculature. Those that have, tend to look at changes during the early radiation reaction with few looking at late changes. Furthermore most studies measure baseline blood flow, with only a few looking at the response of CBF to stress. Results in the literature are not consistent, with both increases and decreases in blood flow being reported as well as the absence of any effect.

In our study only patients with breast cancer who had received the higher doses 60 Gy/25Fx/35 days and 50 Gy/20Fx/28 days (BED 84-98 Gy) demonstrated any change in skin perfusion on heating the skin from 32°C to 40°C. These patients demonstrated a reduction over the irradiated area in the rise in peak blood flow on heating the skin compared to the control site. This resulted in a 21-25% reduction in the fold increase (peak blood flow/ baseline blood flow) in blood flow of the irradiated area compared to the control. All but one of them had clinical evidence of late radiation change in the form of subcutaneous fibrosis and/or atrophy, but not telangiectasia, over the measured irradiated area. A similar reduction was seen in a further seven patients, who had received radiation therapy (BED 81-117 Gy) to a variety of sites, and who all had clinical evidence of late radiation damage. It therefore appears that changes in skin perfusion on heating are only detected in skin once late radiation changes are clinically
evident. Furthermore these changes are only apparent when the cutaneous vasculature is stressed by heating.

In the literature the only other study that used Doppler flowmetry was the one by Amols (1988), which looked at changes in CBF during the early radiation reaction. The author did not specify the actual doses of radiation employed, and the number of patients, fourteen, is small. An increase in CBF during treatment was noted, which rapidly decreased once treatment was finished. However in the nine patients measured a year out from treatment, the blood flow in the irradiated area still remained elevated above the control. Only baseline blood flow was measured, and the study was not extended beyond a year so it is not possible to compare these results with our study.

The removal of a locally injected radioactive indicator from the skin has been used in animal studies as a measure of blood flow in irradiated skin. Results vary depending on the animal studied: for example, a decrease in blood flow clearance rate at about 9-12 months is seen in rodent skin after single fraction doses greater than 1500 R but not in pig or human skin (de Ruiter, 1975 and Keyeux, 1971).

In pig skin following doses of 20.7 Gy given as a single fraction an increase in isotope clearance is seen at week three. This change is associated with, and may be a direct result of, radiation damage to the basal cells of the epidermis. At three months a reduction in isotope clearance was seen. This was felt to be related to direct radiation damage to the vessels or to a reduction in their function. Histologically in irradiated pig skin there is evidence of vascular occlusive changes and of a reduction in vascular density at this time. Over the year the isotope clearance parameters returned to normal (Moustafa, 1975).

Since isotope clearance technique measures clearance per unit volume, the return of clearance parameters to normal could occur as a result of parenchymal atrophy. A similar vascular density has been demonstrated in atrophied irradiated skin and normal pig skin (Moustafa, 1975).

Only a few studies have been undertaken in irradiated human skin. Roswit (1953) studied the clearance of Na\textsuperscript{24} ion from skin showing severe late radiation change in 37 patients treated over the previous ten years. Baseline blood flow measurements were
performed and no difference was seen between irradiated and normal skin. In a small number of cases, patients received histamine by inotrophoresis and showed a similar increase in blood flow over the irradiated and control area; similarly a reduction was seen following adrenaline. Histological sections were taken of the irradiated skin in a number of cases. These showed classic evidence of damage to blood vessels, with some arterioles having obstructed or narrowed lumen. Numerous relatively undamaged capillaries were observed which in some cases appeared in the form of huge endothelial lakes, presumably referring to telangiectatic vessels.

Roswit concluded that the capillaries must dilate because there are fewer channels to handle incoming blood. These dilated capillaries carry a greater volume of blood than the capillaries of normal skin resulting in no difference in blood flow being detected. If this was the case then you would expect that if cutaneous blood flow was maximally stimulated then a difference might be detected.

Certainly in our study we only showed a difference after stimulating the vasculature and de Ruiter (1975) in irradiated mouse skin similarly only detected a decrease in maximal blood flow after stressing the vasculature; however, he used temporary occlusion rather than heating to stimulate blood flow. These two studies would suggest that there is a reduction in vascular capacity but that it is only apparent during situations of high requirement. This reduction may be a result of a decrease in vascular density and/or an impairment of vascular function. Radiation damage to skin vasculature is known to result in narrowing of the lumen of arterioles, due to endothelial proliferation and hyalinisation of the media (Reinhold, 1991). This would impair arteriole dilation on heating the skin, resulting in a reduction in the amount of capillary recruitment and therefore a reduction in the peak rise.

Telangiectasia represents a group of abnormally prominent capillaries, venules, and arterioles that create small focal red lesions in the skin. Histologically the normal vasculature is changed into a maze of coarse widened vessels alternating with narrowed vessels (Reinhold, 1991). Nine patients who had telangiectasia over their breast boost site demonstrated an increase in their baseline blood flow over these areas. Furthermore the greater the density of telangiectasia the more marked the increase in blood flow, with one patient demonstrating a 128% increase in baseline
flow (range 25%-128%) compared to a comparable site in the non treated breast. These results suggest that due to the widening of the vessels the blood flow is increased.

4.3 Prospective study

4.3.1 Skin conductance

Eighteen patients who were receiving post operative radiotherapy for carcinoma of the breast had skin conductance measurements taken during and after their treatment. All received 40 Gy in 15 fractions over 3 weeks followed by an electron boost to the tumour site. A reduction in skin conductance was seen as early as the second week of treatment, despite the fact that there was no clinical evidence of an acute radiation reaction at this stage. Readings continued to fall through out treatment, such that by the end of treatment the average skin conductance of the irradiated area was 43% (range 32-68%) that of the control. This reduction in skin conductance seen with treatment coincides with the progressive dryness of the skin that occurs, as a result of the loss of sweat gland function.

Until recently there was httle information available on the effects of ionising radiation on the eccrine sweat glands in the animal model. Johns has recently measured sweat gland function in the left-hind feet of mice following irradiation. The mice were irradiated with either a single fraction (5.0-13.0 Gy) or a two fraction regime of X-rays (5.8-16.4 Gy). Loss of sweat gland function occurred rapidly within two weeks of irradiating and progressed, resulting in a dose dependent nadir of function at 8 weeks. This was then followed by a gradual recovery that was complete by about 30 weeks after irradiation, leaving a dose dependent residual functional deficit. This pattern matches well the results we have seen with the skin conductance in humans following irradiation.

Little information exists in the literature on the radiobiology of sweat glands. It has been proposed that the early radiation response of eccrine glands is similar to that of salivary glands (Johns). Extensive work looking at the effects of irradiation on the
parotid glands of monkeys was performed by Stephens (1991). He concluded that the early cell death of serous salivary cells following irradiation was a result of interphase cell death occurring by the process of apoptosis. Since there are broad similarities in the structure of eccrine sweat glands and parotid glands this process may well occur in eccrine glands.

The data available on the radiation effects on human sweat glands is very limited. Price (1979) looked at sweat gland function in ten patients receiving electron beam therapy for mycosis fungoides. Patients were treated with a dose of 36 Gy delivered over a ten week period and sweat gland function assessed by the silicon elastomer method. At the completion of treatment there was an approximate 50% reduction in the number of functioning sweat glands, which gradually recovered over the next 6 months to the level seen prior to treatment. The dose delivered in this fractionation schedule was low and probably accounts for the complete recovery of sweat gland function seen.

In our study a range of doses all higher were studied. Recovery of skin conductance occurred in the 6 months following treatment, but complete recovery was not seen in all. Values to within 70-100% that of the control were seen in eight patients while five patients showed little recovery. Patients who showed little recovery tended to be the ones who had the lowest values for skin conductance at the time of completion of treatment.

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 three months and had moderate subcutaneous oedema of the breast.

Results from this technique show that patients with the greatest reduction in skin conductance at the end of treatment tend to be the ones who show little recovery with time. Furthermore by detecting an early reduction in skin conductance during treatment, this technique may be able to single out patients who are sensitive to radiation early on in their course of treatment.
4.4 CONCLUSIONS

In patients treated with radiotherapy more than five years previously for breast cancer measurements of skin conductance, of functioning sweat glands and of skin elasticity show a dose response relationship. Changes were detected in patients receiving the intermediate and even the lowest doses, despite the fact that in the majority of the cases the skin looked normal. These results demonstrate that functional changes can be detected in visually normal looking skin, and that these changes can be quantified, allowing differences to be demonstrated between different fractionation schedules.

Changes in cutaneous blood flow using laser Doppler flowmetry were only demonstrated in patients who had clinical evidence of late radiation damage, following high doses to the skin. Using modern methods few patients show easily discernible late radiation changes of the skin. This technique does not appear to be able to detect changes in cutaneous blood flow over the range of doses used in clinical practice today. This together with the technical difficulties associated with the use of this apparatus, would discourage its use in the measurement of late radiation change.

Of the three techniques, which did show a dose response effect across the ranges of doses used in clinical practice, the Visco-elasticity skin analyser is the simplest one to perform. It is easily portable, enabling measurements to be carried out at peripheral hospitals and in out-patient clinics. Whilst, measurements of skin conductance are easy to perform and reasonably quick (8 minutes) the apparatus which was used was bulky because of the computer needed to record the results. With the introduction of a laptop computer this problem can be overcome.

At a period of five years from treatment, the most sensitive techniques for detecting change in skin function relative to the radiation dose delivered to the skin were: skin conductance measurements and the Visco-elasticity skin analyser measurements.

When measurements of early changes in skin conductance during and one year following radiation treatment for carcinoma of the breast were performed a progressive reduction in skin conductance over the irradiated area was seen during treatment, which became evident as early as the beginning of the second week of treatment.
Patients who demonstrated the greatest reduction in skin conductance at the end of treatment were the ones who did not return to normal over the following 3-6 months. This suggests that the early changes in skin conductance may predict late changes. The only patient who had a marked skin reaction, developing a moist desquamation at the beginning of week four, also showed a marked reduction in skin conductance on day 10 of treatment with the value falling to 33% that of the control. This technique therefore may be able to detect the unusually radiosensitive patient at an early time when modification of the course is feasible.

By day 14 of treatment all patients demonstrated a decrease in skin conductance with on average the skin conductance over the irradiated area being 69% that of the control. This novel technique could provide a means for detecting the unusually sensitive patients early on in their course of treatment and thus allow modification of their treatment regime. This could be tested by measuring the skin conductance of patients on day 14 of their treatment, with late follow up readings to see if the magnitude of change in skin conductance at day 14 predicted for the severity of early and late changes.

Studies which have assessed changes in the skin after radiation have almost entirely relied upon subjective measures for example Bates (1988) used a clinical score of none, mild, moderate and severe to assess subcutaneous fibrosis. Objective methods such as those described in this thesis have great advantages over subjective methods reducing observer bias and detecting change where visually none is evident.

The public today are better informed, more critical about medical practice and have higher expectations. To cure the patient following irradiation is no longer sufficient as the sole objective of treatment. The minimisation of long term cosmetic and functional damage now has a higher profile, than has historically been the case. It follows that a reduction in the incidence of long term morbidity, while maintaining the same level of cure is considered a significant advance in medical practice.

There has been much publicity regarding radiation morbidity following treatment for carcinoma of the breast. In this country over 10,000 women with breast cancer a year receive radiotherapy following a lumpectomy. Since radiation in this setting is used as
an adjunct to surgery it is important that the morbidity associated with radiotherapy which is added to that of surgery be kept at a minimum.

The schedules of radiotherapy used to treat breast cancer across the United Kingdom have been shown to vary widely. Economic pressures have encouraged the use of limited numbers of fractions whereas biological evidence has shown the sparing of late radiation damage with many small fractions. The Royal College of Radiology is currently exploring the possibility of nation-wide studies to determine the best balance between economics and multiple fractionation. The techniques described in this thesis to measure functional change in irradiated skin, can detect sub-clinical change and offer a means of comparing the different fractionation schedules advocated.
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APPENDIX 1.

PROFORMAS USED TO RECORD DATA
Skin conductance and laser Doppler flowmetry

NAME            DATE
hosp no
sex
DOB
Tel

RADIOThERAPY
site
date
total dose	no fractions   dose per fraction   overall treatment time
machine
Boost   BU   machine
no fractions   dose per fraction   overall treatment time

SITE OF MEASUREMENT

Conductance readings 1
Conductance readings 2
Blood flow 1
Blood flow 2
APPENDIX 2.

PROFORMAS USED TO RECORD DATA
Visco-elasticity skin analyser measurement

Name
Hospital Number
Age
Diagnosis
Surgery
Chemotherapy
radiotherapy

SITE OF MEASUREMENT

Appearance
APPENDIX 3.

PROFORMA USED TO RECORD SKIN MORBIDITY

Clinical observations of radiation change.

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<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hosp No</td>
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<table>
<thead>
<tr>
<th>Low dose area</th>
<th>High dose area /boost</th>
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</thead>
<tbody>
<tr>
<td>Erythema</td>
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</tr>
<tr>
<td>Dry desquamation</td>
<td>0-100% of irradiated field</td>
</tr>
<tr>
<td>Moist desquamation</td>
<td>0-100% of irradiated field</td>
</tr>
<tr>
<td>Pigmentation</td>
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</tr>
<tr>
<td>Pallor</td>
<td>0 none, 1 slight, 2 moderate, 3 severe</td>
</tr>
<tr>
<td>Thinning of epidermis</td>
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</tr>
<tr>
<td>Subcutaneous induration</td>
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</tr>
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<td>0 none, 1 &lt;1/cm², 2 1-4/cm², 3 &gt;4/cm²</td>
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APPENDIX 4.
PATIENT INFORMATION AND CONSENT FORM

MEASUREMENT OF CHANGES IN THE SKIN FOLLOWING RADIOTHERAPY TREATMENT

Following radiotherapy there may be small changes in the skin over the area treated such as dryness. We are interested in measuring these changes to see if they are related to the dose of radiation we give. The four measurements we will be recording are 1) Skin moisture 2) Number of sweat glands 3) Skin blood flow 4) Skin elasticity.

Skin moisture
This test takes 8 minutes during which time the patient is asked to lie on a bed. One small pad made of clear plastic with inbuilt metal electrodes is placed over the area previously irradiated and another pad for comparison is placed over a similar area that has not been treated. Moisture collects under the pads leading to an increase in skin conductance which is measured graphically on a computer. This test is non invasive and painless.

Number of sweat glands
The number of sweat glands in an area measuring 3 cm by 5 cm are calculated. This is done by forming an imprint of the skin over the area of interest, each imprint taking 15 minutes to do. Firstly the sweat glands in the area to be tested are stimulated to secrete sweat. This is done by placing a piece of blotting paper soaked in pilocarpine on top of the skin. Using a battery a very small current is passed through the blotting paper for 5 minutes. This draws the drug into the skin to the sweat glands causing them to secrete sweat. Occasionally this results in a tingling sensation. Next a clear liquid is placed over the area which sets in 5-10 minutes forming an impression of the skin. This can be peeled off and the number of sweat glands calculated by counting the number of holes in the impression. On completion there maybe an area of redness over the test site, which settles over 2-3 hours.

Skin blood flow
This test takes approximately 20 minutes and requires the patient to lie still on a bed. Two small applicators are placed on the skin, one over an area of skin previously treated and one over a similar area that has not had any radiation. These applicators warm the surface of the skin to 40 degrees centigrade, which results in a feeling of warmth over the area. Any changes in skin blood flow due to warming the skin is then measured by the applicator.

Skin elasticity
This test takes 10 minutes to do and is completely painless. The area previously treated and a similar area which has not been treated with radiotherapy is marked out and multiple sites within these areas are measured. A small probe is placed on the skin, which generates a mechanical wave in the skin and measures how fast it travels. The slower it travels the more flexible the skin.

I consent to the above
Signature of Patient Date

Signature of Doctor Date
APPENDIX 5.

Silicone elastomer imprints in 38 patients who have been treated with radiotherapy to one side of the chest.

<table>
<thead>
<tr>
<th>Case No</th>
<th>Radiotherapy (Gy/fractions/days)</th>
<th>Control No/cm²</th>
<th>Treated No/cm²</th>
<th>% difference of treated compared with control</th>
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</thead>
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<td>95</td>
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<td>42</td>
<td>-34%</td>
</tr>
<tr>
<td>14</td>
<td>50/25/35</td>
<td>45</td>
<td>7</td>
<td>-84%</td>
</tr>
<tr>
<td>15</td>
<td>50/25/35</td>
<td>58</td>
<td>56</td>
<td>-3%</td>
</tr>
<tr>
<td>16</td>
<td>50/25/35</td>
<td>42</td>
<td>3</td>
<td>-93%</td>
</tr>
<tr>
<td>17</td>
<td>50/25/35</td>
<td>82</td>
<td>30</td>
<td>-63%</td>
</tr>
<tr>
<td>18</td>
<td>50/25/35</td>
<td>86</td>
<td>84</td>
<td>-2%</td>
</tr>
<tr>
<td>19</td>
<td>50/25/35</td>
<td>91</td>
<td>1</td>
<td>-99%</td>
</tr>
<tr>
<td>20</td>
<td>50/25/35</td>
<td>25</td>
<td>6</td>
<td>-76%</td>
</tr>
<tr>
<td>21</td>
<td>50/25/35</td>
<td>22</td>
<td>26</td>
<td>+18%</td>
</tr>
<tr>
<td>22</td>
<td>40/15/21</td>
<td>54</td>
<td>4</td>
<td>-93%</td>
</tr>
<tr>
<td>23</td>
<td>40/15/21</td>
<td>155</td>
<td>77.5</td>
<td>-50%</td>
</tr>
<tr>
<td>24</td>
<td>40/15/21</td>
<td>184</td>
<td>198</td>
<td>+8%</td>
</tr>
<tr>
<td>25</td>
<td>40/15/21</td>
<td>29</td>
<td>25</td>
<td>-14%</td>
</tr>
<tr>
<td>26</td>
<td>40/15/21</td>
<td>100</td>
<td>70</td>
<td>-30%</td>
</tr>
<tr>
<td>27</td>
<td>40/15/21</td>
<td>26</td>
<td>24</td>
<td>-7%</td>
</tr>
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<td>28</td>
<td>40/15/21</td>
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<td>-43%</td>
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<tr>
<td>29</td>
<td>40/15/21</td>
<td>250</td>
<td>50</td>
<td>-80%</td>
</tr>
<tr>
<td>30</td>
<td>40/15/21</td>
<td>164</td>
<td>200</td>
<td>+22%</td>
</tr>
<tr>
<td>31</td>
<td>40/15/21</td>
<td>70</td>
<td>65</td>
<td>-7%</td>
</tr>
<tr>
<td>32</td>
<td>40/15/21</td>
<td>116</td>
<td>66</td>
<td>-43%</td>
</tr>
<tr>
<td>33</td>
<td>40/15/21</td>
<td>34</td>
<td>2</td>
<td>-94%</td>
</tr>
<tr>
<td>34</td>
<td>57/38/17</td>
<td>125</td>
<td>120</td>
<td>-4%</td>
</tr>
<tr>
<td>35</td>
<td>54/36/12</td>
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<td>68</td>
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<tr>
<td>36</td>
<td>54/36/12</td>
<td>140</td>
<td>128</td>
<td>-9%</td>
</tr>
<tr>
<td>37</td>
<td>54/36/12</td>
<td>73</td>
<td>78</td>
<td>+6%</td>
</tr>
<tr>
<td>38</td>
<td>54/36/12</td>
<td>106</td>
<td>97</td>
<td>-5%</td>
</tr>
</tbody>
</table>
APPENDIX 6.

Changes in cutaneous blood flow measured with laser Doppler flowmetry

Change in cutaneous blood flow on heating the skin to 40°C measured with laser Doppler flowmetry. Readings carried out in 33 patients treated with radiotherapy for breast cancer.

<table>
<thead>
<tr>
<th>Dose (Gy/fractions/days)</th>
<th>Control relative increase in blood flow</th>
<th>Treated relative increase in blood flow</th>
<th>Ratio of relative increase in blood flow treated/control</th>
<th>Percentage increase in blood flow of treated compared to control</th>
</tr>
</thead>
<tbody>
<tr>
<td>60/25/35</td>
<td>2.5</td>
<td>1.8</td>
<td>0.74</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>2.8</td>
<td>2.1</td>
<td>0.76</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.0</td>
<td>2.4</td>
<td>1.22</td>
<td>79%</td>
</tr>
<tr>
<td></td>
<td>3.2</td>
<td>2.1</td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.6</td>
<td>1.9</td>
<td>0.72</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.1</td>
<td>1.7</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.8</td>
<td>3.3</td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.6</td>
<td>1.9</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.1</td>
<td>1.4</td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.7</td>
<td>1.6</td>
<td>0.97</td>
<td></td>
</tr>
<tr>
<td>50/20/28</td>
<td>2.1</td>
<td>1.8</td>
<td>0.88</td>
<td>97%</td>
</tr>
<tr>
<td></td>
<td>1.6</td>
<td>1.6</td>
<td>1.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.5</td>
<td>2.3</td>
<td>.93</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.5</td>
<td>2.9</td>
<td>1.14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.7</td>
<td>1.5</td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.3</td>
<td>1.7</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.8</td>
<td>2.8</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.9</td>
<td>1.7</td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.5</td>
<td>2.7</td>
<td>1.08</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.8</td>
<td>1.7</td>
<td>0.94</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.1</td>
<td>2.7</td>
<td>1.25</td>
<td></td>
</tr>
<tr>
<td>50/25/35</td>
<td>2.3</td>
<td>2.3</td>
<td>1.0</td>
<td>97%</td>
</tr>
<tr>
<td></td>
<td>1.9</td>
<td>1.9</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.3</td>
<td>2.3</td>
<td>0.98</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.1</td>
<td>2.1</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.8</td>
<td>1.7</td>
<td>0.97</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.2</td>
<td>1.3</td>
<td>1.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.6</td>
<td>1.5</td>
<td>0.94</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.9</td>
<td>2.2</td>
<td>1.15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.4</td>
<td>2.3</td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.3</td>
<td>1.2</td>
<td>0.93</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.7</td>
<td>1.5</td>
<td>0.89</td>
<td></td>
</tr>
<tr>
<td>40/15/21</td>
<td>2.8</td>
<td>2.4</td>
<td>0.84</td>
<td>97%</td>
</tr>
</tbody>
</table>

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LINEAR QUADRATIC EQUATION

Cell survival curve

A cell survival curve is the relationship between the fraction of cells retaining their reproductive integrity and the absorbed dose. Conventionally survival curves are always plotted on a logarithmic scale of survival. A number of models and theories exist to explain the shape of the survival curve. The linear quadratic equation is the most commonly used especially when considering radiation response in the low-dose region (0-3 Gy).

Linear Quadratic Equation

The linear quadratic model describes a continuously-bending survival curve. It assumes that there are two components to cell killing by radiation, one of which is proportional to dose and the other proportional to the square of the dose (Steel, 1993).

Equation

\[ S = \exp(-\alpha D - \beta D^2) \]

\( S \) = fraction of cells surviving at dose \( D \)
\( \alpha \) = linear component of cell kill
\( \beta \) = quadratic component of cell kill

The linear quadratic model may be explained if it is assumed that two cellular targets have to be inactivated for cell death. This may be achieved through one of two processes. In the first process the two targets are simultaneously damaged in a single physical event (single particle track). Cell death would then occur as a linear function of dose (\( \exp(-\alpha D) \)). In the second process each of the two targets are damaged by two separate particle tracks. The two damaged targets interact to produce lethal damage. The frequency of cell death will then vary with the square of the dose (\( \exp(-\beta D^2) \)).
Figure 33. \( \alpha/\beta \) ratio, a dose which describes the shape of the survival curve.

If the initial slope of the shoulder of the survival curve is compared to the rest of the shoulder a value in Gy can be found at which damage attributed to the process for the linear initial slope is equal to damage attributed to the process responsible for the increasing curving shoulder. This dose is referred to as the \( \alpha/\beta \) ratio and it is this ratio which is used to describe the shape of the survival curve.

The components of cell killing that are proportional to dose and to the square of the dose are equal when:

\[
\alpha D = \beta D^2 \quad \text{or} \quad D = \frac{\alpha}{\beta}
\]
Figure 34. Dose response curves for early and late reacting tissue

The survival curves for early and late reacting tissue differ in their shape with late reacting tissues having a more curved survival curve and consequently a smaller $\alpha/\beta$ ratio (Fig. 34). At clinically relevant doses per fractions early reacting tissues demonstrated predominantly a linear relationship ($\alpha$ component) between dose and effect, while with late reacting tissue a large part of the effect is related to the square of the dose ($\beta$ component). Reducing the dose per fraction should spare late reacting tissue as it will reduce the contribution of the $\beta$ component.

The value of $\alpha/\beta$

Studies in fractionation have been carried out extensively in animals to determine the $\alpha/\beta$ ratio for acute and late responding tissue, however in humans the data is limited. Acutely responding tissues having $\alpha/\beta$ ratios in the range of 7-20 Gy compared to 0.5-6 Gy for late responding tissues.
Early reactions

<table>
<thead>
<tr>
<th>Condition</th>
<th>$\alpha/\beta$ (Gy)</th>
<th>95% CI</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>skin erythema</td>
<td>7.5 (5.4-10.9)</td>
<td></td>
<td>Turesson and Thames (1989)</td>
</tr>
<tr>
<td>skin desquamation</td>
<td>11.2 (7.8-18.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Late reactions

<table>
<thead>
<tr>
<th>Condition</th>
<th>$\alpha/\beta$ (Gy)</th>
<th>95% CI</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telangiectasia</td>
<td>3.9 (2.7-4.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subcutaneous fibrosis</td>
<td>1.9 (.8-3)</td>
<td></td>
<td>Bentzen et al (1989)</td>
</tr>
</tbody>
</table>

Table 21. $\alpha/\beta$ values for human skin

Calculation of isoeffect relationships

The LQ cell survival curve can also be used to describe the relationship between total isoeffective dose and the dose per fraction in fractionated radiotherapy (Fowler, 1989). The biological effective dose (BED) formulae below provides a simple way of calculating isoeffective radiotherapy schedules:

\[
\text{Biological effective dose (BED) Gy} = D \left[ 1 + \frac{d}{(\alpha/\beta)} \right]
\]

- $D = \text{total dose}$
- $d = \text{dose per fraction}$
- $\alpha/\beta = \text{for the specific tissue endpoint}$
APPENDIX 8.

FACTORS AFFECTING THE SKIN DOSE

Introduction

The depth that an X-ray will travel in tissue before being absorbed is directly related to its energy. The higher the beam energy, the more penetrating the beam in tissue (fig. 33). Until the 1950's, most external beam radiotherapy was carried out with X-rays generated with voltages up to 300 kV. These orthovoltage machines gave the highest dose at the surface of the skin. High energy megavoltage machines, such as linear accelerators, which are now in clinical practice generate beams which spare the skin; the dose building up several mm below the surface-the actual depth depending on the energy at which the beam is generated.

1 Skin sparing effect

All incident radiation beams deposit dose in a predictable way within the tissue. The maximum dose Dmax is deposited at a certain depth within the tissue. Beyond this point the dose falls off in a reproducible manner as the beam is attenuated by the tissue it is passing through. The higher the beam energy, the more penetrating the beam and the less the tissue attenuates it, thus the greater the dose at depth.

Before the depth of maximum dose is reached there is a region of dose build up. This can be explained by the fact that as high energy photons enter a patient, high speed electrons are ejected from the surface and subsequent layers and travel deep into the tissue. As they slow down, they deposit their energy at a distance from the surface. This is the absorbed dose, and it increases with depth up to Dmax. The depth at which this maximum dose is deposited increases with the energy of the incident beam and gives rise to this dose gradient, the build up region (fig. 35). This dose build-up effect accounts for the skin sparing effect. For orthovoltage the dose build-up region is negligible, and the maximum dose is essentially at the skin surface (Khan, 1989).
<table>
<thead>
<tr>
<th>Depth (mm)</th>
<th>100 kV</th>
<th>Co$^{60}$ 80 cm</th>
<th>4 MV 80 cm</th>
<th>10 MV 100 cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>18.0</td>
<td>14.0</td>
<td>12.0</td>
</tr>
<tr>
<td>1</td>
<td>70.5</td>
<td>57.0</td>
<td>30.0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>90.0</td>
<td>74.0</td>
<td>46.0</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>98.0</td>
<td>84.0</td>
<td>55.0</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>100.0</td>
<td>90.0</td>
<td>63.0</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>85.0</td>
<td>100.0</td>
<td>94.0</td>
<td>72.0</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>96.5</td>
<td>76.0</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>99.5</td>
<td>84.0</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>73.0</td>
<td>100.0</td>
<td>91.0</td>
<td></td>
</tr>
<tr>
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<td></td>
<td></td>
<td>97.0</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>25</td>
<td></td>
<td></td>
<td>100.0</td>
<td></td>
</tr>
</tbody>
</table>

**Table 22.** Build-up dose distribution in polystyrene for 10×10 cm field for X-rays different energies

**Figure 35.** Build up dose in the skin
2 Electron contamination of the photon beam

Electrons arise from photon interactions in the air, in the collimator, and in any other scattering material in the path of the beam. For example if a shadow tray is used to support beam shaping blocks, secondary electrons are produced by photon interactions in the tray and the air column between the skin. The contamination of a high energy photon beam with secondary electrons reduces the skin sparing effect of megavoltage radiation and increase with field size (Khan, ).

3 Field size

Backscatter is radiation which on entering tissue is scattered back to the surface. The amount of backscatter increase with the area of the field irradiated. It also varies with the energy of radiation reaching a peak with beam quality of .8 mm Cu HVT (150 kV) and falls with higher energy radiation due to the fact that the scatter is increasingly in a forward direction. It also falls with lower energy X-rays as the compton interactions are swamped by the photoelectric effect (Khan, 1989).

4 Obliquity

Jackson (1971) has explained the increase in skin dose with increasing angle of incidence through the concept of electron range surface (e.r.s). The e.r.s. is a three dimensional representation of secondary electron range and distribution produced by a pencil beam of photons interacting with the medium. Electrons generated inside the e.r.s. volume will reach P and contribute to the dose there. The increase in the angle of the incident beam results in additional surface dose at P because of electron contribution from the portion of e.r.s within the tissue.
Figure 36. Use of e.r.s to determine surface dose build up at point P for a beam perpendicular to the surface and for a tangential beam.

For a tangential beam an upper estimate of the dose to the skin may be obtained by the following relationship.

Percent skin dose = \(\frac{1}{2} (100\% + \text{entrance dose})\)

Entrance dose represents the surface dose for normal incidence expressed as a percentage of Dmax.

The skin dose increases with an increasing angle of obliquity because of an increase in the contribution of dose from secondary electrons generated in the tissue. Furthermore as the surface dose increases with the angle of incidence, the depth of maximum build-up decreases.

5 Bolus (tissue compensator)

When using megavoltage radiation, occasionally it is necessary to treat the skin to the full dose, for example where tumour extends to involve the overlying skin. This can be accomplished by the use of bolus, which effectively adds a layer of tissue above the skin, so that the build up region occurs within the bolus and the skin receives the maximum dose (Khan, 1989).
APPENDIX 9.

**Retrospective study:** Skin conductance results related to the biological effective dose delivered to the dermal structures using different a/b ratios.

![Graphs showing skin conductance results for different a/b ratios.]
APPENDIX 10

Calculation of the radiation dose to the dermal structures.

The dose at 1mm was measured using a thin windowed NACP parallel plate ionisation chamber. The graphite front window is 0.6 mm thick, which is equivalent to a water thickness of 1mm. Readings obtained were repeatable to an accuracy of less than 5%

Lung

Patients were treated isocentrically using a 6MV linear accelerator. The dose was prescribed to the isocentre.

For calculation of the dose at a depth of 1mm an average field size of 10 x 10 cm and a separation of 20 cm (range 18-24cm) were assumed.

\[
\begin{align*}
%DD \text{ at } 1\text{mm} &= 40\% \text{ Entrance} \\
%DD \text{ at } 19.9\text{mm} &= 36\% \text{ Exit} \\
\text{Total } %DD &= 76\% \\
\end{align*}
\]

\[
\text{Midline } 10 \text{ cm } F^2 = \left( \frac{f^1 + d}{f^1 + d_m} \right) \left( \frac{f^2 + d}{f^2 + d_m} \right)
\]

\[
F^2 = \left( \frac{100 \times 91.5}{101.5 \times 100} \right) = 0.983 \text{ isocentric}
\]

\[
F^2 = \text{inverse square law correction factor for depth dose}
\]

\[
f^1 = \text{focus to skin distance (100cm)} \quad f^2 = \text{treatment focus to skin distance}
\]

\[
d_m = \text{depth of build up dose} \quad d = \text{depth of interest}
\]

\[
6\text{MV } %DD = 67 \times 0.983
\]

\[
= 65.9\% \text{ from single field}
\]

Total = 131.7%
Therefore skin dose = 76% of 132%
= 57% of the dose prescribed to the isocentre from the anterior and posterior fields.

The variation in the skin dose across this group of patients is less than 10%. Factors contributing to the variation are field size, patients separation and lead shielding (page 155).

**Breast dose**

Patient were treated with a Cobalt 60 machine. The dose was prescribed to the minimum tumour dose. A gradient of 10% across the tumour being acceptable. Wedges were used as tissue compensators.

Patients were treated with a fixed FSD.
For the calculation of the dose at a depth of 1 mm an average field size of 10 x 10 cm was assumed.

Patient with a separation of 20 cm.

Co-60 %DD at 1mm = 80% entrance

%DD at 19.9cm = 28.45 x 0.966 (build down factor, due to lack of backscatter)
= 27.4% exit

Total %DD 1mm below the skin surface = 80% + 27.4% = 107.4%

Midline breast dose = 58% x 2
= 116%

Skin dose at 1mm = 107.4% of 116% = 92.5% of midline dose

Dose prescribed to the minimum tumour dose which was 2-4% higher than the midline dose. Therefore skin dose at 1mm is approximately 94% of the minimum tumour dose.

Variation in the patients separations (range 18-25cm) will result in a variation in the dose at 1mm of 92% -105% of the minimum tumour dose.
GLOSSARY OF TERMS

**α/β ratio**: The ratio of the parameters α and β in the linear-quadratic model.

**Accelerated fractionation**: Reduction in overall treatment time without a significant change in dose per fraction or total dose.

**Apocrine sweat gland (sebaceous glands)**: Glands present in the dermis whose ducts open into the upper hair follicle canal and secrete sebum.

**Applied dose (a.p.d)**: For single fields, the dose may be prescribed as an 'applied' dose, i.e. 100 per cent at the D max. (maximum depth dose) for the machine used.

**Ataxia telangiectasia**: Progressive loss of muscle co-ordination and dilation of the small blood vessels are the symptoms of this autosomal recessive trait.

**Brachytherapy**: Radiotherapy using radioactive sources inserted into a body cavity or through needles into tissue.

**Biologically-effective dose (BED)**: In fractionated radiotherapy, the total dose that would be required in very small dose fractionation's or at infinitely low dose rate, as indicated by the linear-quadratic model. BED values calculated for different α/β ratios.

**CHART**: Continuous hyperfractionated accelerated radiotherapy.

**CHARTWELL**: Continuous hyperfractionated accelerated radiotherapy weekendless.

**Dermis**: The dermis makes up most of the skin's thickness. It is bounded superiorly by the epidermis and inferiorly by the subcutaneous tissue. It is composed of fibrous connective tissue and ground substance and contains the skin appendages, blood vessels and nerves.
Dose-modifying factor (DMF): When a chemical or other agent acts as if to change the dose of radiation, DMF indicates the ratio: (dose without/dose with) the agent for the small level of effect.

“Early” responses: Radiation-induced normal tissue damage that is expressed within weeks to a few months after exposure. Generally due to damage to parenchymal cells. $\alpha/\beta$ ratio tends to be large.

Eccrine sweat gland: Glands which are present in the dermis and open onto the skin surface. They play an important role in temperature regulation and secret sweat.

Epidermis: This is the outer layer of skin and is composed of stratified keratinising epithelium measuring 0.04-1.5 mm in thickness.

Field-size factor: The dependence of normal tissue damage on the size of the irradiated area: also known as the volume factor.

Gray (Gy): Unit of absorbed dose. 1 gray = 1 joule per kg (= 100 rad)

“Hierarchical” tissues: Cell populations comprising a lineage of stem cells, proliferating cells and mature cells. The mature cells do not divide.

Hyperfractionation: Increase in number of fractions and reduction in dose per fraction, within a similar overall time.

Hyperthermia: The use of heat treatments in excess of 42 degree’s centigrade to treat cancer

Hypofractionation: A reduction in the number of fractions, increase in fraction size, within a similar treatment time.

Hypoxia: Low oxygen tension

Intersection dose (I.D.): The dose were two or more intersecting beams cross

Isoeffect plot: A graph of the total dose for a given effect (e.g. ED50) plotted, for instance, against number of fractions, dose per fraction or dose rate.
“Late” responses: Radiation-induced normal tissue damage that is expressed months to years after exposure. Generally due to damage to connective-tissue cells, $\alpha/\beta$ ratio tends to be small.

**Linear-quadratic model (LQ model):** Model in which the effect ($E$) is a linear-quadratic function of dose ($d$): $E = \alpha d + \beta d^2$

**Megavoltage:** High energy X-ray beams. These are either linear accelerators producing X-ray beams of 4-20 MV or cobalt machines containing a source of CO 60, which decays spontaneously to Nickel-60 releasing gamma rays of 1.2 and 1.3 MV.

**Minimum tumour dose (min.t.d):** The minimum dose which encompasses the target volume

**NSD:** Nominal standard dose in the Ellis formula

**Orthovoltage:** X-rays of energy 200-300 kV, which penetrate to a depth of 3 cm.

**Potential doubling time:** A measure of the proliferative activity of the tumour cells taking into account the presence of dividing and non-dividing cells, but assuming the absence of cell-loss.

**Potential-lethal damage:** Cellular damage that is recovered during the interval between treatment and assay

**Quality of an X-ray:** The penetrating ability of the primary radiation beam

**Radio-responsiveness:** A general term, indicating the overall level of clinical response to radiotherapy.

**Radiosensitizer:** In general, any agent that increases the sensitivity of cells to radiation. Usually applied to electron-affinic chemicals that mimic oxygen in fixing free-radical damage.

**Radiosensitivity:** The sensitivity of cells to ionising radiation. Usually indicated by the surviving fraction at 2 Gy (i.e. SF2)
Recovery: An increase in cells survival or decrease in tissue injury as a function of time during or after irradiation

Relative biological effectiveness (RBE): Ratio of dose of a reference radiation quality (usually 250 kV x-rays) and dose of a test radiation that produce equal effect.

Repair: Restoration of the integrity of damaged macromolecules

Skin erythema dose (SED): Defined as that quantity of X-irradiation administered at 23-cm focal skin distance at 180 kV (with 0.5 mm zinc + 3 mm aluminium filtration) to a field of 6×8 cm which produced a reversible skin reaction.

Superficial X-rays: X-rays of energy 50-150 kV, which penetrate to a depth of 1 cm.

Stem cells: Cells capable of both self-renewal and supply of daughter cells that differentiate to produce all the various types of cells in a lineage.

Sublethal damage: Non-lethal cellular injury that can be repaired, or accumulated with further dose to become lethal.

Target cell: Cell whose death contributes to a reduction tissue growth or function

Telangiectasia: A group of abnormally prominent capillaries, venules, and arterioles that create small focal red lesions, usually in the skin and mucous membranes of the body

Therapeutic Index: Tumour response for a fixed level of normal-tissue damage

Tolerance: The maximum level of normal tissue damage produced by radiotherapy that the therapist judges to be acceptable. Usually indicated by dose units, although the actual values will depend on fractionation, field size and concomitant treatments.