Photothermal Treatment of Cutaneous Lesions

A thesis
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the Degree of
Doctor of Philosophy in Physics

by

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Abstract

This thesis reviews the understanding of the processes involved in the laser treatment of cutaneous blemishes. The current treatment protocol for the treatment of vascular lesions – double scanning with transient blanching – used at St George's Hospital is shown to give excellent results. The protocol takes advantage of the precise control provided by the SCANALL automatic scanner and the 5 W, 578 nm output of the copper vapour laser. The clinical endpoint – transient blanching – is shown to be due to a temporary halting of blood flow (probably by vasoconstriction) rather than coagulation necrosis of overlying tissues. Various models of the laser treatment of vascular lesions are presented and examined.

A histological study of the double scanning, transient blanching protocol shows that tissue damage is confined to vascular and perivascular tissue. Cosmetic lightening is due to a reduction in both the number and size of the vessels in the upper dermis.

The protocol is also investigated by interview and postal survey. The incidence of adverse effects is small. For example, there are only two 1 cm^2 adverse skin texture changes in 64000 cm^2 of treated area. Patients receiving treatment for telangiectasia and spider naevus are satisfied with the outcome after one or two treatments, but many with port-wine stain cease treatment after four sessions when government funding runs out. Patient perception of the success is compared with the surgeon's perception. Patients often needed to be reminded of the size and severity of their original lesion with a photograph.

The thesis reports on a parallel investigation of the use of millisecond scale pulses of white light for the treatment of tattoos. A xenon flash-lamp system is designed, constructed, and used in a clinical trial. This includes building pulse forming networks to produce rectangular current pulses of differing lengths.

During the clinical trial the system produced a strong inflammatory response in the skin adjacent to the pigment, and lightening of the tattoo. Modelling, histology and other literature studies lead to the conclusion that the pulse length is too long to cause the explosive rupture of pigment-containing cells observed after Q-switched laser treatment, and too short to cause sufficient necrosis and phagocytosis of the pigment-containing cells for it to be useful clinically.

The thesis also describes the construction of a device to measure muscle tension during tendon transfer surgery. The device uses diffraction to measure the separation of the fundamental unit of muscle tissue - the sarcomere.

Chapter 1

Introduction

Removal of cutaneous blemishes has long been the desire of the afflicted and medical practitioners alike. Until recent times the only solutions available caused significant damage to the surrounding tissue, and thus involved a high probability of scarring. In 1960, the newly invented ruby laser was used to treat pigmented lesions. Within a few years surgeons were using the new technology to treat vascular and pigmented lesions.

The success of laser treatment depends critically on the treatment parameters and protocols. The early laser treatments, with ruby and carbon dioxide (CO_2) lasers caused damage to structures in the skin which are not the cause of the blemish (Goldman *et al*, 1967; Ratz and Bailin, 1987). Often this damage was to dermal collagen, which can lead to scar formation; or to melanocytes, which risks abnormal pigmentation after treatment. For some people, this may be worse than the original blemish. In chapter 2, we describe the physiology of human skin, and also the structure of vascular lesions (such as port-wine stains) and tattoos.

The narrow band of wavelengths produced by lasers is one of their main advantages in the treatment of skin blemishes. For tattoos it was quickly recognised that the 694 nm wavelength of the ruby laser was ideal for treating blue and black pigments (Laub *et al*, 1968). The proliferation of multi-coloured tattoos has seen other lasers used for treatments. The argon-ion (488 nm to 514.5 nm) and alexandrite (755 nm) lasers, along with several others, have been used with considerable success, the different colours allowing a wider range of pigments to be treated.

For vascular lesions, lasers such as the argon-ion (488 nm to 514.5 nm) and the frequency-doubled Nd:YAG (532 nm) were used. Light from these lasers is absorbed by the oxy-haemoglobin (HbO_2) in the red blood cells. Unfortunately, the long illumination times needed for these lasers to deliver sufficient energy to the blood vessels results in non-specific coagulation necrosis of the surrounding tissue (Solomon *et al*, 1968). As well, these wavelengths are well absorbed into the melanocytes in

the skin, leading to hypo-pigmentation. In chapter 3 we summarise the non-specific laser treatments used prior to 1980.

Mathematical modelling has been used in the search for the optimal treatment parameters needed for a laser treatment that specifically targets blood vessels. One of the publications regarded as fundamental to the development of the current widely used pulsed dye laser systems is Anderson and Parrish (1981). This paper concluded that 1-10 ms pulses of 577 nm light would produce damage specific to dilated blood vessels. In chapter 4 we look in some detail at the model presented in their paper. We also review the modelling that was undertaken in this institution in the following decade.

At St George's Hospital, Christchurch, a copper vapour laser has been used for 14 years for the treatment of vascular lesions. Since then, more than 1000 patients have undergone treatment for a variety of vascular lesions. In the literature the copper vapour laser has been associated with the argon laser in producing such complications as atrophic scarring and abnormal pigmentation. Some workers (Alster, 1996, for example) also claim that the copper vapour laser is ineffective in treating pale lesions. Often these claims are based on the use of a hand guided optical fibre delivery system, which produces long illumination times. Since 1990 an automated treatment system, SCANALL, has been used to provide treatments using the optimal illumination times. Prior to the commencement of the research for this thesis the treatment provided to patients was satisfactory for most lesion types. It resulted in good cosmetic clearance of these lesions. However, the processes that occur in the skin as a result of laser illumination were not well understood, and the difficulty in treating pale or pink port-wine stains was unexplained. This thesis reports on research which increases the understanding of the damage and healing processes to an extent that the reasons for the difficulties mentioned are well understood. The treatment is now satisfactory for all port-wine stain types. The adverse effect rate is noticibly lower than for previous protocols. The researchers are convinced that the results we are obtaining are at least as good as those obtained by pulsed dye laser practitioners. The development of pulsed dye lasers, of SCANALL, and of the treatment protocols used are presented in chapter 5.

The treatment protocol used at St George's Hospital involves scanning the lesion then rapidly cooling it using ethyl-chloride spray. After this the erythemetous lesion is rescanned. We show that this protocol increases damage to the vasculature while maintaining the viability of the epidermis. This increases the effectiveness of the

treatment. To investigate the damage caused to the skin by the double scanning protocol a histological series was obtained. The samples were taken over a period of three months from just prior to treatment to when the skin had completely healed. This investigation is presented in chapter 6.

A follow-up survey has been conducted to assess the clinical outcomes obtained by the treatment protocol used in conjunction with the SCANALL system. The results of this survey are presented in chapter 7.

For treatment of tattoos Q-switched lasers have been widely used. These work well when used on blue or black tattoos. However the multicoloured tattoos common in recent years present a problem for laser systems. Systems incorporating several lasers of different wavelengths have been developed to treat such tattoos.

The knowledge obtained from the modelling and treatment of vascular lesions was applied to the treatment of tattoos. For patients with light toned skin (Fitzpatrick Types I and II) most, if not all, of the chromophores in the skin will be HbO_2 and the tattoo pigment. The HbO_2 can be temporarily excluded by gentle pressure applied to the skin surface, leaving only the tattoo pigment to absorb light. Since the only chromophore in the skin is the pigment, there is no need to use a wavelength near an absorption peak of the pigment. Therefore an alternative solution to the problem of multi-coloured tattoos is to use intense pulsed white light, rather than laser light.

Further, since tattoo pigment in the skin is encapsulated in fibroblasts, it was thought to be possible to use longer pulses than are used with Q-switched lasers. Phagocytosis (scavanging of debris by macrophages and fibroblasts) occurs with new tattoos - removing some of the pigment before it becomes encapsulated. The pulse lengths of Q-switched lasers are sufficiently short to shatter micron scale pigment granules, rupturing fibroblasts, and stimulating further phagocytosis. However, thermal rather than mechanical necrosis of the encapsulating fibroblasts will also cause phagocytosis. To thermally necrose a fibroblast, much longer light pulses are needed.

A flash-lamp system was developed by Mrs Huaying Zhang as part of her M.Sc. thesis at this institution. This system was tested on a volunteer. The 550 μs pulse of white light produced severe oedema of the skin adjacent to the pigment. In the 6 months after the treatment, the pigment in the treated area faded considerably, leaving the skin texture normal.

In order to further investigate the use of microsecond scale pulses of intense white light for the treatment of tattoos, as part of the research for this thesis another flash-lamp system was designed, built and tested. This used a pulse forming network to

produce a rectangular current pulse. For a constant input energy, a rectangular pulse allows a lower peak current to be used than the discharge shape of an equivalent single mesh circuit. This increases the efficiency and life-time of the flash-tube. In chapter 8 we present the design and testing of a high-power flash-lamp intended for the removal of tattoos.

A clinical trial was conducted to gauge the effectiveness of the flash-lamp system in removing tattoo pigment. A range of input energies and pulse lengths was tried. Some lightening of tattoo pigment was obtained, but at a rate slower than that achieved by Q-switched laser systems. In chapter 9 we present the methodology and results from this clinical trial and an analysis of why the flash-lamp system is not as effective as Q-switched laser treatment.

Tendon transfer surgery for tetraplegics offers them some mobility in their arms. This helps with every-day actions such as holding a pen, dressing, and wheelchair control. Critical to the success of the surgery is the tension applied to the tendon when attaching it to the muscle. This tension is normally found using the passive tension felt during surgery. However, a quantitative measurement is desirable. In chapter 10 the construction of a device is described which allows the stretch of a muscle to be measured. This device uses interference techniques to measure the separation of muscle sarcomeres, which are the basic unit of striated muscle tissue.

Finally in chapter 11 we summarise the results of this thesis.

Chapter 2

Physiology and Pathophysiology

In this chapter the structure of normal skin is described, along with the pathophysiology of the more common vascular lesions and tattoos. Anatomical terms that will be used freely throughout this thesis will be defined.

2.1 Human Skin

Human skin is the body's largest organ, providing about 10% of body mass. It varies in thickness from 1 mm on the eyelids to 4 mm on the back, palms of the hands, and soles of the feet (Goldsmith, 1983). Skin consists of three main layers: the epidermis, the dermis, and the subcutaneous fat (see figure 2.1).

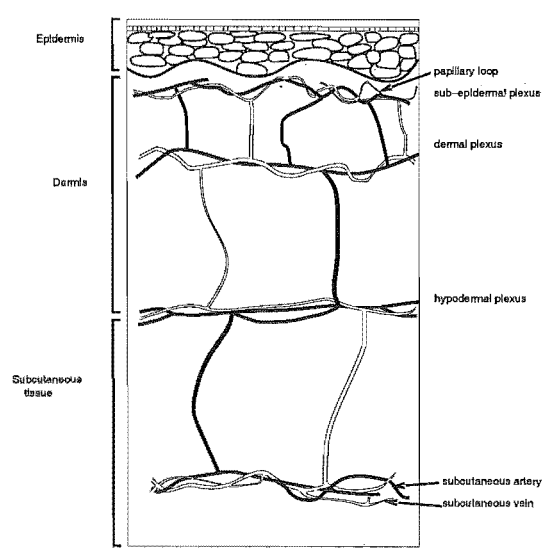

Figure 2.1: The three main layers of human skin.

2.1.1 Epidermis

The epidermis is the most superficial layer of the skin and is between 0.4 mm and 2 mm thick. It is cellular in structure and entirely avascular. The epidermis continually produces new cells whose main purpose is to act as the body's first line of defence. It protects the body from invasion by micro-organisms, prevents loss of fluids from the body, and provides a strong surface covering. The cells at the base of the epidermis continually divide and migrate towards the surface until their nuclei die. Then they become desiccated and are flaked off.

The epidermis is composed of four layers; the innermost is the basal layer, followed by the stratum spinosum, the stratum granulosum, and the stratum corneum or keratin layer. The basal layer is only one cell thick and produces two types of cells: keratinocytes and melanocytes. The keratinocytes produce the cells that form the main structure of the epidermis, namely keratin. The melanocytes produce melanosomes, small (0.3 μm to 1.0 μm) egg-shaped sacks that contain the chromophore melanin. The keratinocytes divide and move upwards toward the skin surface, taking with them the melanosomes which get spread throughout the epidermis. As the keratinocytes progress towards the surface they become flatter and finally die, producing keratin. Keratin is tough, pliable, and relatively impermeable to substances passing in or out of the body. Eventually the keratin is shed. The entire process from basal cell formation to keratin shedding takes 45 to 75 days, depending on the thickness of the epidermis.

The melanin in the epidermis strongly absorbs ultra-violet and visible radiation. It thus provides skin with its yellow, brown, or black pigmentation. The amount of light that reaches the dermis may vary by a large fraction between any two sites on the skin of an individual depending on the melanin concentration at each site. Further, the melanin concentration at any site may change over a period of days or weeks depending on the exposure to the sun the skin receives, and also the biological and hormonal stimulation of melanocytes.

The epidermis also plays a role in tissue healing. After a wound occurs the healing process is as follows.

1. A clot forms
2. inflammatory cells arrive
3. epidermal edges migrate forward to cover the denuded surface
4. fibroblasts and capillaries appear, to form new tissue

5. contractile granulation tissue pulls the wound together.

The clot forms a protective shield over the wound and provides a matrix through which cells can migrate during the healing process. It is also a reservoir for cytokines (soluble proteins which regulate cell biology processes such as growth, division, tissue repair and defence) and growth factors which are released as activated platelets degenerate. Finally it helps to "kick-start" the wound closure process by recruiting circulating inflammatory cells, initiating the re-epithelialisation and connective tissue contraction, and stimulating the growth of new blood vessels.

Once the clot has formed, the process of re-epithelialisation can begin. The basal keratinocyte layer reconstitutes from the edges of the wound, and from stumps of hair follicles and other deeper, undamaged structures. They act as normal wound edges, like an island of good tissue.

Some hours after onset of migration, epidermal cells back from the wound margin undergo a proliferative burst to provide extra cells to replace those lost during the injury. The leading edge keratinocytes cut a way through the clot by dissolving the fibrin barrier.

Once the wound has been coated by a mono-layer of keratinocytes, epidermal cell migration ceases and a normal stratified epidermis starts to form from the wound margin.

2.1.2 Dermis

The dermis contains the bulk of the skin between the epidermis and the subcutaneous fat, and is normally 1-4 mm thick. The epidermal basal layer and the top of the dermis form the epidermal/dermal junction which is characterised by undulations (papilla) which protrude up to 100 μm into the dermis. Between each of these protrusions is the region known as the papillary dermis. The papillary dermis contains the capillaries that provide nutrients for the epidermis. Below the papillary dermis is the layer called the reticular dermis which extends inwards towards the fatty layer, and contains the larger blood vessels.

Both layers of the dermis are comprised mainly of fibrous connective tissue called collagen. Collagen has a high tensile strength which, along with the elasticity provided by elastin, creates a network of strong fibres which are able to protect underlying organs from mechanical injury.

Present within the dermis are several cellular structures. Two of these are fibroblasts and macrophages. The primary function of fibroblasts is to produce collagen

and elastin fibres to repair damaged tissue. Fibroblasts also have a role in scavenging damaged tissue. Macrophages are the main scavenging cells in the skin. They can engulf and digest particulate organic and inorganic materials, disposing of them before tissue regeneration occurs.

2.2 The Cutaneous Vascular System

The cutaneous blood supply serves a dual purpose. First, it provides nourishment to both the surrounding dermis and the avascular epidermis. However the skin has a larger blood supply than is needed to satisfy its oxygen requirements (Wood and Bladon, 1985). The large volume of blood which flows through the skin plays an important role in regulating the temperature of the body. On exposure to heat a larger than normal volume of warm blood flows to the peripheral regions of the body through a widely dilated vascular network. In contrast, the rate of blood flow falls upon exposure to cold.

2.2.1 Blood Vessel Distribution

The distribution of blood vessels within the dermis can be approximated by a tree-like structure (figure 2.2).

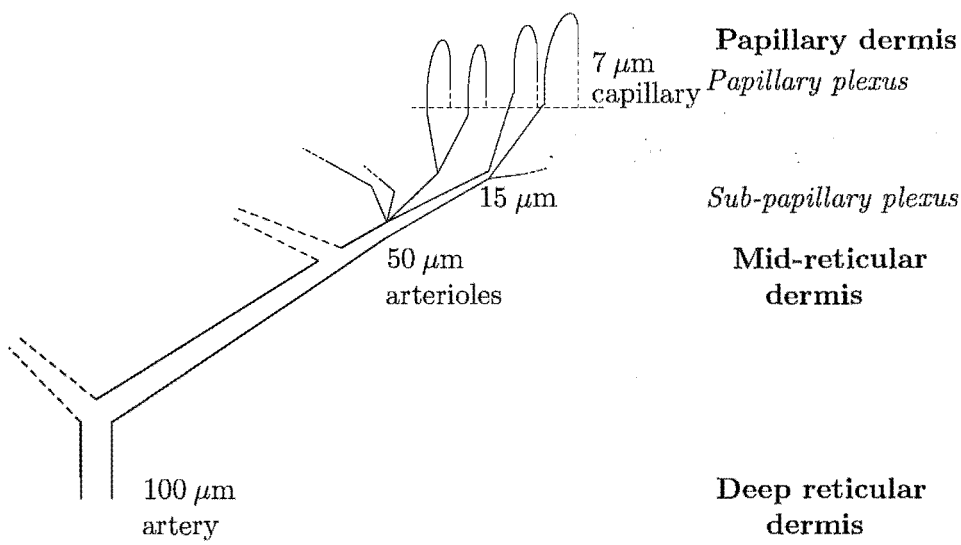

Figure 2.2: Blood vessels form a tree-like structure in the dermis. It is often capillaries in the sub-papillary and papillary plexi that are ectatic (from Ryan, 1973).

An artery approximately 100 μm in diameter enters the lower dermis through

the subcutaneous fat. This artery may divide once or twice before reaching the mid-reticular dermis where the branches are approximately 50 μm in diameter and are now called arterioles. More branching occurs as the arterioles reach upwards until they begin to form one or two plexi (the sub-papillary plexi) of small capillaries that lie approximately parallel to the surface. Extending from these plexi into the dermal papilla are the papillary (or terminal) capillaries. These are vertical loops in the shape of a hair pin (Ryan, 1973) which supply the papillae. The papillary capillaries are only 5 μm to 10 μm in diameter and a typical papilla contains only one such vessel. The capillaries drain into venules which lead to larger and larger veins deeper within the dermis.

Capillaries are formed from a single layer of entwined endothelial cells. Unlike other types of blood vessel, capillaries have no surrounding muscle tissue to control vessel diameter and hence blood flow. Blood flow through capillaries is instead controlled by a pre-capillary sphincter muscle. Only a fraction of the capillaries carry blood at any one time, since there is insufficient blood to fill every blood vessel in the body at the same time (Chaffee and Lytle, 1980). The fraction varies throughout the body and also varies with body temperature and emotional state.

The endothelial cells resemble lightly fried eggs rolled over to form a tube (Ryan, 1973; Rushmer, 1972). The yoke represents the nucleus and may be up to 6 μm thick (Chaffee and Lytle, 1980). The egg-white represents the cytoplasm of the cell. It may be found in any shape and is only 1 μm thick. The volume enclosed by the endothelial cells is called the vessel's lumen. Endothelial cells are semi-permeable and permit the escape of water, sugar, sodium chloride and other nutrients from the blood to surrounding tissue (Best and Taylor, 1961).

Blood, which is contained within the lumen, is a collection of many components but is mainly, by volume, 55% plasma, 40% erythrocytes (red blood cells), and 5% leukocytes (white blood cells). Erythrocytes are bi-concave discs averaging about 7.7 μm in diameter and are about 3 μm thick (Tortora and Anagnostakos, 1984). They move in single file along the capillary, separated by other blood elements. In the process the erythrocyte's outer surface is left in contact with the vessel wall allowing, among other processes, the transfer of oxygen from oxyhaemoglobin (HbO_2) within the cell to the surrounding tissues.

2.3 Vascular Lesions

Vascular lesions are areas of skin with an abnormally red coloration. They vary in size from a few square millimetres to over 10% of the body surface area (approximately 2000 cm^2). Skin displaying vascular lesions contains capillaries within the sub-papillary or papillary plexus which are enlarged, or ectatic. Ectatic vessels are irregularly shaped with diameters ranging from 20 μm to in excess of 150 μm. Barsky *et al* (1980) measured the thickness of endothelial cells to be 4 μm to 6 μm for all ectatic vessels. The volumes of these vessels are typically 5 to 100 times greater than those of normal vessels, hence the erythrocytes no longer move in single file down the capillary. Since the volume of blood within the sub-papillary plexus determines the redness of the skin colour (Chaffee and Lytle, 1980), vascular lesions result. In the following three subsections we describe three of the most common vascular lesions.

2.3.1 Port-Wine Stains

Port-wine stains are salmon pink to purple vascular lesions present in about 0.3% to 0.5% of the population (Carruth and Shakespeare, 1986). The ectatic vessels may occur anywhere between the papillary dermis and the lower dermis. They tend to be darker and more sharply defined than telangiectasias (see figure 2.3).

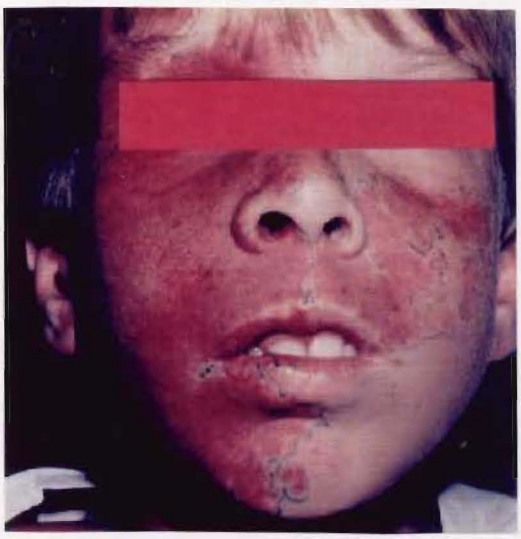

Figure 2.3: A typical, but extensive, red port-wine stain outlined in green ink.

Clinically port-wine stains are usually classified by colour. They vary in colour between salmon pink and dark purple. Children tend to have lighter coloured lesions

than adults, which implies that the colour of a port-wine stain darkens with age. The lighter colour of salmon pink port-wine stains indicates a lower volume of blood present in the lesion.

The physiological reason for the difference in blood volume is not well established. According to Noe *et al* (1980) and Barsky *et al* (1980), the number of ectatic vessels stays the same but they become progressively dilated due to the surrounding collagen degenerating as the patient ages. They also suggest that more of these dilated vessels become full as the patient ages.

Niechajev and Clodius (1990) disagree, claiming the number of ectatic blood vessels which are full of erythrocytes is an unimportant artifact, since this number varies (see section 2.2.1). They also claim that vessel diameter does not increase with age. They suggest that colour differences are caused by differences in vessel diameter, vessel wall structure, depth of the ectatic vessels in the dermis, and the quality of the overlying skin.

The only agreement between the two histological studies is the importance of vessel diameter to lesion colour. Whilst this is sufficient for most modelling purposes, it does not explain the ageing of lesions.

The cause of the ectasia is largely unknown. There is a small tendency for port-wine stains to be hereditary, but no physical reason has been firmly established. However Smoller and Rosen (1986) performed histologies which indicated that ectasia may be caused by a lack of nerves to muscular tissue that controls arteries and arterioles (Rydh *et al*, 1991). These nerves, called sympathetic nerves, control blood vessel dilation, allowing the body to control its temperature. Pickering *et al* (1991) noted that lesions tended to involve singular or adjoining nerve regions of the skin, an observation which supports a link to the nervous system.

2.3.2 Telangiectasias

Telangiectasia is the obvious redness of the lower legs, neck, cheeks, and nose that is common in middle age. It is caused by the loss of papillary capillaries resulting in dilation of vessels in the sub-papillary plexus. This condition has many causes, among them smoking, solar damage, steroid use, and hereditary factors. The ectatic vessels tend to have diameters at the larger end of the scale but are usually well separated. This results in a red discoloration which varies little between patients (see figure 2.4).

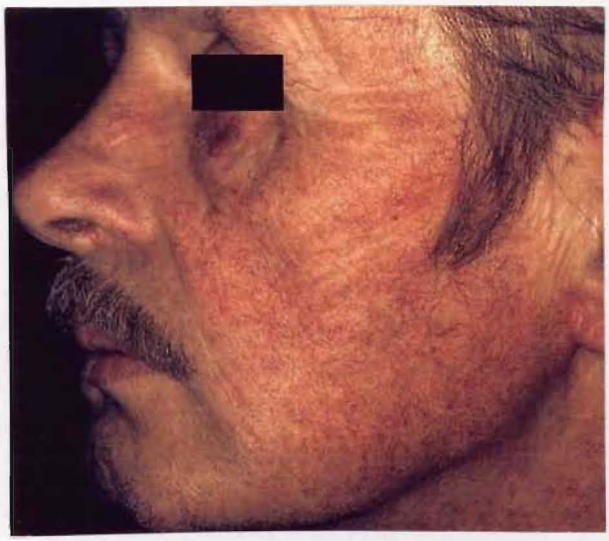

Figure 2.4: A severe telangiectasia. In this case individual vessels can be seen.

2.3.3 Spider Naevi

Spider naevi are telangiectatic vessels in a localised region of the sub-papillary dermis. The dilated sub-papillary plexus is pushed up in to the papillary dermis, resulting in the characteristic red central vessels surrounded by a "blush" of smaller vessels (see figure 2.5). Spider naevi often occur in the young, as a result of trauma (such as a dog bite), or during pregnancy.

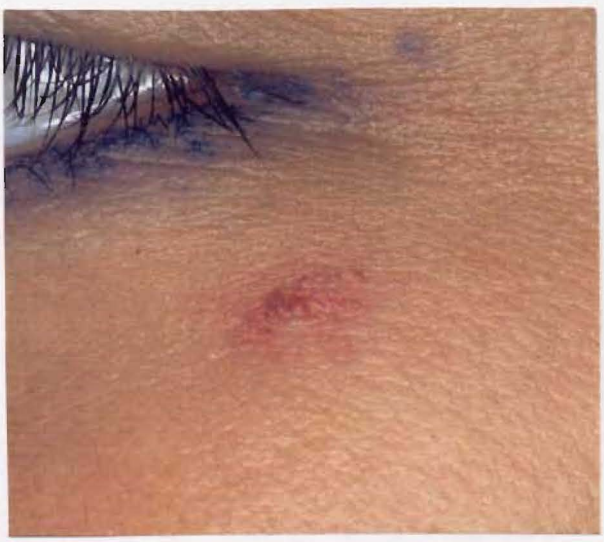

Figure 2.5: A spider naevus

2.4 Decorative Tattoos

Decorative tattoos are formed by the deliberate introduction of pigment into the dermis of the skin. Rather than being uniformly distributed, the pigment tends to accumulate in clusters that are membrane bound, normally in fibroblasts which cluster around blood vessels. These clusters may be up to 30 μm in diameter (Zhang, 1993). Histologically, decorative tattoos may be divided into two categories: professional tattoos, and amateur tattoos.

2.4.1 Professional Tattoos

Professional tattoos are applied by a cluster of needles mounted on an electric vibrator. The needles penetrate an even distance into the skin and when they retract leave behind the tattoo dye. This results in an uniform distribution of pigment clusters superficially within the dermis (Apfelberg *et al*, 1980) with, on average, 70% of clusters ocurring between 5 μm and 15 μm below the dermal/epidermal junction (Zhang, 1993). The method of application also results in even pigment concentration between clusters. Professional tattoos tend to be sharply delineated with little blurring at the edges (see figure 2.6).

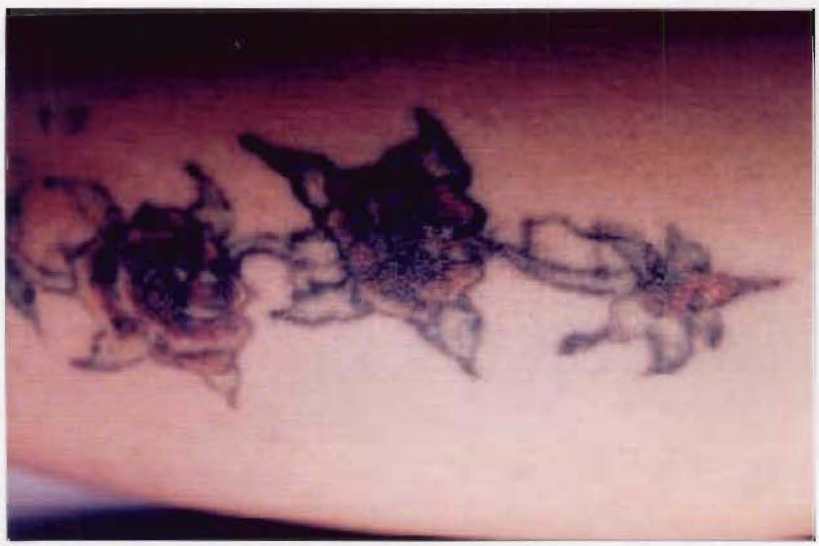

Figure 2.6: A professionally applied tattoo

2.4.2 Amateur Tattoos

Amateur tattoos are applied by the penetration of sharp objects (for example, needles and fountain pens) to a non-uniform depth into the skin (Taylor *et al*, 1990). As a result the pigment varies in concentration from cluster to cluster, and the clusters themselves vary in size. The pigment is often distributed non-uniformly throughout the epidermis, dermis, and the subcutaneous fat, but as a rule is deeper than pigment in professional tattoos. The combination of these factors gives amateur tattoos less distinct, more blurred lines than professional tattoos as can be seen in figure 2.7 (Apfelberg *et al*, 1980).

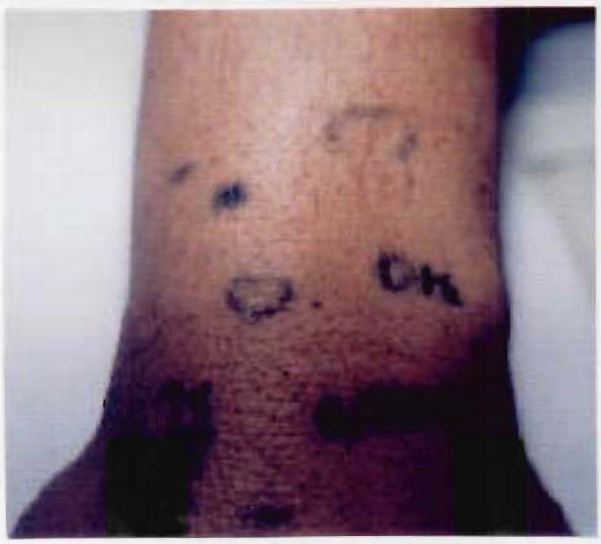

Figure 2.7: An amateur tattoo.

2.4.3 Tattoo Dyes

Nearly one hundred coloured commercial tattoo dyes are available in the major American catalogue (Spaulding & Rogers catalogue 1988, 1989-1990, 1991-1992), and many more are available from other sources. Coloured tattoo dyes traditionally contain metals, such as mercury, iron, aluminium, cobalt, copper, titanium, chromium, lead, and magnesium. These help to make tattoos vivid and more resistant to fading (Loewenthal, 1960; Agris, 1977; Slater and Durrant, 1984). More recent coloured dyes are organic, but tattooists are reluctant to provide precise details.

Indian ink is used for many blue and black amateur tattoos. This is made from candle-black and a binding agent such as gelatin or glue (Hanks, 1988). Another

common amateur pigment is ink designed for use in rotary presses. This contains anti-foaming and anti-flying agents, oils, and varnish, as well as the actual pigment.

Tattoos fade after a number of years. Black tattoos fade to light blue over 20 to 50 years and also become less sharply defined. This is caused by the diffusion of the pigment in the dermis, scavenging by macrophages, and transport out through the lymphatic system. In areas of the skin where the skin is frequently flexed (such as the wrists and knuckles) a black tattoo may fade over 5 to 6 years. Coloured tattoos are generally less resilient than black tattoos and tend to disappear completely after 50 years.

Chapter 3

Treatment Protocols Prior to 1980

In this chapter the motivation for research into vascular lesion removal is presented. Treatments which cause non-vascular specific damage are described.

3.1 Why Do Research Into Vascular Lesion Removal?

Vascular lesions, such as port-wine stain, telangiectasia, and spider naevus are common afflictions. The incidence of port-wine stain has been studied in a number of places worldwide. The studies agree that approximately 0.3% of infants are born with port-wine stain. Telangiectasia and spider naevus are common in later life as the structure of the dermis weakens.

Those afflicted with a vascular lesion on a visible region of the body often suffer from psychological stress. In 1990 Pickering and co-workers from this institution conducted a survey of 242 patients with vascular lesions. The response rate was 72%. They concluded that most patients find their lesions unattractive. Most also found that they had difficulties in interpersonal relationships that they attributed to their lesions (Pickering *et al*, 1990b).

In order to reduce the noticeability of the lesion, and so improve their social interactions, the afflicted are often prepared to incur substantial expenditure. The treatments are usually expensive and medical insurers (at least in New Zealand) are usually not prepared to cover what they consider to be cosmetic surgery. Some people manage to obtain funding through community groups, but such funding is limited.

In the last five years the New Zealand Government has made funding available to a limited number of people who meet strict criteria. People who meet the Ministry of Health's Core Health Services Committee's criteria are funded for up to four 75 minute treatments, irrespective of the size or severity of the lesion. Their criteria are, in order of priority:

1.1) Disfiguring facial port-wine stains, or

1.2) Acute cases where aggressively developing haemangiomas are causing functional impairment

2) Less extensive port-wine stains on the face

3) Port-wine stains elsewhere on the body which have become nodular and prone to bleeding or discomfort

4) Disfiguring hyperpigmented or lesser vascular lesions (generalised telangiectasia on the face).

Our experience since 1986 in the clinic at St George's Hospital is that almost all of our funded patients are from categories 1.1), 1.2) and 2).

It is important therefore that the lesion is improved as much as possible with those four treatments. To optimise the treatment requires research. Research requires funding too, and public funding has been as hard to obtain for researchers as it was for patients. Since vascular lesion removal is usually classified as cosmetic surgery it often "falls through the cracks" between medical and scientific research.

Funding for medical research is targeted towards areas of primary and community heath care, and acute and chronic illness - areas which affect large sections of the community. Approximately 10% of the NZ$36.5M projected expenditure for 1999/2000 by the Health Research Council of New Zealand was allocated to "Biological Systems and Technologies". This category is designed to fund not only medical technology development, but also research that does not fit into any of the other funding categories. Currently there is no "science" funding available in New Zealand that is directly targeted towards research into the removal of disfiguring birthmarks.

3.2 Research Into The Treatment Of Port-Wine Stains

The goal of research into the removal of vascular lesions is to determine the best treatment parameters for each lesion undergoing treatment. In fact, because of the variability of the structure of skin, a given lesion may require the use of different treatment parameters to obtain the best clinical outcome.

An ideal treatment would remove the ectatic vessels without damaging any other structures. Any treatment that predominantly damages the target vessels is called "selective" or "specific".

In practice completely selective treatment is difficult to achieve, and treatments aim rather to damage non-vascular tissue as little as possible. Damage to tissue

typically causes scarring. Small amounts of scar tissue within the dermis may be invisible from the surface, but the more severe the damage the more likely the scarring will be visible and detract from the cosmetic result.

A satisfactory treatment will remove the visible signs of the lesion without causing noticeable scarring or any adverse side effects to the patient's health. The treatment may be considered satisfactory if, for example, the redness of the lesion is reduced, or mild scarring occurs, as these may be less of a burden than the original lesion. Some of the therapies used in the past must be considered unsatisfactory. Two people who have been treated at our clinic had radiation therapy as children. Not only were their port-wine stains largely unimproved, but they suffered deformation of the facial bones as a side effect. Both required reconstructive surgery later in life.

Scientific research into vascular lesion removal falls into three areas - modelling, clinical trials, and histology. In order to understand fully the treatment process all three methods need to be used.

Modelling involves taking known properties of tissue and using them to calculate an optimal set of treatment parameters. These parameters include wavelength, illumination time, energy density (sometimes referred to as fluence), and beam diameter.

Modelling physical processes in the skin is constrained first of all by the simplifications necessary to construct a useful model of the skin structure. Models that can be investigated analytically are based upon simplifications of the skin structure so that the tissue model bears only superficial resemblance to the complex structure of real skin (Anderson and Parrish, 1981). Increasing computing power has made statistical analysis of more complex models feasible (Smithies, 1995). Even such numerical methods of solution require numerous simplifications. In some cases models of only two layers have been used - epidermis and a dermis perfused with blood.

Modelling is also constrained by our limited knowledge of the physical parameters of human skin. These are normally determined *in vitro* and the value of the parameter determined by the experiment often depends on the method of preparation or measurement used (Jacques *et al*, 1987; Graaff *et al*, 1993; Pickering *et al*, 1993; Torres *et al*, 1994).

Clinical trials are perhaps the more traditional medical approach to the problem. Here a therapy is used on a small number of patients and the results observed. From these results the therapy is modified until the best results are obtained.

Histology allows a detailed examination of the physical effects of the treatment. By using combinations of light and electron microscopy changes in the skin can be observed, and related to the treatment parameters used.

More than 15 years of research has been conducted in this institution into the treatment of vascular lesions - in particular, port-wine stain birthmarks. The science that applies to the treatment of port-wine stains has been transferred to the other common vascular lesions - telangiectasia and spider naevus. We have used all three approaches to understanding the treatment of port-wine stains, and this thesis presents our work alongside work carried out in other places. We start with pre-laser (and non-specific laser) therapies, before discussing, in subsequent chapters, the development of current laser treatment protocols.

3.3 Non-Laser Treatments

Until the mid-1970s there existed no satisfactory treatment for large port-wine stains. Indeed Goldman *et al* (1976) regarded port-wine stains as *incurable*. Small lesions could be excised leaving only a small scar. Larger lesions were normally covered by dense theatrical make-up, or tattooed over with flesh coloured or white pigment. Several medical and surgical techniques were used to try to remove the blemishes, among them dermabrasion (whether performed by a surgeon or by the afflicted using an abrasive material such as pumice), skin grafts, radiotherapy, infra-red heating, ruby laser heating and cryotherapy. The histological result of these treatments is damage to normal tissue. This manifests cosmetically as scarring, and in the case of radiotherapy of a child's lesion, deformity of the underlying bone. The result was often no better than, or far worse than, the original lesion. Of these treatments, only excision, either total or serial, and grafting are commonly in use today. Infra-red heating is also occasionally used, using the "Infra-Red Coagulator" (Colver *et al*, 1986).

3.4 Non-Specific Laser Treatments

Early attempts at using lasers to treat port-wine stains followed the clinical trial methodology. It was clear that light, in particular the intense visible light produced by lasers, offered a possible selective treatment (Goldman *et al*, 1976; Noe *et al*, 1980). The lasers were tested on a number of patients, using a wide variety of treatment parameters. Often these early trials had high incidences of scarring and

abnormal post-treatment pigmentation. However, they did produce some progress towards a better treatment. One of the significant benefits was to identify issues that could be investigated using the modelling methodology. A brief summary of the main lasers trialled is presented below.

3.4.1 The Carbon Dioxide Laser

The carbon dioxide (CO_2) laser (wavelength 10600 nm) has been used for the treatment of a number of cutaneous blemishes. Currently it is popular for facial resurfacing and fine-line removal. In the past however, it was used to treat port-wine stains. This wavelength light is strongly absorbed into water. Since skin contains large amounts of water the CO_2 laser can be used to vaporise the skin down to the level of the ectatic vessels forming the lesion. Below this level there is minimal damage. Clinically, there is little difference between this and dermabrasion. Both result in complete epidermal and partial dermal necrosis (Buecker *et al*, 1984; Tan *et al*, 1986). For this to heal, the epidermis lining around deeper structures re-epithelializes the surface and new fibrous tissue forms in the dermis. Associated with this is a relatively high incidence of noticeable scarring. Figures from 8% (Ratz and Bailin, 1987) up to 30% (Olbricht *et al*, 1987) have been reported. There is also a high incidence of hypopigmentation caused by ablation of a fraction of the melanocytes in the tissue (Tan *et al*, 1986).

3.4.2 Nd:YAG Laser

The Nd:YAG laser has a wavelength of 1064 nm. The radiation is produced by neodymium ions doped into a crystal of yttrium aluminium garnet. Like the CO_2 laser, the Nd:YAG laser produces infra-red light but its shorter wavelength means that it is not well absorbed by water. This allows the light to penetrate the epidermis and upper dermis and so reach the blood vessels. Several trials were carried out using this laser (Landthaler *et al*, 1986; Rosenfeld and Sherman, 1986; Dixon and Gilbertson, 1986; Adams *et al*, 1987). All used long illumination times which, as we shall see later, allow significant conduction of heat away from the absorption site. This, in turn, leads to widespread damage to non-vascular tissue, and hence scarring and abnormal pigmentation. In addition to this the long wavelength is not well absorbed by HbO_2, so the absorption is not well localised to blood vessels.

The Nd:YAG laser has also been used "frequency-doubled" to a wavelength of 532 nm. This wavelength is much more strongly absorbed into haemoglobin. How-

ever, this is offset by the reduction in the power available as a result of the doubling process. The lower power output results in long illumination times being necessary to deliver enough energy to thermally necrose ectatic capillaries. Again long illumination times result in general coagulation necrosis, rather than selective thermal damage.

3.4.3 Photodynamic Therapy

One treatment that has shown some promise is photodynamic therapy (otherwise known as photochemotherapy). Here a photo-reactive chemical is applied to the lesion which is then illuminated with the appropriate light, often from a low powered laser. Very little has been published on this technique, but the published results are positive (Orenstein *et al*, 1990; Lin *et al*, 1997).

3.4.4 The Argon-Ion Laser

In 1976 use of the argon-ion laser for treatment of port-wine stains was first reported (Goldman *et al*, 1976). The argon-ion laser is a visible-light laser with a wavelength range of 488 to 514.5 nm. It has been used in both untuned and tuned modes, most often being tuned to 514.5 nm to minimise (for the main laser transition for this laser) the absorption into melanin.

The argon-ion laser was a popular choice until the mid-1980s and many clinical trials were carried out to study its effectiveness as a therapy for a range of vascular lesions. Because of the power densities available, and because the 514.5 nm wavelength is not well absorbed into oxy-haemoglobin (see section 4.1), long illumination times are needed to cause sufficient damage to blood vessels to render them non-viable (van Gemert *et al*, 1991). As with the Nd:YAG laser this leads to significant conduction of heat away from the vessels to dermal tissue. Histological studies showed superficial, non-specific thermal coagulation necrosis (Goldman *et al*, 1976), leading to scarring.

In addition to the low absorption into HbO_2, the 514.5 nm wavelength produces significant absorption into epidermal melanin. Too much heat deposited in the epidermis destroys it, leading to a variety of undesirable side-effects such as hypopigmentation, and atrophic scarring.

Nevertheless, the argon-ion laser can produce satisfactory results. Indeed, as late as 1996 argon laser treatment was still being reported (Trelles *et al*, 1996). Newer lasers have more power available to them. Coupled with an automatic scanner,

such as Hexascan^{TM}, shorter illumination times are achieved. This has significantly lowered the incidence of scarring (McDaniel and Mordon, 1990), but the problem of epidermal damage remains.

In 1982, plastic and reconstructive surgeon Mr E. Peter Walker approached the (then) Department of Physics, University of Canterbury, with a request to use their argon-ion laser to treat port-wine stain birthmarks – the first time such a treatment had been offered in New Zealand. Initially the department's involvement was limited to providing the laser, and some assistance in running the equipment. From 1982 to 1985 Mr Walker achieved some encouraging results particularly when the laser was tuned to 514.5 nm. Powers used at this wavelength varied between 1.5 and 2.5 W (van Halewyn, 1985).

The typical clinical endpoint used with argon-ion laser treatment is blanching, or whitening of the skin. Histologically this is identified with the coagulation necrosis noted earlier (Greenwald *et al*, 1981).

Chapter 4

Laser Treatment Parameters

In this chapter two mathematical models of the laser treatment of port-wine stains are examined. These models are used to calculate a range of optimal treatment parameters. The first use of the copper vapour laser for the treatment of port-wine stains is described.

4.1 The Calculations of Anderson and Parrish

In 1981 Anderson and Parrish published a series of calculations of treatment parameters (wavelength, illumination time, and fluence) that they claimed would maximise damage to vasculature and minimise damage to the surrounding connective tissue and overlying epidermis. This was the first attempt to use a model to quantify the treatment of vascular lesions.

Anderson and Parrish made a determination of the optimal wavelength for treatment of vascular lesions that

> *maximises optimal absorption and heating in a chosen "target chromophore" associated with vessels,* **relative to** *absorption occurring in the other dermal structures and in the overlying epidermis.* (emphasis theirs)

They identified HbO_2 as the target chromophore and regarded the melanin in the epidermis as a filter. They aimed to minimise the absorption into melanin while maximising absorption into HbO_2.

The epidermal melanin, along with the increased penetration into the dermis indicated the α (577 nm) absorption band of HbO_2 rather than the Soret (415 nm) or β (542 nm) bands (see figure 4.1).

The calculation of the optimal illumination time was based on the thermal diffusion equation. In cylindrical coordinates this is

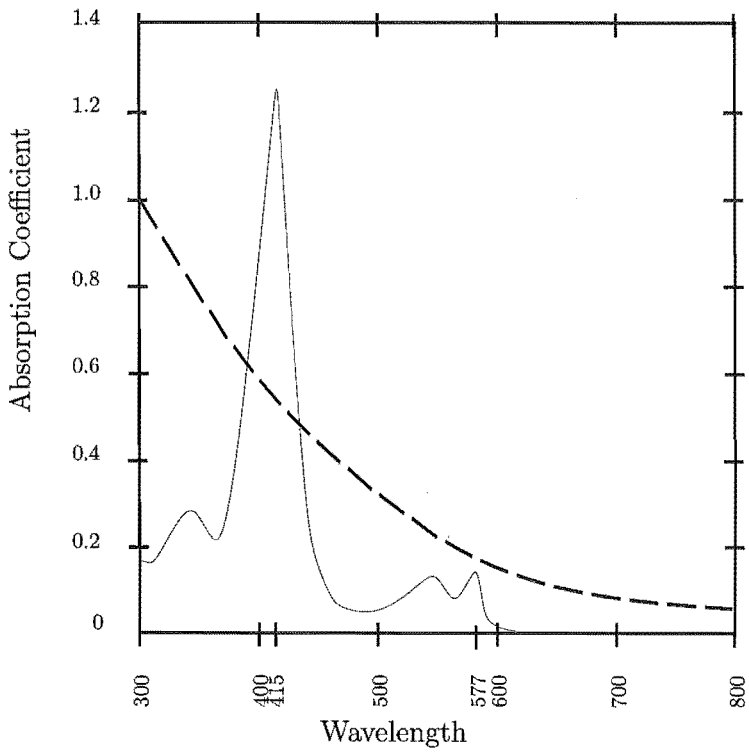

Figure 4.1: Absorption coefficient for melanin (dotted line) and oxy-haemoglobin (solid line).

$$\frac{\partial T(r,\vartheta,\tau)}{\partial \tau} = \frac{\Phi(r,\vartheta)}{\rho C_v} + \frac{\eta}{\rho C_v}\left[\frac{\partial^2 T(r,\vartheta,\tau)}{\partial r^2} + \frac{\partial T(r,\vartheta,\tau)}{r\partial r} + \frac{\partial^2 T(r,\vartheta,\tau)}{r^2 \partial \vartheta^2}\right] \quad (4.1)$$

The coordinates are centred on the vessel, with r being the distance from the origin, and the angle ϑ indicating a point on the circle of radius r. T is the temperature, and τ the time. The fraction $\frac{\eta}{\rho C_v}$ (where ρ, C_v, and η are the tissue density, heat capacity, and thermal conductivity respectively) they called the "thermal diffusivity", and labelled it α.

To calculate the illumination time, they made the assumption that the illumination time is very short, so that conduction of heat away from the target vessel during the illumination time can be ignored. They stated that the illumination time should be less than or equal to the thermal relaxation time – the time taken for the temperature at the centre of the vessel to fall from its peak to half way between the peak temperature and that of its surroundings. Since only cooling is being considered the source term, $\Phi(r,\vartheta)$, is zero. Furthermore, they assumed that the

temperature distribution within the vessel has rotational symmetry. This eliminates the dependence on ϑ. After these simplifications, equation 4.1 reduces to

$$\frac{\partial T(r,\tau)}{\partial \tau} = \alpha \left[\frac{\partial^2 T(r,\tau)}{\partial r^2} + \frac{\partial T(r,\tau)}{r \partial r} \right] \tag{4.2}$$

Their solution to equation 4.2 assumed a Gaussian temperature distribution in the tissue. Changing the time variables such that $t = 0$ at the initial temperature distribution gives the following solution.

$$T(r,t) = k_1 \left[\frac{4}{16\pi\alpha t + \pi d^2} \exp\left(\frac{-4r^2}{16\alpha t + d^2} \right) \right] + T_0 \tag{4.3}$$

In this solution k_1 is determined by the peak temperature in the vessel, and T_0 is the initial temperature of the surrounding skin. The diameter of the vascular lumen is d. After normalising the term in the square brackets, the thermal relaxation time t_r is given by

$$t_r = \frac{d^2}{16\alpha} \tag{4.4}$$

Using this Anderson and Parrish calculated the following table of illumination times for different vessel diameters.

d(μm)	t_r (ms)
10	0.048
20	0.19
50	1.2
100	4.8
200	19.0

Table 4.1: Thermal relaxation times for vessels of varying diameters (from Anderson and Parrish 1981b)

Anderson and Parrish concluded that illumination times less than 1 ms would give the most specific damage to microvasculature, but

> *for exposure durations on the order of 1 to 10 msec, it is possible for thermal damage to be specific for larger vessels, but to perhaps avoid or reduce damage to smaller vessels, which will transfer a significant amount of heat to the interstitial connective tissue* **during** *the exposure time.* (emphasis theirs) (Anderson and Parrish, 1981, p271)

This concept has been labelled "selective photothermolysis of ectatic vessels".

The conclusion quoted above is different from the abstract of the paper which implies that a time less than the thermal relaxation time (*"approximately 1 millisecond"*) is required to produce *"highly specific laser induced damage"*. Indeed, such an illumination time can produce highly specific damage for small (normal sized) capillaries, as their experiment using 0.3 μs on normal Caucasian skin showed. However damage to such small vessels is not the aim when treating port-wine stains.

Some clinicians and advocates (for example salespeople) of the pulsed dye laser have seized upon the abstract of this paper to support the idea that the short illumination times that are provided by pulsed dye lasers are required to give satisfactory treatments. This support is accompanied occasionally by a statement to the effect that continuous wave lasers cannot give these illumination times and are therefore inadequate for port-wine stain treatment. We shall see in the following chapter that this is not the case. Our modelling, and recent clinical evidence from pulsed dye lasers is strongly in favour of illumination times of 2-5 ms, a range consistent with the 1 to 10 ms for selective damage of ectatic vessels advocated by Anderson and Parrish.

4.2 The Copper Vapour Laser

In 1985 my thesis advisor, Professor Phil Butler, and an undergraduate student Mr Chris van Halewyn began to look closely at the treatment performed by Mr Walker. Following the work of Anderson and Parrish they realised that obtaining light near the 577 nm absorption peak of HbO_2 with sufficient power to obtain satisfactory clinical results meant moving away from using the argon-ion laser. It was decided to take advantage of recent developments in metal-vapour laser technology and purchase a copper vapour laser.

A Quentron^{TM} QM90-51C copper vapour laser was purchased from Adelaide, Australia. This was the first medical version of the copper vapour laser in the world. The copper vapour laser is a quasi-continuous wave device producing a train of typically 50 ns pulses of yellow (578 nm) and green (511 nm) light. As purchased the laser used a stable resonator (flat-flat) configuration producing in excess of 20 W of yellow and green at a pulse repetition frequency of 12 kHz. The green (511 nm) light was filtered out and the remaining 8 W of yellow 578 nm light was coupled into a hand held optical fibre and manually scanned across the lesion (see figure 4.2). Care was taken to place the scan lines parallel to the Lines of Langer. This minimises the unevenness which was often noticed after the first treatment. The

laser was used in this manner until 1990.

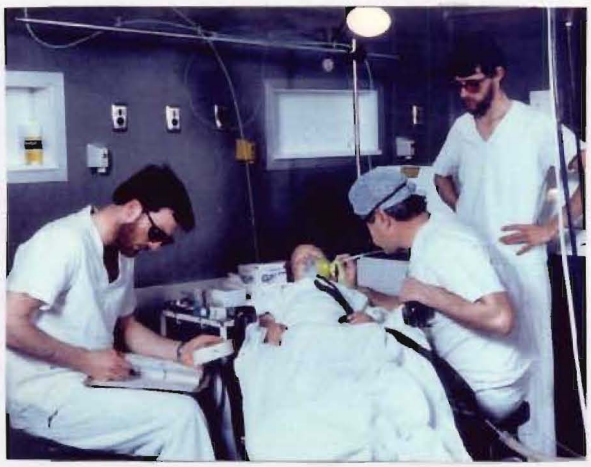

Figure 4.2: Mr Peter Walker using the copper vapour laser with a hand-held optical fibre. Chris van Halewyn records the time taken to treat an area and records this on a map of the lesion. John Pickering looks on.

As with argon-ion laser treatment the clinical endpoint used was minimal blanching of the lesion. For this endpoint the blanching lasts for several minutes (up to an hour) after illumination.

Histological studies were used to investigate the cause of the blanching. (Walker *et al*, 1989). Patients treated with this protocol (60-90 ms, 1.6-3.6 W) showed selective vascular damage with only minimal damage to dermal collagen and adnexal structures. Pickering (1990) attributed the blanching to the protein surrounding the blood vessels becoming opaque, in the manner of egg white when heated.

In 1990 Pickering *et al* conducted a survey of 242 patients treated with the copper vapour laser. The patients had received treatment for port-wine stain, telangiectasia, and spider naevus. The survey, along with observations recorded in the treatment clinic, showed scarring rates (where a scar was defined as any persistent hypertrophic or atrophic mark of any size) of 3.5% per patient, and persistent hyperpigmentation and hypopigmentation rates were 1.4% each. The questionnaire was based on that of Dixon *et al* (1984b) who surveyed patients who had received argon-ion laser treatment. The adverse effect rates for the copper vapour laser treatment were lower than the 5-30% for argon-ion laser treatments (Cosman, 1980; Dixon *et al*, 1984b; Apfelberg *et al*, 1987). The patients' views on the copper vapour laser treatment were very positive. 84% of port-wine stain, 74% of telangiectasia and 81% of spider

naevus patients thought that there had been an improvement in their appearance. Of the port-wine stain patients, 91% said that they would recommend the treatment to others, 84% would have the treatment again, and 60% said that the overall effect of the treatment on their lives was very good.

As part of the clinical observations, Pickering *et al* (1990a) determined that when higher powers allowed the illumination times to be shorter, consistently greater colour changes occurred. This added evidence to support the need for illumination times to be close to, or less than, the thermal relaxation times calculated by Anderson and Parrish. Pickering *et al* (1989a) constructed a theoretical model which allowed them to calculate from a different set of assumptions the optimal treatment parameters.

4.3 The Assumptions of Anderson and Parrish

The oft quoted "optimal parameters"of Anderson and Parrish of 577 nm, and 1-10 ms are often misunderstood. They have been used as hard and fast rules to determine the success or failure of a proposed or even current treatment. Rather they should be regarded as a guide to the appropriate parameters needed for the lesion of a given patient. The "optimal parameters" are really estimates of "optimal ranges" rather than fixed numbers. Even a quick glance at the absorption spectrum of HbO_2 shows that the α band is quite broad. Little absorption is lost within 3-4 nm either side of the 577 nm peak.

Similarly the 1-10 ms illumination times are based on the thermal decay times of a large range of vessel diameters. The relationship between thermal decay times and satisfactory treatment is not yet well understood.

Furthermore, the thermal decay calculations themselves are not a complete solution to the optimisation problem. Some of the approximations that were made to carry out the calculations are not sufficiently accurate.

Anderson and Parrish's calculations of illumination times and fluence are based on raising the temperature of the blood inside the vessel to greater than 70 °C. In fact, heating of the vessel wall to the point of thermal necrosis is the true goal of the treatment. The treatment will not be successful if insufficient thermal damage is done to the endothelial cells, irrespective of the temperature of the blood within the vessel. The calculations of Smithies (1995) showed that using Anderson and Parrish's illumination times and fluences does not raise the temperature of the vessel wall to greater than 70 °C. The question arose as to whether this temperature was in fact

as critical as Anderson and Parrish supposed.

Nilsson *et al* (1997) heated blood passing through a flow chamber and measured the scattering of light from the blood as a function of temperature. They observed that at 45-46 °C the amount of scattered light increased slightly. A white-light transmission microscope was used to observe the red blood cells throughout the heating. At the same 45-46 °C region the blood cells changed in shape from bi-concave discs to spheroids. The temperature range used by Nilsson *et al* (1997) was 25-55 °C. The rate of heating was 0.2-1.1 °C /min. Therefore this research does not investigate temperatures around the presumed critical temperature for port-wine stain treatment of 70 °C.

Nilsson *et al* (1997) also found that the absorption coefficient of blood increases by a factor of 1.9 between 25-55 °C. This was also observed by Verkruysse *et al* (1998). Both of these papers conclude that the optical properties of blood are temperature dependent, but neither explored the 70 °C region, nor worked with endothelial cells rather than red blood cells.

Experimental methods for determining the critical temperature at which the protein within the endothelial cells denatures are difficult to interpret in the context of the rapid heating and small tissue volumes involved in laser treatment. Typically the experimental methods use larger samples and longer, slower, heating methods. To further complicate the interpretation the experiments are done *in vitro*. It is not clear whether results gathered from such experiments are applicable to laser treatments.

Pickering used the damage integral of Henriques (1947) to determine the temperature at which irreversible necrosis occurs for a 50 μm diameter vessel. The integral is

$$\Omega = P \int_0^t \exp\left(-\frac{\Delta E}{RT}\right) dt \tag{4.5}$$

Where

Ω	is an arbitrary function describing tissue injury
T	is the time dependent temperature in K
R	is the universal gas constant
P and ΔE	are experimentally determined pre-exponential constant and experimental activation energy constant respectively

Pickering found that for illumination times between 0.45 ms and 30 ms irreversible necrosis occurs to endothelial cells between 68 and 72 °C. This supports the criteria used by Anderson and Parrish, but unfortunately the treatment parameters

they calculated did not satisfy it. It should be noted that Henriques' damage integral, although based on the standard theory of chemical reaction rates, requires an extrapolation from heating over perhaps hundreds of milliseconds to shorter times.

A difficulty with the damage condition (that the illumination time must be less than or equal to the thermal relaxation time) taken by Anderson and Parrish is that their calculation showed that for vessels larger than 50 μm diameter the thermal relaxation time is longer than 1 ms. If the illumination time is about 1 ms, or longer, then the effects of thermal conduction away from the vessels cannot be ignored, as conduction lowers the peak temperature of the vessel and its walls. The assumption of no conduction was included to simplify the model. Anderson and Parrish's statements have been interpreted incorrectly in the subsequent literature, by assuming as fact that there is insignificant conduction during the illumination time. We shall see in section 4.4 that this is not the case. Indeed, the definition of the thermal relaxation time of a body assumes that there *is* significant conduction of heat away from the body, since the temperature lowers by 50% in this time.

Further, the Anderson and Parrish calculation depends on the arbitrary choice of a 50% reduction on the temperature for the thermal relaxation time. There is no reason that a "half-life" measure should be used rather than, say, a $\frac{1}{e}$ measure of the thermal decay. This may be a good "rule of thumb" (Pickering, 1990) but it should not be used as a necessary condition. It does not guarantee that there will be sufficient heat conducted from the blood to the vessel walls.

4.4 Pickering's Model

Between 1986 and 1990 Pickering *et al* addressed several of the assumptions of Anderson and Parrish by seeking a better solution to the thermal processes. This numerical model of the heating of individual blood vessels in the skin (Pickering *et al*, 1989a,b; Pickering, 1990) gave a sharper definition of the treatment parameters that lead to the coagulation of the endothelial cells.

The Pickering model assumes that if there is negligible scattering of light in the skin, the transfer equation for the intensity of light at a depth x of blood can be reduced to

$$I = I_0 e^{-\alpha x} \tag{4.6}$$

where I_0 is the intensity of the light incident on the surface of the skin and α is the absorption coefficient of blood. Pickering considered an endothelial cell thickness

of 6 μm and required that the endothelial cells at the top of the vessel reach a temperature of 70 °C. This condition was justified by the observation of the tendency for endothelial cells to wrap around vessels. The peak temperature within the vessel was constrained to 100 °C, as exceeding this temperature would cause vaporisation of the blood and mechanical rupture of the blood vessel. This would be seen as haemorrhaging which is not observed histologically when blanching is the clinical endpoint. The skin model was a 65 μm thick epidermis, and a single vessel located 300 μm in to a dermis at a temperature of 35 °C. Vessel diameters of between 30 and 100 μm were used.

The equation was solved using a finite difference method. Temperature profiles were calculated for a vessel cross-section at times during and after the illumination. The results are shown in table 4.2 and are taken from Pickering *et al* (1989a).

Vessel diameter (μm)	Fluence (J/cm^2)	Illumination time (ms)
30	6.3-8.8	5.9
50	4.1-5.7	5.5
80	2.9-4.1	5.0
100	2.8-3.9	5.0

Table 4.2: The results of Pickering's model. The variation in the values of the fluence are cause by allowing for a 30-50% variation in the absorption of light between the skin surface and the blood vessel.

In figures 4.3 and 4.4 we have the profiles for an 80 μm diameter vessel. Figure 4.3 is the temperature distribution immediately after the 5.5 ms illumination time. Here the treatment parameters modelled raised the temperature at a point 6 μm above the vessel lumen to 70 °C. Apart from showing this, there is not much insight gained from this figure. However, by taking a vertical cross-section and looking at the time evolution gives figure 4.4. This shows that the top surface of the endothelial cells reach the coagulation temperature just at the end of the illumination time. At no time does the peak blood temperature go above 100 °C – the vaporisation point. The temperatures well away from the vessel are well below the coagulation temperature.

In this figure it is possible to see the rapid increase of the central temperature and the much slower cooling after the illumination has ended. Note the higher temperature above the blood vessel throughout the heating and cooling processes. This illustrates the departure of this model from the two-dimensional Gaussian profile assumed by Anderson and Parrish.

We can also see from this figure that there is significant conduction occurring during the illumination time. Even using the 1.2 ms thermal relaxation time calculated by Anderson and Parrish, we can see the propagation of the temperature profile away from the blood vessel. Pickering has showed here that in fact 5.5 ms of illumination is necessary to raise the endothelial cell temperature to 70 °C without causing damage to surrounding tissue. In 5.5 ms, thermal conduction has very significant effects.

As can be seen from table 4.2 the dependence of the optimal illumination time on vessel diameter is not strong. Most port-wine stain sized vessels require 5.0-5.9 ms illumination times.

With the manual scanning treatment protocol used with the copper vapour laser at the time, illumination times of 5-6 ms were impossible to achieve while maintaining the accuracy of the scan lines. Even when concentrating on accurately scanning the lesion, some areas were left untreated, in particular the region left between the scan lines to minimise the risk of overlap. Other regions would receive too much energy. This was particularly noticeable at the edge of the lesion where the surgeon would slow down to reverse the direction of the scan. This resulted in blanching that was too severe. Patients routinely had severe blistering and crusting post-treatment. This required careful management to avoid infection, and occasional formation of scar tissue.

Pickering *et al* (1990a) also noted that spongy/salmon-pink port-wine stains gave the poorest cosmetic results. They observed that these lesions tended to blanch quickly and in some cases it was impossible to achieve the minimal blanching endpoint. This they attributed, following Ratz and Bailin (1987), to pink port-wine stains having faster flowing blood. This would provide a less effective target for the light.

They also noted that fewer adverse effects occurred with higher powers from the laser. Higher laser power allowed them to use shorter illumination times. This resulted in the thermal damage being more confined to the region of the vessel.

Despite these concerns the copper vapour laser with manual scanning produced very satisfactory treatments for the patients. For the first time in New Zealand a treatment was available which could improve or even remove port-wine stains without a high risk of unsightly scarring. Approximately 250 patients received this treatment between 1986 and 1991.

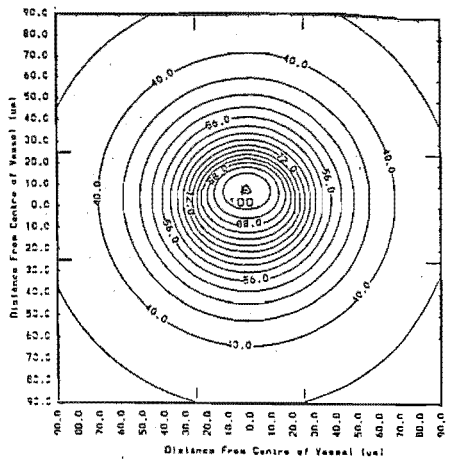

Figure 4.3: Thermal profile after 5.5 ms illumination. The temperature 6 μm above the lumen is 70 °C

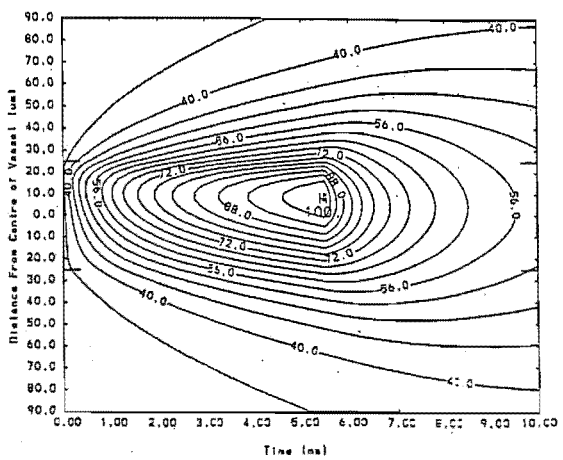

Figure 4.4: Time dependent thermal profile. The peak temperature at the top of the endothelial cells is 70 °C, and at the centre of the vessel is 100 °C

Chapter 5

Laser Treatment in the 1990s

In this chapter the laser treatment of vascular lesions in the 1990s is reviewed. The automated scanning system, SCANALL, is described and compared with pulsed dye laser treatments. The treatment protocol developed as part of this thesis, double scanning with transient blanching, is presented. The causes of different types of blanching are examined.

5.1 Scanners

In 1985 van Halewyn and Butler developed a prototype automated scanner for use with the argon-ion laser at the University of Canterbury. The scanner was designed to *replicate the surgeon's skill, and then to improve upon it* (van Halewyn, 1985). Unfortunately in tests the scanner gave uneven line spacing, due to backlash in the gearing. Apart from a very limited trial this scanner was never used routinely in the clinic.

In 1988, Rotteleur *et al* (1988) described Hexascan^{TM}. This is a handpiece containing an optical fibre which can be moved to 127 different locations within a hexagon. At the time this was connected to an argon-ion laser, and illumination times between 30 ms and 60 ms were used.

In 1990, Chambers *et al* (1990) described CC-Scan, a similar device to Hexascan^{TM} but with the outline being square. Either Hexascan^{TM} or CC-Scan allow tessellation of the treated areas, giving no overlap while ensuring that the entire lesion has been treated.

Butler and van Halewyn (1988) patented in the U.S.A. a device for moving a mirror in a controlled manner while being observed by a CCD camera looking along the laser beam. This allowed laser light incident on the mirror to be moved rapidly across a lesion. The mirror was moved by two stepper motors with a worm drive on

their outputs resulting in rotation about two perpendicular axes. The motion of this scanning mirror was controlled by a program written for an Apple IIe computer.

In 1990, SCANALL was first used clinically (Smithies *et al*, 1991). SCANALL is a development of the scanner built by van Halewyn and Butler. Again there is a single rotatable mirror under computer control. The rotation of the mirror about two perpendicular axes moves the laser spot on the patient. The development of SCANALL allowed the trial of illumination times within the modelled optimal range of 1-10 ms. It incorporated a CCD camera for outlining the area to be treated as described in the patent, but used a different optical arrangement that avoided the use of a dichroic mirror.

5.1.1 SCANALL

In this subsection a detailed description of SCANALL and its use are provided. This device is a critical component of the treatment protocol used at St George's Hospital for the last ten years.

The SCANALL automated treatment device has two critical innovations which make it a successful clinical device. The first is the motorised scanning mirror, the second is the software which drives it. The scanning system is mounted on a rotatable optical bench. An Amiga 2000 computer provides the control and is interfaced with a video camera.

The movement of the scanning mirror is controlled by two linear stepper motors connected to it via universal joints. The mirror is mounted in such a way that it pivots about a point on its front surface. This design reduced the unevenness noted with the earlier version of the scanner. The even scan allows an even distribution of energy over the surface of the lesion.

Figure 5.1 is a photograph of a port-wine stain that has been treated with a manually guided optical fibre. As can be seen the edges of the lesion have been overtreated (indicated by excessive blanching) while there are significant gaps between the scan lines. This is typical of such treatments.

Figure 5.2 shows another lesion immediately after treatment with the SCANALL system. Here the edges receive the same dose as the rest of the lesion. The gap between scan lines is very small. In section 5.5.1 a modification to the treatment protocol is discussed which further minimises the effects of these untreated lines.

The software which controls the motion of the scanner mirror was written initially by Butler. This was modified by Bernie Mentink to allow the surgeon to enter the

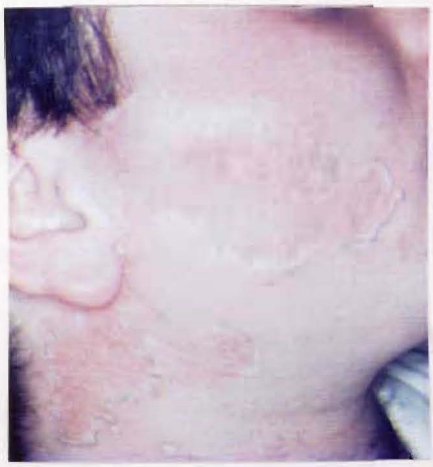

Figure 5.1: A port-wine stain after treatment with the copper vapour laser and a hand-held optical fibre. The lesion is over-treated around the perimeter where the surgeon reversed the direction of the treatment lines.

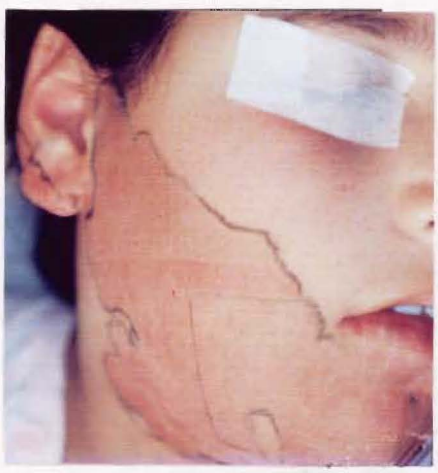

Figure 5.2: A port-wine stain after treatment with the SCANALL system. The treatment lines are evenly spaced and there is no over-treating at the perimeter.

outline of the region to be treated, treat the region, and have the computer store information about the patient and the treatment. After clinical testing showed that the system gave excellent clinical results, the software was re-written by Derek Smithies to make the interface more "user-friendly".

In figure 5.3 the optical system of SCANALL is shown. The lens, scanning mirror, stepper motors, camera system and fluorescent light are all situated on an optical bench mounted on the end of the copper vapour laser. The collimated laser beam passes out through the laser cabinet and onto a mirror mounted at the bottom of a hollow pillar. This mirror (the pillar mirror) reflects the beam to the top of the pillar where it is reflected into the horizontal plane by another mirror. The beam then passes through a lens (focal length 800 mm) and from there onto the scanner mirror. The scanner mirror reflects the beam downwards onto the lesion to be treated. The scanner arm (optical bench) can be rotated about the top of the pillar and also extended away from the pillar. The extension occurs before the lens so the focal point of the beam is not affected. The rotation and extension of the scanner aid the surgeon in manoeuvering the system into the correct orientation for treating the lesion.

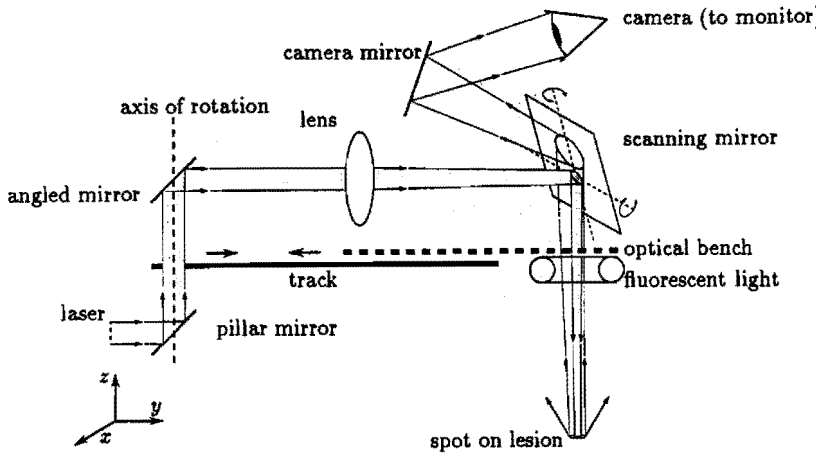

Figure 5.3: The layout of the optical system used in SCANALL.

5.1.2 The Treatment Protocol, 1990 - 1994

The copper vapour laser is situated at St George's Hospital in Christchurch. From 1986 - 1992 the laser was used in a converted recovery room. With the opening of the Day Surgery Unit in 1992 the laser was moved into an operating theatre.

Much of the current protocol is identical to that presented here. The modifications are discussed in section 5.5.1.

After pre-treatment photographs the patient lies on an adjustable bed beneath the scanner arm. The patient is then anaesthetised. For extensive lesions a general anaesthetic is administered (as in figure 5.4). Care must be taken that any general anaesthetic is not a vaso-constrictor (such as sevoflurane) as this will reduce the effectiveness of the treatment. For smaller lesions, particularly in adults, local anaesthetic is preferred. The local anaesthetic used is 2% plain Xylocaine (lignocaine hydrochloride B.P. 2.13%, Astra Pharmaceuticals) given by block anaesthesia or local infiltration. Plain Xylocaine has a mild vaso-dilating effect which increases blood flow to the region thus increasing the available "target". Anaesthesia is important since the patient must be still during treatment so that the scan lines are even and the mapping of the lesion to the motion of the scanning mirror is maintained.

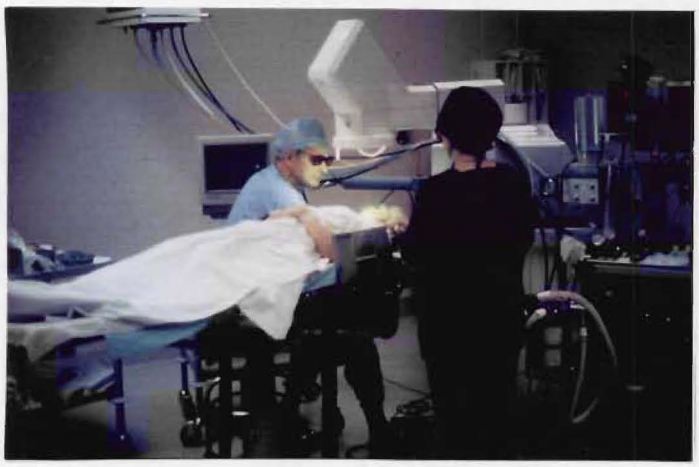

Figure 5.4: SCANALL in use at St George's Hospital. At left is plastic and reconstructive surgeon Mr E. Peter Walker, at right is anaesthetist Dr Susie Newton.

Once the patient is anaesthetised the bed is raised so that the lesion is at the focal point of the laser beam. This point is indicated by a "plumb-bob" suspended from the scanner arm. Care is taken to ensure the area to be treated is near horizontal to maximise both the amount of light penetrating the skin and the penetration depth. The lesion is positioned so that the scan lines will lie along the Lines of Langer.

Normally the surgeon will outline the lesion with ink to make it more visible when displayed by the video camera on the computer monitor. The margin of the lesion is then mapped using the computer's mouse. Once the outline is completed the program determines the best way of filling the outline using a raster-scan pattern.

The treatment is then started. A foot-switch is pressed which operates the laser shutters allowing the beam to enter the SCANALL optical system. The foot-switch also activates the motion of the scanner mirror. If for any reason the surgeon wishes to halt the treatment, releasing the foot-switch closes the shutter and pauses the scanner motion.

From 1991 - 1994 the clinical end point was minimal blanching. The illumination time was adjusted to produce this. For most lesions this was in the range 4.5 - 6 ms for 5 W incident 578 nm light.

The treatment process is repeated on different parts of the lesion until the entire lesion has been treated. The lesion is then dressed with soothing Brulidine® cream (dibromopropamidine isethionate B.P. 1.5 mg/g) and gauze.

No quantitative study was done at the time into the comparative effectiveness of the SCANALL system and manual scanning. As part of this thesis project a follow-up clinic and survey were conducted to accomplish this. The survey and its results are presented in chapter 7. However, both the surgeon and the patients have made some observations about the treatment with the SCANALL system.

Patients who received both manual scanning and SCANALL (minimal blanching protocol) treatments to their lesions reported that the amount of post-treatment blistering and crusting was significantly less with the SCANALL system. This indicates less damage to non-vascular tissue as a result of using illumination times closer to the optimal value for a given vessel size.

From the surgeon's perspective the SCANALL system has made the treatment much less tedious. Manual scanning using an optical fibre was fatiguing, since the fibre needed to be moved as rapidly and accurately as possible whilst maintaining a constant height above the skin.

SCANALL also made precise control of the illumination time possible. Small adjustments to the illumination time can be made during a scan, allowing the thermal damage to the tissue to be increased or decreased to meet the desired blanching end-point.

The evenness of the result is far greater than can be achieved with the optical fibre. There are only very narrow untreated lines and the margin of the lesion is not over-treated.

However, under the minimal blanching protocol the slow response of spongy/salmon-pink lesions still persisted. Frequently minimal blanching was not obtainable on these lesions. The rate of cosmetic improvement was still slow. The danger in

taking a more aggressive approach to the treatment of such lesions (using longer illumination times causing stronger blanching) is the increased risk of causing persistent scarring and/or abnormal pigmentation.

5.2 Pulsed Dye Lasers

5.2.1 Short Pulses

While SCANALL was being developed in New Zealand other researchers and clinicians were using flash-lamp pumped pulsed dye lasers for the treatment of vascular lesions. Anderson and Parrish (1981) tested their theoretical results using 0.3 μs, 300mJ pulses of 577 nm light. They illuminated normal skin on the volar forearms of 10 subjects. The illuminated sites were observed immediately, after 24, and 48 hours post-treatment. Punch biopsies were taken from the treated sites.

The histologies showed a range of thermal and mechanical damage. Immediately after treatment with 2-3 J/cm^2 the damage was confined to the superficial vasculature. They observed rupture and haemorrhage of affected blood vessels, which they attributed to steam formation in the vessels. At 48 hours, some endothelial cells were necrotic, though others had apparently reconstituted. At this stage the haemorrhage was less severe than immediately post-treatment.

At 3 J/cm^2 occasional focal epithelial necrosis and basal cell vacuolisation was observed. Above 3 J/cm^2 damage was observed to non-vascular tissue. At 5 J/cm^2 full thickness epidermal necrosis and sub-epithelial blister formation occurred.

Clinically their results ranged from no response (less than 1 J/cm^2) through purpura formation (2-3 J/cm^2) and "opalescence" of the epidermis (greater than 5 J/cm^2). The purpura formation corresponds to the vessel rupture and haemorrhage observed histologically. This is consistent with the traditional definition of purpura (Miller and Keane, 1987) as extravasation of erythrocytes. We shall see later that the use of this term has been extended to include an intravasular coagulum. This has caused some confusion in the literature.

Hulsbergen-Henning *et al* (1984) used 1 μs pulses of 577 nm light to treat light-coloured port-wine stains on five patients. Fluences of between 0.5 and 3 J/cm^2 were used, with punch biopsies being taken 48 hours after illumination. About 1 minute after the illumination a red-brown spot appeared at the treatment site. This faded away in about 4 weeks. There was no long term cosmetic change to the port-wine stains as a result of the laser illumination.

Histologically, there was no epidermal damage, save for a sub-epidermal blis-

ter in a heavily pigmented patient. There was erythrocyte extravasation to a depth of 0.9 mm but the endothelial cells were intact. Like Anderson and Parrish, Hulsbergen-Henning *et al* (1984) attributed the extravasation to rupture of the endothelium caused by steam formation in the the vessel. The absence of visible tearing in the histology indicates that healing of the endothelium had occurred within 48 hours. There was no indication of thermal necrosis of the vessels.

This study shows the need for more than just mechanical damage to ectatic capillaries. Hulsbergen-Henning *et al* (1984) say

> *"in order to cause obliteration of blood vessels it seems necessary to get a rather massive vessel wall coagulation effect. ... The present opinion is that a complete "cooking" of the whole capillary cross section is a prerequisite for clinical bleaching. Most likely this requires millisecond (instead of microsecond) laser pulses."*

These results illustrate the insufficiency of using the thermal relaxation time as the sole damage criteria. Both of these studies used pulses far shorter than the 48 μs calculated for 10 μm vessels (approximately the size of normal superfical vessels). Neither produced sufficient damage to cause cosmetic improvement.

By 1986 results of experiments using longer pulses were being published. Garden *et al* (1986) used 20 μs and 56 μs pulses of 577 nm light. There was less microvascular rupture and haemorrhage observed, and also an increase in the fluence required to produce purpura. They also used 350 μs pulses to illuminate normal skin on the volar forearms of Caucasian patients. At fluences of 4 J/cm^2 the illuminated skin turned purple in colour, which they called purpura. Histologically there was an intravascular coagulum rather than erythrocyte extravasation.

Morelli *et al* (1986) used 300 μs pulses of 577 nm light. With fluences of 6.5-10 J/cm^2 illuminated skin turned a blue-grey colour within minutes. Their histology showed that within the blood vessels there were agglutinated erythrocytes, and thrombosis of fibrin and platelets extending well into the dermis. Some necrosis of endothelial cells was observed, in proportion to the amount of agglutination. There was some oedema present around damaged vessels.

Tan *et al* (1986) observed that vessels treated with these longer pulses are thermally necrosed. Within a few days of illumination the dermis returns to normal, with the ectatic vessels replaced by normal vessels. This produces a reduction in the severity of the lesion.

5.2.2 Purpura?

The use of the term purpura to refer to both extravascular and intravascular coagula is a cause of some confusion in the literature. It obscures the evidence that to cause optimal improvement, endothelial cells need to be necrosed rather than just mechanically ruptured. Some workers (Bandoh *et al*, 1990, for example) persisted with short pulse pulsed dye lasers for several years after it was well established that longer pulses are necessary. As a result, a large proportion of their patients (up to 19%) show unsatisfactory or no improvement. This is in comparison with the nearer 100% success rates of those who use longer pulses (Tan *et al*, 1989a; Sheehan-Dare and Cotterill, 1994).

5.2.3 Long Pulses

Since the early 1990s, 450 μs has been the standard pulse length used by most clinicians who use pulsed dye lasers (Ashinoff and Geronemus, 1991; Fitzpatrick *et al*, 1994, for example). This pulse length, when combined with 577 nm or, more recently, 585 nm light has been called "the treatment of choice" (Tan and Stafford, 1992; Alster, 1996) for port-wine stain treatment. Wavelengths away from the 577 nm absorption peak are used to give more even absorption across the treated blood vessel, allowing the bottom of the vessel to be thermally necrosed (Tan *et al*, 1990b; Smithies and Butler, 1995). The standard spot size is 5 mm.

5.2.4 Pulsed Dye Laser Protocols

Many patients are treated without any anaesthesia. The sensation of the treatment has been described variously as being like a rubber band being snapped against the skin, or the intense pain of a hot rod being pressed against the skin (Masciarelli, 1992). The tenderness remains from 1 hour to 24 hours post-treatment.

The area of the lesion is covered in a point-wise manner, with the hand-piece needing to be moved between spots. The pulse repetition frequency is determined by the recovery rate of the device, and also the preference of the user.

Both the discomfort experienced by the patient and the point-wise treatment method limit the area that can be treated in one session. If the lesion being treated is extensive, then multiple sessions may be required to treat the entire area. Masciarelli reports attending the laser clinic for as many as seven consecutive weekends.

Since the laser spot is circular, it is not possible to tessellate the treated area. This leaves areas of untreated lesion in between the treated circles. As well as leav-

ing a lattice-like pattern on the post-operative skin it necessitates further treatment to cover the entire lesion. Various schemes for "overlap" have been used to attempt to optimise the clinical results. Overlap amounts have been varied from "minimal" (Tan *et al*, 1989b) to as much as 33% (Reyes and Geronemus, 1990), though it is sometimes unclear whether the percentage refers to beam diameter or area (Kauvar and Geronemus, 1995, for example report an "approximate spot overlap of 10%"). Dinehart *et al* (1994) calculated that 13% diameter overlap provides complete coverage with the least amount of overlap. Their clinical test of this protocol showed no difference in the rate of adverse effects from a non-overlapping protocol. Cosmetically the lattice-like pattern still appears, but it is less obvious than with no overlap.

Verkruysse *et al* (2000) modelled the change in temperature of a blood vessel surrounded by a ring of other blood vessels. They showed that although the central vessel has a lower temperature increase than the ring vessels after a single laser pulse, it also cools more slowly due to thermal conduction from the surrounding vessels. Therefore using a series of pulses (separated by approximately 1 second) causes the temperature in the central vessel to rise more rapidly as opposed to the outer vessels. They note that a similar effect could be caused by pre-heating the dermis with (for example) a Nd:YAG laser. In either case cooling will need to be applied to the epidermis if ulceration is not to occur after such a treatment (Dierickx *et al*, 1995b). We further explore the idea of multiple illuminations during one treatment session in section 5.5.1.

Pre-cooling lesions was first examined by Gilchrist *et al* (1982) who used ice to cool skin prior to argon laser treatment. In recent years, Nelson *et al* (1995) experimented with using a short (20-80 ms) cryogen spurt after illumination with a 450 μs pulse from a pulsed dye laser. The short duration of the pulse was used to confine the cooling to the epidermis. They found that no surface textural changes occurred on the cooled test sites, compared with epidermal necrosis on the uncooled control sites. Six months after treatment the port-wine stain had lightened, indicating that the cooling did not inhibit photothermolysis.

Waldorf *et al* (1997) used a cryogen spray prior to laser illumination. They found that this protocol significantly reduced the pain associated with the treatment without reducing its effectiveness. In most cases the pre-cooling prevented epidermal damage or pigmentation change. Fader and Sax (2000) also reported significant reduction in pain levels due to dynamic cooling prior to treatment. Despite using

10% to 20% higher fluences than normal, almost a 90% reduction in postoperative morphine administration was noted. Postoperative purpura was also less pronounced and resolved more quickly. Pre-cooling needs to be done with care, as White *et al* (1999) reports laser ignition of a cryogen spray used for local anaesthesia.

The clinical results obtained using pulsed dye lasers with 450 μs pulses of 585 nm light are reported by van der Horst *et al* (1998). They follow up 89 patients below the age of 30 and assess the results of their treatments. They report that after an average of five treatments the average reduction of the difference in colour between port-wine stain skin and adjacent normal skin was 40% regardless of the age of the patient. In no patient did this difference reach 0%. Some patients required as many as 25 treatments to obtain the best possible clearance. The best results were on small port-wine stains or superficial lesions with large ectatic vessels. Only 7 of the 89 patients completed treatment during the period of the study. All 7 discontinued because no further clearance had been achieved in 3 consecutive treatments. Four of them described the level of clearance as adequate. The remaining three had incomplete clearance of the port-wine stain after 5-7 treatments.

There was no significant difference in the clearance rates in children an older patients. This calls into question the belief that treating younger children is more efficient than waiting until they are older and conscious of their lesion.

General anaesthesia was used for 16 of 45 children in the study. Without this fewer pulses could be delivered per visit, requiring more visits to completely treat a lesion.

After treatment the patients reported a blue discolouration (purpura) of the skin lasting for 7 to 10 days. This was accompanied by small blisters and crusting. In no case did this result in scarring or infection.

5.2.5 The Need for Longer Pulses

Despite the modelling of Anderson and Parrish (1981) who calculated 1-10 ms as the optimal range of illumination times for port-wine stain treatment, no pulsed dye laser was capable of producing a pulse within that range until very recently. Dierickx *et al* (1995a) states that

> *this exposure time domain is not achieved by any of the lasers currently used to treat PWS.*

This overlooks the use of the copper vapour laser combined with the SCANALL system, which has been in use since 1990.

De Boer *et al* (1996) suggested that pulses longer than 1 ms allow vessels up to approximately 20 μm in diameter to survive laser treatment. This supports the conclusions of Anderson and Parrish (1981) that choosing an appropriate pulse length will allow normal capilliaries to survive while damaging ectatic vessels. De Boer *et al* (1996) suggest that the presence of many small blood vessels may explain the poor response of some patients to laser treatment. They also propose that such patients should be treated with shorter pulses.

By 2000, at least two pulsed dye lasers (Cynosure, Chelmsford, MA, USA; and Candela, Natick, MA, USA) had been developed that allowed the use of 1.5 ms pulses for leg telangiectasia and port-wine stain. The use of these devices is reported in Dover (2000), Geronemus and Quitana (2000), and Buscher *et al* (2000). Dover found that facial blood vessels that were unresponsive to 450 μs pulses were responsive to the 1.5 ms pulses. He notes, however, that *1.5 msec is still shorter than the ideal pulse duration to treat all but the smallest cutaneous vessels.*

5.3 More Modelling

In 1995 Smithies *et al* (Smithies and Butler, 1995) published the results of a model of the distribution of the laser light absorbed within port-wine stained skin. The model was implemented using Monte Carlo techniques and used a skin model that was much more complex that had been used before (figure 5.5).

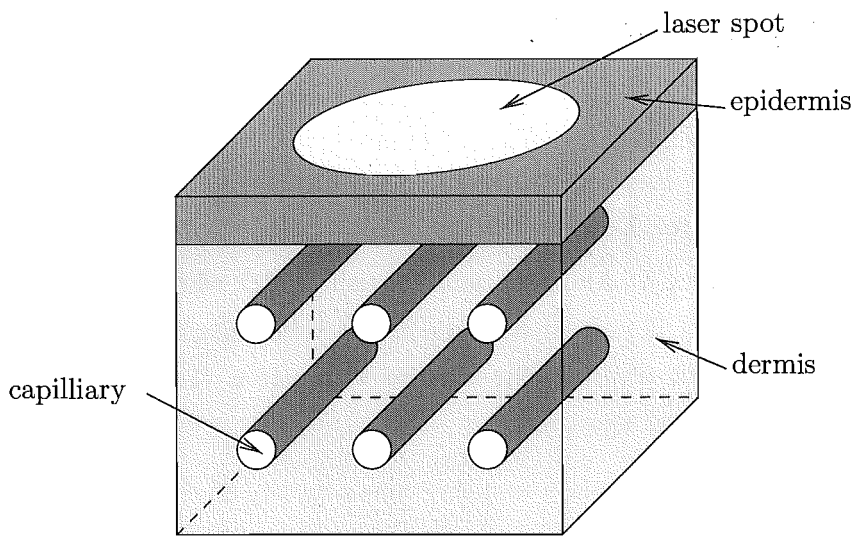

Figure 5.5: Smithies' model of skin

This model had two layers which represented the epidermis and dermis, and multiple layers of individual capillaries which could be varied in diameter, depth, and number. For some simulations more than 500 capillaries were included. In addition both scattering and absorption events could be modelled. This allowed for the effects of different skin types to be calculated. They modelled the effects of

- laser spot diameter
- capillary diameter
- capillary position
- the level of pigmentation in the epidermis
- the wavelength

on the distribution of the absorbed light within the skin.

The distribution of the absorbed light was then used to construct thermal profiles. These indicated that 4 ms was the optimal illumination time for a 50 μm diamater vessel (see figure 5.6). Any shorter and the endothelial cells would not reach a temperature of 70 $^{\circ}$C at both the top and bottom of the vessel. If illumination times significantly longer than this (for example 40 ms) were used, too much heat would be conducted to the surrounding non-vascular tissue. This would cause the widespread coagulation necrosis seen in the histologies obtained after copper vapour laser treatment of port-wine stains with the manually scanned optical fibre. Smithies (1995) supported the use of 1-10 ms illumination times.

Van Gemert *et al* (1997) and Verkruysse *et al* (1997) showed that complex models such as those used by Smithies and Butler (1995) produce much more accurate light distributions within the skin than the models which use a homgeneous blood layer within the dermis. Models with discrete vessels have non-uniform absorption into the blood within the vessels. The blood at the centre of the vessels absorbs less than the blood near the vessel wall. Homogeneous models therefore overestimate the absorption of light into blood from the same number of red blood cells. This explains why models such as Smithies and Butler (1995) more accurately predict the damage depths reported in the histological literature. Van Gemert *et al* (1997) calculate a correction factor that can be used to make homogeneous models more realistic.

The issue of the optimal wavelength is also addressed by van Gemert *et al* (1997). Discrete absorber models show different absorption patterns for wavelengths longer

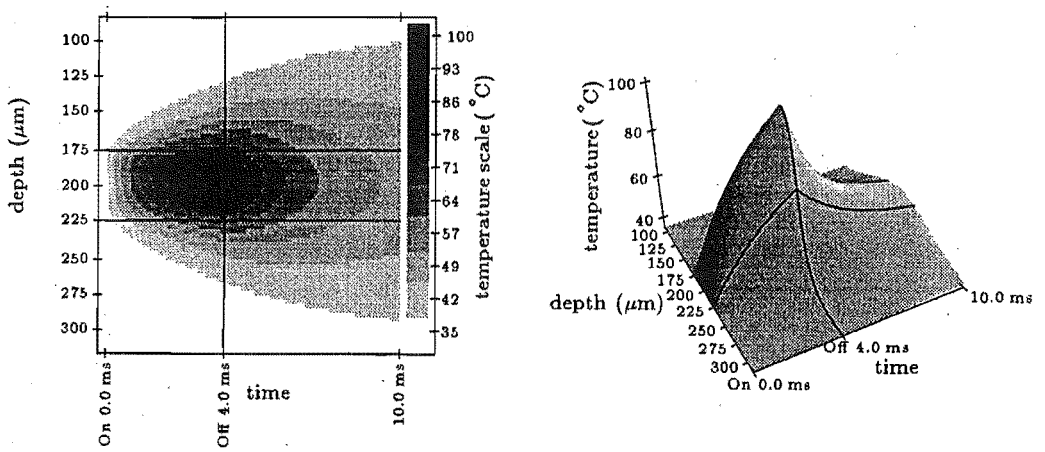

Figure 5.6: The temperature distribution of a 50 μm diameter vessel heated for 4.0 ms.

than 577 nm. In particular they indicate that damage depth increases with the use of wavelengths near 585 nm. The authors conclude that for patients with deep port-wine stain vessels 585-587 nm wavelengths are appropriate. However, if the first layer of vessels is thin (less than 150 μm) and contain vessels less than 25 μm in diameter then 577 nm is appropriate. These conditions are often seen in young children with pale pink port-wine stains.

5.4 The Cause of Blanching

Histological studies by Smithies *et al* (1995) showed that with illumination times of the order of 4 ms thermal damage is restricted to vascular tissue. If little or no collagen is being coagulated then what causes blanching? We noted earlier that Pickering *et al* followed Ratz and Bailin (1987) in attributing blanching to coagulation of endothelial cells. Marini *et al* (1992) proposed a different mechanism. On a visit to the clinic at St George's Hospital Marini observed the rapid onset of blanching after laser treatment. The skin is observed to blanch at the treatment point. Effectively this means that blanching occurs within a few tens of milliseconds after the illumination has stopped. Very shortly after this, bands of erythema form on both sides of the treated line. Marini *et al* proposed that as a result of the endothelial cells being thermally damaged the selective permeability of their cell membranes is irreversibly lost. This allows water, carried by Na^+ ions redistributing according to their concentration gradient, to be ingested by the endothelial cells. The cells then swell. This swelling must be centripetal in nature since the surrounding dermal tis-

sue is essentially rigid. The centripetal expansion blocks the vascular lumen, which is observable as blanching. This process is illustrated in figure 5.7. Damage to the endothelial cells also stimulates the release of vasodilating agents. This produces erythema adjacent to the treated region as part of an acute inflammatory process.

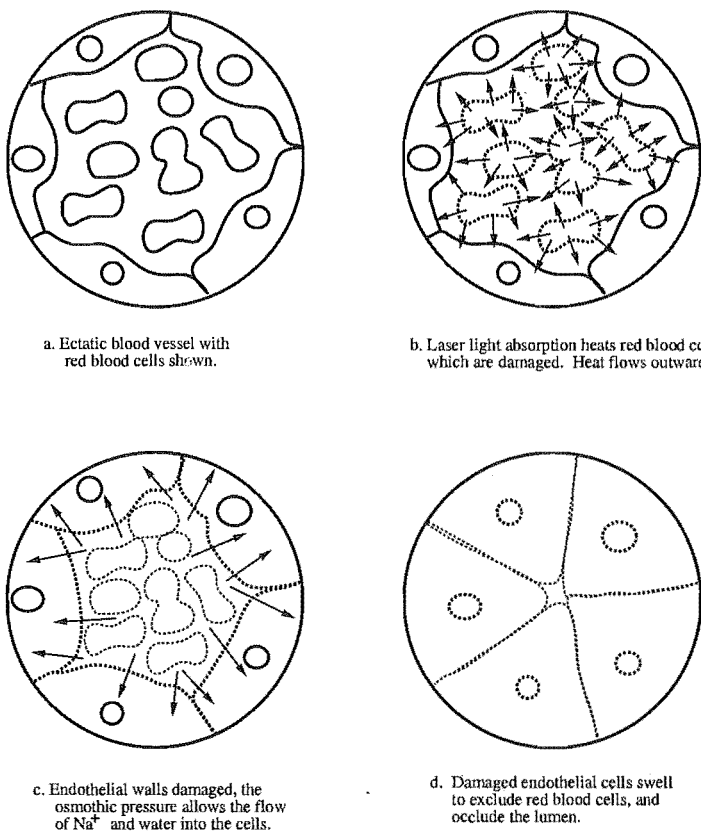

Figure 5.7: The blanching process as proposed by Marini *et al.* (1992).

Flock *et al* (1992) observed blood vessel constriction during copper vapour laser illumination. This was accompanied by a streak of dark pigment (thought to be coagulated red blood cells) moving away from the point of illumination. Flock also observed fresh whole blood in a petri dish while being illuminated by a copper vapour laser. Blood was physically displaced from the point of laser-blood interaction. They concluded that constriction of blood vessels and the movement of the blood was the cause of port-wine stain blanching during copper vapour laser treatment.

5.4.1 Measuring the Blanching Time

In 1992-3 two methods were employed to measure how fast blanching occurs (Mehrtens *et al*, 1997). The first method used a fast photo-diode to measure the intensity of the light which is either reflected off the lesion during illumination or is back-scattered out of the skin. This combination of reflected and back-scattered light will be referred to in this thesis as "remitted light".

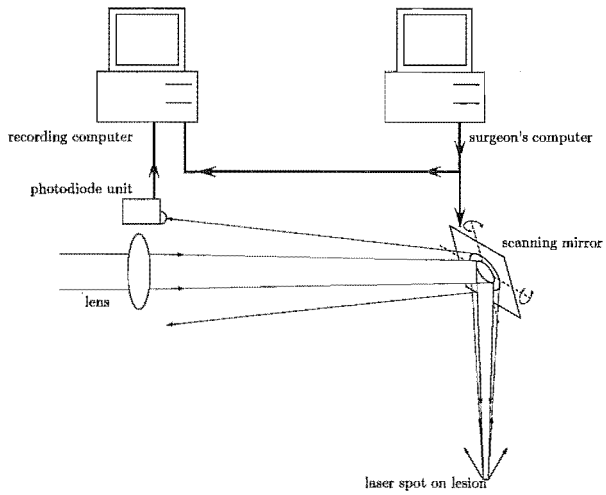

Figure 5.8: The layout of the photodiode measurement of the blanching time.

A diagram of this system is given in figure 5.8. The photodiode unit was mounted adjacent to the path of the laser beam in the scanner arm. The remitted light would travel back along the same optical path as the the outgoing beam, but would not be collimated. The output was recorded by a computer which also received data from the surgeon's computer about the the motion of the laser spot. Since the peak power of the laser (approximately 7000 W) is so high the photodiode could be triggered to only detect the magnitude of the peak levels. Effects from ambient light could then be ignored. The laser beam was kept stationary until the skin had blanched, then moved away. The data from many such spots was collected.

The results from this experiment showed that blanching occurred as soon as 3 ms after illumination started for some pink port-wine stains. The average time for a pink lesion to blanch was (mean $\pm$ standard deviation) 4.0$\pm$3.5 ms, for red lesions 11.5$\pm$3.1 ms, and for purple lesions was 14.5$\pm$4.9 ms.

The second method involved real-time photography of the laser treatment. Using

"slow" film (25ASA) and an intense pulsed white light source (20 μs pulse from an xenon flash-lamp) high resolution photographs were taken immediately after laser illumination had ceased. The camera was connected via a fibre optic cable to the firing circuit of the laser, enabling the laser to be switched off momentarily while the photograph was taken. This prevented the intense laser spot from obscuring the area of interest. The stepper motors were not stopped during this time, so the scanning motion continued even though no light was being emitted from the laser. A single pulse was emitted from the laser a few milliseconds later (while the shutter of the camera was still open) to mark the current position of the laser beam on the skin. The timing of this is shown in figure 5.9. Using the known speed of the laser beam, the photographs could be used to measure the time taken for the skin to blanch after laser exposure.

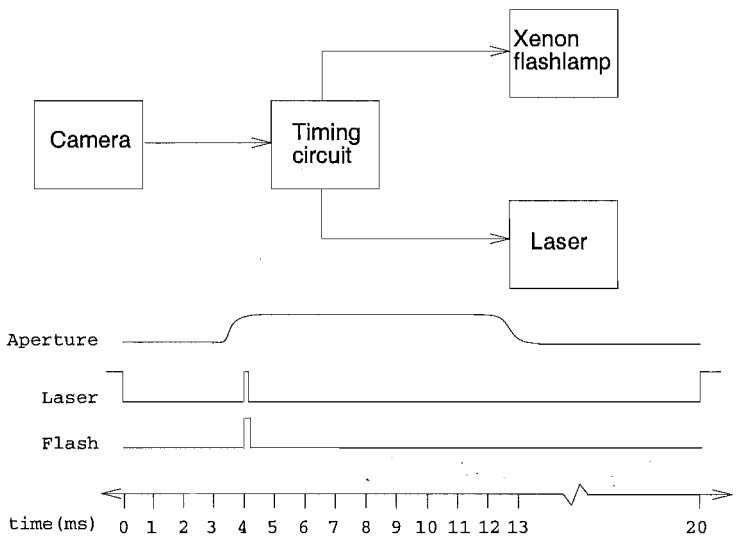

Figure 5.9: Timing diagram for the photographic method of measuring the blanching time.

Results from this experiment confirmed that the time taken for skin to blanch depends on the colour of the lesion. The more red/purple a lesion, the longer the blanching time. Pink lesions blanched on average 8.3±1.5 ms, red lesions 19.5±4.0 ms, and purple lesions 31.5±1.3 ms.

As noted in chapter 2, port-wine stain colour has been associated with vessel diameter, with more purple lesions being linked with larger vessel size. The correlation between blanching time and colour (vessel diameter) tends to support the proposal of Marini *et al* (1992), since the endothelial cells of larger diameter vessels have to swell more to occlude the lumen.

We also noted from the photographs that the erythema often formed within seconds of the illumination ceasing. With slightly lower fluences this erythema not only formed alongside the treated line, but occurred in the treated region too. This would not occur with coagulation (with the associated whitening) of either the overlying dermal tissue or the endothelial cells. The conclusion is that the blood is being forced from the vessels by the constriction of the vessel. These vessels respond to the release of vasodilators by re-opening. The surrounding vessels which were not treated will also dilate.

5.5 The Current Protocol

The broad details of the current treatment protocol at St George's Hospital are the same as those discussed in subsection 5.1.2. However, the blanching times measured during the author's Master's degree research led to signifcant changes being made to the protocol. These changes were made during the term of the research for this thesis. The major development has been the introduction of double scanning. This section describes the application of the knowledge gained during the previous research to the devlopment of the double scanning protocol.

5.5.1 Double Scanning Protocol

It has often been a criticism of copper vapour laser treatment of port-wine stains that treatments of pink lesions have been less successful than those of redder lesions. Since pink lesions are more common in children, and it is perceived to be advantageous to remove port-wine stains while the afflicted person is young, (though this is disputed by van der Horst *et al* (1998)) improving the the results with pink lesions has always been an area of research. We noted earlier that some pink port-wine stains blanch during the normal illumination time. This blanching removes the target chromophore. Any further illumination has no effect. Thus insufficient thermal damage will have been done to the ectatic vessel to cause thermal necrosis. This explains why pink port-wine stains have a higher probability of being non-responsive. It also explains the observation made by Pickering *et al* that the minimal blanching endpoint (blanching which persists for several minutes to hours after treatment) was often difficult to attain.

Since red port-wine stains take longer to blanch, making pink lesions more red before treating allows sufficient heating to occur to cause thermal necrosis. This is accomplished by taking advantage of the erythema formed after a scan is complete.

The dilation of the vessels not only increases the diameter of the treated vessels but also opens new capillaries that had previously been empty (see chapter 2). The erythema which forms is illustrated in figure 5.10. The lesion extends across the chest and onto the shoulder. Before treatment the entire lesion was the colour of the region visible on the shoulder. After one scan of the chest region, erythema formed. There is a sharp boundary between the treated and untreated regions.

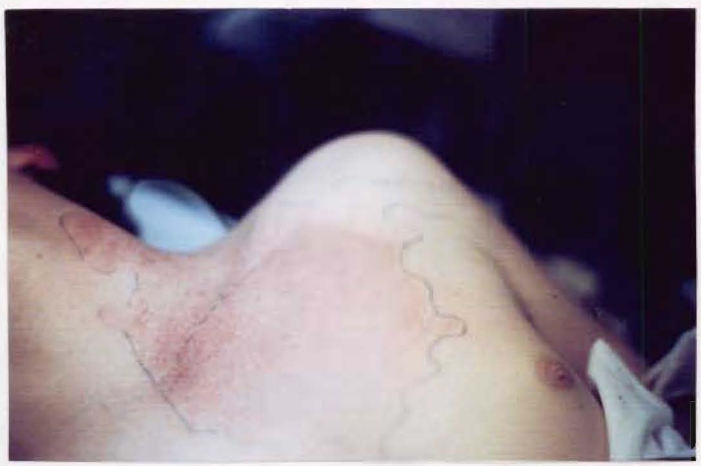

Figure 5.10: Erythema after one scan. The region on the shoulder has not been scanned. The entire lesion was the colour of the shoulder region before being treated.

The epidermis is cooled to preserve its viability, as the epidermis is essential to the healing process (see section 2.1.1). This development occurred at much the same time as dynamic cooling was proposed for pulsed dye laser treatment (section 5.2.4). We therefore rescan the lesion perpendicular to the original scan. This allows more vessels to be treated in one session, and also reduces the visibility of the scan lines post-treatment.

The endpoint for the initial scan is erythema forming within seconds of illumination. The endpoint for the second scan is transient blanching, defined as blanching which only persists for seconds to minutes after illumination. More persistent blanching we believe to be indicative of coagulation necrosis of non-vascular tissue.

The cooling of the epidermis is achieved by application of ethyl-chloride spray. This evaporates rapidly, removing heat from the epidermis, but does not inhibit the formation of erythema. Nor does it reverse the damage inflicted on the endothelium as this damage was done within a few milliseconds of the illumination (see section

5.3). The cooling may not be applied until several seconds have elapsed since treatment. The new protocol is used for all port-wine stains, irrespective of colour since the cooling means that there is no disadvantage to scanning twice, and the extra scan allows more vessels to be treated in one session. This new protocol has been examined histologically. This study is presented in chapter 6.

The double scanning protocol was tested initially on a boy whose father is a general medical practitioner. With consent obtained, one region of this child's pink port-wine stain was treated using the old protocol. The remainder was treated with double scanning with cooling both between the scans and after the final scan. The father reported to us that the area that had been scanned twice had less post-treatment blistering than the control area. When the boy returned for further treatment three months later, the twice-scanned area was almost completely resolved. The control area had faded, but was still clearly visible along with some of the parallel scan lines from the treatment.

Further confirming evidence was obtained from the experience of an associate professor of physics who received treatment for his purple port-wine stain. This man had previously had treatment using the single scan (minimal blanching endpoint) protocol. One week after having received a treatment using the double scanning protocol he wrote to us complaining about the efficacy of the treatment. He believed that not enough damage had been done since he had suffered no post-treatment blistering and the treated areas were still quite red. In response to his letter we offered him a free treatment after three months. When he returned to our clinic his port-wine stain had almost completely resolved. Only a careful examination revealed any lesion left to be treated. The absence of blistering was evidence that the cooling was efficacious. The resolution of his port-wine stain showed that the double scanning protocol could be extended to purple port-wine stains. The free treatment that we gave more than paid for itself in confirming our understanding the processes occuring in the skin during and after treatment, and our ability to predict the effects of the new protocol.

Making lesions more red before treatment has been investigated in other places. Haederdsal *et al* (1998) reports using nicotinic acid to cause erythema before laser treatment. However, an increase in scarring and hyperpigmentation was noted. This has not been our experience. The author of this thesis was involved in almost every treatment session between mid-1993 and mid-2001. This amounts to about 250 treatment days, approximately 2500 hours, during which many more than 2000

patients were treated at St George's Hospital Day Surgery clinic. Most of these patients were having repeat treatment sessions. After the introduction of the double scanning protocol, fewer incidents of hypopigmentation and atrophic scarring were noted on patients returning for further treatment. Almost without exception the skin texture is normal after three months healing time and the clearance rate has increased since the introduction of the new protocol. Chapter 7 investigates the rate of adverse effects under the double scanning protocol.

5.5.2 Injection Sclerotherapy

Injection sclerotherapy is also an important part of the treatment protocol at St George's Hospital. The larger vessels associated with facial telangiectasia respond well to this treatment, and the copper vapour laser is used to treat those vessels too small to inject.

A 3% solution of Sclerovein (polidocanol/ethanol) is injected into the vessels with a 30 gauge needle. The Sclerovein is an irritant to the endothelial cells membranes and causes them to swell. Their surface changes enabling platelets to adhere to the luminal surface of the swollen endothelial cell – effectively stopping the flow of blood. If a port-wine stain has vessels sufficiently large to be injected then injection sclerotherapy is done. Frequently this results in a significant area of the lesion being resolved.

An interesting effect occurs when sclerosed vessels are subsequently treated with the copper vapour laser. Figure 5.11 shows a region of facial telangiectasia that had received injection sclerotherapy minutes before copper vapour laser treatment. The sclerosed vessels show a purpura-like response to the treatment. We believe that this is caused by the flow of blood in the venules having been stopped, or occluded by the swollen endothelial cells. This results in haemoconcentration, or red blood cell agglutination as fluid is withdrawn from the vessels. The stationary erythrocytes denature *in situ* on exposure to laser light (see chapter 6) and the vessels change colour to brown or black.

This supports the model of Marini *et al* (1992). If coagulation of the epidermis, dermis, or endothelial cells was responsible for blanching, blanching would still be observed in the sclerosed case – obscuring the dark vessels. Here, however, the blood has been prevented from leaving the treated region. Not only is the visibility of the stationary coagulum of erythrocytes an indication of the nature of blanching, but it is also evidence that blood flow plays an important part in the blanching mechanism.

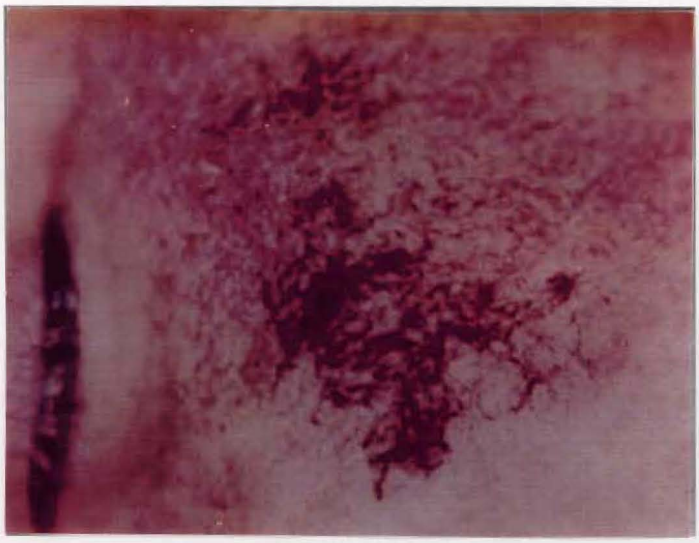

Figure 5.11: The purpura-like response of sclerosed vessels on the upper cheek after copper vapour laser treatment.

5.6 Extending the Protocol

When simplified, the double scanning protocol has two essential features. The first is the heating of the blood vessel walls to greater than 70 °C, while maintaining the non-vascular tissue below 70 °C. This results in damage specific to vascular tissue. The other key compontent to the protocol is the use of erythema to provide new targets for the laser on its second scan. There is no reason why this should be limited to only two scans, provided that non-vascular tissue is kept below 70 °C.

This suggests that the protocol can be extended. If the entire volume of skin containing the ectatic vessels can be cooled to significantly below normal temperature (for example to 20 °C) and the laser treatment can still heat the blood vessels to greater than 70 °C, then the erythema produced by the damage to the blood vessels could be retreated several times. The cooling would inhibit the erythema somewhat, but it will still form. Erythema is a response to damaged tissue, and the stimulants are still released even though the surrounding tissue is immediately cooled. We observe this in the operating theatre while using the double scanning protocol. It is also observed when a superficial burn is held under cold water for several minutes. The affected tissue can still be quite red.

Cooling for this new protocol could be achieved using a flow of cooled air. Dr Lou Reinisch (private communication) indicated that he has a device which directs

a flow of chilled air onto the skin prior to pulsed-dye laser treatment. Using cooled air has advantages over chemical coolants:

- it would not interfere with the transmission of the laser light to the patient
- it would be more effective at maintaining the temperature of the non-vascular tissue since the tissue would be cooled continuously rather than several seconds, or even tens of seconds, after treatment
- coolant spray causes irritation if it gets into the eye of the patient when used in the peri-orbital region
- it completely eliminates the fire risk present when using flammable chemicals such as ethyl-chloride, and
- it is friendly to the environment.

This proposal is left for further research.

Chapter 6

Histology

To investigate the effect of the double scanning protocol on port-wine stain skin a series of biopsies were taken for microscopic examination.

6.1 Method and Results

5 mm punch biopsies were taken from a previously untreated port-wine stain on the volar forearm of a consenting patient. Nine samples were taken. The first was a control sample on untreated port-wine stain. Then two samples were taken immediately post-treatment. The first was after a single scan with 11 J/cm^2 fluence (4.1 ms illumination time). Having taken this sample, the skin was cooled with ethyl-chloride spray and retreated with the same treatment parameters. After again cooling with ethyl-chloride the second sample was taken. Biopsies were then obtained after 24 hours, 48 hours, 4 days, 1 week, 3 weeks, then 3 months post-treatment. The samples were stained using toluidine blue and examined using light microscopy.

The control sample (taken from untreated port-wine stain skin) showed normal skin, except for dilated capillaries in the papillary and reticular dermis (see figure 6.1). Some of the capillaries contained red blood cells.

After one scan minimal epidermal oedema was observed with slight separation of keratinocytes. One blood vessel showed early clumping of red blood cells. The dermis was normal.

After the second scan there were fewer red blood cells in the vessels of the reticular dermis. Those vessels that did contain blood showed coagulation of the red blood cells, along with the blood plasma. The endothelium appeared degenerated (see figure 6.2). There was separation of keratinocytes in the epidermis indicating oedema (see figure 6.3).

After 24 hours the endothelial cells were breaking down, and contained no nuclei. There was oedema of the surrounding connective tissue. The epidermis was

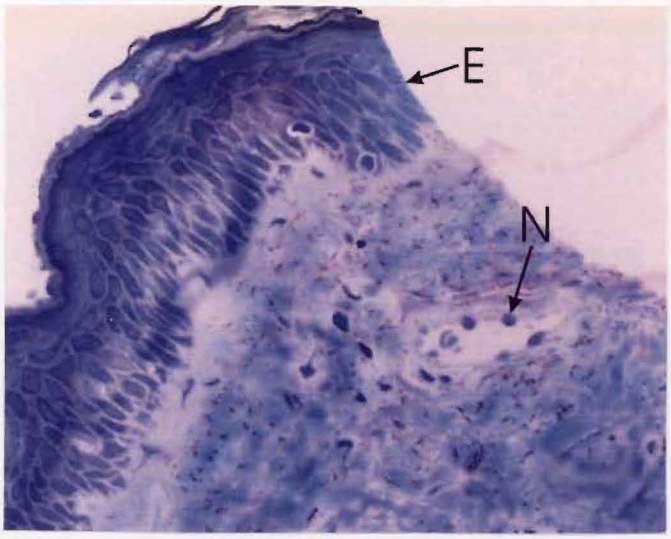

Figure 6.1: Pre-treatment skin showing normal epidermis (E) and an ectatic capillary with healthy endothelial cells (N) (x40 original).

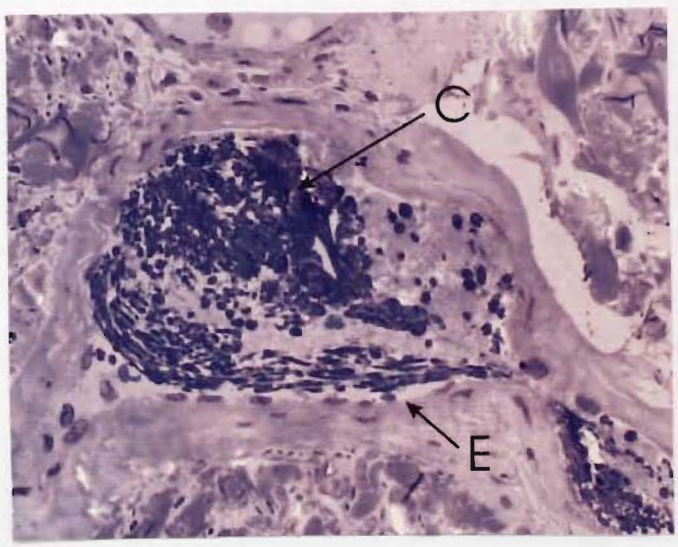

Figure 6.2: Skin after two scans separated by cooling. Blood and plasma has coagulated inside the lumen (C), and the endothelial cells show signs of degeneration (E) (x40 original).

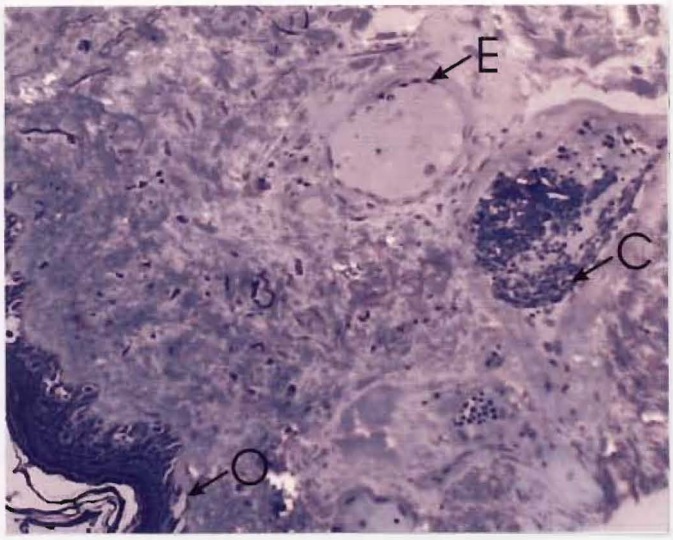

Figure 6.3: Skin after two scans separated by cooling. The epidermis is oedemetous (O). The blood vessel (C) is the same on as in figure 6.2. Blood vessel (E) has no coagulated red blood cells in the lumen, but the endothelial cells show signs of degeneration (x20 original).

oedemetous, and lifting from the dermal junction.

At 48 hours post-treatment the endothelial cells had disappeared. The dermal connective tissue showed signs of fibrosis and oedema. There were vesicles and oedema in the epidermis.

By the fourth day the epidermis was intact once again. The capillaries had constricted and appeared as slits without endothelial cells. There was considerable fibrosis around the capillaries (see figure 6.4).

One week after treatment, the sample showed a low grade inflammation. The blood vessels were slits but had regenerating endothelial cells. The dermis contained numerous macrophages, neutrophils, and active fibroblasts. The epidermis appeared normal.

After 3 weeks, the epidermis appeared normal. There were few blood vessels. Those that were visible did not appear dilated and had new endothelial cells. There was new wavy collagen in the perivascular region. Macrophage activity was still evident.

After 3 months (at which time, according to the double scanning protocol we would re-treat the lesion) the skin appeared to be normal (see figure 6.5). The epidermis was undamaged. The blood vessels in the papillary dermis were narrow and surrounded by mature collagen. The endothelial cells were normal. The fibroblasts

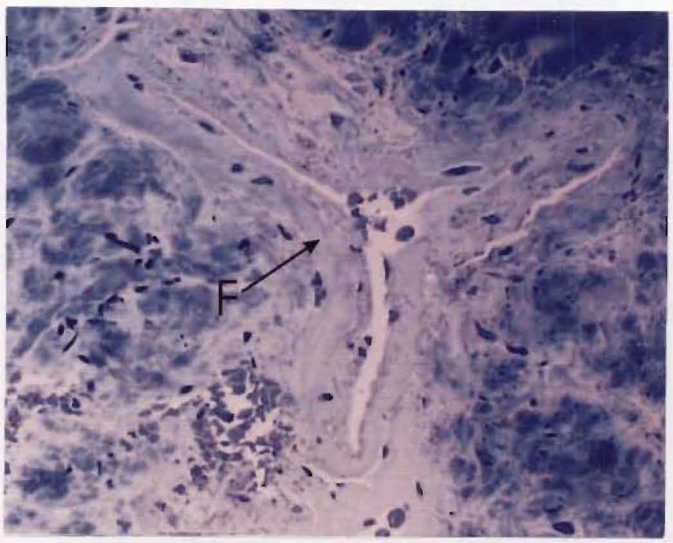

Figure 6.4: On day 4, capillaries appeared as slits without endothelial cells. There is fibrosis around the vessel (F) (x40 original).

had become thin – transforming into resting fibrocytes. Cosmetically the treated lesion had lightened significantly.

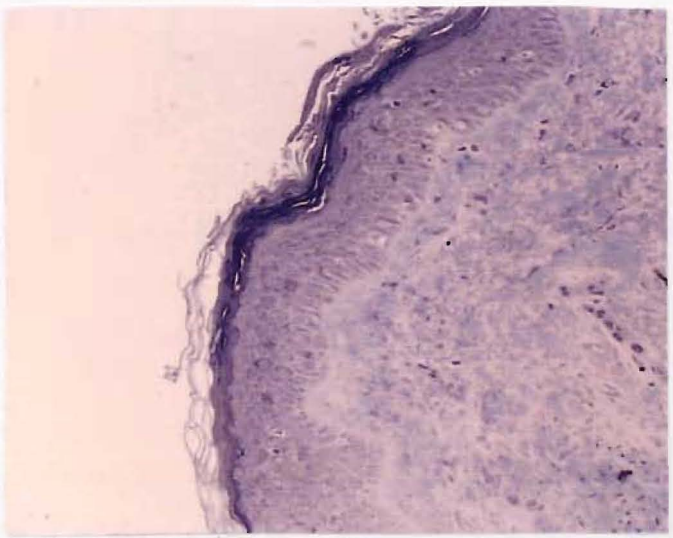

Figure 6.5: Three months after treatment the skin appears normal. (x20 original).

6.2 Discussion

Other copper vapour laser treatment protocols have been investigated histologically. Walker *et al* (1989) used a hand guided optical fibre to produce 30-50 ms illumination

times. After 24 hours they observed a sub-epidermal blister and acute inflammation in the dermis. Parts of the papillary and reticular dermis were degenerate. After 3 months the skin appeared normal. Some vessels were filled with collagen.

Neumann *et al* (1993), with Hexascan and 50-200 ms illumination times, took samples after treating with a variety of fluences. Using 10 J/cm^2 they observed thermal damage confined to blood vessels and a small region of collagen around the endothelium. With 20 J/cm^2 a diffuse cone of non-specific epidermal and dermal coagulation necrosis was observed. This was sharply delineated from the viable surrounding tissue.

Smithies *et al* (1995) performed electron microscopy on skin treated with the SCANALL system and 4 ms illumination times. After 24 hours there was necrosis of endothelial cell walls which were infiltrated with platelets and stratified basement membrane collagen. They saw no damage to either non-vascular structures or epidermal cells.

Tan *et al* (1990a) examined samples taken after 360 μs exposures with either 577 nm or 585 nm light from a pulsed dye laser. With 577 mm light thermal damage was confined to vascular tissue. Samples taken 30 minutes after treatment with 585 nm light they observed that perivascular collagen had denatured. Red blood cells had agglutinated within denatured vessels.

Walker *et al* (1989) and Neumann *et al* (1993) used blanching as a clinical endpoint. The transient blanching used as part of the double scanning protocol does not produce the degeneration in the dermis that is observed with minimal and stronger forms of blanching. As mentioned in section 5.4, transient blanching produces a constriction of the heated blood vessel, temporarily forcing out blood from the lumen at the point of illumination.

The cosmetic lightening of the lesion after 3 months corresponds to fewer capillaries visible in the papillary and reticular dermis. The capillaries that could be seen were slit-like. They were surrounded with a perivascular cuff of new collagen. This is consistent with the findings of Walker *et al* (1989), Smithies *et al* (1995), and Chung *et al* (1996) who observed a ring of damaged collagen around treated vessels. The reduction in vessel diameter reduces the volume of blood flowing through the affected region of skin, reducing the redness.

The mild damage to the epidermis healed quickly and cleanly. There was no scarring or abnormal pigmentation. Epidermal damage occurs either following excessive thermal conduction from vascular tissue to surrounding structures, or as a result

of direct heating of pigmented structures in the epidermis itself. Excessive thermal conduction is a result of long illumination times, as seen by Neumann *et al* (1993). The amount of photothermal heating of the epidermis depends on the amount of pigment therein. Chung *et al* (1996) examined the copper vapour laser treatment of port-wine stains on the brown skins of Korean patients. They observed that a fluence of 15 J/cm^2 produced diffuse necrosis of the epidermis in Caucasian skin, as opposed to 6-8 J/cm^2 in Korean skin.

The blood vessels that contained a coagulum after the second scan are occasionally visible after the treatment. Injection sclerotherapy (see section 5.5.2) followed by laser treatment increases the number of these vessels, resulting in the purpura-like effect.

6.3 Conclusion

The results obtained from the samples taken after port-wine treatment using the double scanning protocol indicate that it does not excessively damage either epidermal or dermal non-vascular tissue, while producing thermal necrosis of ectatic capillaries. Reduction in the volume of blood in the skin is achieved by reducing both the number and size of capillaries within the papillary and reticular dermis.

Chapter 7

Clinical Follow-up

This chapter describes a clinic and postal survey used to gather information about the effectiveness of the copper vapour laser treatment of vascular lesions.

7.1 Motivation

In the decade since the SCANALL system was introduced much of the physics of the treatment process has been well analysed. We also have extensive treatment notes for several hundred patients, with photos at every treatment. As part of the work of this thesis a survey was conducted to provide data relating to the effectiveness of the treatment, the immediate response of the lesion to treatment, and the reasons that patients ceased treatment.

For most of the first half of the 1990s many of our patients were from outside the local area. Few would consider travelling to Christchurch for a consultation just to assess the response of the lesion to treatment. If they returned for further treatment then photographs were taken. Straight after the pictures were taken the lesion received another treatment. If the patient did not request further treatment then this was often the last that was seen of them. In most cases no reason was given for not requiring further treatments. Thus we could only judge the effectiveness of the treatment by those who returned for more sessions.

Given that the patients treated for spider naevus and telangiectasia received an average of one treatment only, there was no certainty as to the effectiveness of the treatment. Similarly for port-wine stains. The average number of treatments for this condition is four. This is also the number of treatments currently funded by the Health Funding Authority. Were the patients ceasing treatment because the treatment was not working, because it worked so well that four treatments were sufficient, or because they could not afford to continue after public funding ceased?

To assess the effectiveness of the SCANALL system a follow-up clinic and survey

were conducted. The clinic was used to trial the questions to be used in the postal survey. Only those in the local area (approximately a 100 kilometre radius from Christchurch) were approached to take part in the clinic. All of the other patients treated with the SCANALL system were included in the postal survey.

7.2 Method for Clinic

A database of all patients who had received treatment with the SCANALL system was constructed by the author. This database contained information concerning the type, colour, and location of the lesion, the number treatments received, the dates of the first and last treatment, and any other relevant notes. This database made grouping of the patients into categories simple. A letter inviting attendance at the clinic was sent to 123 patients who had received treatment with the SCANALL system alone. Many of our patients in the early 1990s had received some of their treatments using the manually scanned optical fibre. The lower precision of the movement of the laser beam and the length of the illumination times caused some overtreatment. These patients were unsuitable to take part in an assessment of the SCANALL system.

Of the 123 invitations, 44 (36%) attended. Of these, 10 had port-wine stain, 14 had telangiectasia, and 16 had spider naevus, the rest had miscellaneous vascular conditions such as angiofibroma, tuberous sclerosis, and Campbell de Morgan spots.

A written questionnaire was designed following those used by Dixon *et al* (1984b) and Pickering *et al* (1990a). At the clinic, the patients were given the questionnaire to complete. They then discussed their answers with the surgeon, who also took photographs of the treated areas. The author was present to assist the patients with any difficulties in answering the questions and to assess the suitability of the questions for the postal survey. The discussions gave an indication of the difference between patient perceptions of their lesions and the surgeon's perception.

The questionnaire asked questions in the following areas.

- The healing processes after their treatment
- Past and present colour and texture of the lesion
- The patient's perception of the effectiveness of the treatment with respect to both colour and size
- The patient's reason for stopping treatment

All questions but that regarding the reason for stopping treatment were constructed on a bipolar scale allowing a choice of at least three answers. There was also space given for other comments to be made if the patient felt that none of the answers provided adequately described their response.

7.3 Method for the Postal Survey

The results of the follow-up clinic were used to judge the effectiveness of the questionnaire. In a postal survey the questions need to be clear and able to be easily answered. In the event the only substantial change made was to the question about the skin texture (see subsection 7.4.2).

A total of 251 patients were sent survey forms. Of these 85 were port-wine stains, 79 were telangiectasia, and 75 were spider naevus. The remaining 12 had miscellaneous vascular lesions such as Campbell de Morgan spots, hereditary haemorrhagic telangiectasia, and angiofibroma. Two months after the initial questionnaires were posted, a follow-up letter and another question form were sent to those that had not replied to encourage them to participate in the survey. Replies were received from 42% port-wine stain, 46% telangiectasia, and 27% for spider naevus patients. Of the 159 non-respondents, 30 were returned "address unknown" and 2 had died since receiving treatment. The other 127 patients sent surveys either never received them, or they chose not to answer for one reason or another.

The numerical data obtained from the survey was entered into a Microsoft Excel spreadsheet to allow summary statistics to be prepared.

7.4 Results

Since both the questions and the results of the clinic and survey are similar they are presented together.

7.4.1 Response of the Lesion to Treatment

The first question concerned the physical response of the lesion in the first few days after treatment. The four responses asked about were

- Blistering
- Weeping or discharge from the skin
- Scabs

- Puffed up eyes

Blistering, weeping, and scab formation represent a time during healing when the treated lesion has a higher risk of scar formation if the lesion receives any trauma. During this time the patient needs to keep the region dressed, or at least protected from scratching or bumping. The results gathered from these questions allows better information to be given to patients with respect to post-treatment care.

The question was *"How much of the following did you experience in the first few days after your treatment?"*

	Not Experienced	Mild Amount (lasting 2-5 days)	Moderate Amount (lasting 5-9 days)	Severe Amount (lasting 10-14 days)
a.Blisters	1	2	3	4
b.Weeping or discharge from the skin	1	2	3	4
c.Scabs	1	2	3	4
d.Puffed up eyes	1	2	3	4

Blistering

	Clinic	Postal Survey
Lesion Type	Mean ± Standard Deviation	Mean ± Standard Deviation
PWS	1.3± 0.5	2.1 ± 0.9
Tel	1.4 ± 0.5	1.7 ± 0.8
SN	1.4 ± 0.8	1.3 ± 0.5

Discharge from the skin

	Clinic	Postal Survey
Lesion Type	Mean ± Standard Deviation	Mean ± Standard Deviation
PWS	1.3± 0.7	1.9 ± 0.7
Tel	1.6 ± 0.9	1.6 ± 0.7
SN	1.0 ± 0	1.2 ± 0.4

Scabbing

	Clinic	Postal Survey
Lesion Type	Mean ± Standard Deviation	Mean ± Standard Deviation
PWS	1.9± 0.6	2.8 ± 0.8
Tel	1.5 ± 0.5	1.7 ± 0.9
SN	1.5 ± 0.6	1.4 ± 0.6

Patients reported mild to moderate blistering, weeping and scabbing. This is consistent with the results of Pickering *et al* (1990b) who asked similar questions of patients treated using the copper vapour laser and hand-held optical fibre. Consistent also is the observation that the scabbing is slightly more severe than blistering and weeping. For port-wine stains 59% reported blistering, 45% reported weeping, and 78% reported scabbing after treatment.

The results for discharge from the skin should be correlated to the results for blistering. Blisters which get broken will cause weeping. For port-wine stains and telangiectasia this can be seen. For spider naevus, no-one observed any weeping at all. Possibly this is due to the much smaller areas being treated. A typical spider naevus involves less that 1 cm^2 of skin, while a port-wine stain or telangiectasia may involve large areas of the face. The bursting of a single blister formed over a treated spider naevus may be less noticeable than the moisture from a large treated area.

Scabbing, or crusting, was observed by approximately half of all patients who had received treatment for telangiectasia and spider naevus. However 78% of those with port-wine stain had scab formation. Port-wine stains are normally more red or purple in colour than either telangiectasia or spider naevus. The greater amount of blood near the skin surface gives higher absorption of laser light. However, only 1 patient reported them being anything more than mild.

Puffy Eyes

	Clinic	Postal Survey
Lesion Type	Mean ± Standard Deviation	Mean ± Standard Deviation
PWS	1.6± 1.3	1.6 ± 0.8
Tel	2.1 ± 1.2	2.0 ± 0.8
SN	1.4 ± 0.7	1.2± 0.5

When the treatment is near an eye, the peri-orbital tissues may swell up in the first day after the treatment. Occasionally during a prolonged treatment session (for example where the telangiectasia being treated extends over the entire face) the puffiness can be seen forming. This can persist for several days. Several patients with

port-wine stain and telangiectasia reported severe puffiness. The higher incidence of puffiness resulting from treatment for telangiectasia reflects the propensity for this condition to involve the anterior cheeks and nose. Again the smaller size of a typical spider naevus means that the total damage to tissue is smaller, resulting in less risk of puffiness.

7.4.2 Skin Texture

Clinic

This question investigated the issue of atrophic scarring and the "orange-peel" effect that has been reported in the literature.

The question used at the clinic was *"If you run your hand over the treated area, how does it feel?"*

1	2	3	4	5
Much rougher than normal skin	Slightly rougher than normal skin	Like normal skin	Slightly smoother than normal skin	Much smoother than normal skin

The results for this question are shown below.

Lesion Type	Mean ± Standard Deviation
PWS	3.1 ±0.3
Tel	3.0 ± 0
SN	3.0 ± 0

All patients who attended the clinic, with one exception, said that the treated region felt like normal skin. The only patient who said otherwise was a young girl who had received 14 treatments to a port-wine stain on her nose. She reported that the skin was slightly smoother than normal. After the plastic surgeon examined the patient, he commented that the skin had now softened and become pale. The quality of the skin was good. Her treatment record showed that on her first treatment more blanching was observed than is normal for the "transient blanching" endpoint. This had resulted in a blister which had become infected, resulting in the scar. The endpoint used for this treatment was minimal blanching, which is more severe than the transient blanching endpoint now used.

For the postal survey a question was inserted which asked about the pre-treatment texture.

The question was *"Before treatment if you ran your hand over the treated area,*

how did the skin feel?"

1	2	3	4	5
Much rougher than normal skin	Slightly rougher than normal skin	Like normal skin	Slightly smoother than normal skin	Much smoother than normal skin

This was followed by *"If you run your hand over the treated area now, how does it feel?"*

1	2	3	4	5	6
Much rougher than normal skin	Slightly rougher than normal skin	like normal skin	slightly smoother than normal skin	Much smoother than normal skin	The same as it felt before treatment

The patients at the clinic often said that the lesion felt the same as before treatment. Often this meant that it felt normal both before and after. Therefore this option was included to make the question easier to answer. A response of this type needs to be considered in the light of the response to the pre-treatment question.

Without being able to see the patient, there is no way of telling whether a response indicating an abnormal post-treatment texture reflects a scar, or just the "normal" texture of the lesion. For example, many of the port-wine stains that are treated in the Christchurch clinic are nodular. A response indicating that the post-treatment texture is rougher than normal may not be evidence of a scar, but rather that the nodular texture persists.

Pre-treatment (Postal Survey)

Lesion Type	Mean ± Standard Deviation
PWS	2.5 ±0.7
Tel	2.8 ±0.7
SN	2.7 ±0.5

This shows the tendency of port-wine stains and spider naevi to be nodular. 39% of port-wine stain patients, and 35% of spider naevus patients reported that prior to treatment their skin felt rougher than normal skin. This is compared to 8% of telangiectasia patients.

Post-treatment (Postal Survey)

Lesion Type	Mean ± Standard Deviation
PWS	3.0 ±0.4
Tel	3.0 ±0.3
SN	3.0 ±0

The increase in the average response here shows the effectiveness of the SCANALL system in reducing the nodularity of the lesions. 93% of those port-wine stain patients, and 100% of spider naevus patients, who indicated that their lesion was rougher than normal skin before treatment indicated that it had become like normal skin (or in once case gone from much rougher to slightly rougher than normal).

Only one port-wine stain patient who responded to the postal survey indicated that their previously normal textured skin was now slightly rougher than normal, and made the comment that the mark was very small. The patient believed that a scab had been scratched off, which led to the scar forming. Over both follow-up surveys then, only two out of 46 port-wine stain patients reported possible hypertrophic scars, a rate of 4.3% per patient. Again, the accuracy of this figure is limited by the low response rate to the surveys.

No telangiectasia or spider naevus patients reported that their skin was rougher than normal after the treatment. Two telangiectasia patients (4%) reported that their skin was now smoother than normal.

7.4.3 Pigmentation

One possible adverse effect observed with all cutaneous laser treatment is abnormal pigmentation. We asked the patient to assess whether the treatment had caused this.

The question was *Is the colour of the skin in the treated area browner or paler than the surrounding skin?"*

1	2	3	4
No such areas	Skin colour more brown than normal	Skin colour normal	Skin paler than normal

The results were

	Clinic	Postal Survey
Lesion Type	Mean ± Standard Deviation	Mean ± Standard Deviation
PWS	3.1 ±0.3	2.1 ± 0.5
Tel	3.1±0.3	2.0 ± 0.4
SN	3.0 ± 0	2.1 ± 0.3

Most patients report no change in the pigmentation of their skin as a result of laser treatment. For port-wine stain 15% reported hypopigmentation, and 4% hyperpigmentation. Most of those who reported hypopigmentation had treatments before the double scanning protocol was introduced. The cooling of the skin that occurs as part of that protocol is to protect the epidermis from the excessive damage that occurs when too much heat is absorbed by the melanin, or is conducted from the dermis. Of those who received only the double scanning protocol, only 4% reported hypopigmentation.

Two patients at the clinic reported hypopigmentation following treatment. One had both received treatment for port-wine stain and the other for telangiectasia. Both have poikiloderma on the neck and anterior chest. Poikiloderma is a condition involving a combination of vascular and pigmented lesions. The treatment for the vascular lesion also removed some of the poikiloderma which left an area of normal skin surrounded by the darker skin of the poikiloderma. Both patients commented that the area did not cause any difficulties as it was easily concealed with make-up.

Several others recalled that there had been regions of hyperpigmentation that had resolved within about 6 months of the last treatment. For telagiectasia 3% reported hypopigmentation and 6% hyperpignemtation. 6% of spider neavus patients reported hypopigmentation, none reported hyperpigmentation.

7.4.4 Residual Striping

The raster-scan nature of the SCANALL protocol could lead to some "stripiness" on the lesion, where the path of the laser light has travelled. The small gap left untreated between the scan lines may be visible.

The question was *"During the treatment the laser was scanned across the lesion in evenly spaced lines, are these lines visible now?"*

1	2	3	4
Extremely visible	Moderately visible	Only just visible	No striping

None of the patients at the clinic reported any striping at all. This was confirmed on inspection by the plastic surgeon. No striping was visible when viewed from a distance of approximately 20 cm.

Lesion Type	Mean ± Standard Deviation
PWS	3.8 ± 0.4
Tel	4.0 ± 0.4
SN	4 ± 0

16% of port-wine stain patients and 2% of telangiectasia patients reported that

they had some striping which was only just visible. No patients treated for spider naevus reported any striping. When patients return for further treatment occasionally these stripes can be seen when the lesion is closely examined. They are almost always unnoticeable from 1 metre away, particularly if the patient has had more than one treatment. All of those patients who reported visible striping were treated before the double-scanning protocol was established. Scanning a second time in a direction perpendicular to the original scan reduces the visibility of the striping.

7.4.5 Size

This question, and the one following, investigated the patient's view of the effectiveness of the treatment. The patients had difficulty with the initial form of the first question which asked them to give a percentage change (within 5 bins). The question was modified to allow a less quantitative alternative. The patients seemed to be more comfortable with the modified question. However they seemed comfortable with the second question (relating to colour change) in the original form.

The question was *How much has the lesion decreased in size because of the treatment?"*

1	2	3	4	5
Same size as before treatment	Mild decrease in size (1%-30%)	Moderate decrease in size (30%-60%)	Large decrease in size (60%-90%)	Completely gone

The results were:

	Clinic	Postal Survey
Lesion Type	Mean ± Standard Deviation	Mean ± Standard Deviation
PWS	3.2±0.9	2.7 ± 1.2
Tel	3.3±1.4	3.3 ± 1.2
SN	4.6±0.9	4.6 ± 1.2

7.4.6 Colour

The question was *How much lightening of the colour (redness) of the lesion has there been?"*

1	2	3	4	5
No change	(1%-30%)	(30%-60%)	(60%-90%)	Completely gone

The results were:

	Clinic	Postal Survey
Lesion Type	Mean ± Standard Deviation	Mean ± Standard Deviation
PWS	3.4 ± 0.7	3.0 ± 1.0
Tel	3.3±1.2	3.1 ± 1.2
SN	4.6 ±0.9	4.8 ± 0.7

The results from the clinic to these two questions show similar features. 75% of patients who were treated for spider naevus believed that their lesion had completely gone. 93% only had one treatment. This shows that the protocol for spider naevus treatment is very effective. There were no reports of any adverse effects and for most patients one treatment is sufficient.

In contrast only 21% of patients with telangiectasia, and none of those with port-wine stain believed that their lesion had disappeared completely. Most considered that their lesion had been reduced by 30%-60% in both size and colour.

Some port-wine stains will never be completely removed. It is common in the clinic to see lesions corresponding to the "deeply located" classification of Ohmori and Huang (1981). Many of these go through the full thickness of the skin. For example, a lesion may involve the full thickness of a patient's cheek and be visible inside the mouth.

It was noted that for port-wine stain and telagiectasia patients, the surgeon's assessment of the changes in size and colour often differed, with the surgeon tending to rate the treatment as being more successful. One interpretation of this is the distance at which the assessment is made. The patient normally judges this while looking in a mirror, where as the surgeon looks from one to two metres away. From the surgeon's perspective if the lesion is not noticeable from that distance then the treatment has been a success. The patient may judge the amount of success to be less, since it is still visible when looked for at close range, for example, in a bathroom mirror. In some cases the patient thought that there had not been much change until they were shown a pre-treatment photograph. For example, one patient with telangiectasia on the nose considered that the redness had only decreased by 20%. The surgeon's assessment was 80%. After showing the patient the pre-treatment photographs, he agreed with the surgeon's assessment.

One factor which some patients did not take into account was the boundary and patchiness of the lesion. A port-wine stain with a very distinct border between "normal" skin and the lesion is considerably more obvious than one where the colour change is gradual. For some patients the area enclosed by the outline of the lesion

does not change much with treatment, but within that area there may be patches of normal skin showing through. The effect of the patchiness and boundary to the cosmetic disfigurement has been noticed by other researchers. In particular, Koster *et al* (1998a,b) attempted to quantify the factors contributing to disfigurement. Their results are presented in the following table (table 7.1).

Size	45.9%
Colour	18.7%
Boundary	12.4%
Patchiness	3.3%
Hypertrophy	3.2%
Surface	1.7%
Shape	1.7%
Unexplained	13.1%

Table 7.1: Perecentual contribution of each of the port-wine stain characteristics to overall stain disfigurement. (from Koster *et al* (1998b))

Boundary and patchiness contribute almost 16% towards the disfugurement of port-wine stains. In one case in the clinic, a patient considered that the lesion had shrunk by less than 20% in area. The surgeon's assesment was 60% taking into account the reduction in sharpness of the border and areas of normal coloured skin within the lesion. Another patient, who had facial telangiectasia, considered that her lesion was still present having faded approximately 75%. The surgeon's assesment was that the remaining colour was normal. The patient was asked about what she considered a complete removal to be. Her opinion was that there should be no redness at all in her cheeks.

While these differences did not cause much difficulty in the clinical follow-up, it is expected that the postal survey results will reflect the "harsher" standard of the patient.

7.4.7 Reason for Ceasing Treatment

For this question, the patients were presented with a range of options, and also given opportunity to make an alternative response. The question asked was *"Why did you stop treatment?"*

1	2	3	4	5	6	7
Haven't stopped, treatment still continuing	Lesion completely removed and satisfied with the result	Lesion not completely removed but satisfied with the result	No further improvement seen	Could not afford to continue	Treatment did not work at all	The treatment was inconvenient

The percentages of those patients who came to the clinic with each lesion type are given below.

Response	1	2	3	4	5	6	7
PWS	20	0	30	10	20	0	10
Tel	14	21	43	0	29	0	7
SN	6	75	6	0	0	0	0

The corresponding results for the postal survey were

Response	1	2	3	4	5	6	7
PWS	6	8	42	11	50	0	6
Tel	3	8	28	0	25	0	0
SN	0	85	10	0	10	0	0

Several patients gave more than one response to this question. For example, they gave a combination of 3 and 5, indicating that if they could afford to return they would prefer more treatment, but meanwhile they were satisfied with the appearance of their lesion.

Cost seems to be a major factor in port-wine stain and telangiectasia patients' reasons for stopping treatment, with 50% of the postal survey respondents including it as at least part of their reason. Approximately 13% of those patients indicated that they were satisfied with the outcome, but if money was available they would continue. Many of the reasons given for ceasing because of the inconvenience were also cost related, such as not being able to afford time off work, the cost of travel. Other reasons included the discomfort (likened to severe sunburn (Pickering *et al*, 1990b)), and the need to wear dressings for a few days.

7.5 Discussion

The response rates to the clinic and the postal survey were less than obtained by Pickering *et al* (1990a) and Dixon *et al* (1984b), whose surveys were carried out soon after or during treatment. It is not possible to get from the results a reliable

estimate of the statistics that are used in the literature to assess a treatment, such as the adverse effect rate.

Since the introduction of the double-scanning protocol with transient blanching as the endpoint we have observed very few patients returning for treatment with any form of adverse effect. Even patients who requiured quite high fluences to achieve the transient blanching endpoint returned with normal textured skin and no signs of abnormal pigmentation. Under the minimal blanching endpoint we saw patients with persistent hypopigmentation, crepey-textured skin, and visible hypotrophic and hypertrophic scars.

Although no precise statistics are available for the adverse effect rates an estimate can be made. The patients who responded to the clinic and survey had a total treated area (including double scanned areas) of approximately 64000 cm^2. The two scars reported had a combined area of less than 2 cm^2. This gives a scarring rate of less than 1 cm^2 for every 32000 cm^2 treated. Treatment of vascular lesions with the SCANALL system is a very safe procedure for our patients. They can be confident that the probability that any adverse effects will occur is low.

We can see that the SCANALL protocol provides satisfactory treatment for vascular lesions. This is particularly noticeable for spider naevus. For telangiectasia, the percentage is lower, but none the less more than half believed that their lesion had lightened 30-60% with only one treatment. Since some "blush" of the cheeks is considered normal in western society, a complete removal of telangiectasia may not even be desired by the patient. Conversely, some patients prefer no colour in their cheeks at all and perceive "normal colour" as an incompletely removed lesion.

For port-wine stains the follow-up shows that patients are generally satisfied with the treatment. No patient indicated that the treatment did not work at all, and only 11% stopped treatment due to a lack of response of the lesion to a later treatment session. The most common reason that people ceased having their port-wine stain treated was the cost. The publicly funded four treatments are often insufficient to satisfy the patient, who may then not be able to afford to fund their own treatment.

With this data we can now give prospective patients much better information than before, particularly regarding the immediate response of the lesion to treatment, and the number of treatments required for satisfactory treatment.

Chapter 8

Tattoo Removal

In this chapter the development of a flash-lamp based tattoo removal system is described. The design, construction, and laboratory testing of the system are presented.

8.1 Why Do Research into Tattoo Removal?

In recent years tattooing has become more common, having perhaps lost some of the social stigma of the past. However, many people who have tattoos wish to have them removed - ideally without causing disfiguring scarring in the process. Their reasons for wanting tattoo removal vary. Some people have hypersensitive reactions to the tattoo dyes (Lehmann and Pierchalla, 1988) and removal offers relief. Others find that a tattoo which is visible to the public is a hindrance to finding or changing employment. Many former prison inmates find that tattoos that they received "inside" inhibit their rehabilitation, and removal would distance them from their past. For those who see tattooing as an art form, treatment offers the opportunity to create a clean "canvas" or remove a tattoo that they find displeasing. For many though, it is merely regret of having a tattoo that motivates them to seek treatment.

Whatever the motivation, tattoo removal has never been an easy goal to achieve. As already seen with vascular lesions, damage to cutaneous tissue at, or below, the basal layer of the epidermis causes scarring. Since tattoo pigment is placed into the dermis, it must be removed with minimal damage to adjacent tissue if scarring is to be minimised. Indeed some scarring may be already present, due to the mechanical nature of the tattoo application, particularly for amateur tattoos.

Traditional treatments aimed at removing tattoos such as excision (Lindsay, 1989), dermabrasion (Clabaugh, 1975), and laser ablation (Brady *et al*, 1979; Reid and Muller, 1980; Apfelberg *et al*, 1985) all cause damage to dermal tissue and hence produce scars.

One of the first laser treatments used was the ruby laser (694.3 nm). Goldman *et al* (1965) reports on experiments using the ruby laser in first the long-pulse mode (1.5 - 2.5 ms) and then in Q-switched mode (10-30 ns). Long pulses were associated with skin damage and slough of tissue (Laub *et al*, 1968). Using Q-switching improved the ink removal and cosmetic outcome. The Q-switched ruby laser is still one of the most popular options for tattoo removal.

Modern tattoos are very often multicoloured. This can complicate the removal process. For example, the ruby laser is ineffective in treating red tattoos since the 694.3 nm wavelength is not well absorbed into red pigments (Laub *et al*, 1968). Thus several other laser types are also used for the removal of tattoos. The most popular are the Nd:YAG (1064 nm), and the alexandrite (755 nm) lasers. Both of these are used in the Q-switched mode and many systems based on these lasers are available commercially. Indeed, several systems contain more than one type of laser in order to cater for the need to treat pigments of different colours.

A previous student in this Department, Zhang (1993), investigated a new device for removing tattoos. Her proposal was that any device that delivers sufficient energy to destroy the cells containing the tattoo pigment should provide an alternative to multi-laser systems. White light will be absorbed by all pigment colours. Zhang used a high-powered xenon-filled flash-lamp to produce intense pulses of white light. Based on similar mathematical models to those discussed in chapters 4 and 5, her thesis explored using pulse lengths between 20 μs and 550 μs. 20 μs is the thermal relaxation time (see section 4.1) of a structure approximately 6 μm in diameter, 550 μs corresponds to approximately 45 μm.

Using a 550 μs pulse, giving an energy density of 8 J/cm^2 on the skin, she treated a professional multicoloured tattoo on the leg of a volunteer with Fitzpatrick skin type II. The result is shown in figure 8.1. Immediately after the treatment there was oedema and erythema localised to the treated area. A sizable blister formed, but no infection developed. This clinical trial was conducted at the very end of her research.

Three months after the trial the author had an opportunity to inspect the treated area. There was noticeable reduction in the pigment in the test region. The skin texture was normal. This result provided the motivation to explore tattoo removal with intense white light and illumination times of the order of one millisecond, rather than pulses in the microsecond domain.

Millisecond scale high-energy flash-lamp pulses are rarely described in the liter-

Figure 8.1: Test patch treated on the leg of a volunteer. The pale diagonal area in the lower centre of the figure is the area treated with the flash-lamp. (1.5x actual size)

ature. These pulses are expected to result in short tube life-times and a high risk of explosive failure. In order to understand the behaviour of flash-lamps under extreme operating conditions a literature review was undertaken. A summary of this is presented in the next section.

In the mid-1990s, a new cutaneous treatment device appeared in the literature, the PhotoDerm (Energy Systems Corporation - ESC Medical, Haifa, Israel). This is described as an intense pulsed light source (Foster and Gold, 1996) which uses white light. PhotoDerm is most commonly used for vascular lesions, but its use for tattoos and hair removal are occasionally reported. For pigmented lesions (such as tattoos) the PhotoDerm is reported as being comperable to Q-switched laser systems (Hellwig *et al*, 1995).

Very few technical details were published until 1999 when the manufacturers published a clinical application note (Wilder, 1999). The available treatment parameters are:

- Standard Head Spectrum: 515 - 1200 nm
- Delivery: Direct coupling through coated-filter light guide
- Energy Density (fluence): 30-90 J/cm^2
- Pulse Sequence: 2 to 5 pulses

- Pulse duration: 2.5 - 16 ms
- Delay between Pulses: 1 - 300 ms
- Spot Size: 8 x 35 mm

The electrical and optical design of this system is not known, but it appears to be a xenon flash-lamp device.

8.2 Flash-Lamp System Design

8.2.1 Xenon Flash-Lamp Characteristics

Xenon flash-lamps are made to produce light by passing a current through a tube filled with the inert gas xenon. Xenon is used as it is the most efficient of the inert gases at converting electrical energy into light. Xenon flash-lamps are capable of producing both pulsed and continuous illumination. In pulsed mode, a capacitive discharge circuit is the normal configuration of the power supply. Pulse widths from less than 1 μs to more than 50 ms are obtainable, with energies ranging from millijoules to kilojoules per pulse.

In its most simple form a linear flash-lamp works in the following way. A capacitor, C, is connected in series with an inductor, L, and the flash-lamp (see figure 8.2). The purpose of the inductor is to tune the circuit to give critical damping which

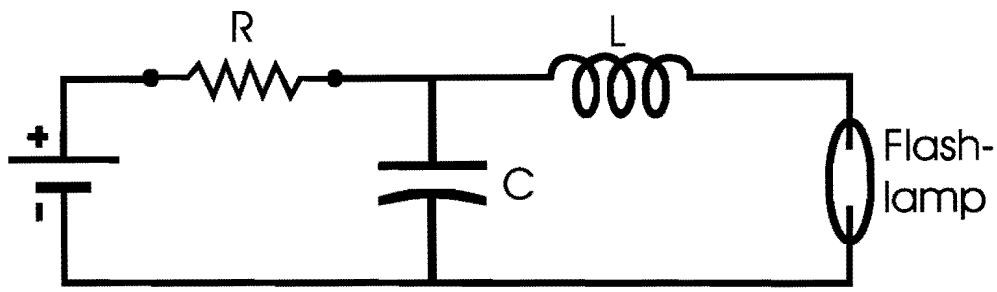

Figure 8.2: Simple L-C circuit for flash-lamps

gives the most efficient energy transfer from the capacitor to the flash-tube. Initially the xenon in the tube is non-ionised, giving the tube a high impedance. As the voltage, V, across the capacitor is increased it reaches a voltage, V_0, at which the xenon in the tube begins to ionise. The ionisation causes the impedance to start to drop. A short time later enough xenon atoms are ionised to form a low-impedance path between the tube electrodes. Current flows along this path through the tube. As it

does so more atoms are ionised until the arc fills the bore of the tube. Eventually the energy in the capacitor is expended, the current reduces and the gas de-ionises. Once the low-impedance path has disappeared, the capacitor begins to charge again.

In practise the low-impedance path is not usually formed in this way. "Over voltage" triggering, as it is known, is inconsistent since the breakdown voltage, V_0, is not precisely the same every time the tube ignites. Thus synchronising the pulse with other equipment is very difficult, and the repetition frequency tends to be variable. This method also is impractical for applications where a high repetition rate is required, since most xenon flash-tubes have a high breakdown voltage. A switch (such as a mercury ignatron, a hydrogen thyratron, or a triggered spark gap) can be used to control the over voltage triggering, but it is still unreliable when the maximum voltage is close to V_0. Miss-fires are are common in this case.

In these applications a separate trigger circuit is employed. These take two forms: series triggers and external triggers.

In a series trigger a potential is applied directly to a tube electrode from the secondary of a transformer connected in series with the flash-tube. The secondary windings must therefore be capable of taking the full current pulse from the flash-lamp, and can take the place of the choke in the supply circuit. The applied trigger voltage lowers the voltage required from the capacitor to ionize the xenon.

External triggering produces a low impedance path between the tube electrodes by applying a high voltage trigger pulse to a third electrode placed outside the tube. This electrode can be a thin wire wrapped around the tube, a rod running along the tube, or a metallic reflector, provided that the electrode covers the entire distance between the tube electrodes. This triggering design is very flexible since the trigger circuit is not part of the main discharge circuit.

External triggering is often used in conjunction with "simmering". Simmering involves passing a dc current along the low-impedance path formed by the trigger. This maintains the ionised state of the xenon and allows for a stable and uniform arc (which can be made to fill the bore) to be formed before the main pulse is enabled. Without this the arc is normally thin and runs along the tube wall (Fang and Lee, 1986). This procedure can increase the electro-optical efficiency by 30-50% due to uniformity of current and plasma density (Ornstein and Derr, 1974). This allows the tube to be operated at lower input energies, thereby increasing the lifetime of the tube. The dc currents may be of several amperes, depending largely on the pressure of the xenon gas. The disadvantage of simmer triggering is that it creates

considerable heat. In the confined space of a reflector this produces high tube and optics temperatures. These can be reduced by cooling either with forced air flow, or by encasing the tube in a water jacket.

The output spectrum and efficiency of the discharge depend strongly on the current density during the discharge. Goncz (1966) showed that

> *at low current density, the spectrum consists of continuum plus lines with prominent features occurring at strong xenon lines between 800 and 900 nm. As the current density is increased, the spectrum changes continuously in a manner such that the continuum rises to mask out the lines and the spectral peak moves to shorter wavelengths.*

Lower current density discharges also improve the lifetime of the tube since the flash-tube operates at a lower fraction of the "explosion energy" of the tube.

Buck *et al* (1963) found that high fill pressures also increase the efficiency of flash-tube operation. Therefore maximizing the efficiency of the system involves using a high pressure xenon tube, with external triggering, simmering, and current densities as low as possible.

The useful lifetime of flash-tubes is limited (Goncz, 1966). One mode of failure is cathode splutter, where material from the electrodes is deposited on the walls of the tube. Initially this causes opacity of the walls and thus a reduction in light output. Eventually enough material can be deposited to "short" the electrodes together, preventing the formation of an arc.

Another influence on the lifetime is the quality of the electrode seals. Failure of these produces contamination of the xenon resulting in the inability of the flash-tube to trigger, simmer, or ignite.

The most spectacular mode of failure is explosion. The severity of this ranges from hairline cracks appearing in the wall of the tube, to explosive shattering of the tube. Empirically, the "explosion energy" of a flash-tube has been found to be given by

$$U_{ex} = kdl(t_{\frac{1}{3}})^{\frac{1}{2}} \tag{8.1}$$

where

- U_{ex} is the explosion energy in joules
- $k = 90$, an experimentally derived constant, this value holds when

- d (the bore diameter) is expressed in millimetres, and
- l (the arc length) is expressed in inches, and
- $t_{\frac{1}{3}}$ (the current pulse width) is expressed in milliseconds

This relationship is based on a linear fused-quartz tube wall, uncooled and not enclosed in any form of reflector. Cooling increases the explosion energy. Placing the tube in a reflector (for example in laser applications) decreases the explosion energy as it increases the joules-per-unit-length loading on the quartz. The pulse shape also has an impact on the explosion energy. The current pulse produced by a single branch capacitive discharge circuit has a higher peak current than that produced by a multi-branch circuit providing the same input energy and pulse length.

The lifetime is given to within an order of magnitude by

$$lifetime = (\frac{U_{in}}{U_{ex}})^{-8.5} \tag{8.2}$$

where U_{in} is the input energy. Thus, using 50% of the explosion energy would allow a lifetime of between 100 and 1000 pulses.

8.2.2 Design Requirements

In order for the system to be a candidate for an effective tattoo removal device several conditions need to be met. Some of the conditions are needed to remove ink from skin, while others are to make the system "user-friendly". Many hundreds of hours in an operating theatre using laser systems for vascular lesion removal has shown the importance of having a system that is safe, reliable, and easy to use.

The necessary conditions for removing ink are

- The system needs to have as much of the light delivered onto the skin to be in the visible region of the spectrum, especially wavelengths longer than 500 nm
- The pulse length must be suitable

Wavelengths less than 500 nm are very well absorbed into melanin (see figure 4.1). Damage to melanin-containing cells can result in abnormal pigmentation post-treatment. Exposure to ultra-violet light also needs to be minimised.

Initially the pulse length was set to 1 ms. The initial trial with 550 μs encouraged the belief that long pulses could be effective in removing tattoo pigment. Short (microsecond) pulses target individual ink granules inside the skin. Millisecond scale

pulses target fibroblasts inside the skin. These fibroblasts contain many ink granules and histologically they appear as one macroscopic ink granule. It was decided to see if a longer, higher energy pulse would improve the clearance rate.

The requirements to make the flash-lamp device user-friendly in a clinical trial are

- The flash-tube must have a reasonable lifetime
- The system must be operable by a single person
- The system must be safe for both patient and operator.

Since high-power flash-tubes are costly (the tubes for this system cost US$1000 each) they must have a reasonable lifetime. While what is "reasonable" is not easy to define, every attempt needs to be made to maximise the number of pulses from a tube.

Since laser tattoo removal systems are made for solo operation, the flash-lamp system had to have that capability as well. In the initial stages this condition was ignored in the interest of producing a functioning system. A later rebuild of the system modified the controls to make it usable by a single operator.

Obviously the system must be safe for both patient and operator. Operating a high-power flash-lamp safely involves electrical, mechanical, and optical safety.

8.2.3 Flashtube Design

As part of Zhang's research, two high pressure (3 atmospheres) xenon-filled tubes had been purchased from Xenon Corp (Woburn, MA, USA). These had a 2.5 cm long active region, and were designed for an 80 μs capacitive discharge (single mesh) pulse (see figure 8.3). The internal diameter of the tube was 7 mm.

A British flash-tube manufacturer (Laser SOS, Cambs, England) was contacted regarding the capabilities of the Xenon Corp flash-tubes (Xenon Corp being unwilling to discuss their design). Since more tubes were to be ordered Laser SOS were prepared to provide information and suggestions about flash-tube design and operation. The only modification to the tube design Laser SOS thought was necessary was the replacement of the electrode seals with re-entrant seals. Re-entrant seals are less likely to fracture during operation, leading to contamination of the xenon and failure of the tube. With this modification Laser SOS felt that their tubes would be suitable for a trial at 1 ms pulse length and 800 J input energy. However, in order to extend the lifetime of the tubes it was recommended that

Figure 8.3: The xenon flash-tube used for the first part of the trial. (0.7x actual size)

1. the power supply design incorporate simmer triggering (see subsection 8.2.1) to reduce the shock to the tube
2. forced-air cooling be used to maintain the tube and surrounding optics at reasonable temperatures.
3. that the peak power to the flash-tube be minimised.

The most effective way of minimising the peak power is to deliver the energy to the tube via a rectangular pulse of current.

8.2.4 Rectangular Pulse Shapes

Circuits producing rectangular pulse shapes have been analysed by Perlman (1966), White *et al* (1948), and Goncz (1966). These researchers all used multi-branch *L-C* pulse forming networks. Such networks behave as artificial transmission lines. The deposition of energies from several parallel-connected capacitors into the flash-tube are delayed by inductors to (by superposition) form a output pulse that closely simulates the pulse formed by the discharge of an equivalent coaxial transmission line. The following discussion on pulse forming networks is adapted from the above sources.

Let L_t and C_t be the total network inductance and capacitance respectively. Then the characteristic impedance of the network is

$$Z_0 = \sqrt{\frac{L_t}{C_t}} \tag{8.3}$$

and the pulse length, T, is

$$T = 2Z_0C_t = 2\sqrt{L_tC_t} \tag{8.4}$$

Since the energy in the network is given by

$$U_{in} = \frac{1}{2}C_tV^2 \tag{8.5}$$

the operating voltage, V, can be expressed in terms of the input energy, network impedance, and pulse length as

$$V = 2\sqrt{\frac{Z_0U_{in}}{T}} \tag{8.6}$$

Equation 8.6 is a useful design equation since for efficient energy transfer the flash-tube resistance, R, ought to be equal to the network impedance. This will ensure that reflections do not occur. Since the pulse is rectangular, for most of the duration of the pulse the discharge current will be approximately constant. Therefore R can also be approximated to be constant throughout the discharge.

The resistivity of xenon plasma has been shown to vary as the square root of the current density, J. The dependence is

$$\rho = \frac{1.13}{\sqrt{J}} \tag{8.7}$$

where ρ is the xenon plasma resistivity (Ω-cm) and J is the current density (A/cm^2). The constant in equation 8.7 was experimentally determined for a wide range of arc diameters, lengths, and current densities (Goncz, 1965). The tube resistance is then

$$\begin{aligned} R &= \frac{\rho L}{A} \\ &= 1.13\frac{L}{\sqrt{IA}} \end{aligned} \tag{8.8}$$

where L is the arc length, I is the instantaneous current, and A is the cross-sectional area.

The peak current, I_p, is then

$$I_p = \frac{V}{Z_0 + R} = \frac{V}{Z_0 + \frac{\kappa}{\sqrt{I}}} \tag{8.9}$$

where

$$\kappa = 1.13\frac{L}{\sqrt{A}} \tag{8.10}$$

Solving for I_p yields

$$I_p = \left(\frac{-\kappa \pm \sqrt{\kappa^2 + 4VZ_0}}{2Z_0} \right)^2 \tag{8.11}$$

The subtractive solution may be ignored since it leads to values of the peak current greater than the short circuit current ($\frac{V}{Z_0}$) which are not possible.

White *et al* (1948) presented several alternative designs for pulse forming networks which produce rectangular pulses. These were produced by numerical models of the circuits. Attempting to produce the infinitely sharp rise and fall times of a rectangular wave results in overshoots near the beginning of the pulse and excessive oscillations during the main part of the pulse. Guilleman (1944) overcame this by allowing finite rise and fall times. Networks based on this principle are known as Guillemen networks. They are further subdivided in to types "A" through "F", depending on the arrangement of the capacitors and inductors within the network. The first networks were designed to give a trapezoidal pulse shape with a rise time of approximately 8%. Five and seven section networks were modelled, but the improvement gained by the seven section networks were negligible. Reducing to fewer sections was found to deteriorate the pulse appreciably.

For a given pulse shape, some of the Guilleman types may not be producible in practice since they may have negative values of inductance or capacitance. The choice of Guilleman type for a particular application depends upon the capacitors and inductors available. One of the more "buildable" designs is the type E, shown in figure 8.4. This has sections of equal capacitance, which makes obtaining the capac-

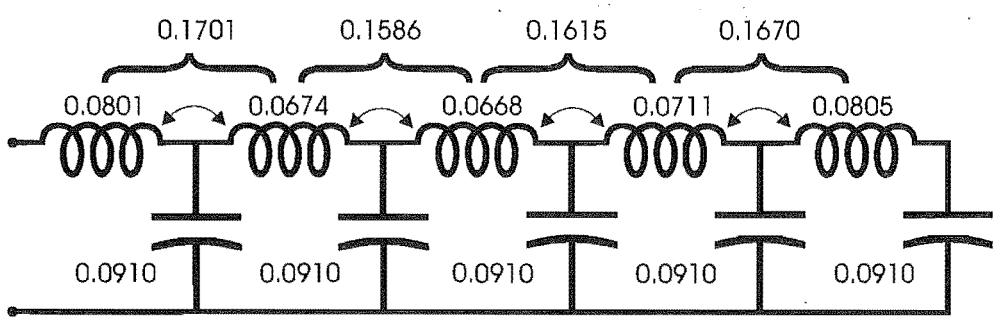

Figure 8.4: Type E Guillemin network with equal-capacitance mutual inductance sections. (From White, 1948, p. 205). To obtain the inductance and capacitance values multiply the "inductances" by TZ_0 and the "capacitances" by T/Z_0.

itors much easier. Slight variations in the values of the inductances are introduced to improve the pulse shape.

In practise the inductances are formed by a continuous solenoid wound in such a way that its total inductance is

$$L_t = \frac{TZ_0}{2} \tag{8.12}$$

The total network capacitance

$$C_t = \frac{T}{2Z_0} \tag{8.13}$$

is divided equally among the sections and each capacitor is connected to a tap on the solenoid. The inductances are not equal with the end sections having 20-30% more self inductance. The length to diameter ratio of the coil is chosen to give a mutual inductance which is 15-20% of the self inductance for the middle sections.

8.2.5 Power Supply Design

Based on the preceding analysis of a five-branch L-C network the power supply for the tattoo-removal flash-lamp was designed. First, an approximation was made for the value of the resistivity of xenon plasma. For pulses over 1 ms the resistivity is approximately 0.027 Ω-cm (ILC Technology, 1986). This leads to a tube resistance during the discharge of 0.18 Ω. Then, for a 1 ms critically damped pulse, the characteristic impedance for the network must be

$$Z_0 = 0.18\,\Omega$$

From equation 8.4 the total capcitance must be

$$C_t = 2800\,\mu\text{F}$$

and the total inductance is

$$L_t = 89\,\mu\text{H}$$

The circuit of the form showed in figure 8.4 was modelled with the circuit simulation program, PSpice. The flash-lamp was approximated using a non-linear resistor of resistance 0.18Ω. The capacitance and inductance were as in the previous section. The standard switch simulations used in PSpice have far too much resistance to adequately simulate the relays used in the real circuit, so the simulation switches were modified to produce very low resistances.

The simulated output of the pulse forming network is presented in figure 8.5. The current pulse is rectangular with some small oscillations during the pulse. This is close to the shape predicted theoretically. The negative currents after the main pulse

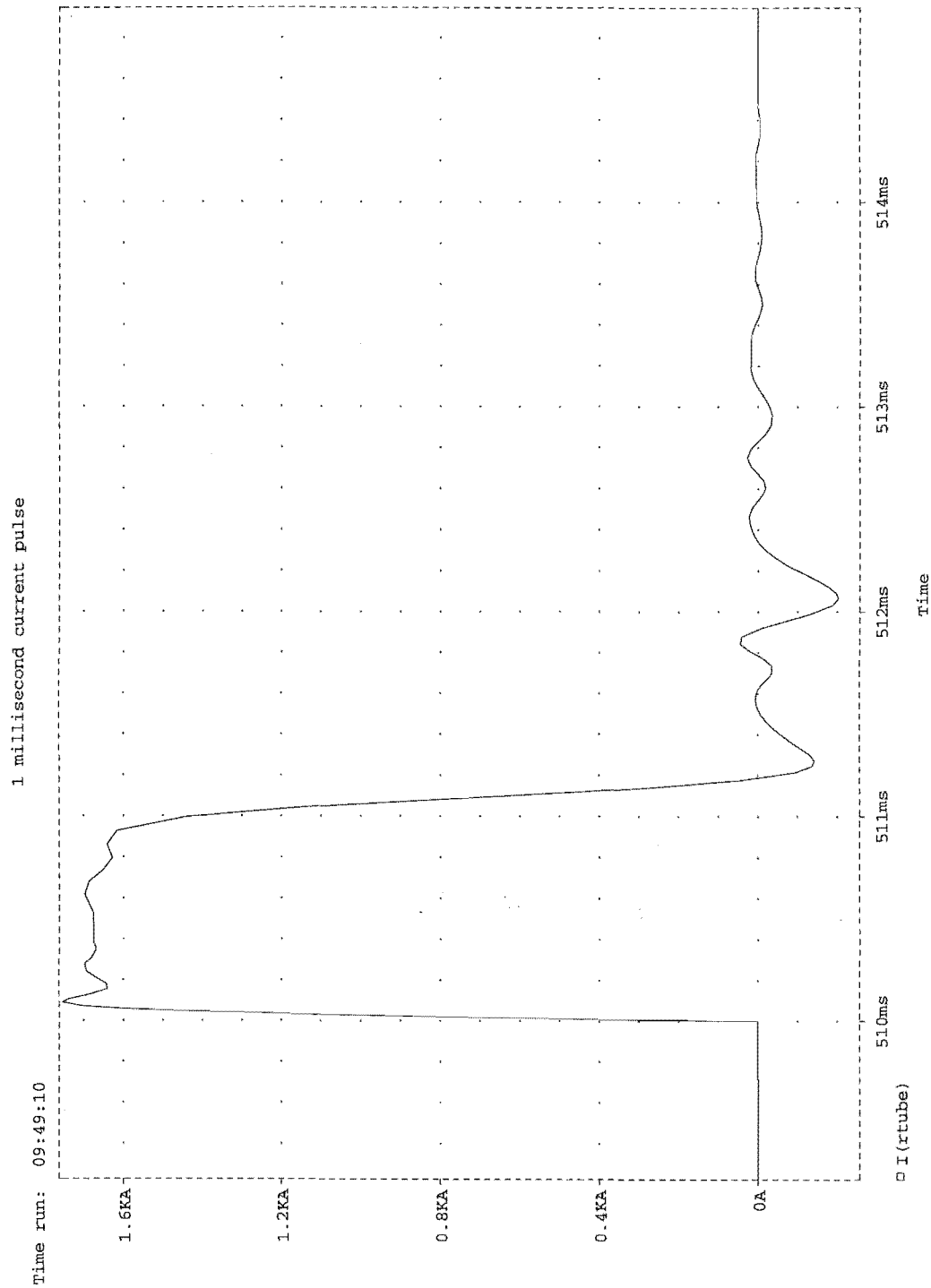

Figure 8.5: Simulated current pulse from the pulse forming network

do not occur in the real circuit. They are an artifact of simulating the flash-tube as a resistor. In practise the reverse voltage across the flash-tube quenches the ionisation and prevents the reflections. The pulse length produced in the simulation was 1 ms as expected. Having established that the L-C network produces the required pulse the real circuit needed to be produced.

8.2.6 The Pulse Forming Network

The author designed the inductor design followed Langford-Smith (1957). Wheeler's formula

$$L = \frac{a^2 N^2}{9a + 10l} \tag{8.14}$$

was used to determine the coil diameter (a) to length (l) ratio. This was 1:2.05 (for the end inductors, which have a larger inductance). Rather than having separate inductors, one long inductor was constructed and tapped at appropriate intervals for the capacitors.

Because of the high currents that would flow through the inductor, it needed to have low DC resistance. Therefore 8 mm diameter solid copper rod was wound onto a 125 mm outside diameter former. 64 turns were required to give 89 μH inductance.

The next stage of the power supply design was to determine the voltage that would provide a reliable external trigger for the flash-tube. Because the flash-tube is high pressure, it requires a high external trigger voltage to ionise the xenon. Experimentally it was found that a 25 kV pulse generated using a car ignition coil was sufficient to initiate ionisation in the flash-tube when the voltage was applied to a metallic rod running along the outside of the flash-tube, between the electrodes.

Having established ionisation in the tube, this need to be maintained with a DC simmer current. It was found by experiment that a 2 kV potential difference was necessary to expand the initial spark into a streamer that could be maintained using a 2 A DC current. Once the current is established the 2 kV starting supply is isolated from the discharge.

The pulse forming network, the external triggering and the summer supply form the three main component of the flash lamp power supply design. The control circuitry for these elements was designed in consultation with the electronics workshop in the Department of Physics and Astronomy. The author provided the requirements for successful operation of the system. These requirements were

- that the pulse forming network could be charged quickly from the mains supply, the voltage being variable and displayed on a meter

- once the network was charged the charging supply needed to be isolated from the circuit to protect it from the main current pulse
- the flash-tube had to be triggered and the simmer current established
- the presence of the simmer current needed to be detected before any further operation would go ahead.
- if the simmer current was present an isolating relay would switch the simmer-start supply out of the circuit and the pulse forming network could be discharged through an SCR switch
- at the end of the pulse the negative voltage from the discharge would quench the DC simmer current, terminating the firing cycle.

These requirements were taken and a control circuit was designed and built to specification. The trigger circuit is shown in figure 8.6. The main control circuit is

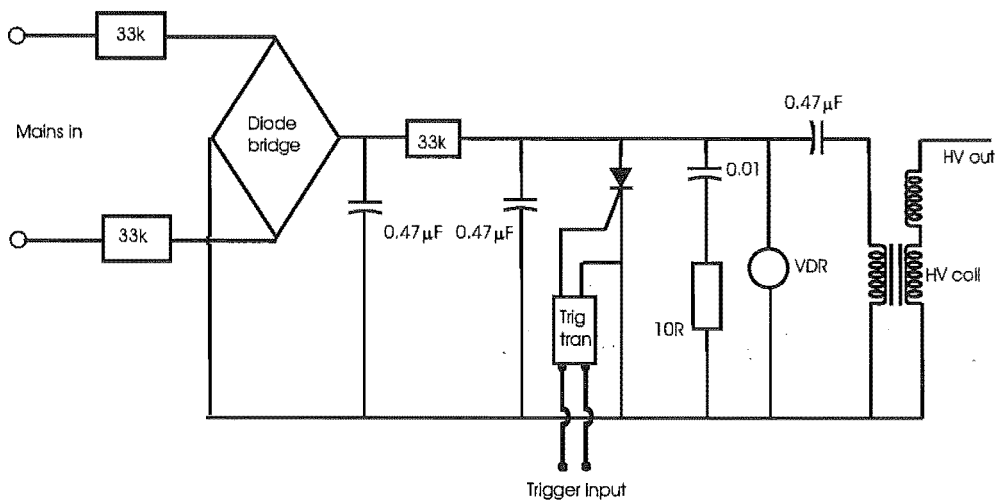

Figure 8.6: Trigger schematic.

shown in figure 8.7.

The initial prototype was laid out with the pulse forming network lying horizontally. The trigger and simmer supplies were in a separate box which was on top of the pulse forming network box. This prototype required two people to operate it, one to use the handpiece described in section 8.2.7, and the other to charge the pulse forming network and operate the controller.

Once the system was constructed it was tested in the laboratory. Figure 8.8 is a

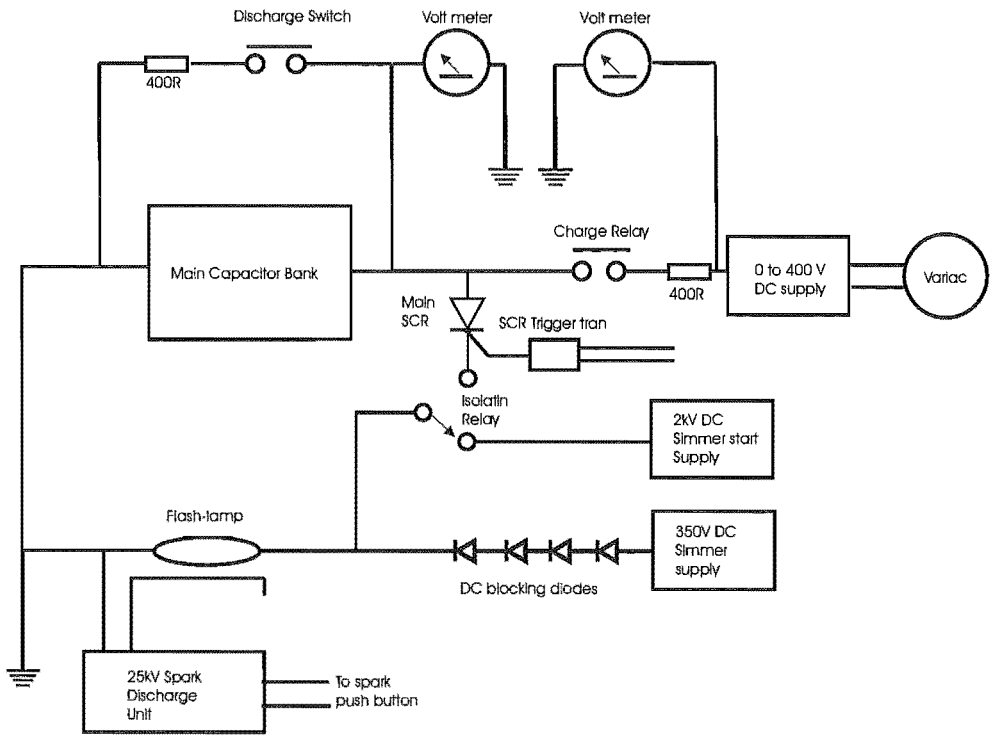

Figure 8.7: Supply schematic.

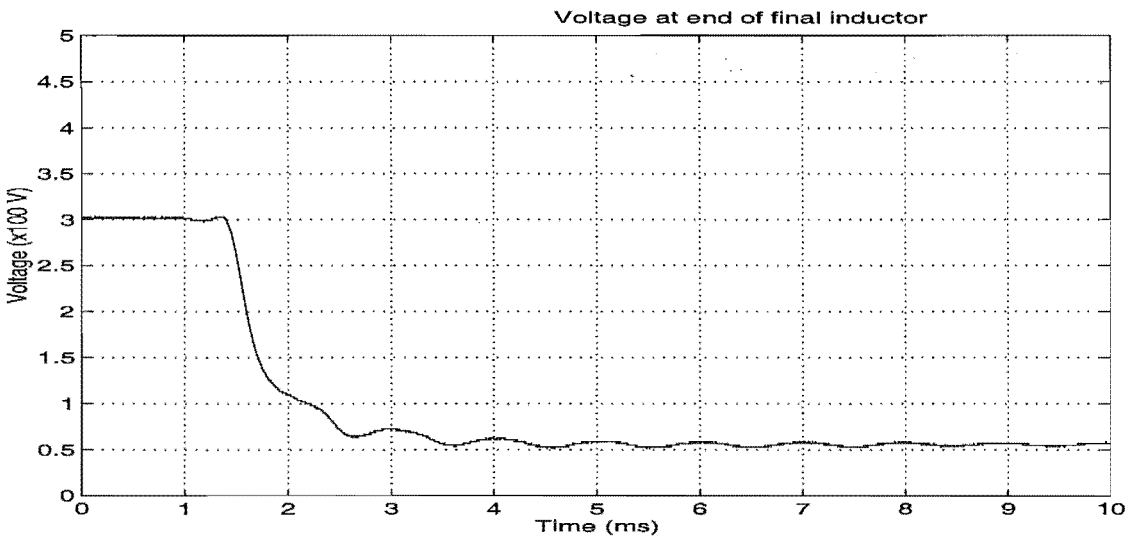

Figure 8.8: Current pulse from the pulse forming network

trace of the voltage at the end of the inductor nearest the flash-tube as a function of time. The trace starts at 250 V, which was the voltage across the capacitors. This prevents the rising edge of the pulse being observed. At $t = 0.5$ ms the SCR was triggered.

This system produced the light pulse shown in figure 8.9. This was measured

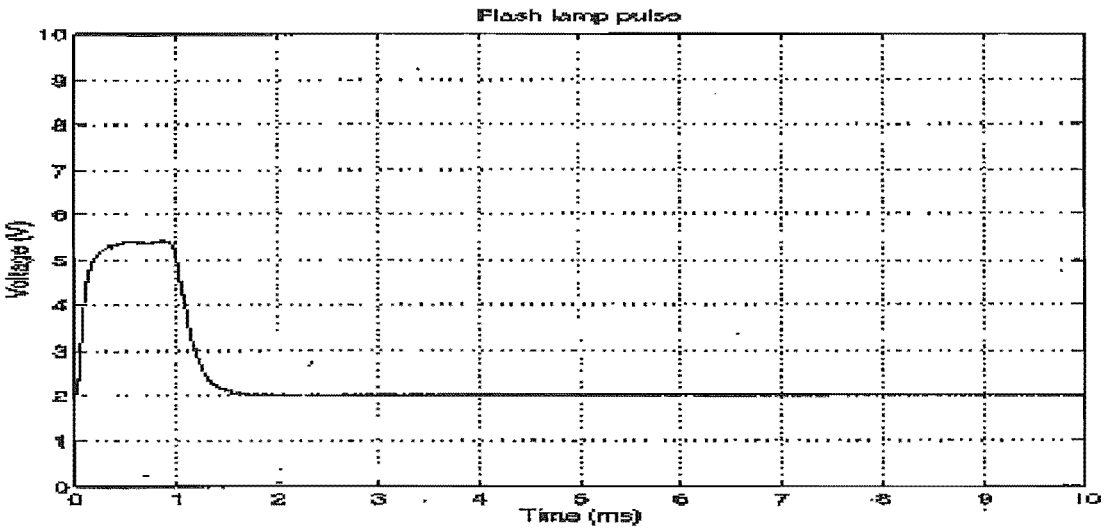

Figure 8.9: Light pulse from the pulse forming network

with a fast photodiode (the same as was used in Mehrtens *et al* (1997)). The shape and duration of the pulse meet the design specifications of a 1 ms pulse of light with a square temporal profile.

8.2.7 Hand-Piece

The design for the reflector followed Siegrist (1976). Conventional reflectors, such as semicircular, parabolic, and plane-corner mirrors, reflect some of the light emitted from the tube back into the plasma. Emmett *et al* (1964) showed that at high current densities xenon plasma is essentially opaque to wavelengths longer than 500 nm. Siegrist used ray tracing to show that a cusp reflector formed from an involute of a circle the same diameter as the plasma directed most, if not all, of the light away from the plasma region. The equations for such a surface in cartesian co-ordinates are

$$\begin{aligned} -x &= r\cos\phi + r\phi\sin\phi \\ y &= r\sin\phi - r\phi\cos\phi \end{aligned} \tag{8.15}$$

where r is the radius of the tube and ϕ is a parameter. This is plotted in figure 8.10.

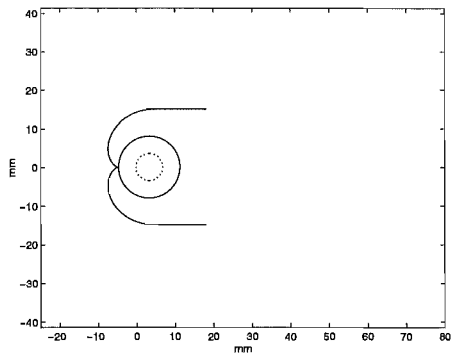

Figure 8.10: Diagram of the reflector system. The dotted circle is the plasma region, the solid circle is the maximum diameter of the tube

If the reflector is not placed precisely at the cusp some light will re-enter the plasma, but at the less optically-dense edges of the discharge. Siegrist found that cusp reflectors gave a 9.6% advantage over plane corner reflectors, and 8.4% over parabolic mirrors.

The reflector was modelled with AutoCAD and ray-tracing was done to determine whether light from the plasma would indeed miss the plasma and be reflected to emerge from the aperture. Initally it was thought that the aperture could be narrowed using plane mirrors converging from the ends of the cusp to produce an aperture 1 cm wide. However the ray-tracing showed that most rays that reflected off the plane mirrors stalled and re-entered the area around the flash-tube. This idea was discarded in favour of close-coupling the cusp/flash-tube with the aperture, so as to maximise the intensity of the direct rays from the flash-tube to the target.

This design was first modelled using silvered mylar on a polycarbonate and wax former. The tube was inserted in this and fired. The high temperature caused by the simmer current and also the flash evaporated much of the reflective coating off the mylar and melted some of the mylar. Further work on reflector shape was done using polished aluminium.

The output aperture measured 30 mm x 30 mm. Although the active region of the flash-tube was 25 mm, some light is produced in the adjacent plasma ballast regions between the active region and the electrodes. This light was also directed towards the patient.

The polished aluminium reflector was then connected to the trigger supply to determine its suitability as a trigger electrode. Tests showed that the cusp was sufficient as an electrode provided it was placed almost in contact with the tube. This meant that a separate trigger electrode is unnecessary with this design.

The flash-tube and reflector system were contained within a black polycarbonate shield (see figure 8.11). The shielding was designed to protect the operator from the

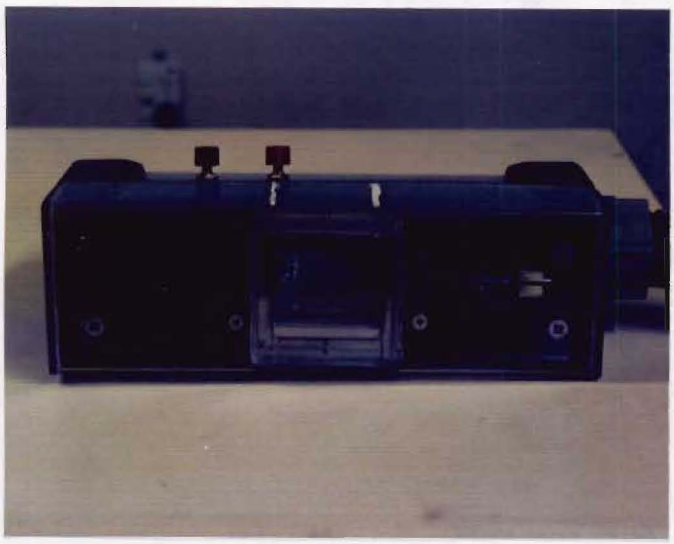

Figure 8.11: The hand-piece, showing the output aperture with polycarbonate shielding

possibility of injury from both an exploding tube and light leakage from the optical system. Polycarbonate has very impact resistance so the energy from an exploding tube would be absorbed by the polycarbonate. The high voltage areas of the hand-piece were well separated from the users and shielded by the polycarbonate.

This sheilding was connected to a handle, making a device that looks similar to an iron. This is connected via a long hose to the pulse forming network and power supplies. Inside this tube run heavy welding cables to carry the current.

In order to keep the hand-piece cool and to increase the life of the flash-tube the hot air from around the tube and in the reflector needed to be removed. This was achieved with a flow of compressed air. This was piped through the same hose as the welding cables and injected through a small hole in the side of the reflector.

8.3 Flash-Lamp Testing

The system was tested on red cardboard. At 400 J input energy much of the red dye was vaporised (see figure 8.12). After the pulse there was a strong smell of ozone,

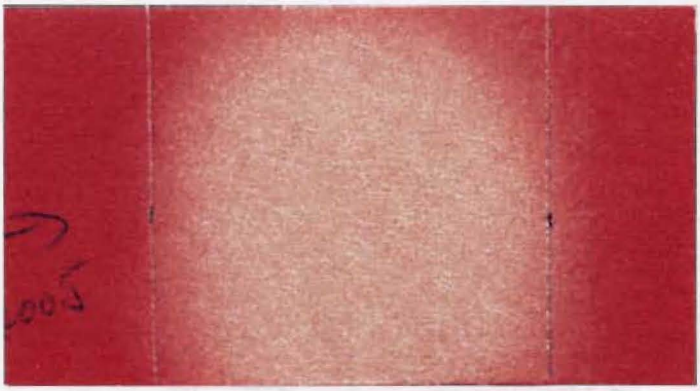

Figure 8.12: Red cardboard after illumination with a 400 J pulse. (1.7x actual size)

indicating that, as expected, there was UV light being produced by the discharge, and was forming ozone in and around the hand-piece.

The UV filter put between the tube and the patient also had to be able to protect the patient from the possibility of the tube exploding during a discharge. Polycarbonate is a suitable material for the mechanical shielding. To investigate its optical properties a transmission spectrum through 2 mm thick polycarbonate sheeting was obtained (figure 8.13). Below 380 nm the transmission is essentially zero, providing protection from UVC (100-280 nm), UVB (280-315 nm), and almost all UVA(315-400 nm). Glass has a similar shaped spectrum, but the cut-off wavelength is approximately 300 nm. These results indicated that a polycarbonate cover for the treatment window would provide sufficient protection for the patient. Having put the polycarbonate shield in place more red cardboard was treated. The result is shown in figure 8.14. Less of the red dye was vaporized.

The amount of dye removed from the cardboard is similar to when the copper vapour laser is tested on red cardboard at treatment fluences. This indicated that the flash-lamp was producing sufficient energy to have a physiological effect on skin.

8.4 Clinical Use

This first prototype was used for the first two months of the clinical trial. It required two people to operate: one to operate the controls, the other to position the

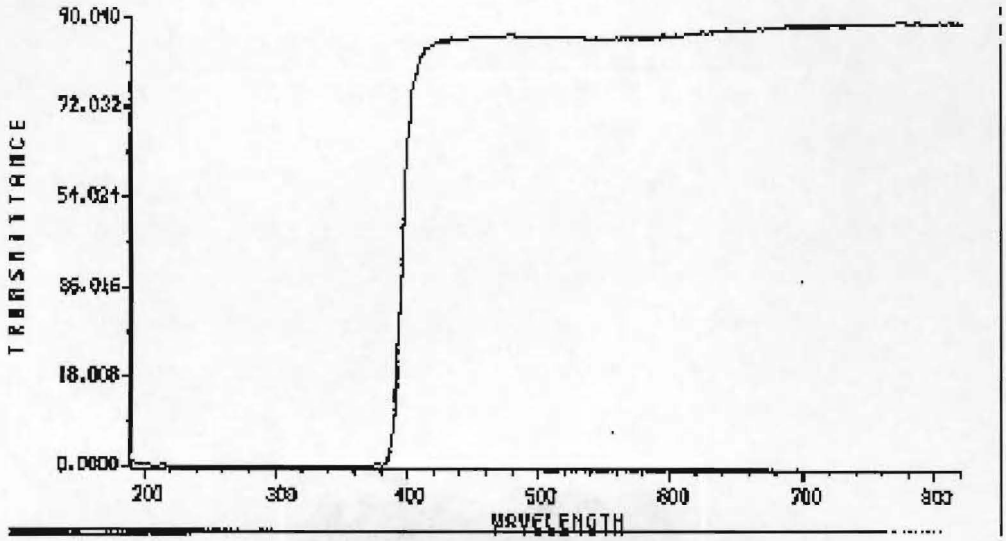

Figure 8.13: The transmission spectrum of 2 mm thick polycarbonate.

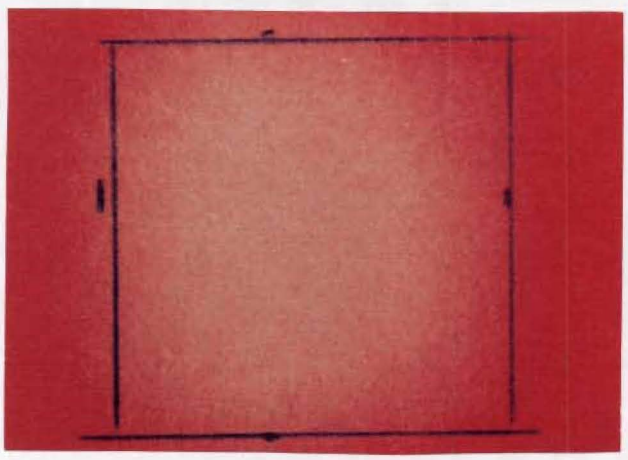

Figure 8.14: Red cardboard after illumination with a 400 J pulse through 2 mm of polycarbonate.(1.7x actual size)

hand-piece on the patient. This was inconvenient. In the break between successive treatments for the patients the system was remodelled. There were two parts to this reconstruction. The first was to make the system vertical with the control units and power supplies being mounted above the (now vertical) pulse forming network, and in the same box. This reduced the footprint of the device to make storage and moving easier.

Second, the charging and firing controls were moved to the hand-piece with buttons on the side of the hand-piece underneath where the operator's fingers rest. This allows the entire system to be operated from the hand-piece once the required voltage was set. The system could therefore be operated by one person and is shown in figure 8.15. This prototype was use for the remainder of the clinical trial described in chapter 9.

Figure 8.15: The second prototype of the flash-lamp tattoo treatment system.

After the first set of clinical trials it was decided to reconfigure the pulse forming network to halve the pulse length to 500 μs, thus doubling the power. This was achieved by halving the network capacitance while keeping the inductance the same. This method did cause some deterioration of the pulse shape. In particular the impedance matching of the circuit was affected leading to underdamping. The effect was modelled with PSpice, and is shown in figure 8.16. Once again, in practice the reverse voltage quenches the discharge, thus suppressing the reflections.

This system was used in a short clinical trial. However it quickly became apparent that the shorter pulses produce excessive cathode splutter. Electrode material

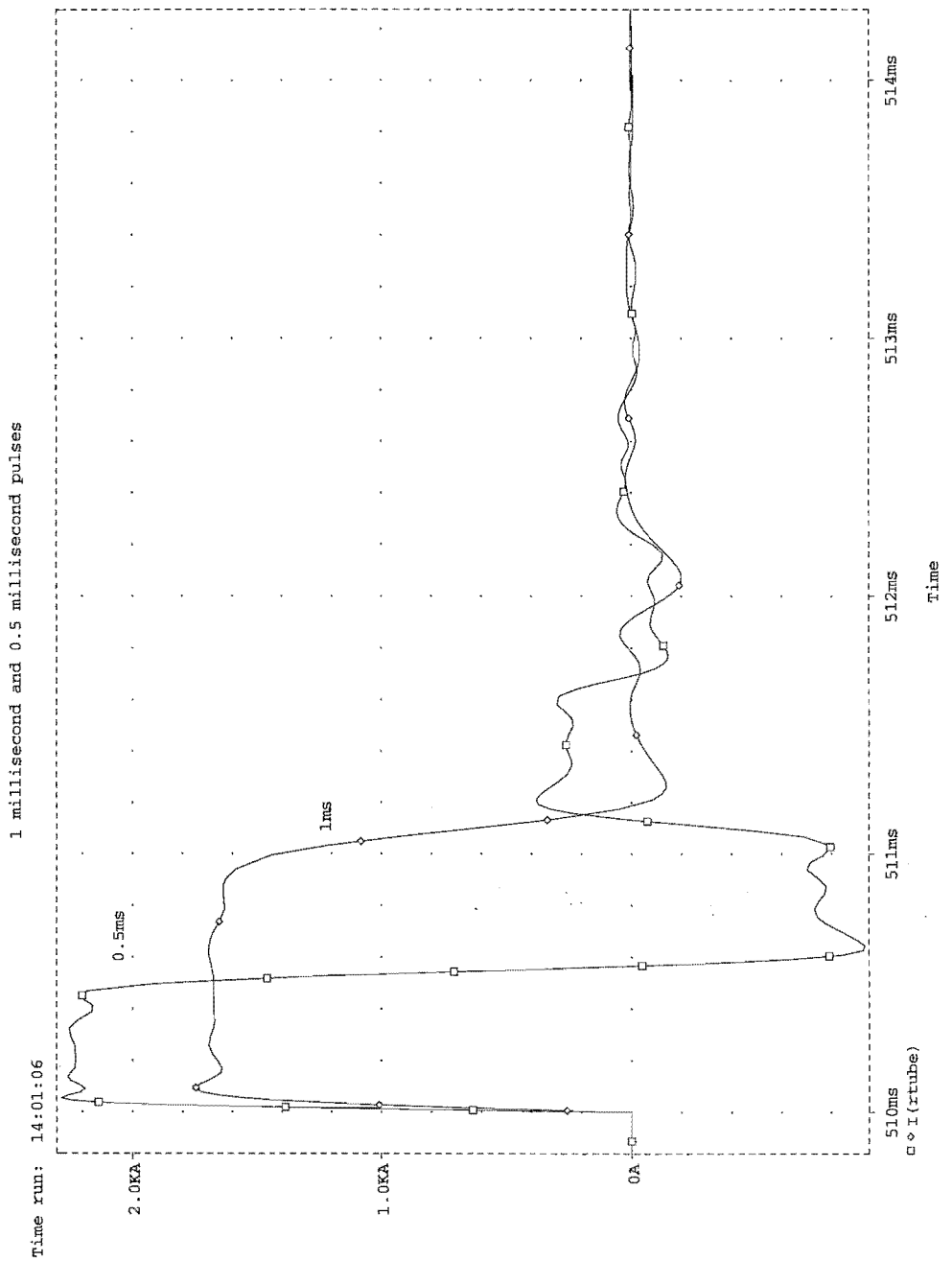

Figure 8.16: A comparison of the 1 ms and 500 μs pulses. The shorter pulse has substantial reflections.

deposited on the wall of the tube formed a conducting path between the electrodes, causing failure of the tube.

Chapter 9

Clinical Trial

Having constructed the flash-lamp system and tested its output in the laboratory, the system needed to be evaluated with respect to its clinical effectiveness. The author gained approval for a clinical trial from the Canterbury Ethics Committee of the Southern Regional Health Authority, and from the Human Ethics Committee of the University of Canterbury. The consent covered the treatment itself, and also allowed for biopsies to be taken. Several patients had pre-treatment, immediately post-treatment biopsies, and then biopsies at varying intervals thereafter.

9.1 The Patients

Twelve people who had presented to Mr E. Peter Walker for tattoo removal gave informed consent to take part in the trial. Each patient was given a document containing detailed information about the clinical trial, the treatment process, and what we believed would occur after their treatments. They were asked to read, consider, and discuss this information with whoever they wished before giving consent. A list of these patients, along with a description of their tattoos is given in table 9.1. To minimise the amount of melanin over the tattooed areas, all were asked to avoid sun exposure if possible and to use sun-block over their tattoos.

Several of these patients did not complete the full course of the trial. One (HS) decided to proceed with a serial excision, another (NM) left the district for employment reasons. RL, CN, and AT failed to appear for follow-up appointments and attempts to contact them were unsuccessful.

Initials	Sex	Skin type	Description of tattoo
KB	M	II	Professional multicoloured tattoos, left forearm, right and left lateral arm, right posterior arm. Amateur india ink tattoo left first web space
LB	F	IV	Professional blue/black tattoo left upper arm. Treated with tannic acid 2 years prior to the trial leaving scar in the middle of the tattoo.
HB	F	II	Professional over amateur multicoloured tattoos both wrists
DD	F	I	Professional blue/black tattoo right upper chest. Tannic acid treatment 4 years prior to trial, and ruby laser treatment 2 years prior to trial. Hypotrophic scar secondary to tannic acid treatment, and hypopigmentation secondary to ruby laser treatment.
DH	M	II	3 pale india ink amateur tattoos wrist. Ruby laser treatment 1 year prior to trial.
VL	F	I	Professional multicoloured tattoos left forearm and upper right breast.
RL	M	III	Amateur india ink tattoos arms and face
NM	M	IV	Blue/black amateur tattoos left hand and arm. Some hypertrophic scars on volar forearm secondary to infection after tattooing.
NMc	F	I	Professional blue/black tattoo posterior right shoulder
CN	F	IV	Professional and amateur blue/black tattoos hands and arms.
HS	F	I	Black professional tattoo left posterior shoulder.
AT	F	I	Professional multicoloured linear tattoos upper chest and stomach

Table 9.1: Patients in the clinical trial of the flash-lamp system.

9.2 Treatment Protocol

The area of skin to be treated was shaved. Having hair in the area is undesirable as it absorbs some of the light, reducing the fluence that is incident on the tattoo itself.

Initial testing on the investigators showed that the treatment caused a mild stinging sensation, like being slapped. Therefore no anaesthesia was used for the treatments in the clinical trial, except where a punch biopsy was taken. Then Xylocaine 2% with adrenalin (Astra Pharmaceuticals) was given as a block anaesthesia. Several of the patients reported that the tattooing process itself was more painful than the treatment.

At the initial treatment session the plastic surgeon, Mr E. Peter Walker, was present to administer the treatment and to take the skin biopsies. The flash-lamp system was operated by the author. At subsequent treatments with the first prototype device, which required two operators, the author operated the system while the hand-piece was positioned by Professor Bulter. Once the firing controls were put on the hand-piece the author was responsible for all treatment sessions. The patients were advised to contact Mr Walker immediately if they had any concerns in the post-treatment period. Since they were part of the clinical trial there was no charge for consulting with Mr Walker, beyond the fee for the initial consultation.

The hand-piece was held against the tattoo. Where the area to be treated involved fine lines of ink, polished aluminium masks were used to shield "normal" skin. Sufficient pressure was applied to blanch the blood vessels in the tattooed area. The tattoo was then treated.

Following the treatment a soothing cream (Brulidine® cream, dibromopropamidine isethionate B.P. 1.5 mg/g) and gauze were used to cover the treated tattoo. The patients were asked to be careful not to knock or otherwise cause trauma to the treated area. This has been associated with a higher incidence of scar formation (Dixon *et al*, 1984a).

The patients were given a form to take home, which asked them to record regular observations of the appearance of the skin in the 48 hours after the treatment. They were also asked to return to have photographs taken during the healing process. Detailed notes were kept by the author and shown to Mr Walker at regular intervals. Those patients having biopsies taken saw Mr Walker in his clinic for the procedure.

Initially the pulse length was set to 1 ms, with the input energy being 300-400 J. During subsequent treatments the input energy was increased to 550 J. Later in the

trial the pulse length was shortened to 0.5 ms and the input energies increased to a maximum of 1000 J.

9.3 Results

9.3.1 Immediate Response to Illumination

All the patients reported a slapping sensation, likening it to a sharp snap with a large rubber band, or hot needles being inserted into the skin. For a few hours thereafter a tingling or burning sensation was noted.

At 300 J input energy erythema and oedema over the ink were noted within 30 seconds of illumination. With higher energies, this time was markedly reduced, with erythema forming within 5 seconds on occasion, and oedema (raised 1 mm from the surrounding skin) soon afterwards (figure 9.1).

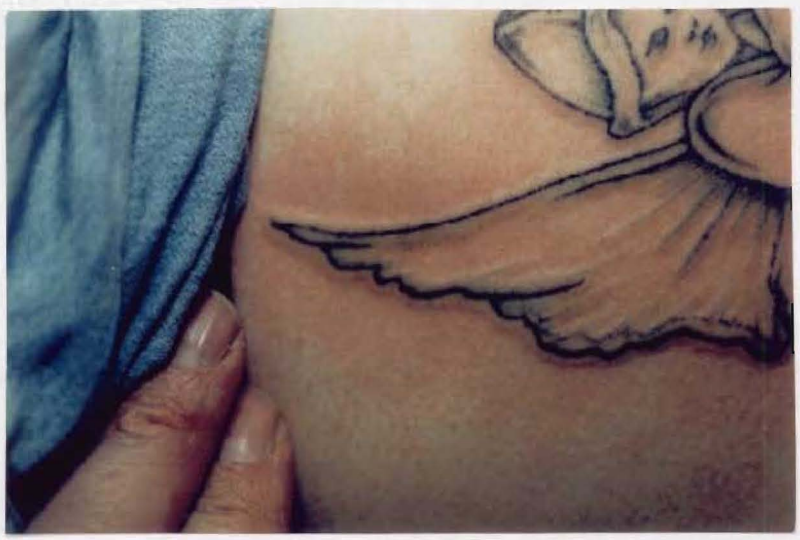

Figure 9.1: Erythema and oedema 2 minutes after treatment (AT).

In the 24 hours after treatment, some of the patients had blisters form on the inked areas. Regions of treated "normal" skin adjacent to tattoos had no blister formation. One patient (KB) had strong blister formation. He burst the blisters which led to an infection occurring. This resulted in mild atrophic scarring and hyperpigmentation at the site of the infection (figures 9.2, 9.3, and 9.4). The hyperpigmentation had resolved at 6 months.

The marked oedema persists for up to 8 hours, though more general swelling lasts for up to 24 hours. The erythema fades over the course of 2-3 days, much like

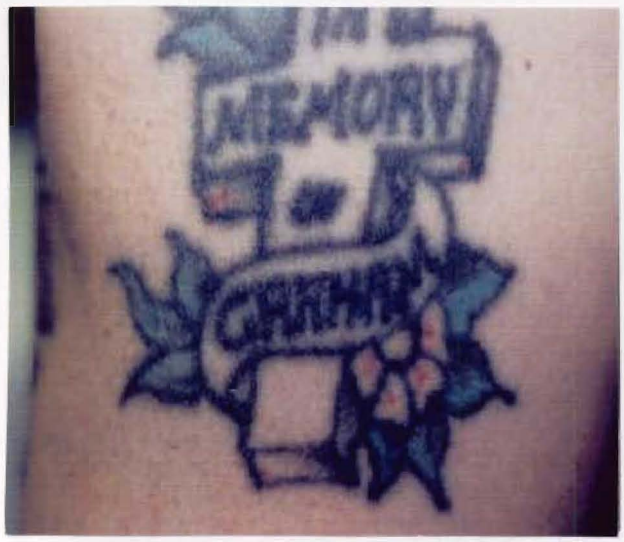

Figure 9.2: Tattoo on the right bicep, pre-treatment (KB).

a sunburn.

Half of the patients treated had mild epidermal peeling a few days after treatment. Those patients with Fitzpatrick skin type IV had peeling that extended beyond the margin of the ink. The rest (skin types I and II) had pin-head sized scabs in inked areas, which then peeled (figure 9.5).

9.3.2 Cosmetic Results

With the pulse length set to 1 ms there was no indication of any tattoo fading, even after repeated treatments with the maximum input energy (550 J). After the modification of the system to use 0.5 ms pulse length and higher input energies some fading was seen on 3 of the 12 patients. However, even after as many as 10 treatments the fading was not satisfactory.

One of those three had atrophic scarring following an infection. The scabs which formed were blue/black, suggesting the presence of ink. The other two patients had no scab formation, so any ink removed is likely to have been via macrophage activity (see subsection 9.3.3).

The patients who had their tattoos fade were LB and NM. Both have heavily pigmented skin (type IV).

LB has a tattoo of a leopard on her left upper arm (figure 9.6). After 10 treatments with the flash-lamp system the tattoo has faded noticeably, but is still plainly visible. The ink seemed to be less dense and the detail of some of the leopard's

Figure 9.3: Tattoo (right bicep) with infection.

Figure 9.4: Tattoo (right bicep) after 2 months. There is mild atrophic scarring and some hyperpigmentation remains

Figure 9.5: The "forehead" of the tattoo shows pinhead sized scabs (the dark areas on the ink). The scars on the left side are punch biopsy sites.

"musculature" is less defined (figure 9.7).

NM has a tattoo of a skull in his right shoulder (figure 9.8). After 5 treatments with the flash-lamp system the tattoo was paler (figure 9.9). This is particularly noticeable on the right of the skull, adjacent to the eye.

9.3.3 Why Does The Flash-Lamp System Not Work?

The clinical trial was terminated when it became apparent that the lifetime of the flash-tube was significantly shortened by using the shorter pulses. After only a few dozen pulses cathode splutter was coating the interior walls of the tube. This led to shorting between the electrodes and ultimately tube failure. The shorter lifetime coupled with the slow response rate of the tattoos indicated that the system was unlikely to provide a satisfactory treatment for tattoos.

Histologies taken immediately after flash-lamp treatment (1 ms illumination time) showed little rupturing of cells containing ink. These cells (primarily fibroblasts) have a long lifetime in the skin. One pre-treatment sample showed fibroblasts containing large amounts of ink. The pathologist expressed surprise that such a cell could still remain viable. This may indicate that severe damage is needed to destroy such a cell.

Histological studies of pigment-containing cells after Q-switched laser treatment indicates that explosive rupture occurs (Taylor *et al*, 1991; Zelickson *et al*, 1994,

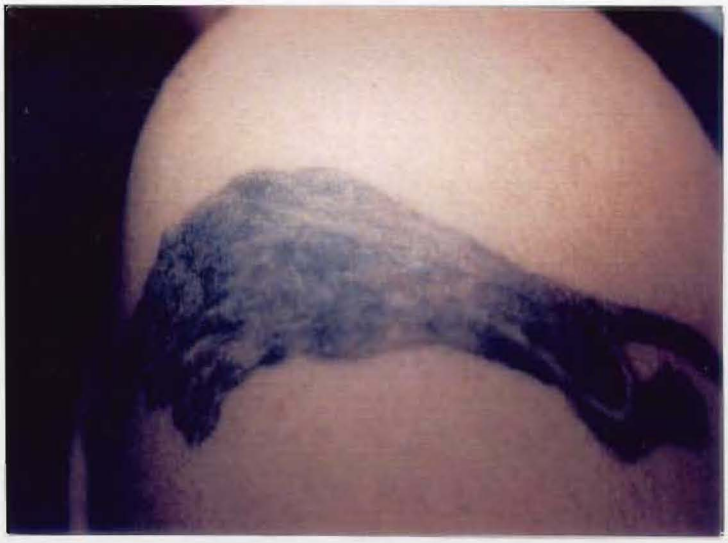

Figure 9.6: Tattoo on the left shoulder, pre-treatment

for example). Histologies taken immediately after illumination show extracellular pigment in the vicinity of cellular debris, or pigment within damaged cells. After eleven days the pigment was once again intracellular - in fibroblasts, macrophages, and mast cells. These cells have an important role in the inflammatory response and phagocytosis. One "speculation" on the mechanism for the clinical lightening of laser-treated tattoos (Taylor *et al*, 1991, p 135) was that the *"process of inflammation and phagocytosis reduces the overall amount of tattoo pigment, and that some pigment is eliminated during desquamation of epidermis during repair."* This is illustrated in figure 9.10.

The histology taken after the (1 ms) flash-lamp treatment showed that pigment-containing fibroblasts had been damaged, but not explosively ruptured. Ink granules were still intracellular. Later samples showed no cellular debris, indicating that cells may have repaired themselves with little or no reduction in the amount of pigment.

The PhotoDerm PL, which also uses non-laser light, has the ability to use far longer pulses lengths (up to 16 ms) than the flash-lamp system developed here, with correspondingly higher fluences. These may be enough to cause thermal necrosis (without the explosive rupture produced by Q-switched lasers) of the pigment-containing fibroblasts in much the same way that heating red blood cells causes thermal necrosis of endothelial cells in the laser treatment of port-wine stains.

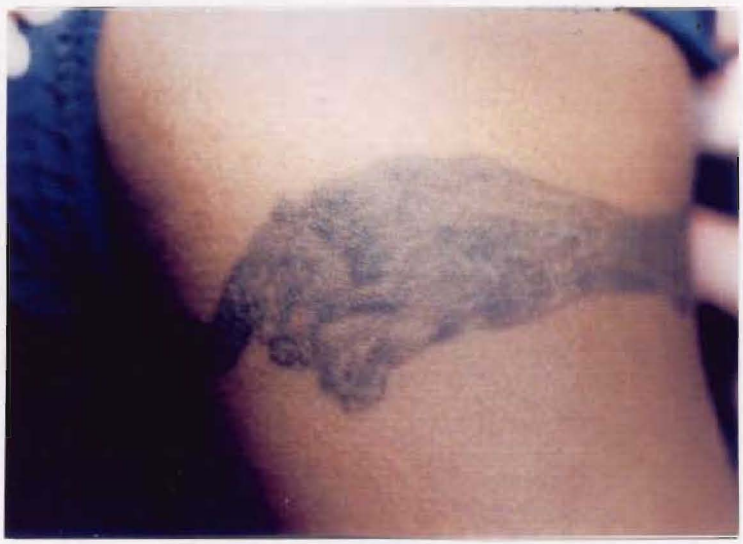

Figure 9.7: After 10 treatments with the flash-lamp system. There is noticeable fading and blurring of the tattoo.

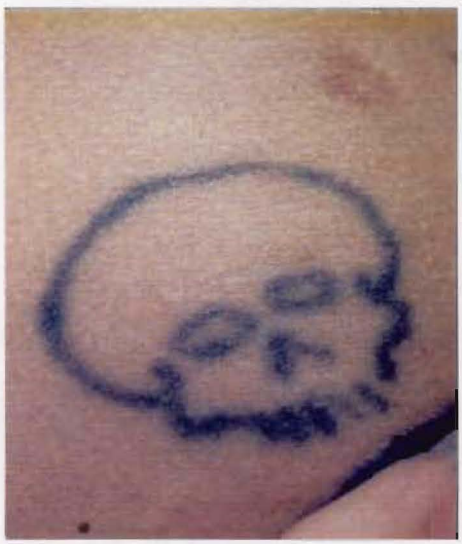

Figure 9.8: Tattoo on the left bicep, pre-treatment.

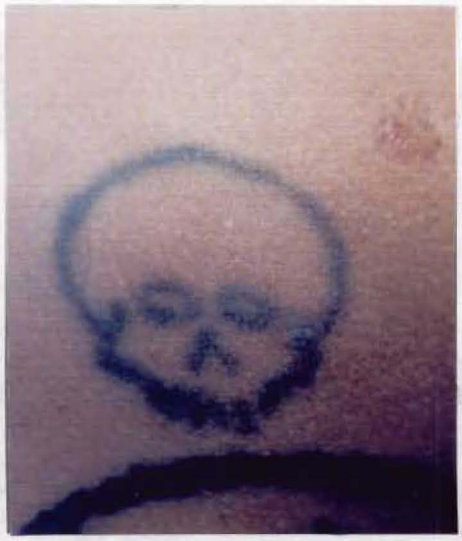

Figure 9.9: After 5 treatments with the flash-lamp system. The area to on the right of the skull, adjacent to the eye, showed noticeable ink loss.

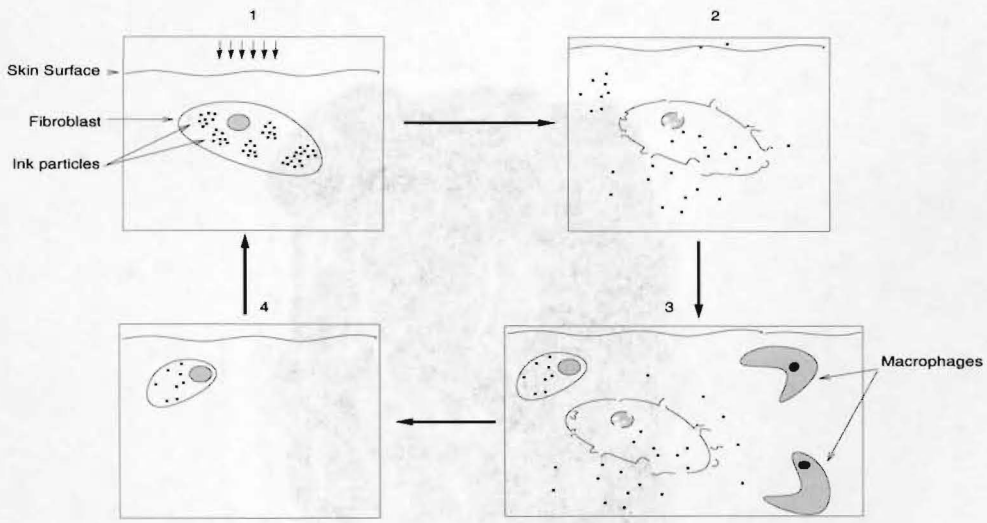

Figure 9.10: 1) A short pulse of light is incident on a fibroblast, 2) rupturing it and scattering pigment into the adjacent tissue. 3) Desquamation of the epidermis and phagocytosis remove some of the pigment, 4) while the rest is re-encapsulated in fibroblasts.

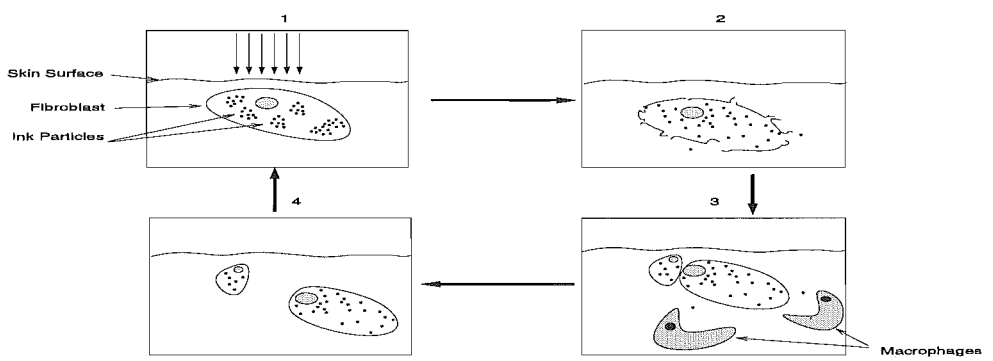

Figure 9.11: 1) A pulse of light from the flash-lamp is incident on a fibroblast. 2) The cell suffers thermal damage, but remains viable. 3) Phagocytosis removes any pigment that has become extracellular. 4) The fibroblasts may have slightly less pigment encapsulated.

Chapter 10

Tendon Transfer Technology

This chapter describes the development of an instrument to measure the stretch of a muscle undergoing tendon transfer surgery.

10.1 Introduction

Tetraplegia is caused by injury to the spinal cord in the neck. Depending on the location of the injury some limited movement in the shoulder and arms may still be possible. However, tetraplegics are rarely able to straighten their elbows, raise their forearms, or use their thumbs and fingers to grasp objects. This makes a tetraplegic almost completely dependent on others for day-to-day care.

Tendon transfer surgery offers some hope for those tetraplegics who have the ability to move their shoulders. A deltoid-triceps tendon transfer involves taking a tendon from a patient's shin and placing it in their upper arm. Mobility is achieved by attaching one end of the tendon to the still functioning posterior deltoid muscle, and the other end to the tricep. After extremely intensive physiotherapy the posterior deltoid can be trained to operate the tricep muscle enabling the patient to straighten their elbow, and raise their arm above their head. With this movement the patient can lift and push, which are important for wheelchair propulsion.

Once this motion is possible, forearm surgery is an option. This surgery also requires at least one strong forearm muscle, supple thumb and finger joints, and preferably a strong wrist extension. A tendon is attached from the strong forearm muscle to the hand. This enables the patient to grasp objects using thumb and fingers. The patient's ability to feed, grip a pen, and dress is restored - all actions which were previously impossible.

Tendon transfer surgery is not new, having been offered in Christchurch since 1992 at Burwood Hospital. The surgeons conducting this surgery are Professor Alistair Rothwell, an orthopedic surgeon, and plastic and reconstructive surgeon,

Mr Stuart Sinclair.

Both operations are most successful when the tendon is attached such that the muscle tension is optimal. Too much tension on the muscle and the muscle loses some of its strength, just like overstretched elastic. An under-tensioned muscle requires too much movement before the desired action is obtained. The correct muscle tension is normally found using the passive tension felt during surgery (Fleeter *et al*, 1985). This requires considerable skill and experience on the part of the surgeon. Even so, consistancy is hard to achieve. It is desirable the tension on the muscle be quantified *in situ* so that the best result can be achieved as often as possible.

10.2 Muscle physiology

Bulk muscle tissue is composed of fasciculi, which are the strands visible to the naked eye in red meat. Within each fascicle there are smaller fibres (myofibres) separated by a membrane. These myofibres are 10-50 μm in diameter and 1-40 mm in length. The myofibres are made of myofibril bundles surrounded by a plasma membrane. These myofibrils are approximately 1 μm in diameter.

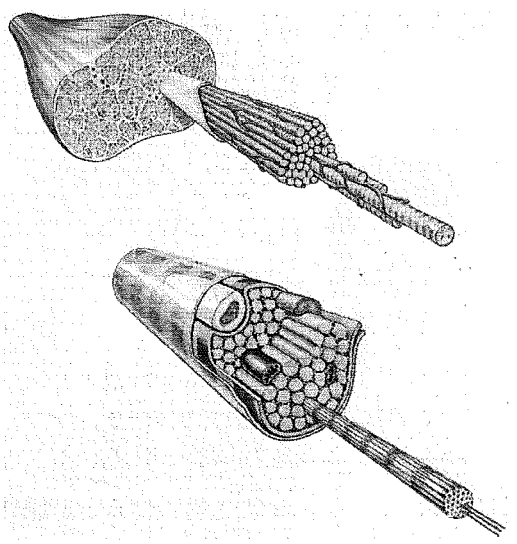

Figure 10.1: The structure of bulk muscle tissue. Muscle is composed of successively smaller bundles of fibres, from the whole muscle to fascicoli, myofibres, myofibrils, and protein filaments. A sarcomere is a section of myofibril containing one light and one dark region.

Myofibrils are composed of the contractile proteins actin and myosin which alternate along the length of the myofibril. Actin is a thinner filament than myosin

and gives the myofibril a periodic light and dark appearance. A length of myofibril containing one section of actin and one section of myosin forms the basic unit of striated muscle - the sarcomere.

Muscle contraction and extension are produced by the actin and mysin filaments sliding past one another. This shortens or lengthens the sarcomere. Figure 10.2 is a micrograph of striated muscle myofibrils. The periodic stucture of light and dark

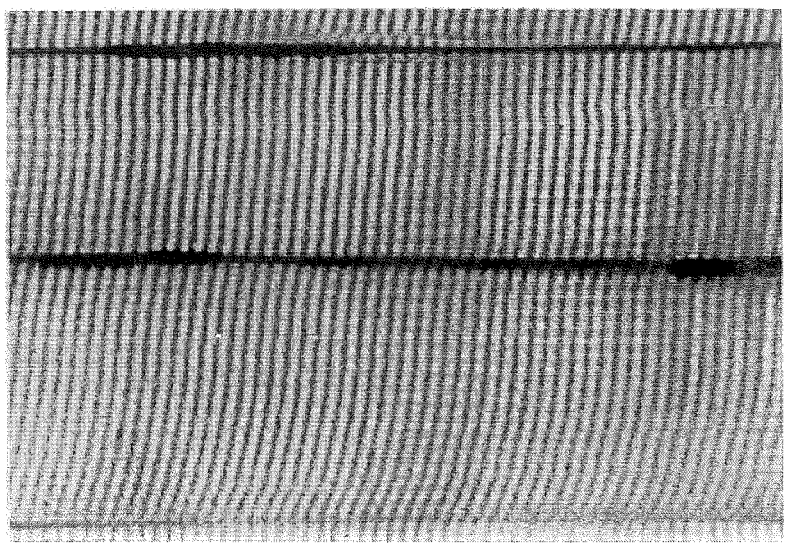

Figure 10.2: Light micrograph.

regions can be seen. Between myofibrils the sarcomere domains are offset, causing the disruption in the periodic structure seen in the micrograph.

10.3 The muscle as a diffraction grating

The series of light and dark bands of the sarcomere unit is reminiscent of a diffraction grating. When monochromatic light is passed through muscle fibres, a diffraction pattern can be observed.

These patterns can be seen in the laboratory using muscle fibres from fresh meat stretched out over a microscope slide. When illuminated from below with a He-Ne laser a diffraction pattern can be projected onto a screen. The diffraction can be quite sharp, so long as the screen is close to the fibres, the fibre bundle is thin, and the meat is very fresh. Refrigerated meat is normally not suitable unless the fibres are taken from the interior of the bulk muscle. Samples tend to dry out over a period of ten minutes, and the diffraction pattern will decay over this time.

It has been shown on whole muscle fibres (Sandow, 1936) and single fibres (Buchthal and Knappeis, 1940) that the diffration maxima spacings satisfy

$$m\lambda = d\sin\theta \tag{10.1}$$

where

m	= diffraction order
λ	= light source wavelength
d	= sarcomere length
θ	= diffraction angle

A former student of this department, Mr Peter Love, constructed a prototype device, shown diagramatically in figure 10.3, to measure the sarcomere length *in vivo*. This instrument was based on the work of Lieber *et al* (1984) who produced

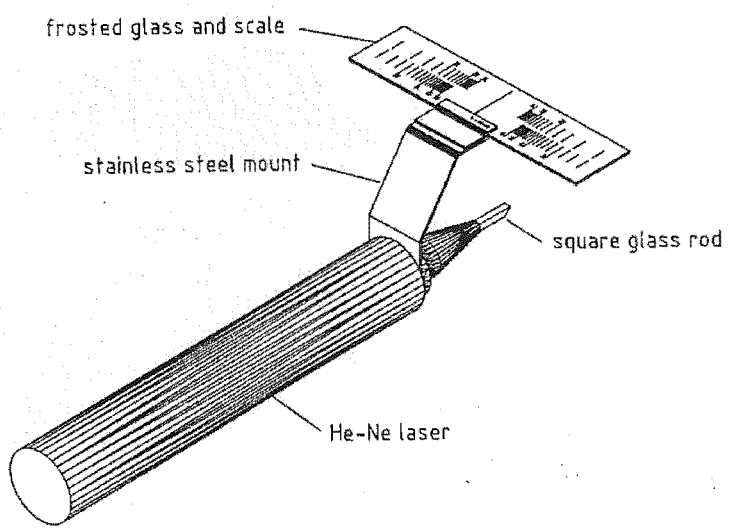

Figure 10.3: The instrument built by Peter Love.

the first such instrument. The device is designed to pass a He-Ne laser beam through a rectangular glass rod and internally reflect it off a 45° face ground onto the end. The beam then passes through a small bundle of fibres positioned on the upper surface of the rod. The diffraction pattern is projected onto a frosted-glass screen which enables the surgeon to observe the diffraction pattern from above. There was a scale printed on the screen so that the sarcomere length could be read off in micrometres. Two scales were used, one each for the first two diffraction orders. The first order scale gives more precise readings for short sarcomere lengths, and the second order scale for the longer sarcomeres of stretched muscle.

The 45° face was coated with aluminium to reflect all the light through the muscle bundle. If the surface is not coated moisture or other contaminants on the surface prevent the total internal reflection, destroying the diffraction pattern.

At the conclusion of Mr Love's research, the device was not suitable for use in a clinical environment. There were several problems.

1. the aluminium coating on the glass rod could not survive the autoclaving necessary to sterilise the instrument.
2. the laser was plastic and thus could not be sterilised either
3. optical alignment was difficult
4. the screen was too far away from the fibre bundle to give a clear diffraction pattern.

The author, along with Professor Butler undertook to redesign the prototype device and produce a clinically useable product for the surgeons.

10.4 Sterilisation

The aluminium coating on the glass rod was protected by painting over it on all but the upper surface of the glass rod. The author repeatedly autoclaved a test rod and showed that the painting protected the aluminium coating. No degradation of the reflection was observed even after 10 cycles through the autoclave.

Since the plastic casing of the laser could not be sterilised, a stainless steel casing was made into which the laser could be inserted. The casing (figure 10.4) was designed by the author and Professor Butler and constructed by Robert Thirkettle of the Mechanical Workshop of the Department of Physics and Astronomy. The stainless steel block, complete with the glass rod in position, could be put through an autoclave prior to the operation. Immediately before use the sterile casing could be held by a scrub nurse while the laser was carefully inserted into the tube by the circulating nurse, who would not touch the stainless steel. The entire device would then be placed in a sterile clear plastic camera cover, preventing accidental contamination of the surgical field by the mains cable to the laser.

10.5 Alignment

One of the critical requirements was that the rod and laser could be removed and reinserted without severely disrupting the optical alignment. To achieve this the rod

Figure 10.4: The final version of the instrument.

needed to be coaxial with the laser. The aperture end of the stainless steel housing was tapered so that the laser would settle in the same place every time. The slot into which the rod is placed was machined to be aligned with the laser. Minute adjustments to the alignment could be made at the rear of the laser using a tripod of screws.

The system was easily sterilised and assembled before use without contamination of the sterile field. The device was aligned prior to sterilisation, and after autoclaving and re-assembly did not effect the alignment significantly.

10.6 Clinical Use

The device was tested during a deltoid-triceps tendon transfer operation. It was easily sterilised, assembled, and used by Professor Rothwell to measure the extension of the triceps muscle when attaching the tendon. Relatively clear interference fringes were seen. The spacing of these was measured using the scale on the frosted glass screen. We concluded that the device satisfied the design requirements.

However, the surgeons felt that the device was difficult to use clinically. Isolating a small bundle of fibres from the muscle and positioning them on the glass rod was difficult. Also the bundle tended to dry out before the muscle could be stretched and the new measurement made. Therefore they have preferred to rely on their previous methods of estimating the correct tension.

One suggestion for overcoming these difficulties is to use reflection rather than transmission interferometry. This would remove the need to isolate a fibre bundle, simplifying the use of the device. This possibility is left for further research.

Chapter 11

Conclusion

11.1 Vascular Lesions

This thesis reviewed the development of the understanding of the processes involved in the optimal laser treatment of port-wine stains and other vascular lesions. Early research was largely a random exploring of the parameter space based on availability of lasers, with associated randomised trials. This has changed to a systematic measure, model, predict, design, re-measure cycle. It is worthy of note that the science has reached the level of understanding of the process to be able to make a prediction of a better treatment protocol, and our first two trial treatments (one of which was a blind trial) gave a clear confirmation of the prediction.

The better treatment protocol – double scanning with transient blanching – was developed and tested as part of this thesis. The protocol involves two treatments of the lesion with 578 nm light from a computer guided scanner (SCANALL), each followed by cooling with a cryogen spray. The first scan causes some damage to blood vessels, producing erythema. The cooling preserves the epidermis allowing for a second scan which treats those vessels dilated by the erythema. Treating the erythemetous vessels enhances the treatment of pale lesions especially. These had previously been resistant to copper vapour laser treatment.

This resistance to treatment was expecially apparent when using a hand guided optical fibre to deliver the light to the lesion. The minimal blanching endpoint was often difficult to obtain. We have concluded that during the early part of the illumination time, the small ectatic vessels would constrict, forcing the blood from within the lumen, thereby robbing the laser light of its target. Because the absorption was decreased, insufficient energy was deposited in the vessels to necrose them.

The illumination times used for the double-scanning protocol are within the 1-10 ms range first calculated by Anderson and Parrish (1981) to be optimal, now

confirmed by other workers, in particular Pickering *et al* (1989b) and Smithies and Butler (1995) from this institution. The later work suggests that 2-5 ms is best. Pulsed dye lasers, which are popularly regarded as the treatment of choice for port-wine stains, have typically used 0.45 ms illumination times. The models since 2000 have been able to use 1 ms illumination times.

A histological study was performed on a patient treated with the double scanning protocol. The study showed that the treatment causes damage to ectatic blood vessels and a small region of collagen around the necrosed vessels. Cosmetic lightening of the lesion is accomplished by a reduction in both the number and size of the blood vessels in the papillary and reticular dermis. The transient blanching is caused by blood flow through the treated vessels being temporarily obstructed, rather than by coagulation necrosis of overlying tissue. The obstruction may be caused by vasoconstriction as predicted by Marini *et al* (1992) and observed by Flock *et al* (1992). Injection sclerotherapy causes a larger fraction of treated vessels to contain a coagulum of red blood cells. These form a purpura-like effect after the treatment.

A clinical assessment by interview and postal survey was conducted. This indicated that the protocol reduced the adverse effects of abnormal pigmentation and scarring that were observed with the previous, minimal blanching, protocol. Residual scan lines visible after the treatment are also reduced. The immediate effects of treatment were also documented.

The assessment also provided new information about the average number of treatments received for the lesions most commonly treated. Cost is seen to be a major factor for patients ceasing treatment for port-wine stain. Public funding (where available) stops after four treatments and many patients stop treatment at this stage. For telangiectasia and spider naevus, most patients were satisfied after one or two treatments.

The follow-up clinic held showed clearly that patient perception of the success of laser treatment is harsher than that of the surgeon. Patients tend to forget the severity of the lesion before treatment and are surprised when they see their pre-treatment photographs. They also assess the progress of the treatments in conditions that are harsher than most others see them, such as in well lit bathroom mirrors. Those who responded generally indicated satisfaction with the treatment.

A new treatment protocol is proposed, extending the double scanning protocol. Provided that the volume of skin containing the ectatic vessels is kept below the

damage threshold, the vessels can be treated more than two times in one treatment session. The cooling could be provided using a flow of chilled air. After the first treatment, erythema would form, allowing further vessels to be treated. This cycle could be repeated, effectively giving the equivalent of several current treatments in one session.

11.2 Tattoos

The knowledge obtained from the modelling and treatment of vascular lesions was appled to the treatment of tattoos. Following a single clinical trial of a prototype on a volunteer, a xenon flash-lamp based system was built to investigate the use of millisecond scale pulses for the removal of tattoos. The system used an artificial transmission line pulse forming network to produce a pulse of white light with a rectangular temporal profile. This causes less stress on the flash-tube than an equivalent single-mesh discharge of the same input energy. The light was reflected towards the skin by a cusp-shaped reflector. Ultra-violet light was filtered out by a polycarbonate filter, which also provided protection for both patient and operator in the event that the tube exploded. The light was sufficiently intense to bleach coloured cardboard.

A clinical trial was conducted to assess the effectiveness of the device. Initially a 1 ms pulse length was used. The treatment caused an inflammatory response in the skin adjacent to the pigment, and histology showed some damage to fibroblasts. Later samples showed that the pigment was once again encapsulated in fibroblasts. Little lightening of the tattoos treated was observed. The pulse length was reduced to 500 μs, which produced fading of tattoo pigment in 3 of the 12 patients in the clinical trial. However, the fading observed was too slow to be comparable to Q-switched laser systems. The shorter pulse length reduced the life-time of the flash-tubes to unacceptable levels, and the trial was terminated.

One possible cause of the slow rate of fading was the pulse length. Pulses of the order of 0.5-1 ms are too long to cause the explosive rupture observed following Q-switched ruby laser treatment, and too short to cause necrosis of pigment-containing cells as after PhotodermPL treatment. Either form of damage is necessary to make pigment granules extracellular, thus stimulating phagocytosis and subsequent pigment removal.

11.3 Tendon Transfer

Interference techniques were used to measure the stretch of a muscle undergoing tendon transfer surgery. A device was designed and constructed to shine laser light through a bundle of striated muscle fibres. The interference pattern created by the periodic structure of the myofibrils was projected on to a screen, allowing the order spacing to be measured. The device satisfied the design criteria, but was difficult to use in practice. Isolating a bundle of fibres was difficult, and the bundle tended to dry out during the measurement process, destroying the interference pattern. We have proposed that interference by reflection rather than transmission may overcome the clinical difficulties.

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that you've given me. I hope that I can repay your kindness.

Finally, thanks to the various groups that have provided me with financial support. Medical Laser Developments has been generous with its support, both in providing a scholarship and work at St George's Hospital. It is a shame that so few others get to work with the SCANALL system, which I believe provides treatment at the very least the equal of anywhere else in the world. Thanks also to the Department of Physics and Astronomy for providing funding through a Teaching Assistantship, and support which enabled me to attend the ACPSEM Conference in Queenstown in 1995.

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