ELECTRICAL STIMULATION
OF
CHRONICALLY DENERVATED MUSCLE

By

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Doctor of Philosophy

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ABSTRACT

Electrical stimulation of denervated muscle offers similar potential benefits as that for paralysed innervated muscle, such as enhanced tissue viability, cosmesis and retained contractile function. For acute nerve injuries, these benefits may enhance functional re-innervation. Appropriate stimulation parameters are, however, essential in each case to optimise benefits and minimise tissue damage.

This pilot study has concentrated on the therapeutic benefits of charge balanced, long pulse, biphasic stimulation treatment of peripheral limb muscle, denervated for more than three years, with quantitative assessment of some clinically important tissue changes. The five study subjects include complete and partial limb denervation arising from T12 level spinal cord, peroneal nerve, and brachial plexus injuries. Treatment consisted of two sessions each day of up to 30 minutes, stimulating a single muscle group with surface electrodes with the contra-lateral limb as control. Non-invasive evaluation measurement of tissue thickness, resting limb segment blood flow, resting skin temperature and muscle excitability occurred before and at regular intervals throughout the 6 month treatment and 6 month follow-up periods. The custom designed portable stimulator unit issued to each subject, was programmed from the clinician’s personal computer, allowing on-line change of treatment parameters and Strength-Duration testing.

Pulse widths of 100ms or greater were required initially in all cases, eliciting only twitch contractions. Muscle responsiveness progressively increased, such that tetanic contractions were possible after approximately ten weeks and limited limb movement by the end of the treatment period, but no functional use. Trapezoidal, instead of rectangular, shaped pulses were used initially in cases of partial limb denervation to minimise co-contraction, but nerve accommodation was not possible at tetanic frequencies.

No significant changes in resting tissue property measurements occurred and those that did, were confused by high measurement variability including artefacts. However in the case, where treatment was most consistent, some positive changes were detectable in all measurements, suggesting that greater benefit may accrue from a more prolonged treatment period. Subjects remained enthusiastic about the treatment and of its perceived beneficial effects.
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### Electrical Stimulation of Chronically Denervated Muscle

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1. **INTRODUCTION**

In the UK there are an estimated 1000 new spinal cord injuries (SCI) per year and 40,000 people are living with the condition; in the US numbers may be 10 times greater. [Hammell, 1995]. Of these 10%\(^1\) or more have T12/L1 level injury with possible lower motor neurone damage resulting in flaccid paralysis. In addition, there are an estimated 15,000 peripheral nerve injuries (PNI) in the US per year [Zanakis, 1990] and in the UK, 350 severe brachial plexus lesions [Wynn Parry, 1994]. Despite the sophistication of modern surgical techniques, there remain areas of concern to clinicians following lower motor neurone damage;

- During the period of nerve re-growth, the prospects of successful functional recovery may be limited by deterioration of the target muscle tissue.
- In cases where re-innervation is limited or absent, the limb undergoes severe atrophy and skin deterioration, leading to poor cosmesis with greater risk of ulceration and circulatory disorders.
- In cases of impaired function, especially mobility, disuse of the muscle or limb can further compound these effects.

For each of these, appropriate electrical stimulation of the denervated muscle has been shown to have positive benefits in at least some cases, however such treatment remains far from routine. For acute nerve injuries, this is largely due to the continued controversy over its effect on nerve growth and re-innervation. For long-term denervation cases, this is due to the ineffectiveness of infrequent treatment with the traditional low frequency 'galvanic' stimulation (e.g.\(100\)ms, \(1\)Hz twitch contractions). In addition, there is a lack of awareness of and availability of home-use stimulators for the more recent, long pulse biphasic stimulation treatment (e.g.\(20\)ms, \(20\)Hz tetanic contractions), for which beneficial effects have been demonstrated. Alternative treatment options for denervated muscle are limited and often not continued on a long term basis beyond the expected period for re-innervation due to the absence of significant functional benefit. The possibility of therapeutic value from improved tissue viability and cosmesis appears to be of lesser concern, but may ultimately result in greater health care cost savings and quality of life to the individual. Chronically denervated muscle is therefore typically allowed to atrophy and deteriorate, with consequent physiological and psychological impact on the person.

Cases of lower motor neurone damage may also become apparent from referrals for restoration of function by Functional Electrical Stimulation (FES) at centres like the Medical Physics and Biomedical Engineering (MPBE) department at Salisbury District Hospital (SDH)\(^2\). However the absence of a functioning lower motor neurone precludes these cases from such treatment.

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\(^1\) Estimated from the proportion of intake at Duke of Cornwall Spinal Treatment; Salisbury District Hospital,

\(^2\) Salisbury District Hospital, Salisbury, Wiltshire, SP2 8BJ, UK
In view of this clinical situation and following the beneficial effects demonstrated in other studies of direct electrical stimulation of denervated muscle using long duration biphasic pulses, a small pilot study was conducted at Salisbury district hospital using this technique [Taylor and Ewins 1992]. This involved two typical long term post injury patients, one with flaccid paraplegia following SCI and the other 'flail arm' following brachial plexus Lesion (BPL) and also produced encouraging improvements in mean skin temperature and muscle thickness (§3.4.2).

Based on this experience, the aim of the present project was to investigate further the therapeutic value of electrical stimulation of chronically denervated muscle through research of existing studies and if necessary through clinical study. The hypothesis being that;

*electrical stimulation treatment can produce clinically significant benefits to the tissue properties of complete and partially denervated limbs. Also, that functional benefits may be evaluated as appropriate.*

The outline of the project and following chapters of this thesis is

§2. Familiarisation with muscle denervation and reinnervation processes.

A review of peripheral nerve injuries, the recovery process and failures causing chronically denervated muscle with the resulting changes to tissue properties. Also some clinical means of assessing the state of innervation are discussed.

§3. Review of studies of stimulation of denervated muscle in animals and humans.

To identify any further clinical investigations necessary, the likely stimulation treatment pattern, suitable evaluation measures and the requirements for stimulation equipment

§4. Design of the experimental clinical study, treatment and evaluation protocols.

An outline of the clinical investigations conducted for this study into the therapeutic benefits of stimulating chronically denervated muscle

§5. Stimulation equipment specification, design and testing.

A technical description of the stimulator unit produced to perform the clinical study

§6. Analysis of study results and observations.

§7. Discussion of study results.

§8. Conclusions of the study with suggestions for improvements and further investigations.
2. **BACKGROUND**

2.1 The Neuromuscular System

The nervous system initiates and co-ordinates contractions of the muscles in the body to achieve movement and posture control (skeletal muscle), internal functions such as digestion and circulation (smooth muscle) and those of the heart (cardiac muscle). Skeletal muscle is controlled by the Central Nervous System (CNS) and the Peripheral Nervous System (PNS), which provide a form of feedback control system (Fig.2.1.1).

![Neuromuscular System Schematic for Knee Flexion Control](image)

**Figure 2.1.1** Neuromuscular System Schematic for Knee Flexion Control

The brain normally acts as the central processing unit, generating the movement demand signal which is conducted via the efferent nerves cells (motor axons or neurones) to the muscle to produce a proportionate contraction. Feedback signals are relayed back to different levels of the CNS via afferent nerves providing, for example; the extent and rate of contraction from spindles within the muscle and golgi organs within the tendons, the limb position from proprioceptors in the joints, touch sensing organs in the skin as well as special sense organs (eyes, ears). Integration of these signals is distributed within the CNS forming a hierarchy of closed loop control. The inner most loop of the 1a afferents and lower motor neurones (LMN) is completed at the corresponding level in the spinal column, forming the reflex arc, so that the rapid muscle contraction can be achieved autonomously, usually to withdraw the limb in response to a noxious stimulus. The brain therefore normally provides control signals to inhibit this and initiate contractions appropriate to the desired
movement and feedback awareness. It can also adjust the 'feedback gain' and sensitivity of the system, such as muscle spindles by means of gamma motor-neurones. [Tortora and Grabowski 1993]. A wide range of neurological impairments can result from partial or complete failure of the various parts of the nervous system. Loss of voluntary control is referred to as paralysis, either central paralysis when it occurs in CNS (upper motor neurone) or peripheral paralysis when it occurs in the lower motor neurone. Terms also refer to the affected limbs; paraplegia when both lower limbs are affected, quadriplegia or tetraplegia when all upper and lower limbs are affected and hemiplegia when one side of the body is affected [Maynard, Bracken et al. 1997].

Figure 2.1.2 Peripheral Neurone Cell and Fibre Structure [after Michael 1996 and Lundborg 1988]

Each nerve consists of many separate neurone cells, which form the basic unit of the nervous system (Fig.2.1.2). Signals are received directly from peripheral sensors or other neurones by the dendrites or cell body and the resultant is conducted down the axon to be relayed to other neurones. The method of conduction is by means of adjusting the electrical potential of the cell membrane (axolemma) which is determined by the relative concentrations of Sodium (Na+) and Potassium ions (K+) on either side. Normally the membrane is dynamically maintained at a negative resting potential (RP of approximately 75mV) by ionic pumps controlling the in and out flow of ions. Separate Na+ and K+ voltage gated channels allow the adjustment of concentrations to generate a momentary positive membrane action potential (AP) typically in less than 1ms, a process known as
depolarisation. Once the RP is raised above a certain threshold, the AP is automatically generated and propagated along the axon to its termini. The absolute refractory period is the time taken for the RP to decrease to this threshold once more, during which period the cell cannot be excited and varies from 0.4 to 4ms depending on the axon diameter. Although still excitable thereafter, a further, relative refractory period is required to fully restore the resting RP. The speed of conduction is directly proportional to axon diameter; the largest A fibres are largely motor efferents to skeletal muscles and sense afferents with diameters between 5 and 20μm and conduction speeds of 12 to 130m/s, B fibres (up to 3μm diameter and 15m/s speed) are predominantly autonomic efferent and somatic afferents, and C fibres (0.5-1.5μm diameter and 0.5-2m/s speed) are visceral efferent and somatic afferents. Conduction speed is increased for group A and B fibres by a discontinuous myelin sheath formed by successive Schwann cells along the length of the axon. This permits ionic current flow in the extra-cellular fluid, so that depolarisation need only occur at successive Nodes of Ranvier, a process known as saltatory propagation. Signals are transmitted between neurones at a synapse (Fig.2.1.2). On reaching the axon terminal, the action potential causes release of neurotransmitter, Acetylcholine (ACh) being the most common in peripheral nerves. When sufficient of these reach the receptors (e.g.AChR) on the receiving neurone, it becomes depolarised and propagates its own action potential. A synapse may involve axon terminals of neurones from various sources, relaying action potentials having different significance, and thus integrated processing is achieved in the nervous system. To prevent subsequent repeated depolarisation, neurotransmitters are removed from the synapse and returned to the termini by esterase enzymes (e.g.AcetylcholineEsterase AChE) [Tortora and Grabowski 1993].

All axons are surrounded by concentric layers of Schwann cell cytoplasm, myelin, and basal lamina, together with capillaries, endothelial cells, fibroblasts and collagen which form the supporting endoneurial tube or sheath. A number of such fibres are closely packed together in nerve fascicles or funicles and surrounded by a perineurium, a lamellated sheath that acts as a diffusion barrier to maintain the ionic environment of the endoneneurial space. Myelinated A and B nerve fibres are associated with only a single Schwann cell at any one level, whereas other Schwann cells surround a number of unmyelinated C fibres. The nerve fascicles, grouped into bundles, are embedded in the epineurium, a loose, soft connective tissue also containing the main vascular vessels and the outer layers of which are condensed into the nerve trunk sheath. The epineurium protects the fascicles against trauma and movement and is especially abundant around joints. The main metabolic processes of the neurone are concentrated in the cell body, which may be as much as 5000 cell diameters away from its most peripheral parts. In addition to the conduction of electrical signals, both fast and slow forms of axioplasmic flow transport nutrient and neurotransmitter supplies along the axon, to its distant synapse. There is evidence that the cell's anabolic processes are also regulated by neuronotrophic factors (NTF) synthesised by the muscle target tissue or components of the nerve trunk, such as Schwann cells [Lundborg 1988].
The final synapse in the conduction path is that between the lower motor neurone and the muscle fibre cell, referred to as the neuromuscular junction (NMJ) or motor endplate. Here release of neurotransmitter initiates similar depolarisation of the muscle fibre membrane (sarcolemma) which propagates along its length, including the transverse tubules and resulting in contraction of the fibres' contractile elements (Fig.2.1.3). These consist of interleaved layers of particular proteins (Actin and Myosin) which have a characteristic banded structural appearance. Their contraction arises from a biochemical reaction initiated by release of calcium from the sarcoplasmic recticulum (SR) and re-circulating energy in the form of adenosine triphosphate (ATP). The ATP is derived anaerobically from creatine phosphate and glucose reactions or aerobically from the blood by mitochondria. All these elements are contained within each muscle fibre cell (myofibre) which includes a number of myofibril contracting elements [Tortora and Grabowski 1993].

In mature muscle, each fibre has only one endplate so is controlled by only one neurone, but each neurone may innervate several thousand muscle fibres, which form a motor unit. Motor units are smaller, where fine movement control is required, such as of the face and of only 2 or 3 fibres in laryngeal or ocular muscles. However all the muscle fibres of a single motor unit are of the same type as they receive the same action potential stimulus or ‘firing’ pattern. Muscle fibres are classified according to their contraction speed, predominant energy metabolism and histological colour; type I are slow contracting oxidative 'red' fibres, type IIA are fast contracting fibres with some oxidative metabolism and an intermediate colour, type IIB are fast glycolytic 'white' fibres usually located superficially. The type IIB fibres are faster acting both because of the greater conduction speed of their larger axons and their glycolytic energy metabolism, however they also
fatigue faster. Muscles usually consist of a mixture of motor units of each type distributed throughout the muscle, which are recruited asynchronously in order to achieve a graded movement. The smaller, slower, fatigue resistant motor units are recruited first as these can sustain a contraction, followed by the larger, more powerful fast fatigable motor units to supply greater force. Each fibre has a finite refractory period during which it can remain contracted and then recover. To maintain sustained muscle contraction, motor units are fired asynchronously in rotation order according to their refractory intervals. The firing of muscle fibres can be monitored from their electrical signals, known as Electromyography (EMG) [Tortora and Grabowski 1993].

A single action potential results in a twitch contraction of the muscle fibre. A sufficiently small interval between consecutive action potentials results in a cumulative increase in muscle tension as the muscle fibre does not return to its resting tension or length in between. Above a certain frequency (typically 30Hz in skeletal muscle) individual twitch responses can no longer be identified and summate into a smooth continuous tetanic contraction. The generated muscle force increases with frequency as does fatigue, but also depends on the proportion of fibre types of the muscle [Solomonov, 1984 quoted by Rattay 1990].

2.2 Peripheral Nerve Injuries (PNI)

The peripheral nervous system may be subject to a wide range of both sensory and motor neurone damage as described in detail elsewhere [Schaumburg, Spencer et al. 1983; Ashbury and Gilliatt 1984]. This text is concerned specifically with the impairment of lower motor neurones and therefore muscular function, which may be partial or complete, sudden or progressive, temporary or permanent and primarily through trauma or degeneration of the lower motor neurone cell itself.

2.2.1 Causes of Peripheral Nerve Damage

Non traumatic peripheral nerve damage occurs from a range of causes and tends to be of a progressive nature, initially reducing conduction speed with resultant muscle weakness, and often accompanied by general fatigue. Eventually muscle fibre denervation may occur if degeneration is persistent. Viral infection, such as Herpes in the facial nerve and subsequent inflammation can lead to complete paralysis of one side of the face, Bells Palsy [Wynn-Parry and Cowan 1994]. Poliomyelitis results in temporary denervation of some muscle fibres which may be reinnervated by colateral sprouting of remaining motor units (§2.2.3). Post polio syndrome (PPS), characterised by muscular weakness, pain and atrophy, occurring decades after an original attack of paralytic poliomyelitis, is thought to be due to NMJ transmission defects and ineffective lower motor neurone conduction following degeneration of these massively enlarged motor units [Trojan,
Peripheral Nerve Injuries

Gillan Barre Syndrome (GBS) also thought to be of viral origin, causes widespread inflammation and PNS demyelination with very sudden but usually temporary, muscle weakness, often to the extent of loss of muscle function with the absence of EMG signals. This is largely due to reduced conduction velocity but fibrillation (§2.3.2) may also occur indicating denervated fibres. Metabolic neuropathies occur with diabetes mellitus, affecting sensory and motor nerve fibre conduction velocities with associated ischaemia become more susceptible to subsequent trauma. Hereditary neuropathies are often degenerative diseases and include Charcot Marie Tooth (MCT) and peroneal muscular atrophy (PMA) which result in progressive distal muscle weakness, severely reduced conduction velocities, increased depolarisation thresholds and loss of anterior horn (LMN) cells. Progressive degeneration of anterior horn cells also occurs with motor neurone diseases such as amyotrophic lateral sclerosis (ALS) and congenital spinal muscle atrophy (SMA). These are again characterised by reduced muscle bulk and strength and partial innervation of muscle fibres with some evidence of denervated fibres (§2.4). Neuropathies also occur from nutritional deficiencies, alcoholism, drugs and other toxic agents [Schaumburg, Spencer et al. 1983; Lenman and Ritchie 1987; Gilbert 1996].

Traumatic peripheral nerve damage usually results in more immediate loss of function and the causes of which are very varied; lacerations (e.g. knife or glass wounds), missile injuries (e.g. gunshot), traction or stretching (e.g. motor cycle accidents), fractures leading to traction or compression, compression ischaemia including from entrapment or inflammation oedema, injection injuries, electrical and burn injuries or radiation [Kaye 1991]. The axonal length of most lower motor neurones make them particularly vulnerable and common pathologies relate to the site of injury. The nerve roots may be affected by spinal cord injury especially at the level of the Cauda Equina (T12/L1) [Maynard, Bracken et al. 1997] and cervical levels [Mulcahey, Smith et al. 1999]. Nerve root avulsions, ruptures and trauma are also common at cervical level resulting in a complexity of brachial plexus lesions [Wynn-Parry and Cowan 1994]. Individual peripheral nerves commonly affected are the medial nerve (most frequently at the wrist and forearm) ulnar (wrist, forearm and elbow), radial (midarm and shoulder), sciatic (hip) and peroneal (knee, head of fibula and gluteal region), tibial nerve (medial malleolus) [Lenman and Ritchie 1987]. The extent of the resulting impairment to upper or lower limbs depends largely on the level of nerve injury and the particular nerve fibres within the nerve bundle affected. For instance trauma of the peroneal nerve and resultant loss of dorsiflexion function, commonly referred to as 'dropped foot' can result from trauma in the spine or more distally. Nerve trauma also commonly occurs during childbirth resulting in impaired sphincter muscle control and subsequent incontinence [Monk, Mills et al. 1998]. Trauma to the child during birth can result in damage to the brachial plexus (e.g. Erbs Palsy, Klumke's paralysis) and in some cases a complete flaccid paralysis of the arm, with subsequent diminutive growth [Kaye 1991].
2.2.2 Types of Peripheral Nerve Injury

A classification of nerve injuries developed by Seldon in 1943 and supplemented by Sunderland in 1951 describes the extent of damage, the degree of impairment and process and prospects for recovery [Irwin 1999],(Fig.2.2.1). In Neurapraxia, (class 1) such as occurs with compression of the nerve, conduction is blocked by transient ischaemia or paranodal demyelination. However as the continuity of the axon is preserved, once the compression is removed function is restored, within hours in the mildest form or after remyelination, usually within 6-8 weeks. Autonomic function is usually preserved. In Axonotmesis,(class 2) such as from a crush or blow injury, traction or ischaemia or closed fracture, it is the continuity of the axon which is interrupted which degenerates. Continuity of the Schwann cell, basal laminar and endoneurial tissue are preserved and these guide the regenerating axons to reinnervate the muscle fibres, with typically complete recovery. Class 3 injuries involve axonal disruption and partial tear of the endoneurial tube, whereas with class 4 injuries, only the epineurium remains intact. In Neurotmesis (class 5), all neural and connective tissues are severed. The formation of fibrosis scar tissue hinders regeneration and if the nerve is completely divided (class 4 & 5), a neuroma forms in the proximal stump preventing reinnervation unless removed surgically. Neurotmesis often results from laceration and missile injuries as well as traction or crush injuries [Schaumburg, Spencer et al. 1983; Kaye 1991; Wynn-Parry and Cowan 1994]. A sixth class has been introduced to cover combinations of these damage classifications [Irwin 1999].

Figure 2.2.1
Peripheral Nerve Injury Classification
1 Neurapraxia,  
2 Axonotmesis  
3 Neurotmesis

[after Schaumburg et al. 1983]
2.2.3 Peripheral Nerve Regeneration

Following division of the axon with injury, the proximal and distal segments retract with leakage of axoplasm. Isolated from the cell body and the CNS, the nerve stump distal to the site of injury continues to function until its metabolic and neurotransmitter supplies are exhausted which therefore depends upon the stump length (2hrs/cm) and the level of synaptic activity. Without axoplasmic replenishment, and typically after 10 days, Wallerian degeneration of the axon occurs progressively along the stump, phagocytosed by macrophages and Schwann cells. The degeneration also triggers proliferation of fibroblast and Schwann cells, forming a new endoneurial tube for the regenerating proximal nerve to the original muscle fibre endplate and including Bands of Bungner to bridge the gap at the lesion site [Vrbova, Gordon et al. 1994; Irwin 1999].

The proximal nerve stump degenerates to the next proximal node of Ranvier, but injuries close to the cell body can lead to complete neuronal death. Within 12 hours, neurotransmitter synthesis decreases in favour of protein synthesis, triggered, it is suggested, by interruption of the axioplasmic transport or degeneration of the distal stump. With this, the cell changes function, from one of a transmitting and conducting channel to a growing state. Sprouting occurs from the growth cone, with daughter axons attracted by neurotropic substances to grow down the distal stump endoneurial tubes to the endplate, bridging gaps of up to 1-2cm is possible but with more variable recovery. Elongation is initially slow and accelerates to a constant velocity by day 3 after injury [Sjoberg,1990 quoted by Vrbova,Gordon et al. 1994 p200]. The growth rate decreases with lesion distance from the cell body, from 2.5mm per day in the upper arm or leg to 1mm per day in the wrist and ankle [Sunderland 1978]. At this rate, the hand for instance, may remain denervated for up to a year following a brachial plexus injury.

Re-generating nerves may have up to 100 branches and may innervate more muscle fibres to form a larger motor unit than normal, in order to compensate for the reduced number of axons. These can exhibit specificity of target organ in terms of tissue, motor or sensory or topographically [Irwin 1999], however this is rare clinically [Lundborg 1999] and inappropriate matching of neurone and muscle fibre type can occur [Vrbova,Gordon et al. 1994 p200]. Prolonged denervation can result in the failure of the regenerating axon to locate the original endplate, which instead forms an ecptic endplate. However, the plasticity of the motor neurone is less than that of muscle fibres [Gordon 1988], and it determines the fast or slow type of new neuromuscular junctions, whereas existing junctions retain their original type [Waerhaug, Lomo et al. 1994]. If maintenance of fast muscle contraction properties is as neural dependant as in post-natal differentiation [Vrbova, Navarrete et al. 1985], then impairment due to nerve-muscle incompatibility on re-innervation may be greater in fast then slow muscle. The extent of re-innervation (at 100dy) was found to be greater in soleus...
Peripheral Nerve Injuries

2.2

Peripheral Nerve Injuries

(2.2) than peroneus tertius (mixed) [Brown and Ironton 1977a] or flexor digitorum longus (FDL) (fast) muscle [Luff and Torkko 1990].

In addition to terminal sprouting of the regrowing original nerve axon, muscle fibre reinnervation can also occur by collateral sprouting of functional axons innervating adjacent fibres. A small amount of sprouting occurs in normal muscle [Barker 1966 quoted by Brown and Ironton 1977a], but is greatly increased with prolonged inactivity, inflammation, or the interruption of neuronal or trophic axon conduction. Numerous neurotrophic factors and other biochemical agents have been proposed as stimuli to nerve sprouting, growth and reinnervation including the endoneurial Schwann cells [Lundborg 1988] and the denervated muscle fibre membrane associated with its increased extrajunctional AChR density (§2.3.2) [Pestronk and Drachman 1978]. The latter stimulus is considered to operate only in very close proximity to the muscle fibres (0.01µm [Eberstein and Eberstein 1996]) to enhance both terminal sprouting of the regenerating nerve and collateral sprouting from innervated fibres. It appears that these neuronal growth factors (NGF) also sustain the functioning contact of the neurone by retrograde axonal transport and without which, neurones withdraw from the muscle fibre. By this means, polynuclear reinnervation is suppressed, to ensure each muscle fibre is under the control of only a single nerve preferably of the appropriate type, in a similar manner to embryonic muscle [Lundborg 1988; Gates and Ridge 1992].

2.2.4 Prognosis for Functional Reinnervation

The extent of muscle reinnervation depends upon the ability of neuronal cells to maintain growth synthesis capability, the quality and length of the endoneurial tube through which they must grow and the capability of the muscle fibre to receive reinnervation and reverse its atrophy, each of which declines with prolonged denervation. [Vrbova,Gordon et al. 1994 p210].

The duration of denervation and therefore the extent of the atrophy is related to the type of nerve injury and associated tendon and soft tissue damage, the quality of the nerve repair, the distance for nerve re-growth as well as many other factors such as the age and health of the patient [Williams 1996a]. The regeneration time varies between sites, typically 6 months for median, ulnar and peroneal nerve injuries and up to 21 months for brachial plexus and sciatic nerve injuries making appropriate or any re-innervation less likely [Boonstra, Van Weerden et al. 1987]. Nerve growth may be hindered by endoneurial gaps, the neuroma scar, blood clots, and tension induced perfusion loss or ischemia [Irwin 1999]. Although muscle fibres denervated for a year have been shown to be capable of still accepting reinnervating nerve fibres [Fu and Gordon 1995], the prospects of successful reinnervation after 18-24 months are considered almost impossible, due to irreversible changes in the muscle cells [Wilgis 1982 quoted by Lundborg 1988 p197]. However the primary cause of poor recovery is cited as the profound reduction in the number of successfully regenerating axons due to deteriorating intramuscular nerve sheaths. Even the ability of axons to reinnervate
three to five times more muscles fibres than normal, does not compensate for this or the incomplete
recovery of muscle fibres from denervation atrophy [Fu and Gordon 1995]. In cases of partial
denervation, enlargement of still functioning motor units can compensate for up to 80% neurone
loss, and complete recovery is probable with less than 85% denervation [Gordon, Yang et al. 1993;
Gordon and Mao 1994].

2.2.5 PNI Intervention Treatments

The prognosis for peripheral nerve injuries may be improved by a number of means, aimed at
enhancing the nerve re-growth, the epineural tube through which it grows or the target muscle
fibre. Micro-surgical nerve repair has been refined to improve both the prospects and quality of
functional recovery, typically involving nerve grafts, transplants or artificial implants and suturing
of either of both perineurium and epineurium, as reviewed extensively in the literature [Lundborg
1988]. Interestingly, allowing up to 5mm gap between nerve endings inside a silicon tube has been
found to be more successful than close apposition [Lundborg 1999]. However, despite the
sophistication of such techniques, functional recovery from PNI is usually less than complete (19-
65%) especially in high level lesions [Williams 1996a].

A number of methods and substances have been found to enhance nerve regrowth and it is probable
that their effect is linked to the multitude of factors which initiate and control the process of the
nerve growth and re-innervation of the endplate. Nerve growth factors (NGF) have been identified
including, fibronectin, gangliosides, adrenocorticotropic hormone (ACTH). Nerve sprouting is
increased by a second injury and has been used advantage surgically, by conditioning a nerve graft
prior to transplant by a period of degeneration [Lundborg 1988].

Peripheral nerve growth has also been shown to be enhanced by pulsed electromagnetic fields and
direct currents of a few micro-amperes passed through the re-growing nerve tip [reviewed by
Lundborg 1988 p183]. The latter is usually generated by implanted simulators and nerve growth is
specific to the direction of a distally placed cathode and to the initial regenerative period [Siskin
1983; Zanakis 1988; Zanakis 1990]. The effect is attributed to an increase in endoneurial vessels
improving the ischaemic state of the damaged nerves and enhancing their degeneration and
regeneration processes [Shen and Zhu 1995].

Physiotherapy of peripheral nerve injuries has traditionally been conservative, with positioning and
passive exercises. These are aimed at maintaining the muscle tissue and limb condition during the
period of nerve re-growth, seeking to minimise muscular atrophy and contractures and preserve
mobility. Active exercises and re-education is undertaken on recovery of function [Cummings 1985;
Wynn-Parry and Cowan 1994]. Artificially induced muscle contractions by electrical stimulation has
also been employed and will be the subject of following sections.
2.3 Denervated Muscle Properties

Without connection to a functioning lower motor neurone, muscle fibres are said to be 'denervated'. This may be temporary while awaiting nerve regeneration, or permanent when reinnervation fails, and may affect some or all of the fibres in a particular muscle or muscle group. A functioning nerve conducts both neuronal (electrical) signals and trophic (metabolic) substances to the muscle fibres [Vrbova, Gordon et al. 1994 p145] and their absence or restriction, results in bio-chemical, electrical and morphological changes. Their extent and reversal or modification with reinnervation, depends on the duration of denervation and the degree of loss of muscle activity, which is thought to be the predominant influence [Eberstein and Eberstein 1996]. Co-incident with the fibre degeneration and dependant on the proportion of fibres affected, is the loss of voluntary control of the contraction of the muscle or limb, its progressive atrophy, reduction in blood flow and deterioration in tissue quality. These clinically significant changes are described briefly here and in greater detail in other texts [Sunderland 1978; Vrbova, Gordon et al. 1994]; some also provide means of assessing the extent of denervation (§2.4).

Much of the analysis has been conducted in the animal model involving histological methods and invasive tests, however there is some evidence from biopsies of human muscle [Williams 1996a; Neumayer, Happak et al. 1997]. Differences between studies therefore occur due to response variation with species and muscle type [Frykman, McMillan et al. 1988; al-Amood and Lewis 1989] and the techniques of denervation and analysis. Methods of denervation include cutting, crushing or excising the nerve, or blocking its conduction, mechanically [Gruener, Baumbach et al. 1974] or by drugs. The latter act on the nerve itself (e.g. tetrodotoxin (TTX), or at the motor endplate synapse, inhibiting neurotransmitter release (e.g. Botulinum Toxin) or its reception by the muscle fibre (e.g. α-bungarotoxin) and are mainly derived from snake venoms. The relevance of the results of these studies is determined by the extent to which these techniques simulate the conditions of human peripheral nerve injuries and the subsequent clinical treatment.

2.3.1 Contraction Response

The most obvious consequence of central and peripheral nerve injury is the loss of voluntary control of the muscle or limb. With central or spastic paralysis, the reflex arc of lower motor neurone and afferent fibres (Fig.2.1.1) remains intact and the absence of the normally inhibitory signals from the CNS results in spontaneous, transient contractions of the muscle, termed spasms, which can help to maintain muscle, skin and bone condition. In contrast, lacking both background tone and spasms, denervated muscle is often referred to as flaccid paralysis, with poorer tissue condition and appearance.
The contraction characteristics of denervated muscle have been deduced by externally applied electric fields (§3), inducing either single twitch contractions or sustained tetanic contractions, and observations depend upon the stimulation parameters employed. Some of the changes in contraction characteristics observed are associated with other changes in the muscle, though unfortunately, few studies have correlated the morphological, physiological and functional changes.

Isometric contraction speed is quantified by twitch duration, which is dependant upon twitch time to peak tension (TPT) and half relaxation times (RT) of the decline in tension, measured for isometric twitch contractions. Denervation results in a decrease of contraction speed, though greater in fast muscle (rabbit extensor digitorum longus (EDL) at 4wk post denervation (EDL) TPT +50%, 1/2RT +100% [Nix 1990]) than slow muscle (rat soleus and gastrocnemius at 6wk post TPT +17%, 1/2RT +30% [Wicks and Hood 1991]). However there is evidence in later stages of denervation of a spontaneous slow to fast transformation of slow muscle (TPT-16% at 15wk post relative pre-denervation levels) and associated with changes to fast myosin [al-Amood, Finol et al. 1986].

Latency is the delay between the nerve or electrical impulse and the contraction of the muscle fibre. Latency increases on denervation due to membrane changes [Nix 1990] to 20ms or more compared to 2-8ms in normal muscle [Raimbault 1984, Petrofsky 1991] and accounts for the 'sluggish' response of denervated muscle to stimuli. Fibre refractory period also increases on denervation [Mihelin, Trontelj et al. 1991]. Denervated muscle therefore tetanises at lower frequencies (8-12Hz) than normal muscle albeit with longer stimuli [Eichhorn, Schubert et al. 1984].

Isometric contraction force is measured for both twitch and tetanic contractions, and may be expressed as specific tension, the force per unit muscle fibre area. On denervation, tetanic tension decreases exponentially before equilibrium is reached after approximately 4months (EDL ~0.75% of control, soleus~0.2-0.3%) [al-Amood, Lewis et al. 1991] Twitch tension is initially little changed after denervation [Finol, 1981 quoted by Vrbova, Gordon et al. 1994 p155], probably due to prolonged contraction time. It then decreases (in rat soleus to 25% at 6wk [Wicks and Hood 1991], and to 5% at 9wk [al-Amood and Lewis, 1987], perhaps less so in fast muscle (to 50% at 4wks in rabbit EDL [Nix 1990].

Fatigue is the decline in muscle force or tension during a sustained contraction. Fatigue resistance is greater in oxidative than glycolytic fibres but is not necessarily related to the oxidative capacity of the whole muscle [Degens and Veerkamp 1994]. Fatigue susceptibility index (§3.5.9) increases on denervation (from 35% to 62% at 4wks after complete denervation of rabbit fast EDL muscle [Nix and Dahm 1987] with a corresponding decrease in oxidative metabolism [Nix 1990].
2.3.2 Membrane Excitability Changes

Denervation results in the loss of muscle fibre membrane conductance and neuromuscular transmission, though this occurs gradually as a result of many individual changes. The decline in non-quantile ACh neurotransmitter release from the endplate is probably the first detectable change [Stanley 1986 quoted by Hülser, Wissmeyer et al. 1997]. The motor endplate shrink [Jones, Tuffery et al. 1973] and the miniature endplate potential (MEPP) from spontaneous ACh release, ceases faster [Vrbova, Gordon et al. 1994 p166] with a decrease in amplitude and frequency as neurotransmitter supplies diminish [Jacob and Robbins 1990]. Conversely, it increases progressively at newly formed junctions and has been used to indicate reinnervation [Brown and Ironton 1977a].

On denervation the Na, K, Ca and Cl ion transfer capabilities of the muscle fibre membrane and its ability to spread irritations are reduced [Hülser, Wissmeyer et al. 1997]. Membrane resting potential decreases almost immediately [Thesleff 1974 quoted by Eberstein and Eberstein 1996], associated with the decline in transport down the axon of a proposed regulator factor [Hülser, Wissmeyer et al. 1997].

The less efficient sodium transport with prolonged outflow [Vrbova, Gordon et al. 1994 p170] results in spontaneous variation in the reduced membrane potential and asynchronous contractions of individual fibres, visible as a persistent fine rippling of the exposed surface of denervated muscle, and known as fibrillation. That, this ceases following application of calcium ions onto the muscle or injected into the blood stream, implies a link with the calcium dependant contraction mechanisms, though it was not stopped by dietary application [Speilholtz 1987]. Fibrillation potentials are a characteristic feature of the EMG signal obtained from denervated muscle (§2.4.3), but as these originate only at the neuromuscular junction (NMJ) zone, the concurrent disseminated ACh hypersensitivity is not thought to be the cause of fibrillation [Kimura 1983]. In animal studies, fibrillation has been observed to commence 3 days after denervation [Vrbova, Gordon et al. 1994 p18,170], with a peak at 5-10 day [Midrio 1992 quoted by Eisenberg and Hood 1994] and decline thereafter, depending on species [Robinson, Tufft et al. 1991]. In human muscle it commences after approximately 20 days, and continues as long as fibre contractile ability remains but is barely detectable after 1 year [Barwick, 1981 quoted by Eberstein and Eberstein 1996]. The frequency of fibrillation (typically 2-16Hz) is proportional to the membrane potential and changes in twitch speed. It is greater in fast than slow muscle and also varies with species [Robinson, Tufft et al. 1991], the NMJ acting as a pacemaker [Belmar et al (1966), Purves et al (1974) quoted by Speilholtz 1987]. Fibrillation as an indicator of continued membrane excitability can be interpreted as its ability to accept re-innervation and its persistence is prolonged by mechanical working of the muscle by physiotherapy or electrotherapy [Rainbault 1984].

In normally innervated muscle, Acetylcholine neurotransmitter receptors (AChR) are localised in the NMJ by an apparently activity mediated neurotrophic element [Andreose, Fumagalli et al. 1995].
The repression in extra-junctional locations is associated with the activation of protein kinase C (PKC) [Changeux 1991]. The number of AChR per junction is regulated by these neurotrophic factors by a continuous process of degeneration and subsequent regrowth [Vrbova, Gordon et al. 1994] and varies with fibre diameter [Andreose, Fumagalli et al. 1995]. The innervating motor neurone also metabolically stabilises the AChR by muscle activity via calcium-dependent reactions [Caroni, Rotzler et al. 1993].

Removal of this neural control on denervation, therefore results in a dramatic increase ACh sensitivity in extra-junctional areas [Axelson and Thesleff 1959 quoted by Lomo and Rosenthal 1975] including the re-appearance of fetal ACh receptor δ subunits [Changeux 1991]. Conversely, junctional AChR numbers remain unchanged for up to 3 weeks after denervation and decreases to 35% of normal after 8 weeks [Andreose, Fumagalli et al. 1995]. In animals, the disseminated ACh hypersensitivity commences 2-3 days after nerve section, [Lomo, 1976 quoted by Eberstein and Eberstein 1996], with a peak at 3-4 day [Jones, Tuffery et al. 1973] and no further increase in adult rat muscle when fibrillation commences [Jones and Vrbova 1970]. In human muscle the increase occurs 5-10 days after injury [Sunderland 1978]. AChR destabilisation also occurs about 3 days after denervation [Andreose, Fumagalli et al. 1995]. The removal of activity mediated ACh receptor stability results in a reduction in their half life up to day 33 post denervation [Fumagalli, Balbi et al. 1990].

![Figure 2.3.1](https://example.com/image.png)

**Figure 2.3.1** Muscle Fibre Membrane ACh Hypersensitivity following Denervation

[after Lomo and Rosenthal 1975]
2.3.3 Muscle Fibre Type

Muscle fibres are classified according to their contraction speed, contractile protein isoforms and their energy metabolism. (§2.1). Transformation of fibre type in terms of myosin isoforms or metabolic enzymes following denervation, may accompany the changes in muscle contraction speed, but not necessarily [Reichmann 1985 quoted by Mokrusch, Engelhardt et al. 1990] and unfortunately few studies include concurrent measurement. Changes in the proportions of different fibre types within a muscle following denervation may occur due to conversion of fibre type or by preferential atrophy or growth of one fibre type over another (§2.3.5).

Myosin is one of the predominate proteins in muscle and is formed into molecular chains which interact with those of other proteins in a layered structure to achieve the contraction. Heavy and light myosin chain isoforms occur in muscle and differ between slow and fast muscle and during muscle fetal differentiation. The slow to fast transformation of muscle type contraction speed observed in denervated slow muscle, after 15 weeks (§2.3.1) is accompanied by changes to fast myosin [al-Amood, Finol et al. 1986]. There is also evidence of a changed myosin phenotype and re-innervation in partial denervated muscle results in multiple myosins forms including pre-natal type [Sawchak, Simeon et al. 1989].

Myogenin and MyoD are proteins that bind to the regulatory regions of a battery of skeletal muscle genes and can activate their transcription during muscle differentiation. Transcript levels of each begin to increase 8-16 hr and 16-24 hr respectively after denervation and reach levels approximately 40 and 15 fold higher respectively than those found in innervated muscle and changes are some of the earliest changes after nerve injury [Eftimie, Brenner et al. 1991].

Muscle fibre metabolic enzymes are considered to be regulated by neural control of muscle contractile activity as they can be transformed by cross innervation or different exercise pattern or external stimulation pattern [Nemeth 1982]. Most forms of long term exercise of normal muscle increase oxidative capacity [Brown, Cotter et al. 1976] but without fibre transformation as fibre recruitment is normal [Vrbova, Gordon et al. 1994 p120]. Chronic denervation results in anaerobic to anaerobic metabolic transformation with decreases in oxidative enzyme activity and mitochondria [Nemeth 1982; Wicks and Hood 1991; Eisenberg and Hood 1994].

However, the study by Mokrusch et al. [Mokrusch, Engelhardt et al. 1990] of fast rabbit flexor digitorum sublimis muscle denervated for 4 months, perhaps illustrates the discrepancies between studies and analysis methods. Histological staining with myofibrillar ATPase showed a shift in fibre type composition towards type II, (type I:II 18.7:81.3 changes to 24.5:75.5) which also showed greater diameter reduction (I 51.3%, II 71.1%). However analysis with NADH dependant tetrazolium reductionase identifying type I, IIA and IIB fibres, showed nearly equal diameter
reduction (60%) but dramatic decrease in glycolytic white (IIB) fibres an increase in oxidative intermediate (IIA) fibres (21.9:23.7:54.4 to 33.7:64.2:2.1). A predominance of type II fibres was also observed with paralysis, though greater in spastic (84%) than denervated (73%) in vastus lateralis muscle [Neumayer, Happak et al. 1997].

In reinnervated muscle, fibre metabolism is dictated by the neurone type. As the reinnervated motor units may be larger to compensate for the fewer nerves, the balance of fibre types and metabolism in the overall muscle may be altered. A homogeneous type I histology (previously mixed fibre type) was observed in reinnervated rat soleus muscle, attributed to reprogramming by the soleus motor-neurone [Davis, Harris et al. 1991]. Conversely in denervated superficial mouse tibialis anterior muscle, glycolytic type IIB fibres were virtually restored within 2 months of reinnervation due to the activity of peripheral and deep muscle fibres or perhaps a resistant phenotype [Parry and Wilkinson 1990]

2.3.4 Blood Flow and Tissue Perfusion

Denervation, as with any limb immobilisation, results in loss of muscle pump action leading to potential prolonged intramuscular vascular stasis (pooling of blood in muscle) and thrombosis [Speilholtz 1987]. For instance, amongst chronic SCI paraplegics (on average 6.7 years post injury), thigh blood flow is reduced to approximately 65%, with lower, but not significantly different cardiac output; though the analysis did not differentiate flaccid from central paralysis [Taylor, Ewins et al. 1993]. Peripheral blood flow is further diminished by vaso-motor spasticity. Conversely, removal of autonomic neural vaso-constrictive tone resulted in an immediate increase in tibialis anterior blood flow to 10 fold at day 7 after denervation and remained elevated until reinnervation and followed closely the timing of sympathetic innervation. However during contractions, muscle metabolic influence predominates (e.g. adenosine, K+, H+, CO2) and muscle blood flow is more closely related to endurance performance than oxidative capacity [Eisenberg and Hood 1994]. In terms to muscle perfusion, the ratio of perfused microvessels per muscle fibre (PV/F) decreased with denervation [Clemente and Barron 1993].

2.3.5 Muscle Atrophy and Fibre Structure

Muscle atrophy is perhaps the most visible physical change with denervation, and can be viewed macroscopically in terms of the muscle weight, thickness or volume and microscopically in terms of the diameter or cross sectional area of muscle fibres their structure and quality. Non-muscle elements (connective tissue, blood vessels and fat) constitute a proportion of this, which may increase with denervation and so fibre calibre is considered a more accurate measure of denervation changes [Speilholtz 1987].
Sunderland produced a summary of muscle weight loss on denervation as an initial rapid decrease of 30% in the first month, 50-60% after 2 months and thereafter the process slowed and reached an approximately stable value of 60-80% after 3 months [Speilholtz 1987]. The residual weight is attributed to the non-muscle elements. The rate of decline is thought to be related to metabolic rate, and is therefore greater in fast muscle [Wicks and Hood 1991]. It also varies considerably between species, individuals, muscles in the same individual, even between fibres in same muscle [Eberstein and Eberstein 1996]. For instance, in rat soleus muscle, the initial decrease to 50-60% after 7-14 days was followed by a more gradual decline to stable value of 20-30% after 45 days and 18% after 6-10 months [Schmalbruch, al-Amood et al. 1991]. Whereas the loss in humans may be less, but dependent on the type of injury. The decline in quadriceps muscle thickness amongst a sample of acute SCI paraplegics was compared with that of age matched normals, though without differentiation between spastic and flaccid paralysis [Taylor, Ewins et al. 1993]. Four cases were monitored from the day of injury and showed a 16% reduction in muscle thickness and 6.5% reduction in subcutaneous fat over the first five days. Over 20 days post injury, this extrapolates to a loss in thickness of 50% in muscle and 14% in fat, as confirmed by measurements in 16 cases from day 5 to day 20. No further significant reduction occurred in another six cases monitored to 40 days post injury, though is possible in cases of flaccid paralysis.

The atrophy and degeneration of muscle fibres is attributed to the impaired nutritional state from reduced circulation but also as a consequence of subsequent trauma, including from temperature changes and potentially from induced contractions [Speilholtz 1987]. The extent of atrophy is affected by the nature of the injury, changes in proportions of non-contractile elements, endogenous hormones, blood flow and the degree of passive stretching of the immobilised muscle which affects protein composition and synthesis rate [Eberstein and Eberstein 1996 quoting others]. The process of fibre atrophy is one of progressive degeneration. Initially simple fibre atrophy arises from loss of myofibrillar material, protein synthesis and intracellular structure. Myofibrillar content decreases with fibre diameter progressing from peripheral to central [Vrbova, Gordon et al. 1994 p159&164]. By 2-4 months, necrosis degeneration occurs, with disruption of fibre organisation, and migration of cell nuclei from the cell periphery to centre (Fig.2.3.2). This leads eventually to cell destruction, which by 4-6 months is extensive but species dependant [al-Amood, Lewis et al. 1991]. The myofilaments of the remaining muscle cells do not form a regular sarcomere structure without the stimulus of activity or stretching [Schmalbruch, al-Amood et al. 1991], such that striations begin to fade after a year in human muscle and the fibres fragment to be replaced by fat cells. However, contractile function by external stimulation can be possible 3 years after denervation [Eberstein and Eberstein 1996]. Therefore initial loss of muscle bulk is due primarily to atrophy of fibre diameter [Anzil 1989 quoted by Vrbova, Gordon et al. 1994 p159] followed by a reduction in the total number of muscle fibres (>50% in rat soleus after 6-10 months [Schmalbruch, al-Amood et al. 1991].
§2.3 Denervated Muscle Properties

Langley (1916) established that the atrophy of denervated muscle is not entirely due to its inactivity but the suggestion that it might be due fibre fibrillation has been refuted [Speilholtz 1987]. Nemoto et al (1988) differentiated between atrophy due to muscle disuse predominately of type I fibres and atrophy as a consequence of denervation occurring mainly in type II fibres, though no explanation of the possible mechanism for this was provided. If atrophy is related to metabolic rate, greater atrophy would be expected in type II fibres, which are also more dependant on neuronal input. However there is conflicting evidence [Speilholtz 1987; Eberstein and Eberstein 1996] (e.g.Mokrusch et al (1990) §2.3.3) and some concluded no evidence of preferential atrophy between fibre types [Wicks and Hood 1991]. Some of this variation is attributed to differences in the amount of passive stretch of the muscle affecting the rate of protein synthesis, muscle activity from surrounding functional muscular, endogenous hormones and blood flow levels and other influencing factors (§2.3.1) [Eberstein and Eberstein 1996].

2.3.6 Chronic Denervated Muscle Conditions

Chronic denervated muscle condition arises from the failure of the peripheral nerve to regenerate or to achieve functional reinnervation following injury, and if it has not occurred after typically 2 years is unlikely to do so (§2.2.4). This risk is obviously greatest, with most proximal injuries, where regeneration distances are greatest, following damage at the nerve root or plexi. Common, chronically denervated muscles are those of the lower limb following cauda-equina (T12/L1) SCI, tibialis anterior causing 'dropped foot' from peroneal nerve damage and upper limb muscles following brachial plexus lesion or cervical level SCI. Partial denervation of sphincter and facial muscle paralysis can also become chronic as can denervation from the progressive deterioration of the nerve from disease or infection (§2.2). Some of the changes and symptoms observed in denervated muscle may also occur with muscle weakness inactivity or enforced immobilisation due to other causes, referred to disuse atrophy.
Secondary complications of flaccid limbs include subnormal temperature, susceptibility to infection and contractures due to unopposed antagonist muscles in cases of partial limb denervation. As many cases of flaccid paralysis are also or become wheelchair bound, then additional secondary conditions include decubital ulcers from impaired circulation, urinary infections from residual urine and kidney damage from bladder dysfunction [Critchley, Eisen 1997].

2.3.7 Treatment of Denervated Muscle

Whereas, in acute PNI cases, treatment is aimed at maximising the prospects of functional recovery through re-innervation, by assisting nerve re-growth and maintaining muscle fibre integrity (§2.2.5), with chronic denervation conditions, the objective of treatment is to minimise the secondary complications arising from the muscle immobility, tissue atrophy and reduced blood flow. Skin quality deterioration may also affect cosmetic appearance of the affected limb and further compound the psychological impact of the condition. Contributing to this is any resulting functional impairment and associated disability.

In some cases of partial limb denervation it is possible to restore limb function by transfer attachment of the tendon attachment of an innervated muscle to that of the denervated muscle, which may then be operated voluntarily or by means of electrical stimulation. [Adams and Wood 1981; Wiessemann 1981]. Another means of restoring function, is the use of orthoses, such as those for the ankle and foot (AFO) in the case of dropped foot from peroneal nerve injury. Although this can aid mobility, it does not enhance the tissue properties or circulation and is often not liked by the users, because of resulting muscle cramp in remaining functional muscles, the discomfort of wearing, and the need for larger shoes. Similar splints may be used in the upper limb to supplement wrist or finger control. Larger, exoskeletal devices (e.g. Reciprocating Gait Orthosis RGO) enable a limited degree of independent mobility for SCI cases and offers the advantage of a period of vertical posture and activity, though opinions vary over the benefits regarding circulation and bone density [Nene, Hermens et al. 1996].

Physiotherapy applied to denervated muscle is aimed at preserving the range of movement of joints to avoid any disabling contractures especially in cases of partial limb denervation, by stretching and heat therapy, however there is concern regarding ‘over-use’ damage of muscles weakened by peripheral neuropathies [Herbison, Jaweed et al. 1983]. Passive standing in suitable support frames is advocated for the benefits to internal organs including bladder drainage, of weight bearing and to help prevent ankle contractures. Attempts to enhance blood flow in denervated limbs, is largely through artificial means of assisting venous return, such as pneumatic cyclic pressure devices (e.g. Flowtron). There is evidence that contraction of muscles induced by electrical stimulation may enhance muscle bulk, blood flow and skin temperature (§3.4) and forms the basis for this study, but this is not in routine clinical use in the UK for chronically denervated muscle.
2.4 Clinical Assessment of Muscle Innervation

The changes in properties and contraction characteristics of muscle once denervated provide a means of assessing the extent and progress of any re-innervation. Some of these techniques may therefore provide means of assessing the effects and effectiveness of any intervention treatments on nerve growth and re-innervation, though no one single parameter is recommended [Frykman, McMillan et al. 1988]; clinically available methods are described here.

2.4.1 Ultra-structural Analysis

A muscle biopsy is the removal of small amount of tissue by the insertion of a needle for histological and microscopic analysis for fibre size, metabolism and structure. Clinically, this can obviously only be performed at irregular intervals. Histological staining can delineate the endplate area and sprouting termini, allowing determination of the sprouting index (average number of terminal branches in a muscle * average endplate length) [Pestronk and Drachman 1978]. Electron and light microscopy has also been used to visualise endplate re-innervation [Frykman, McMillan et al. 1988; Ribaric, Stefanovska et al. 1991].

Increased ACh sensitivity or extra-junctional AChR density is associated with the production of a nerve sprouting stimulus. However the relationship to actual nerve terminals is largely through correlation of results rather than causal [Brown, Holland et al. 1978] and re-innervation has been reported to be independent of extra-junctional ACh tension [Frank, Jansen et al. 1975]. AChR density and stability (half-life) may be determined in vitro and in vivo by labelling with radio-active (125I) α-bungarotoxin which binds with AChR [Andreose, Fumagalli et al. 1995]. AChR sub types can also be identified in vivo and in vitro with molecular probes [Changeux 1991] and adenovirus [Bessereau, Stratford-Perricaudet et al. 1994].

Biochemical assays for myelin may have a direct relationship to nerve regeneration and assays for collagen may indicate scar formation hindering axon re-growth [Frykman, McMillan et al. 1988].

2.4.2 Muscle Cross Section Imaging

Non-invasive, macroscopic imaging of muscle cross section is possible with magnetic resonance imaging (MRI) and is particularly suitable for accurate location in repeated measures, albeit at considerable expense and inconvenience. The technique has been shown to identify sub-acutely denervated muscle (1-12 months post injury) by hyper-intensity of the image, perhaps by increased extra-cellular water content, but is not condition specific, as this also occurs with post trauma oedema. Conversely, acutely denervated muscle shows no unique image characteristic, and chronically denervated muscle is only identifiable by muscle atrophy and fat infiltration. However
in determining the extent of atrophy, the method does confirm the absence of reinnervation or allow its reversal with reinnervation to be monitored. In this it has proved useful in cases where the motor unit anatomy is unconventional resulting in fibre denervation in unexpected locations and thereby directing EMG evaluation and surgical repair [Fleckenstein, Watumull et al. 1993]. Ultrasound imaging (§3.5.1) has also been used in muscle denervation examination [Gunreben 1991 quoted by Fleckenstein, Watumull et al. 1993].

2.4.3 Muscle Electrical Characteristics

Electromyography (EMG) is the recording of the electrical signals produced by the muscle fibres as a result of the action potential depolarisation process during contraction. It may be detected either by skin surface electrodes or by percutaneous needle electrodes. By correct positioning, the latter can detect the signal from individual muscle fibres in a selected part of the muscle, needle or single fibre electromyography (SFEMG). However this is invasive, potentially painful and therefore unsuitable for evaluation of certain subjects, such as young children or those on anti-coagulant drugs. It also relies upon conventional innervation pattern and the operator for precise location of electrodes, which are not confirmed independently, nor easily reproduced for serial evaluation [Fleckenstein, Watumull et al. 1993].

The signal obtained transcutaneously is a compound signal from an indeterminate number of mainly superficial fibres and therefore known as the Compound Muscle Action Potential (CMAP). Analysis of this 'raw EMG' signal is either of its frequency components allowing identification of some individual motor units or from the amplitude of the 'integrated EMG'. In addition to EMG recording of voluntary contracted muscle, it may also be monitored following contraction induced by electrical stimulation, though electronic blanking is usually employed to minimise the stimulation artefact. This technique is obviously of relevance to denervated muscle, and employed by Nemoto et al. (1988) stimulating the nerve distal to the site of nerve injury. However the long pulse duration typically for transcutaneous stimulation treatment of denervated muscle (§3.2), can mask out the signal of interest from the muscle fibres.

The needle EMG signal recorded from denervated muscle (Fig.2.4.1) is significantly reduced and characterised by occasional positive sharp waves and fibrillation variation, known as pathological spontaneous activity (PSA) and increased latency (§2.3.1). This is the first detectable in the muscle about 14 days after injury and the amount of activity is influenced by the muscle fibre type [Hülser, Wissmeyer et al. 1997] With partial denervation high amplitude potentials indicate the enlargement of some motor units [Raimbault 1984]. Reinnervation is indicated by the absence of the characteristic PSA and progressive return of a mixed interference EMG pattern [Boonstra, Van Weerden et al. 1987]. Vain and Humal have derived the oscillating period (T) and common logarithm (O) to characterise the biomechanical status of abnormal muscles [Lasn 1995].
2.4 Assessment of Muscle Innervation

Normal Muscle

Motor unit A

Motor unit B

Denervated Muscle
Surviving motor unit A has taken over two of the fibres supplied by the dying fibre B

Denervated, atrophied fibre, probably responsible for fibrillation

Normal EMG

Rest

Slight activity

Maximal contraction

Chronic Partial Denervation

Rest

Slight activity

Maximal contraction

Reduced pattern

Figure 2.4.1 EMG Characteristics of Denervated Muscle [after Patten 1977]

The CMAP amplitude is also decreased by nerve injury, dependent upon its severity and can occur within 2 days, therefore preceding changes in needle EMG signals. It has advantages of being non-invasive, and less sensitive to electrode positioning that component EMG analysis. However it is a comparative rather than absolute measure, and therefore for diagnosis relies upon the contralateral side having the same pattern of innervation and being unimpaired [Hülser, Wissmeyer et al. 1997]. The progressive increase in compound action potential from recruitment of individual motor units in response to incremental increases in stimulation level, allows estimation of their number and size and therefore any progress of reinnervation. Automated measurement has been developed to compensate for the effects of fibre position relative to the electrodes, for errors due to units with the same or very similar thresholds and intra-operator variability [McComas, Galea et al. 1993].

2.4.4 Electrical Muscle Stimulation Testing

The response of any tissue to an applied electric field is determined by its excitability (in terms of the intensity required for a given stimulus duration), its refractory period (the time after being excited before further excitation is possible) and its capability or not to accommodate to the stimulus [Cummings 1985]. A number of diagnostic techniques have been developed based upon the response of muscle tissue to externally applied electrical stimuli, the principles of which are described elsewhere (§3). The axolemma is depolarised by smaller electric fields than the sarcolemma and so innervated muscle fibres respond to stimuli of smaller duration and intensity than denervated fibres. These tests can therefore provide an indication of the extent of denervation of a muscle, though not the exact quantification offered by electromyography. However they have the advantage of being non-invasive, convenient and require minimal equipment or operator training. They are perhaps most useful as comparative measures, in monitoring the progress of innervation following injury or application of treatment.
Muscle Excitability Testing - Strength Duration Curve

Muscle excitability is assessed by using isolated stimuli and therefore without the influence of refractory or accommodation mechanisms. The Strength-Duration or Time-Intensity curve is a graphical characterisation of the excitability of a muscle or muscle fibres, in terms of the relationship between the intensity and the duration of stimuli. Typically, surface electrodes are used to apply isolated, uni-polarity (monophasic), rectangular stimulation pulses of approximately 10 to 20 different widths between 10μs and 300ms. For each width, the intensity of stimulation required to just elicit a minimum contraction of muscle is plotted and the resulting curve has an exponential shape for normal skeletal and cardiac muscle [Geddes and Bourland 1985]. The stimulation threshold intensity diminishes as pulse width increases, for innervated muscle until approximately 3ms and thereafter remains approximately constant at a value referred to as the Rheobase. The pulse width corresponding on the curve to twice the Rheobase intensity, is known as the Chronaxie, which is typically less than 1ms in innervated muscle. For denervated muscle fibres, depolarisation and subsequent contraction necessitates longer pulses, so the curve is shifted to the right, with increase in Chronaxie to typically 10ms (Fig.2.4.2).

The Rheobase value is influenced by a wide variety of factors and cannot be used as a quantitative measure. Chronaxie does provide some independence from these effects but can only be used reliably to identify denervation. Attempts have been made to produce other quantitative values from the curve [Geddes and Bourland 1985] and a single point value at 1ms has been employed to successfully diagnose sphincter muscle dysfunction [Monk, Mills et al. 1998]. However, it is generally accepted that the usefulness of the curve for PNI treatment is derived from its overall shape when monitored serially. In cases of partial denervation/reinnervation, a combined characteristic is obtained; the nerve and therefore the innervated fibres are excited by the shorter pulse widths, whereas the denervated fibres are excited only by the longer pulses. The resulting 'kink' in the curve appears typically 6-8 weeks before the first voluntary movement and can be used to monitor the progress of innervation though it does not guarantee the eventual functional outcome (Fig.2.4.2). In some cases this does not occur, for instance, in larger muscles where the reinnervated fibres are deep and not reached by the stimulation. Conversely the curve may indicate small regions of denervation before onset of muscle weakness [Lenman and Ritchie 1987 p.96-100].

The threshold measurements are influenced by a wide variety of factors, such as the equipment output impedance, the electrodes used, the skin condition and impedance, the patients state, and the measurement environment. In addition there is inter-rater and intra-rater variability some of which is attributable to the method of detection of contraction, either by palpation or visually. Even so, with experience and careful technique, clinically useful results can be obtained [Alexander 1974; Arsenault and Stevens 1979; Low 1979; Lenman and Ritchie 1987; Monk,Mills et al. 1998].
§2.4 Assessment of Muscle Innervation

**Ischaemia: Polymyositis**

**Participation innervation**

\[
10 \quad 30 \quad 100 \quad 300 \quad 0 \quad 0.1 \quad 0.3 \quad 1 \quad 3 \quad 10 \quad 30 \quad 100 \quad 300
\]

\[
20 \quad 24 \quad 20 \quad 0 \quad 0.1 \quad 0.3 \quad 1 \quad 3 \quad 10 \quad 30 \quad 100 \quad 300
\]

\[
\text{Volts} \quad \text{Volts}
\]

\[
0.01 \quad 0.03 \quad 0 \quad 1 \quad 0.3 \quad 0.03 \quad 0.3 \quad 0.0
\]

\[
\text{Electrode seconds}
\]

**Figure 2.4.2** Strength Duration Curves [after Lenman and Ritchie 1987]

Note: Curves in left plot may correspond to different patients or different measurement conditions, thereby accounting for the location of the curve for partial innervation above that for denervated muscle

**Muscle Refractory Period Measures**

The refractory period is the period after one stimulus before the muscle fibre is able to respond to the next. Muscle action potential duration has been shown to increase from 5ms to 16ms with denervation [Petrofsky 1991]. Hence denervated muscle looses the ability to respond to repetitive (faradic) stimuli and requires progressively longer and stronger (galvanic) stimulation pulses. This **Faradic-Galvanic** response test of the absence of response to faradic stimulation to the normal limit of tolerance of the individual, has been used from the earliest days of stimulation, and remains the easiest way to discriminate innervated from denervated muscle. However tetanic contractions can be achieved in denervated muscle given sufficient pulse width (§3.2), and without standardisation, the test is only correct in 50% of cases and has no value in assessment of prognosis [Lenman and Ritchie 1987 p.87].

A more quantitative measure is the **Intensity-Frequency curve**, a plot of the intensity for a minimum contraction at a given frequency of stimulus. This is typically performed with sinusoidal alternating current, but is then a combined accommodation measure, as the intensity rise time varies with frequency and the optimum frequency, of lowest intensity, occurs when these two effects balance. Although this minimum is not sharp and varies by about 20%, it is approximately 60Hz for normal muscle and 2Hz for denervated muscle. However, with continuous alternating current, the risk of tissue damage is significant and may exceed the tolerance of the patient [Lenman and Ritchie 1987 p.103].

**Muscle Accommodation Measures**

Not only is the axolemma more excitable than sarcolemma, it is also more accommodating to gradually changing stimuli, a fact that can be taken advantage of in both diagnosing and treating denervated muscle. The **Galvanic-Tetanus ratio** is the ratio of intensity of contraction threshold of
a twitch contraction from a single stimulus compared to that of a continuously increasing stimulating current. In normal muscle this ratio is about 5, in denervated muscle about 2. The form of the stimuli is not defined and again there is danger of skin burns [Lenman and Ritchie 1987 p.102].

In **progressive current testing** the comparison is between an instantaneous stimuli and one which increases gradually, according to a set pattern, linearly, exponentially or logarithmically. This enables the denervated muscle to be stimulated without the innervated muscle (Fig.2.4.3.b). For instance, Le Flohic (1994) finds a linear slope of 20% is necessary to accommodate innervated muscle. However it is essential that the rate of decrease of the stimulus is equal to its increase, to avoid a 'break effect' of rapidly reduced intensity [Lenman and Ritchie 1987 p.102]. More useful in monitoring the progress of innervation is a Strength/Intensity-Duration curve for such accommodating stimuli, which in the case of the triangular pulse Intensity-Duration curve shows a clearly differentiable minimum between innervated and denervated muscle (Fig.2.4.3.a).

![Figure 2.4.3 SD Curves for a) Triangular Stimulation Pulses -b) Exponential Pulses](after Stephens 1973) [after Cummings 1985]

**2.4.5 Sensory Innervation Assessment**

Re-generation of sensory neurones can accompany that of motor neurones, through re-innervation of the target organ may not be concurrent. However, since monitoring the progress of sensory neurone re-growth is in some respects easier than that of motor neurones, it may give a useful indicator regeneration. In particular the Tingel-Hoffman sign is a means of monitoring the sensory nerve as it regrows by percussion of the skin [Sunderland 1978; Buck-Gramcko and Lubahn 1993]. Sensory evoked potentials allow determination of nerve conduction to the sensory cortex. Tactile sensation sensitivity and distribution can be determined statically and dynamically with two point discrimination [Chassard, Pham et al. 1993] and monofilaments [Bell and Tomancik 1987].
3. REVIEW OF LITERATURE

3.1 Neuromuscular Electrical Muscle Simulation

Neurones can be depolarised by externally applied electric fields (Fig.3.1.1). The action potential then propagates in the normal manner to cause muscle fibre contraction referred to as indirect electrical stimulation. The generating electrodes may be attached to the skin superficial to the nerve for transcutaneous stimulation or now more commonly, implanted beside or surrounding the nerve to reduce the required stimulation intensity and improve selectivity. With subcutaneous stimulation, the stimulating device is also implanted or with percutaneous systems connections are made externally. As the membrane is bi-directional, the action potential of depolarised afferent neurones also propagates proximally to the cell body and may cause a second, later contraction via the spinal reflex arc.

The current density at the membrane surface from the externally applied field is influenced by the electrode size and orientation, the impedance of the skin interface and intervening tissue, and the nature of the stimulus itself. With electrodes placed too close together the current may only pass through superficial tissue and not penetrate to deeper neurones. Nerves are most easily depolarised at their endplate termini, where unmyelinated. Commonly referred to as the motor point, this is the usual position for the negative active electrode. Current density at the electrode is increased by decreasing its size, but if not optimally located over the motor point, then excessive levels may be required to obtain effective stimulation, causing patient discomfort and possible tissue burns. Unequally sized electrodes are also less suitable for biphasic stimulation when the direction of the applied field is reversed during the pulse, so that no net current flow occurs. This prevents possible deterioration of electrodes and tissue, from migration of ionic concentrations. The stimulation current applied is discontinuous to allow repolarisation of the neurone between pulses. Pulse frequency is determined by the refractory period for the fibre type and typically 10-40Hz. Typical pulse widths for transcutaneous stimulation are 100-300μs, the intensity requires varies with pulse width according to the Strength Duration curve (§2.4.4), and is typically 20-50mA [Baker, McNeal et al. 1993].

Recruitment order is the reverse of normal physiology. The larger diameter axons innervating fast-type II muscle fibres are depolarised by lower stimulation intensities because of their lower threshold and their more superficial location in the nerve bundle [Baker, McNeal et al. 1993]. For maximal contractions, all fibres are recruited synchronously, rather than normal asynchronous recruitment. Both of these effects lead to fatigue of the induced muscle contractions sooner than normal physiology. Techniques to alleviate this include using stimulation patterns derived from a
normal EMG signal [Kidd and Oldham 1988] or with varying frequency, making use of the 'catch like' property of muscle, and its dis-habituation properties [Michael 1996]. Alternatively, multi-polar implanted electrodes have been developed to provide selectively depolarisation in terms of axon diameter, allowing selective recruitment of particular muscles fibres or particular muscles [Rattay 1990].

The precise control of sustained muscle contraction and consequent limb movement, with minimal fatigue is required for the application of functional electrical stimulation (FES) to achieve functional outcomes such as compensation for 'dropped foot' following peroneal nerve damage, multiple sclerosis or stroke, standing and walking for cases of paraplegia, or arm, hand and respiratory control for cases of tetraplegia. By use of appropriate stimulation frequency and pattern, transformation of muscle type and metabolism can also be achieved, for instance, slowing the contraction speed of fast type skeletal muscle for cardio or aorta myoplasty [Salmons 1995].

Stimulation has been employed for therapeutic benefits for SCI and other neurological conditions to compensate for reduced or absent muscle contraction by improving the quality and viability of tissue with increasing bulk and perfusion with some evidence of a prophylatic effect towards pressure sores [Rischbieth, Jelbart et al. 1998]. Through bicycle ergometry, it can also acts as cardiovascular exercise [Baldi, Jackson et al. 1998]. Neuromuscular stimulation has also been shown to assist contracture prevention, tremor alleviation for Parkinson's disease, spasticity reduction in stroke and SCI cases and for neurological re-education following stroke [Baker, McNeal et al. 1993]. All of these techniques rely on the depolarisation of a functional lower motor neurone and in the absence of which direct muscle stimulation is required.

![Figure 3.1.1](image-url) Transcutaneous Neuromuscular Stimulation [after Baker, McNeal et al. 1993]
§3.2 Direct Stimulation of Denervated Muscle Techniques

Reid in 1841, is credited with the first published work on electrotherapy for denervated muscle and advocated it in order to prevent atrophic changes [Mokrusch and Neundorfer 1994]. Erb in 1868, documented that denervated muscle retains its excitability to electric current, though compared to normal muscle, its response is no longer instantaneous but, slow and sluggish [Cummings 1985]. Also observed, was that to elicit a contraction, the stimulating current is required to be of greater intensity, duration and applied to the denervated muscle directly, not indirectly through the nerve, as with innervated muscle. This technique of applying electric fields to depolarising the muscle fibres themselves because of the absence of a functioning lower motor neurone has therefore become known as direct electrical muscle stimulation.

Such stimulation has been suggested as a treatment for denervated muscle on the assumption that muscle activity rather than neurotrophic influence is the most important factor in regulating muscle fibre physiological and bio-chemical properties such that the changes on denervation may be reversed by artificially induced contractions. In reviewing 25 years of studies mainly in the animal model, Eberstein and Eberstein [1996] concluded the evidence is that direct electrical stimulation can indeed to a large extent substitute for innervation to preserve and restore normal muscle properties providing appropriate stimulation parameters are employed. This is aimed at the clinical objective; for acute nerve injuries, of minimising muscle atrophy in order to maximise function recovery on re-innervation, and for chronic denervation cases, of enhancing tissue viability with respect to secondary complications and where appropriate achieving functional muscle contractions. However, contractile activity is not the sole determinant of muscle properties and the multiplicity of influencing factors may account for some of the difference in effect of stimulation observed between studies (§3.3). The Eberstein’s went on to highlight that, at that time, the appropriate stimulation techniques for human denervated muscle (§3.4) had yet to be fully prescribed.

Changes in the electrical properties of the sarcolemma with denervation diminish its ability to propagate the depolarisation action potential. The stimulation electric field is therefore required to cause localised release of calcium ions, it is suggested, by permeating throughout the membrane as in smooth muscle, rather than by their normal release from the SR cisterns [Eichhorn, Schubert et al. 1984]. Deterioration of the muscle fibre contractile protein structures and fibrosis of the muscle tissue, also contribute to the progressive decrease in the muscle excitability with denervation and this is influenced by the degree of immobilisation, the action of surrounding functional musculature and movement impeding contractures. The duration and amount of stimulation charge flow is greater than that with indirect stimulation to ensure sufficient penetration, to recruit deeper fibres.
§3.2 Direct Stimulation of Denervated Muscle

3.2.1 Stimulation Pulse Width

The stimulation pulse width (PW) required to achieve a contraction increases with the period of denervation as demonstrated by the Strength-Duration curve (§2.4.4) especially during the first two weeks, such that tetanic contractions are no longer possible. After 2 years post injury, reinnervation is unlikely (§2.2.4) and the condition is considered chronic. Pulse widths of 100-300ms are then typically required with surface electrodes to achieve a muscle contraction, with Chronaxie used as the minimum or guide value [Cummings 1985; Boonstra, Van Weerden et al. 1987; Campbell and Meadows 1995]. However it has been found that continued treatment with stimulation increases the excitability of the muscle with the membrane resting potential and capacitance are restored [Westgaard 1975 quoted by Nemeth 1982]. The muscle fibres then respond to progressively shorter pulse widths down to the order of 10ms (transcutaneous) and eventually permitting frequencies of tetanic contractions, typically up to 20Hz (§3.4.2). The improved response may be attributed to reversal of some of the fibre changes with denervation; in the electrical properties of the sarcolemma, the contractile proteins and tissue fibrosis tissue and in the fibre metabolism and perfusion (§3.3). Pulse widths required with implanted electrodes are much lower than with surface electrodes, and typically less than 1ms (§3.4.1).
§3.2 **Direct Stimulation of Denervated Muscle**

### 3.2.2 Stimulation Pulse Shape

The contraction of denervated muscle results in fatigue to a greater extent than innervated muscle. In addition to the non physiological recruitment, this may be due to the altered biochemical mechanisms of contraction, which may lead to the temporary exhaustion of calcium supplies, especially if the return mechanisms are impaired [Eichhorn, Schubert et al. 1984]. The transfer to largely anerobic fibre metabolism, with reduced mitochondria and perfusion (§2.3) may also contribute to fatigue. With indirect stimulation, it is important to ensure no net transfer of charge into the tissue to avoid altering the ionic balance of the axon membrane, which could eventually fatigue contractions [Baker, McNeal et al. 1993]. This is commonly achieved passively, by allowing the body to discharge into the stimulator, however with pulses of 100 to 1000 times longer used for direct stimulation, it is quite probable that some ionic effect may occur during the pulse. Active charge balancing, achieved with symmetrical biphasic (opposite polarity) impulses (Fig.3.2.1), has been shown to avoid fatigue in sustained tetanic contraction of denervated muscle, attributed to variations in the tissue current flow paths with the reversal of polarity, causing different fibres to be recruited [Eichhorn, Schubert et al. 1984]. Charge balancing also reduces the risk of skin damage at tetanic frequencies probably from excessive heat [Guttmann 1976, p.573].

Stimulation pulse shape has generally been rectangular as this maximises the tissue current flow for a given pulse width. However the near instantaneous application of current, and resulting sudden, non-physiological contraction, it is thought, may over fatigue and damage the denervated muscle [Cummings 1985]. This is avoided with indirect faradic stimulation, by gradually increasing the intensity of successive pulses within the stimulation burst envelope (§3.2.4). For the pulses of longer duration required for stimulation of chronically denervated muscle the intensity of the pulse can be gradually increased or decreased, either linearly [LeFlohic 1994], exponentially [Cummings 1985][Carraro & Zrunek quoted by Mokrusch, 1994] or sinusoidally [Osborne 1951; Petrofsky 1991]. In cases of partial denervation, this can have the significant advantage of selectively contracting the denervated muscle fibres, while the still innervated fibres accommodate to the stimulus (§2.4.4). These fibres would otherwise contract at lower intensities than the denervated fibres, resulting, either in their possible damage from fatigue or the ineffectual contraction of the denervated fibres [Cummings 1985]. Nerve accommodation requires linear rates of change of less than 20% [LeFlohic 1994], or 30*Rheobase/s [Stephens 1973] as reflected in their respective Strength-Duration curves (Fig.2.4.3). Stimulation pulse widths to achieve LMN accommodation are typically 300-1000ms for which inter-pulse intervals 4-5 pulse widths are recommended [Thom, 1955 quoted by Cummings 1985].
3.2.3 Stimulation Pulse Pattern

Considerable investigation has been undertaken, largely in the animal model, to identify the effects of particular stimulation patterns on denervated muscle, mainly in respect of contraction characteristics and atrophy. Contrasting results, have led opinions to vary as to the relative importance of the frequency or the total number of impulses, the duration of bursts of impulses or the interval between them. In reviewing these, Eberstein and Eberstein [1996] concluded that the optimum stimulation for fast muscle is intermittent bursts of impulses at high frequency (e.g. 100Hz), and for slow muscle is continuous low frequency pulses (e.g. 10Hz). Some researchers have advocated a stimulation pattern derived from the normal EMG signal of the particular muscle [Petterson, Smith et al. 1994]. However the duration of stimulation pulse required for transcutaneous direct stimulation of chronically denervated muscle (> 100ms), limits the frequency to 2Hz or less, producing a series of twitch contractions which has been the conventional electrotherapy employed. Even with the conditioning effect of treatment (§3.2.1), pulse widths of greater than 10ms are required to ensure all fibres are depolarised, and so limits the range of possible variation in parameters for tetanic contractions, though fusion frequency is reduced (§2.3.1). Frequencies of 5-8Hz, producing 'shaking' clonus type contractions have also been employed as an intermediate treatment between twitch and tetanic contractions to account for different rates conditioning between muscle fibres [Kern, Hofer et al. 1999].

There seems general agreement that tetanic are more effective than twitch contractions at preserving muscle fibre properties. Denervated rat muscle weight increased by 10% with transcutaneous stimulation by 100ms at 2Hz but by 10-30% with 25ms at 20Hz [Herbison, Teng et al. 1971]. Studies in human muscle also confirm the absence of effect on atrophy of twitch contractions [Boonstra, Van Weerden et al. 1987] compared to significant benefit from tetanic contractions, albeit necessitating biphasic pulses (§3.4).

3.2.4 Contraction Pattern

The tetanic contractions are sustained for a short period by employing a burst of the stimulation pulses the trend of the intensities of which form the stimulation envelope (Fig 3.2.1). With indirect stimulation, this envelope is often trapezoidal in shape. Compared to rectangular envelopes, the gradual increase and decrease of the consequent contraction more closely resembles physiological muscle contraction force and helps to minimise muscle spasm. A typical pulse train envelope shape for indirect quadriceps stimulation muscle training is 4 seconds of ramp up of intensity, 4 seconds at peak intensity level and 4 seconds of ramp down followed by 12 seconds off-period with zero
intensity of stimulation\(^1\). This form is based on typical physiological muscle use for standing, as for functional stimulation the envelope is of necessity defined by the desired functional outcome. The envelope off-period (Fig.3.2.1) is intended to allow for reperfusion of the muscle, which is more than likely ischaemic during the contraction. However, it is suggested that off-periods of minutes are required for reperfusion and that any less time is equivalent to ischaemic continuous stimulation [Lexell, Jarvis et al. 1997]. This study also revealed that fibre damage induced by indirect stimulation was less with intermittent (1hr on/1hr off) than continuous 10Hz, suggesting that reperfusion following the ischaemic contractions, is not responsible for the damage.

Stimulation patterns used with denervated muscle vary considerably. Some have adopted those used for indirect stimulation [Taylor, Ewins et al. 1992] or rectangular envelopes of 6 seconds [Mokrusch and Neundorfer 1994][Müller, 1970 quoted by Herbison, Jaweed et al. 1983]. Off-periods between contractions are at least equal to or double contraction duration. A quite different approach has been adopted by Kern et al.[1995] in using a series of 6 to 8 contractions of 2 seconds duration with 2 sec off period and a minute or two rest between consecutive sets of contractions (§3.4.2).

3.2.5 Treatment Pattern

The treatment patterns adopted have been dependent on the stimulation pattern. The majority of animal studies employed continuous stimulation whereas clinical studies largely used session based stimulation for practical reasons. Mokrusch et al. [1990 and 1994], demonstrated that atrophy benefits may be obtained by relatively short periods of treatment each day (6min per muscle twice/day) with near maximal contractions. Williams [1996a,b] applied continuous treatment but at a low contraction duty cycle (e.g.0.1s every 4s) with minimal contractions. Both claim the key to success being that all fibres were stimulated, the former transcutaneously using long pulses (20ms), the latter using subcutaneous wire electrodes and less then 1ms pulse width. Wakim and Krusen [1955] demonstrated that over 25-30 days, 5 minutes of stimulation every 30 minutes for 8 hours per day, was just as beneficial as longer sessions at the same frequency and more beneficial than 30 minute sessions once or twice a day [Speilholtz 1987]. The considerable variation in stimulation and treatment pattern may account for the differences in response observe between studies, and means there is as yet no definitive treatment protocol for clinical application.

3.2.6 Electrode Type and Location for Direct Stimulation

Electrode location is optimum for transcutaneous indirect stimulation over the motor point (§3.1), whereas with direct stimulation, electrodes are positioned at either end of the muscle belly to

\(^1\) Quadriceps training pattern used at SDH for FES.
maximise the field distribution along the fibres [Eichhorn, Schubert et al. 1984], and the response of
denervated fibres is generally accepted to be indifferent to polarity [Sunderland 1978]. A
compromise in electrode positioning may be required in the case of partially denervated muscle, so
as to optimise recruitment of the innervated or denervated fibres according to the treatment aim.
Generally surface electrodes have been employed for clinical applications of direct stimulation,
however these necessitate much greater pulse widths and intensities to reach all fibres. There is the
potential for tissue damage at the skin interface and the intensity may be limited by patient
tolerance. Gutmann [1976] minimised this by moving the electrode position during treatment,
which also altered the current path to different fibres. Some researchers have sought to improve the
field distribution, especially in the less superficial fibres by super-imposing fields from a number of
pairs of electrodes. [Arndt, Eichhorn et al. 1987] and this has also been suggested as a means of
minimising antagonist co-contraction [Mokrusch and Neundorfer 1994].

Implanted electrodes permit the use of smaller pulse widths and therefore offer greater flexibility in
stimulation pattern parameters. However percutaneous systems introduce the risk of wire breakages
and infection, whereas fully implanted, subcutaneous systems eliminate any problems of animal or
patient compliance but at the expense of greater technical complexity. Implanted electrodes have
generally been employed on the stimulation studies in animals probably for practical reasons given
that stimulation has often been continuous, though they have also been advocated over surface
electrodes by some to ensure all fibres are contracted [Nix and Dahm 1987]. Conversely, others argue
the intensities required to reach all the fibres of larger muscles have the potential for tissue damage
with implanted electrodes from excessive localised current density [Eichhorn, Schubert et al. 1984].
Clinical implantation has been employed successful for continuous stimulation using wire
electrodes along the length of the forearm and hand muscles [Williams 1996a], which may ensure a
more uniform current distribution, though the response in these acute nerve injuries, may also be
due to the greater retained muscle excitability.

Attempts have been made to model the fields within the tissue induced by direct stimulation and to
produce an electrical circuit model of surface direct stimulation [Reichel, Mayr et al. 1999]. However
as yet there are few studies relating the measured stimulation current flow to the biochemical
processes occurring during stimulation induced contractions, in order to facilitate optimisation of
the stimulation parameters, electrode design and location.

3.3 Effects of Stimulation of Denervated Muscle

Much of the early work focused on whether stimulation could retard muscle atrophy and the
conflicting observations were inconclusive [Speilholtz 1987]. Research in more recent decades has
also included the selection of stimulation parameters to best achieve the effects of clinical benefit,
Effects of Denervated Muscle Stimulation

in terms of muscle properties and reinnervation [Mokrusch, Engelhardt et al. 1990; Eberstein and Eberstein 1996]. This has necessitated invasive histological analysis in various animals to permit the frequency of measurement and statistically significant sample sizes. A few studies in humans have included analysis of muscle biopsies, though of necessity, these are limited to samples before and after treatment. Unfortunately few of the studies correlate the structural and functional measures. This section details some of the results of the animal studies pertaining to those of the clinical studies (§3.4).

The effect of stimulation is predominately on those denervation changes occurring due to the absence of muscle contraction, (§2.3), and therefore greatly influenced by the stimulation, contraction and treatment patterns employed (§3.2). Also important is the muscle loading and length during contractions, which is known to influence protein synthesis rate and damage mechanisms (§2.3). In some studies, the muscle was partly or wholly excised from the animal for post treatment evaluation measurements, which are influenced by the extent to which normal blood supply is preserved, the maintenance of body temperature by artificial means and the use or otherwise of anaesthetic. The duration of denervation and immobilisation of the muscle determine the extent to which tissue properties deteriorate or alter and the effect of stimulation depends on whether these are reversed or compounded [al-Amood and Lewis 1987]. The observed effect of treatment is also influenced by the proportion of fibres stimulated, the level of blood, and hormone perfusion [Eberstein and Eberstein 1996]

The clinical relevance of many studies has been questioned in terms of how representative they are of typical nerve injuries [Speilholtz 1987]. The stimulation treatment employed in many animal studies applied continuously for periods of days or weeks, whereas reinnervation in humans is typically months or up to a year. As with studies of denervation tissue properties (§2.3), variability between studies is introduced by differences in the methods of denervation and histological techniques employed. Direct comparison of studies in animals and humans must also be done with caution given the large differences in parameters required to produce tetanic contractions, especially between transcutaneous and subcutaneous stimulation and because of differences in muscle physiological response to denervation (§2.3). This complexity of influencing factors, makes comparison of individual studies and their conclusions on the effectiveness of stimulation parameters, difficult to correlate and draw overall conclusions from, not least because of the variability of detail in the information [Speilholtz 1987; Eberstein and Eberstein 1996].

3.3.1. Contraction Characteristics

Chronic stimulation of long-term denervated muscle almost completely restored the specific tension of fast and slow muscle fibres (tension per unit fibre area) but overall muscle tension was still about 5% of normal as fibre atrophy was not fully reversed [al-Amood, Lewis et al. 1991]. The
Effects of Denervated Muscle Stimulation

The effect of stimulation on tension in fast muscle is largely related to the frequency correspondence of normal physiological firing rates. High frequency stimulation is required for maximum contraction force [Gunderson and Eken 1992; Vrbova, Gordon et al. 1994 p72]. No significant frequency dependence was observed in stimulation of slow muscle [al-Amood and Lewis 1987].

In some studies, the decrease in fatigue resistance with denervation was reduced by low frequency stimulation [Stein 1982 quoted by Vrbova, Gordon et al. 1994 p238] in others, it had no observed effect [Nix 1990]. This is related to the extent of increase in oxidative capacity and fibre metabolism. Stimulation can either maintain an existing muscle fibre type or effect a change, in its contractile structure, metabolism or contraction characteristics. This plasticity of muscle to its activity pattern, has been used to greatly increase the fatigue resistance of skeletal muscle by indirect stimulation for its application in cardiac assistance and considerable research has been undertaken into the optimum indirect stimulation pattern especially for minimising muscle damage [Salmons 1995].

In denervated slow muscle stimulation produced an increase in contraction speed (decrease in twitch TPT and RT) though some is attributable to denervation changes (§2.3.1). Gunderson and Eken [1992] reported a frequency dependency, with a progressive increase in muscle twitch speed with increasing frequency (20, 75, 150Hz) but similar increase in isotonic shortening speed with all frequencies. al-Amood et al. [1987] observed a similar response (though greatest with 40 & 60Hz) providing intermittent stimulation was used. Only continuous (10Hz) stimulation maintained or restored normal slow muscle contraction speed contrary to denervated changes. They therefore consider the time interval between contractions (contraction frequency) to have greater influence on muscle contraction speed than stimulation pulse frequency, postulating a chemical agent which falls below a critical level when the interval is too great as in all but continuous stimulation [al-Amood, Finol et al. 1986; al-Amood and Lewis 1987]. Similarly, others reported that 10Hz direct stimulation maintained denervated rat soleus and that 100Hz transformed it from slow to fast muscle irrespective of the total number of impulses [Mokrusch, Engelhardt et al. 1990 quoting Lomo. 1980, 1985].

In denervated fast muscle, Gunderson and Eken [1992] suggest a dependence on the amount of stimulation (number of pulses) rather than their frequency. Low frequency intermittent stimulation (20Hz) produced a slight increase in twitch TPT and no change in isotonic shortening velocity. With high frequency intermittent stimulation (150Hz), twitch TPT was unchanged but isotonic shortening velocity was decreased. Using physiologically based high frequency (100Hz) intermittent burst stimulation (average 1.6 Hz) produced no significant effect on latency or contraction speed of rabbit EDL [Nix 1990]. The increase in refractory period of the fibre membrane with denervation, is considered to limit the effect of fast stimulation patterns, which cannot respond to every pulse. Whereas, with innervated muscle the synapse acts as a filter, such that both high and low frequency stimulation can produce a slowing of muscle [Nix 1990].
§3.3  Effects of Denervated Muscle Stimulation 3-11

3.3.2 Membrane Electrical Changes, Nerve Sprouting and Reinnervation

The muscle fibre membrane passive electrical properties and resting potential are restored to normal values by stimulation, and attributed to the muscle activity rather than regulation by neurone derived agents [Lomo and Rosenthal 1975]. Stimulation has also been shown in many studies to suppress the disseminated ACh sensitivity into extra-junctional areas of denervated muscles, producing a rapid increase in PKC activity (§2.3.2) in the chick muscle nucleus within 10min [Huang, Tong et al. 1992]. The level of ACh sensitivity, increased following denervation, is reduced by stimulation in slow and fast muscle (rat soleus [Jones and Vrbova 1970], mouse soleus and peroneus tertius [Brown and Ironton 1977b], rat EDL [Gruener, Baumbach et al. 1974]. Indirect stimulation of rat soleus distal of a nerve block started after 4 days was shown to reverse the extra-junctional supersensitivity, and to prevent it altogether when started earlier. Direct stimulation of the muscle proved only slightly less effective at his suppression but ACh sensitivity of the original endplate was of the order of normal muscle [Lomo and Rosenthal 1972] (Fig.3.3.1). This suppression of ACh hypersensitivity was shown to occur with only very small amounts (average 0.005Hz) of stimulation but occurred at an increased rate with increasing frequency, (up to 100Hz) and also dependent on the interval between bursts [Lomo and Rosenthal 1975]. These authors suggested this accounts for the greater extra-junctional sensitivity in normal slow muscle than fast, regulated by free calcium released by muscle activity.

Figure 3.3.1 Muscle Fibre Membrane ACh Sensitivity following Stimulation (Lomo et al.1975)
§3.3  

**Effects of Denervated Muscle Stimulation**  

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Similarly junctional AChR numbers were maintained at normal levels for at least 2 months in rat soleus muscle by 100Hz but not 10 or 20Hz stimulation, and only when started on the day of denervation and with progressively less effect thereafter, to none if started after 7 days. These authors postulated that such muscle activity is able to maintain a trace of, but not replenish, the neuro-trophic element regulating AChR distribution, which otherwise disappears within a week of denervation [Andreose, Fumagalli et al. 1995]. Metabolic stability of AChR has also been maintained at normal levels by immediate stimulation of rat soleus [Andreose, Xu et al. 1993], by activation of additional calcium channels [Caroni, Rotzler et al. 1993]

Hence electrical muscle stimulation can, to varying degrees, reverse the activity related AChR changes with denervation by limiting AChR to junctions and increasing their half-life, however that this is specific to the type of activity is indicated by the concurrence of fibrillation and hypersensitivity [Lomo and Rosenthal 1972]. However, Gruener, Baumbach et al. [1974] reported that the suppression of ACh hypersensitivity by both subliminal and maximal stimulation induced contractions, suggested a non-activity specific regulation, as does the absence of hypersensitivity following immobilisation from tenotomy [Lomo and Rosenthal 1972]. Therefore, stimulation does not overcome the effect of non-activity dependant ACh regulators such as nerve degeneration products, which may still cause increasing effect on ACh sensitivity [Vrbova, Gordon et al. 1994].

The association of extra-junction ACh hypersensitivity with innervation is suggested by its suppression following cross-innervation by a foreign nerve at ectopic junctions [Frank, Jansen et al. 1975]. Electrical stimulation, known to suppress the ACh extra-junctional sensitivity, also suppressed foreign nerve cross-innervation, whereas regeneration and reinnervation by the original nerve was unaffected [Jansen, Lomo et al. 1973] and occurs without measurable extra-junctional sensitivity [Frank, Jansen et al. 1975]. As noted above, junctional ACh sensitivity is maintained at normal levels during stimulation. It therefore appears that the effect of simulation is mainly to inhibit colateral sprouting and reinnervation at ectopic junctions, probably by suppressing the growth stimuli associated with the increased extra-junctional AChR. Whereas the regenerating nerve is less affected in seeking to reinnervate the original junction, where ACh declines more slowly and may even be enhanced by stimulation [Andreose, Fumagalli et al. 1995]. This was also suggested in the study of Brown and Holland (1979) who observed a reduction (11 cf 62%) in terminals with sprouts due to high frequency (100Hz and 150Hz) intermittent burst stimulation in mouse soleus partially denervated by spinal root section. However indirect stimulation of the innervated fibres alone produced no significant reduction in sprouting, leading the authors to authors conclude that activation of the denervated fibres suppressed a sprouting agent they would otherwise release and induce sprouting from neighbouring innervated muscle fibres. Similarly, direct stimulation of the muscle completely denervated by nerve crush produced no significant reduction in muscle tension, and was taken as indication of no effect on sprouting. Stimulation
current was therefore assumed not to have damaged the regenerating nerve, as also indicated by the positive benefits demonstrated of micro-ampere direct currents (§2.2.5).

Other studies have also demonstrated successful reinnervation with stimulation, largely attributed to the preservation of fibre properties [Williams 1996a,b]. Williams adopted a clinical model, in which the nerve injury was repaired using normal micro-surgical techniques and stimulation continued until EMG changes occurred or nerve stimulated contractions were possible. Stimulation consisted of 0.1s or 1.5s bursts of 36 or 85Hz pulses, and 2.5% or 6.25% burst duty cycle, applied continuously through implanted wire electrodes along the muscle length. Reinnervation took 8 weeks for the rabbit femoral nerve severed 40mm from the rectus femoral muscle, 16 weeks for a 120mm growth of the common peroneal nerve in dogs and 10 months for re-innervation of the frontalis muscle following facial nerve severing and cross facial nerve grafting. Unfortunately the course of reinnervation of the unstimulated controls was not described [Williams 1996b]. A previous study with similar protocol but higher frequency (130Hz) demonstrated fibre changes, but failed to show any signs of reinnervation after 8 weeks, for the common peroneal nerve severed 40mm from the peroneus longus muscle in dogs [Nemoto, Williams et al. 1988].

Conversely other studies have reported detrimental effects of stimulation on innervation, prompting the controversy over its efficacy. However, it has been noted that where nerve growth and reinnervation was affected by stimulation, it was reduced rather than abolished completely, perhaps because not all fibres were stimulated; for instance Hennig [1987] observed that long term stimulation in rats prevented reinnervation in 5-20% of muscle fibres [Eberstein and Eberstein 1996]. If stimulation suppresses collateral reinnervation but enhances regeneration reinnervation by retarding atrophy changes, then it poses a dilemma as to the timing and efficacy of treatment, as both have limitations. Colateral reinnervation is limited by the extent of motor unit expansion possible. Regeneration reinnervation is limited by the process of nerve regrowth, and in some instances, the appropriateness of reinnervation (§2.2.3). Where the prospects of nerve regeneration and successful re-innervation are high, then arguably stimulation should not be applied if it is likely to hinder this process in any way. For instance, collateral cross-innervation may maintain the muscle fibre condition until reinnervation by the regenerating nerve at the original endplate, and therefore advocates no or delayed start to stimulation. However for complete proximal nerve lesions, where collateral innervation is limited or absent, muscle fibres will be subject to denervation for up to a year with consequent severe deterioration in condition limiting the prospects of full functional recovery (§2.2.3). Stimulation treatment commenced as soon as possible after injury would take advantage of the continued muscle fibre excitability to maintaining muscle fibre properties, with almost complete prevention of atrophy achieved when started immediately and diminishing results thereafter [Eberstein, and Eberstein 1996 quoting others]. Also, Andreose et al.[1995] showed the regulatory mechanism maintaining junctional AChR only appear
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to be susceptible to influence by stimulation during the first weeks after denervation, though muscles fibres are still capable of reinnervation after a year of denervation [Fu and Gordon 1995].

However it was apparent that the stimulation pattern is critical to its effect on ACh hyper-sensitivity and various techniques have been adopted clinically (§3.4.1). Some have demonstrated functional reinnervation to be at least not prevented and in cases, enhanced by the stimulation treatment, though none of these studies evaluated colateral sprouting or motor unit count. The studies by Williams [1996a] and Mokrusch and Neundörfer [1994] used similar protocols of stimulation in animals and humans with similar beneficial results. With Williams’ studies, this was despite the use of high frequency stimulation suggested by Lomo and Rosenthal [1975] as most detrimental to ACh hyper-sensitivity, albeit at threshold contraction strength.

3.3.3 Muscle Fibre Type

For denervated muscle, the retarding of muscle and fibre atrophy and the preservation of contractile ability is probably of greater clinical importance to the recovery prognosis than preservation of the normal fibre type balance of the muscle, given that muscle plasticity will probably allow reversion of fibre type if nerve reinnervation occurs. However inappropriate reinnervation is common following facial paralysis, and therefore is a consideration for stimulation treatment applied in such cases. Changes in the fibre type proportion and contraction characteristics of a particular muscle may occur through transformation of fibre type or through preferential hypertrophy of one fibre type over another (§3.3.5). Whether these effects are observed depends greatly on the stimulation pattern. Some of the reported effects of stimulation are in fact a reversal of the changes occurring with denervation which results in a dominance of fast, fatigable type IIB fibres with anaerobic metabolism and fast contraction speeds (§2.3).

Myosin Contractile Proteins

Denervation changes in contractile myosin are enhanced when stimulation increases the rate of protein synthesis and therefore the generation of new myosin. These are of fast isoforms which become predominant over, no longer replenished, slow forms [al-Amood and Lewis 1987]. Conversely, fast to slow fibre transformation with stimulation is associated with changes in heavy and light myosin chains to slow or hybrid forms [Pette 1992 quoted by Jones, et al. 1994] concurrent with changes in myogen [Carraro, Catani et al. 1986], SR system, Z-band thickness and mitochondrial volume [Eisenberg and Salmons 1981]. These have not been observed in all studies perhaps because of insufficient stimulation duration [Mokrusch, Engelhardt et al. 1990].
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Myogenin and MyoD Proteins

Electrical stimulation produces an immediate decline in the denervation increase in myogenin subunit mRNAs and MyoD transcripts [Eftimie, Brenner et al. 1991]. However, that the increase is only partially repressed by stimulation activity, implies an additional neurotrophic regulation factor [Maltin, Delday et al. 1993].

Muscle Fibre Metabolism

Direct electrical stimulation results in a biochemical change from anaerobic to aerobic metabolism [Mokrusch, Engelhardt et al. 1990], including in human muscle [Eichhorn, Schubert et al. 1984]. Glycolytic enzymes are reduced [Weber and Pette 1990] and oxidative enzymes increased within a few minutes of stimulation [Eichhorn, Schubert et al. 1984] especially in fast muscle fibres [Khaskiye, Sine et al. 1990] though not necessarily in the muscle as a whole [Nemeth 1982]. Mitochondria volume, as shown by electron microscopy, is also increased [Eisenberg and Salmons 1981], especially in the subsarcolemmal space [Mokrusch, Engelhardt et al. 1990]. The increase in enzymes was not correlated to fibre diameter or necessarily to contraction speed. [Nemeth 1982]

Muscle Fibre Type Composition

These changes in fibre metabolism are reflected in the relative proportions of fibre types within the muscle. Twice daily tetanic contractions of rabbit fast muscle (flexor digitorum sublimis) produced a predominance (91%) of fast, mitochondria rich intermediate fibres (type IIA) compared to both normal and denervated muscle apparently due to a transformation of type I and type IIB fibres controls [Mokrusch, Engelhardt et al. 1990]. Others reported this accompanied by changes in myosin [al-Amood, Finol et al. 1986]. Type II fibre increase was also observed in dog orbicularis oculi muscle [Salerno, McClellan et al. 1991] and human quadriceps muscle [Neumayer, Happak et al. 1995].

This transformation is attributed to the nature of fibre recruitment with supra-maximal stimulation, that is all fibres/motor units simultaneously rather than in physiological size order from type I to type II, oxidative to glycolytic. Type II fibres are recruited for much longer periods and this may promote enrichment of the oxidative processes and mitochondria of type IIB fibres [Pette and Tyler 1993 quoted by Mokrusch, Engelhardt et al. 1990]. Conversely, Nemoto et al (1988) reported an increase in the proportion of type 1 fibres, even to the extent of being significantly greater than normals (46%(stim), 28.4%(control), 33.7% (normal)) in mixed peroneus longis muscle in dogs, with an associated rise in fatigue resistance. This may be attributable to the high frequency (130Hz), low burst rate (1.5s in 60s) stimulation pattern, causing prolonged twitch type contractions.
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3.3.4 Muscle and Limb Perfusion

Indirect electrical stimulation is capable of producing an increase in overall blood flow due to the greater muscle activity as well as increasing the blood capillary capacity associated with the transformation or predominance of oxidative fibre metabolism. However these are dependent on an appropriate stimulation pattern and visible tetanic contractions were found necessary for oxidative increases [Clemente and Barron 1993]. A delayed or reduced increase in capillary density occurred with intermittent compared to continuous 10Hz indirect stimulation. The absence of change with intermittent 40Hz or 50Hz stimulation is attributed to blood supply occlusion during contractions. The increase in capillary density is prompted by increased muscle activity and the resulting increased oxygen availability in turn prompts the increased oxidative capacity of the muscle cells [Brown, Cotter et al. 1976]. Limb blood flow typically decreases to 65% of normal following SCI. This was restored by indirect stimulation and correlated to increase in muscle bulk [Taylor, et al. 1993].

3.3.5 Fibre atrophy, Structural Changes and Damage

The atrophic effects of denervation may be reduced by stimulation patterns and contractions appropriate to the muscle type. Atrophy in slow muscle is largely prevented by any stimulation pattern but this may also be associated with transformation of fibre type and at high frequency, firing becomes irregular [Vrbova, Gordon et al. 1994 p83]. Results in fast muscle are more variable. Short term low frequency stimulation reduced atrophy by 10% (7ms,1Hz, 20 min/day) [Nix and Dahm 1987] and tetanic frequency by up to 40% (20ms, 25Hz 6min/day) [Mokrusch,Engelhardt et al. 1990, Herbison, Teng et al. 1971]. Conversely high frequency (100Hz) had no effect [Nix 1990 quoted by Eberstein and Eberstein 1996] In mixed peroneus longus muscle in dogs, 130Hz, 24hr/day burst stimulation produced a 14% increase in weight compared to unstimulated control contralateral up to 67 of normal [Nemoto, Williams et al. 1988]. Greatest preservation of muscle weight (up to 80% normal) was achieved by similar technique continued to the time of muscle reinnervation [Williams 1996b]. The failure to fully prevent atrophy is attributed to the inability of stimulation to provide the neurotrophic control of muscle fibres causing denervation atrophy as opposed to disuse atrophy [Nemoto, Williams et al. 1988] and where current penetration is insufficient to effect all fibres [Eberstein and Eberstein 1996]. Induced damage (metabolic or structural) may also be a cause of the lack of observed beneficial effect of stimulation treatment, for instance strong tetanic contractions at 40Hz resulted in severe fibrosis [Nix and Dahm 1987].

Some of these changes in muscle weight were also correlated to increases in fibre diameter in slow muscle (rat Soleus with 100Hz [al-Amood,Finol et al. 1986] and fast muscle (rabbit EDL, 1Hz [Nix and Dahm 1987]. However the response is not uniform, with hypertrophic (32%), atrophic (31%) and normal (35%) fibres arising from stimulation [Nemeth 1982]. The largest fibre diameters were
observed close to electrodes due to the greater current density and strength of contractions [Nix and Dahm 1987 quoting Gutmann 1944, Schaffer 1954]. The number of muscle fibres was increased [Nemeth 1982] or restored to approximately normal levels by stimulation [al-Amood, Lewis et al. 1991]

A preferential effect on one fibre over another was not consistently observed and probably highly dependent on the stimulation pattern used. Pachter et al. [1982] [quoted by Speilholtz 1987] observed retarded atrophy in both types but to a greater extent in type II fibres and this is consistent with their increase in the proportion of fibres. Girlanda, Dattola et al. [1982] observed accentuated atrophy in type I fibres, whereas Nemoto, Williams et al. [1988] observed their greater preservation.

The stretch activity is thought to restore the sarcomere structure of the myofilaments and thereby increasing the contraction force [Schmalbruch, al-Amood et al. 1991]. However contractions should not be so as to cause fatigue and thereby prevent proper contraction: Short tetany (40Hz) in fast muscle resulted in atrophy and joint contracture due to connective tissue proliferation together with laceration, microtrauma and single fibre rupture [Nix and Dahm 1987]. A chemical agent released by fibres is postulated to induce connective tissue growth also released by intensive exercise. Stimulation induced increase in perimysial is attributed to abnormal contraction (increased heat, blocked blood flow) and therefore minimised to the extent that the stimulation is able to mimic normal contraction [Nemeth 1982]. Appropriate stimulation can therefore decrease connective tissue, fatty degeneration, central cell and fibre necroses [Mokrusch, Engelhardt et al. 1990] and restore the filament order [Schmalbruch, al-Amood et al. 1991][al-Amood, Lewis et al. 1991], with fewer atrophied fibres and less fibrosis compared to controls [Nemoto, Williams et al. 1988].

**Muscle fibre damage**

Muscle fibre damage by indirect stimulation induced contractions, when it occurs, is clearly evident with histological staining techniques, in terms of disturbed internal fibre architecture, rounded cross-sectional appearance, activated macrophages and lysosomes within and between fibres, increased RNA and the presence of neonatal myosin isoforms in some fibres. This was quantified as the volume percentage of degenerating muscle fibres within a sample area, and varied considerably between animals (of the same species), between muscles (TA>EDL), between locations in the same muscle (proximal > distal in EDL) and with the stimulation pattern. The damaged observed was after 9 days of continuous stimulation and was reported to subside to almost zero after 3 weeks. This type of damage has a similar time course to the transformation of fibre type, but as it affects far fewer fibres, is not thought to be the mechanism of transformation [Lexell, Jarvis et al. 1997].
Observed fibre damage may be due to excessive contraction strength or duration, excessive pulse
duty cycles or just excessive periods of stimulation. Some evidence refutes the suggestion of
reperfusion damage following ischaemic contractions induced by indirect stimulation [Lexell, Jarvis
et al. 1997] (§2.6.1), however it is possible that the diminished perfusion and metabolism of
denervated muscle fibres may make them more susceptible to such damage. Certainly, it is known
that various damage effects occur from muscle overuse of weak or denervated muscle [Herbison,
Jaweed et al. 1983]. However Guttmann [1976] concluded the fatigue response of normal muscle is
highly variable and that excessive caution with regard to denervated muscle had hindered the
application of effective stimulation treatment. Research has also been conducted into the effects of
nutritional deficiency during indirect stimulation however there seems little evaluation of the
nutritional, fatigue or damage mechanisms in the stimulation of denervated muscle and warrants
research.

3.3.6 Conclusions from Animal Studies

The general conclusion from the animal studies is that stimulation can have beneficial therapeutic
effects on denervated muscle but this has done little to direct the potential clinical applications, and
further research was necessary to conclude the optimum parameters for human muscle [Eberstein
and Eberstein 1996]. More pessimistically, Spielholtz [1987] observed that stimulation at best only
retarded muscle atrophy and degeneration due to denervation and could never replace the
neurotrophic loss, so complete degeneration is inevitable if reinnervation does not occur. In
identifying those in whom reinnervation was delayed beyond 24 months as most in need of the
treatment, he pointed out that issues of finance and patient compliance to the rigorous treatment
pattern may well preclude its viability. However, far more promising results were produced
subsequently by the clinically based model of Williams [1996b], leading to reinnervation and
functional recovery.
3.4 Clinical Application of Denervated Muscle Stimulation

Clinical application of direct electrical stimulation to denervated muscle has been both as a diagnostic tool (§2.4.4) and treatment for peripheral nerve injuries. Early work occurred around the first world war and the second world war prompted considerably more research [Speltholtz 1987]. Studies in animal models questioned the efficacy of such stimulation given its ineffectiveness at retarding atrophy and evidence of its deleterious effect on nerve regeneration, however more recent studies have demonstrated favourable effects (§3.3). Reinnervation stimulation treatment is aimed at retarding muscle atrophy and fibrosis following nerve injury and thereby maintaining the muscle fibres and connective tissue in a state suitable for reinnervation [Campbell and Meadows 1995]. Latterly these aims have been extended to the therapeutic stimulation treatment of chronically denervated muscle where reinnervation is not expected, and the objective is to maintain tissue viability. In some cases, researchers have gone on to seek to restore function to chronically denervated limbs through functional electrical stimulation treatment, as now employed routinely for innervated paralysed muscle (§3.1).

3.4.1 Reinnervation Stimulation Treatment

The conventional clinical treatment of denervated muscle has employed transcutaneous galvanic stimulation, producing low frequency twitch contractions. Typical treatment involved pulses of 100-500ms at 0.5Hz or less for 15 minutes a day, 3 times a week [Kern, Hofer et al. 1999]. This was largely based on the assumption that over-fatiguing of the muscle would exacerbate atrophy, a suggestion dismissed by Guttmann [1976] who advocated that its ineffectiveness was due to its insufficiency of intensity, number of contractions and frequency of treatment sessions, which led many to question its clinical benefit [Mokrusch and Neundorfer 1994]. The infrequency of treatment can be attributable to the reliance on a therapist, given the danger of skin damage from inappropriate use and the unavailability of home-use stimulators.

Guttmann [1976] advocated treatment once or preferably twice per day, initially of 15 minutes with 50-100 contractions and building up to 30-45 minutes with 600-800 powerful contractions and a few seconds rest in between. To minimise the ionising effect of unidirectional current, balanced pulse galvanism was recommended with the high amplitude rectangular stimulating impulse followed by a subliminal amplitude impulse of opposite polarity and longer duration [Wickham 1948 quoted by [Guttmann 1976]. Electrode positions were moved during the session to minimise skin damage and to recruit more muscle fibres. The treatment is advocated for acute cases as soon as possible after injury, including with faradic stimulation where possible. For partial lesions non-rectangular pulse shapes may be employed to minimise sensation.
In terms of quantitative studies, that by Jackson [1945] on 54 patients including ulnar nerve injuries is highlighted amongst the early research [Guttmann 1976; Boonstra, Van Weerden et al 1987]. Using treatment of 30 contractions at 0.5Hz, 3 times each day, 6 days a week. Jackson claimed beneficial effect on atrophy, though this was measured volumetrically and therefore did not account for changes in other tissue. A study by Roselle et al [1977] on over 300 patients concluded in favour of stimulation, but did not precisely define the treatment pattern of the outcome measures [Mokrusch and Neundörfer 1994]. Clinical galvanic stimulation treatment has been conducted for the past 20 years by LeFlohic [1994] for a wide range of acute nerve injuries including more than 130 individual nerves following surgical repair. Treatment is commenced within 1.5 months of the lesion, initially daily and subsequently 3 times a week as outpatient. Using widths of 100-300ms and inter pulse intervals of at least 3 times this, 20 reasonable strength contractions are conducted at each location before moving the electrodes to another sector of the muscle. Trapezoidal shaped pulses are used to selectively stimulate muscles in partially denervated limbs. A number of muscle excitability tests are used to monitor the progress of recovery but measurements of nerve growth or atrophy were not reported. Functional reinnervation has been achieved, it is claimed, in 80% of cases but the author has not published a case control trial.

More quantitative evaluation was conducted by Boonstra, Van Weerden et al. [1987], who studied 81 nerve injuries on 73 patients, including medial, ulnar, brachial plexus and peroneal injuries, the majority following primary repair, and starting treatment on average 7 weeks later because of immobilisation for suture healing. Evaluation measures were EMG pattern, handgrip force, muscle grading and muscle bulk by CT or Ultrasonography. Control groups with each type of injury received no stimulation. Treatment consisted of one session per day for 5 days until a mixed interference EMG pattern or no further change revealed reinnervation. Treatment sessions consisted of 30 contraction at 1Hz with pulse width at 70, 100 or 200ms according to the muscle excitability. For the medial and ulnar nerve injuries, there were sufficient cases to permit additional treatment groups receiving two sessions of 60 contractions each day, 7 days a week, and for each treatment pattern, one group continuing treatment until reinnervation, and one group until muscle grade 2 was achieved. A subjective assessment of the quality of the contraction and the patient compliance indicated that treatment 7 days a week until reinnervation was more effective. Only two statistical differences were found in the qualitative measures between control and treatment groups, either as individual groups or collectively. Stimulation reduced the frequency of the EMG pattern in totally denervated cases. In ulnar nerve injury cases, stimulation reduced the mean period to achieve muscle grade 4- of abductor digiti V by almost half, from 46 to 24 weeks, though the eventual numbers reaching the grade were the same. The authors therefore concluded no beneficial effect on muscle atrophy had been demonstrated by this stimulation treatment and did not recommend it clinically, though no detrimental effect on nerve growth had occurred.
Given the confusion surrounding the efficacy of stimulation in the animal model, there seemed insufficient justification for clinical application of the subcutaneous stimulation that would permit tetanic contractions. However, the studies by Williams [1996b] showed significant improvements in muscle bulk and contraction force, without hindering reinnervation and a clinical study was conducted based upon these [Williams 1996a]. By using high frequency (130Hz), low burst rate (1.5s every 25.5s) continuous stimulation, the treatment pattern is in fact similar to that of the galvanic stimulation but with tetanic contractions at the isometric threshold. The programmable implanted system with wire electrodes passed 1-2cm apart through the muscle of interest allowed a pulse width of 1ms and continuous (24hour) stimulation at the level of isometric contraction. The 13 cases included injuries to the medial, ulnar, medial and ulnar and radial nerves, all of which had been micro-surgically repaired previously. Although treatment is advocated as soon as possible after injury, the stimulator was implanted on an elective basis from 3 to 101 days after repair and treatment started 7 to 10 days thereafter. It was stopped when there were signs of muscle reinnervation from muscle movement or EMG assessment. This varied from 123 to 317 days, corresponding to nerve growth rates of approximately 1mm/day. Assessment of the effect of the stimulation was in terms of muscle bulk (method not stated) and fibre structure from biopsies, muscle contraction grading and functional measures of handgrip; all where expressed as a percentage of the uninjured contralateral. Reinnervation occurred in all cases with a remarkable restoration of function, with the majority graded as good to excellent. Muscle bulk was restored to 100% of normal in 8 cases, greater than 92% in 3 cases and hypertrophy (105%) in 2 of the radial nerve cases. The histological analysis showed a near normal fibre structure. Comparison of results was made with 5 concurrent and 20 retrospective cases of the same clinic that did not receive the stimulation treatment. Results of the functional measures were reported as inferior to those stimulated, the biopsies showed degenerated fibres with centrally placed nuclei, great variability in diameter, with fibrous and fatty infiltration (Fig.2.3.2). The authors cited a number of other reviews of nerve injury repair without stimulation treatment had resulted in both a lower proportion of cases recovering function and poorer quality of recovery, than in their study. The authors attribute the success of the functional restoration to the near complete prevention of muscle atrophy during the period of nerve re-growth. The preceding animal studies showed that it is type 1 fibres disuse atrophy that is reduced by this stimulation pattern, though the histological analysis to confirm this was not reported on. This is somewhat surprising given the high frequency of the impulses especially given the deterioration in muscle for those commencing treatment 103 days after denervation. Direct comparison with the results of transcutaneous stimulation studies is difficult. The rate of reinnervation appears unaffected by the stimulation but the prevention of atrophy and quality of restored function is remarkably good. That this was achieved with far less vigorous contractions than employed with transcutaneous stimulation, is probably attributable to its continuous application for which the implanted system has very significant advantages.
Kim and Kim [1999] have also reported similar improvements from stimulation treatment in the quality and speed of restored function from reinnervation following brachial plexus injury. However, their study differs from Williams, in that the percutaneous electrodes were implanted in 18 acute cases into the nerve at the proximal point of suture repair, primary with a view to enhancing nerve regeneration, rather than muscle atrophy, though the ground electrode was located more proximally at the shoulder. Stimulation was applied intermittently with 5s on, 5s off for six, 30min sessions each day, and consisted of 0.2ms pulses at 20Hz of 1V amplitude. Comparison with other non-clinical studies of stimulation for nerve regeneration (§2.2.5) is difficult without in vivo measures and calculation of the currents and fields involved. However, compared to 24 unstimulated cases (matching not stated), initial biceps motor recovery commenced after 3.4 months instead of 9.1 months, initial medial nerve sensory recovery commenced after 4.5 instead of 9 months and elbow flexion and shoulder abduction strength remained greater throughout the 2 year follow-up period. 2 sub-acute cases (2 year post injury) with poor biceps muscle power recovery were also treated with the electrode positioned at the muscle motor point and improvement was reported within 2 months [Kim and Kim 1999].

Mokrusch and Neundörfer [1994] treating cauda equina and brachial plexus lesions by transcutaneous stimulation with long biphase pulses and tetanic contractions (§3.4.2), commenced stimulation, in some cases within one month after injury, with confirmation of muscle denervation. In three of the brachial plexus lesion cases, sensory reinnervation occurred during the course of the treatment (7, 9 and 21 months after start of treatment, 8,20 and 27 months respectively after injury). No motor reinnervation occurred, which is said to be common after nerve transplant. Motor nerve growth was not measured so the effect of the stimulation cannot be judged. However in the case of a partial lesion, evidence of increased innervation was cited in terms of increased peroneal nerve action potential 26 months after trauma. These cases at least demonstrate that sensory reinnervation was not inhibited by the stimulation treatment.

Partial Denervation Treatment

The work of LeFlohie [1994] cited above is predominately with cases of partial limb denervation and trapezoidal shaped pulses are used to selectively stimulate the denervated muscle by means of accommodation (§3.2.2). Similarly, Cummings [1985], citing the work of Kowarschik [1952] and Thom [1955], recommended the use of exponentially progressive current stimulation, as effective at retarding atrophy in such cases, though no details of clinical results were given.

Denervated facial muscles do not atrophy as rapidly, probably because of the good blood supply and passive movement of underlying muscle activity [Lenman and Ritchie 1987 p.100]. However their treatment with stimulation is particularly difficult as sensory innervation of the overlying skin by the trigeminal nerve is often preserved, and the minimum of pulse width and intensity is
recommended [Campbell and Meadows 1995]. Some have not observed any benefit effect of stimulation [Wynn-Parry and Cowan 1994]. A stimulation pattern based on the EMG pattern of normal muscle has been advocated by others for the treatment of facial paralysis arising with Bells palsy and this has restored function and resolved much of the typical inappropriate reinnervation [Farragher, Kidd et al. 1987]. Similar, Patterned Neuromuscular Stimulation (PNMS) has been shown to reverse the denervation type EMG pattern and increase the CMAP of first dorsal interosseous muscle (FDI) in the case of a wasted and weakened hand following ulnar nerve entrapment and subsequent nerve transplant 2 years previously [Peterson, Smith et al. 1994]. The pulse width employed in this case was 80μs, it is unclear whether the resulting palpable contraction is due to denervated fibres or any remaining innervated muscle fibres. It is possible that this type of stimulation avoids the detrimental effect on collateral sprouting (§3.3.2), which is particularly important in cases of partial denervation, but it has been less successful with the larger, quadriceps muscles (§3.4.5). Another form of stimulation with parameters derived from the muscle EMG signal has been applied to large segment nerve-muscle transplants to the upper limb, while awaiting reinnervation [Lasn 1995].

These clinical studies have contributed further to the debate on the effect of stimulation on muscle reinnervation (§3.3.2). Many of the above clinical studies have continued stimulation, throughout the period of nerve regeneration and reinnervation until muscle movement is possible, without apparent adverse effects on nerve growth and perhaps even enhancement, though this was not monitored directly. Both the time to functional reinnervation and the eventual functional outcome was improved in studies by Williams [1996b] and Kim and Kim [1999], but not with the low frequency stimulation used by Boonstra, Van Weerden et al [1987]. The multiplicity of influencing factors makes the selection of matched controls almost impossible and so a multi-centre trial has been planned [Williams 1996b] which should provide additional evidence. That, nerve growth has not been inhibited by the stimulation used would seem to advocate its commencement as soon after injury as possible, however its effect on the initial period, when collateral sprouting may be expected has not been evaluated. Also of interest, is whether the benefits achieved by Williams with subcutaneous stimulation, may also be obtained by transcutaneous stimulation without effecting nerve growth, and the necessary parameters and treatment pattern required. With a pragmatic approach, Mokrusch and Neundörfer [1994] and Valencic and Vodovnik [1986] both argue that the proportion of the day for which stimulation is applied (say 1hr = 4%) is insufficient to have any effect on nerve growth, though the above observations refute this, and it is not applicable to the continuous stimulation applied by Williams.
3.4.2 Therapeutic Direct Stimulation Treatment

In cases of chronic denervation, typically greater than 2 years post injury, where reinnervation has not occurred, then stimulation treatment is aimed at the long-term maintenance of the muscle and extremity and the prevention of secondary complications (§2.3.6). The effects on muscle atrophy and fibre degeneration are therefore of primary importance, which may be related to restoration of contraction force. Also of relevance is the effect on blood flow, tissue perfusion and in many cases the cosmetic appearance of the limb. As transcutaneous galvanic stimulation appears only to delay muscle atrophy, then, although potentially useful for acute reinnervation therapy, it has not been considered of benefit or practical for chronic cases [Mokrusch and Neundörfer 1994]. This is attributed to the small size of electrodes the low stimulation intensities and the infrequency of the treatment sessions and the stimuli [Kern, Hofer et al. 1999], with higher frequencies limited by muscle fatiguing and potential skin damage.

Eichhorn, Schubert et al. [1984] avoided these limitations by using symmetrical rectangular biphasic pulses to ensure charge balancing and stimulator devices suitable for use by patients at home. Although initially pulse widths of 100ms or more were required, with continued treatment, this was reduced until tetanic contractions were possible with 20ms at 15-20Hz. Two or three, 1 minute contractions each day were sufficient for a stable condition and patients used a home-use stimulator device and surface electrodes of 2-3cm diameter. Successful treatment of Erb’s palsy in children is cited, with the treated arm attaining the length and circumference of the normal arm, whereas without treatment this remained diminished. The stimulation was also shown to increase the limb blood flow and aerobic metabolism for up to 30 minutes after the treatment but no increase in the resting value was reported. Unfortunately none of the articles published in English contain details of larger scale studies or clinical application of the treatment, however equipment was developed to exercise denervated muscles in a functional manner (§3.4.3).

Mokrusch and Neundörfer [1994], working out of the same laboratory, refined the application of this daily biphasic transcutaneous stimulation treatment and undertook a clinical investigation following favourable results from animal studies [Mokrusch, Engelhardt et al. 1990; Mokrusch, Engelhardt et al. 1992]. The majority of limbs receiving treatment were completely denervated and to maximise the overall benefit, stimulation was applied separately to extensor and flexor muscle groups via 4 sets of electrodes on upper and lower limbs as appropriate. Each was activated in turn for 10s, with an overall contraction time per muscle group, per 48min session, of 2-6 min, which represents 12 to 36 contractions. Pulse width was initially 70ms and reduced to 50ms, as the muscle became more excitable. As the interval between pulses was the same as the pulse width (50% pulse duty cycle), frequency was initially 7Hz, then increasing to 10Hz. Of the cases of complete limb denervation, 3 suffered bilateral lower limb denervation following cauda equina lesion and 10 were
upper limb following brachial plexus ruptures and/or multiple root avulsions with age from 17 - 46 years. Sensory loss was complete and motor denervation was confirmed before and during treatment by the absence of tendon reflexes, muscle action potentials (including in response to proximal stimulation), cortical somatosensory evoked potentials, F-wave or Hoffmann's reflexes. Treatment was started 1-21 months after trauma and continued for up to 38 months. Contraction force and endurance of foot and hand flexors was measured by portable dynamometer and muscle volume of lower limbs by MRI.

It is claimed that all patients benefited from the treatment with a distinct reduction in foot oedema, panaritia occurrence and improved trophism. Muscle volume increases of between 9 and 29% in the calf and between 33 to 84% the thigh were obtained. Contraction force increases of between 16 and 400% were obtained, up to one third of normal values in foot flexors and up to one half in hand flexors. Contraction endurance increased by between 13 and 135%. The response of extensor groups was delayed compared to that of flexor groups in one case by up to a year. In another case, when treatment started, 15 months after trauma, no visible quadriceps muscle contraction occurred initially, but after 6 months of treatment, 90° knee flexion was possible and after 38 months, this could be maintained for over a minute. Interruption of treatment, lead to a rapid decline in muscle force, though some contractile ability was retained initially. The greatest increases were seen during the initial 3 months and especially the first week, with two sessions per day. The reason for reducing the sessions to one a day is not given. One patient withdrew after 8 months due to lack of motivation, and 4 other patients of younger age withdrew from the trial after 6 months treatment or less for unspecified reasons. In 3 other cases involving nerve transplantation, treatment was ceased after sensory reinnervation occurred (§3.4.1), observation continued, but without motor reinnervation. It was not stated whether the withdrawal of treatment was because the stimulation became intolerable, or so as not to affect possible motor reinnervation.

Apparent from this study, is that beneficial results can be achieved from a quite minimal treatment regime, even within 12 months, however it left several questions unanswered as to the general applicability of the treatment. As a therapeutic treatment, it was unfortunate that blood flow and skin temperature were not reported in this study. Also, that muscle bulk measurements were not conducted on arm cases or progressively through the course of treatment period to know when most changes occurred. The muscle volume changes recorded, although significant, may not be sufficient to fully halt the progressive denervation atrophy. Surprisingly, it was stated that muscle volume increases were not correlated to force increases, which therefore questions the relevance of the latter as a therapeutic outcome measurement with regard to tissue viability. It was also pointed out that the contraction forces of one third of normal are still insufficient to permit functional use and more intensive treatment would be necessary, however those of the hand flexors were greater. For those for whom treatment was interrupted, the force regained on subsequent occasions was
never as great as at the initial occasion, which would appear to advocate as early intervention as possible to achieve functional objectives, and for which confidence about the absence of effect on reinnerviation would be required.

Some of these deficiencies were addressed in the study by Kern et al. [Kern 1995; Neumayer, Happak et al. 1997] in which similar biphasic rectangular pulse stimulation was applied to spastic (10) and flaccid (4) paralysis patients concurrently. The quadriceps muscles of the 4 cases of complete, chronic lower limb denervation following conus cauda injury, were stimulated using large flexible conductive rubber electrodes of 200cm² surface area and a constant voltage output stimulator. Cases were on average 3.4 years post injury with advanced muscle fibre atrophy or approximately 25% of normal (50% in spastic cases). For the first two months a pulse duration of 200ms at 1.25 Hz was required, but thereafter 30ms applied at 20Hz with a 2-3s on, 5s off periods for 30 minutes (15 minutes initially), twice a day for 8 months (1.3ms at 27Hz for spastic cases). Measurement was made of muscle cross sectional area (CT), isometric knee extension force, skin perfusion (IR thermography) and muscle perfusion (thallium scintigraphy) before and after 8 months of treatment. Muscle biopsies of vastus lateralis, also allowed examination of structural changes.

In reviewing the results, it is interesting to compare those of the denervated and spastic (in parenthesis) cases. By the end of the 8 months, the denervated cases where able to achieve full knee extension against gravity; (the spastic groups achieved this after 2 months and after 6 months were able to lift 3-5kg). The average cross sectional area of the quadriceps femoris was increased by 10% (27.5%) and the adductor and flexor muscles by 7% (22%). However the increase was concentrated beneath the electrodes, proximal 12% and distal 8% compared to only 1.8% in between. This led to the conclusion that electrodes should cover as large an area of the muscle as possible. Average fibre diameters increased by approximately 72% (+42%) although remained at about half that of normal muscle. The mean diameter of type II fibres increased to a greater extent than type I fibres in denervated muscle, 67% cf. 54% (34% cf. 65%), the reverse of spastic muscle, though their initial atrophy was greater. In the denervated muscle, the proportion of type II fibres increased from 73% to 81% (84% unchanged). The smaller relative change in muscle cross sectional area compared to fibre diameter probably reflects a decrease in the amount of connective and fat in the muscle, which was not reported on in detail. Both aerobic and anaerobic enzyme activity increased by 60% (53%) almost to the levels of normal muscle Quardiceps muscle perfusion increases of 500% (950%) were reported but not stated whether this was resting or in response to stimulation. Small but not significant increases were also observed in the lower leg. Skin perfusion measurements were not cited for denervated subjects. Skin hyperemia of the order of 1.6°C occurred in the thigh region after about 25 minutes and lasted for up to an hour, but did not spread to the lower leg.
Comparing these results with those of Mokrusch and Neundörfer [1994] for similar patients shows a smaller increase in muscle cross sectional area despite a more intensive treatment regime. However, given the small numbers, individual responses dominate and this may reflect differences in measurement technique and the greater initial atrophy with longer denervation periods in the study by Kern et al. (1995). Unfortunately, the force measurements are not comparable as only stated for spastic cases and limb blood flow was not measured to correlate with the dramatic increases in perfusion.

Kern et al. have subsequently refined this biphasic stimulation technique for chronic lower limb denervation [Kern, Hofer et al. 1999] with the primary objective of achieving functional stimulation (§3.4.3). The training period aimed at developing the required muscle strength is typically 2 years. As previously, patients start with twitch contractions from pulse widths of 120-150ms at 1-2Hz. Once the muscle membrane has stabilised and metabolism increased, unfused, clonus type contractions at 5-8Hz with 70-80ms pulse width are employed for a while before progressing to tetanic contractions at 16-25Hz with 35-50ms pulse width. In transitioning between these stimulation modes, two may be used concurrently, which helps to ensure all fibres are conditioned. The major difference from previously is the use of 80% pulse duty cycle for tetanic contractions (e.g. 40ms pulse width at 20Hz) compared to the more typical 50%, although contractions are only sustained for 2s with 2s off period in between. Increasing the pulse width thus, has been found to maximise the contraction force and reflects the primary functional aim. Despite the intensity of treatment, the average increase in quadriceps muscle cross sectional area is 48%, which perhaps reflects that atrophy in chronically denervated muscle cannot be entirely reversed. Muscle density recorded by the CT increased by 62% indicating an improvement in the quality of the muscle. The less intensive stimulation (1x/d 15min) of the lower leg and gluteal muscles is not able to prevent mild atrophy. However the primary aim is to increase the generated force to 1/4 of body weight to permit standing, and average increases of 53-73% have been achieved over 24 months. The format of this training is a series of 6 sets of 15 (initially 8) isotonic tetanic contractions of 2s with 2s off and 2min between sets (usually while training the other leg), initially against gravity and then with weights on the leg.

The intensity of the stimulation pattern, with near continuous current flow (albeit biphasic) and minimal reperfusion time between contractions within each set, raises the question of possible inducement of structural or metabolic damage which might hinder muscle development. As yet muscle biopsies have not been performed, but the general absence of fatigue during sets of contractions and progressive increase in muscle strength, is taken by the authors as indication of the absence of adverse muscle damage. However they also stress the importance of the preceding, prolonged twitch and shaking stimulation treatment periods to condition the muscle fibre structural and membrane properties. When fatigue does occur, the muscle is rested for several days to
recuperate, without apparent permanent damage. The treatment appears successful as a preliminary training for the eventual functional aims, however it is possible that it is not optimum for therapeutic purposes, in terms of the limb as a whole and it is unfortunate that measurement of resting blood flow and skin perfusion are not reported.

Taylor and Ewins et al. [1992] confirmed some of the therapeutic value of the transcutaneous biphasic technique by evaluating the effect on muscle bulk by ultrasound, resting skin temperature asymmetry by IR thermography and resting limb blood flow by impedance plethysmography. Stimulation of the lower arm of a subject with a brachial plexus lesion 8 months post injury with rectangular biphasic pulses of 10 ms at 10 Hz, twice a day for up to 15 minutes for 8 weeks, produced an increase in muscle bulk of 22% and an increase in resting skin temperature asymmetry of 3°C, but no significant change in resting limb blood flow. Similar treatment of the quadriceps muscles of a subject with a T12 level SCI, 3 years post injury, resulted in an increase in muscle bulk of 23%. Prior treatment with 30 ms monophasic pulses at 0.5 Hz for 7 weeks produced no detectable changes in the tissue measurements [Taylor, Ewins et al. 1992].

Petrofsky [1991] has also confirmed the efficacy of transcutaneous biphasic long pulse stimulation treatment but using sinusoidal current of 20 ms period at 10 Hz. The denervated quadriceps muscles of 11 paraplegics following SCI at L1 level at least 2 years post injury, were treated for 15 min/day, 3 day/wk for 6 months. The stimulation current was increased gradually over 3 s up to 100 mA followed by a 3 s off period before repeating the sequence. Measurements were made of isometric knee extension tension at the ankle, limb girth around the midpoint of the quadriceps correlated to body weight and EMG single fibre action potential amplitude at the beginning and end of the treatment period. During this period the muscle tension from stimulation at 20 ms and 250 μs doubled and the frequency of maximum response increased from 10 Hz to 20 Hz and 15 Hz respectively. Response to frequencies greater than 35 Hz remained negligible. This change in the muscle fibre electrical characteristics was reflected in the duration of the action potential, which decreased from 16 ms to 8 ms, nearer to the 5 ms of normal muscle and indicates a decrease in refractory period. From mere muscle bulging at the start of treatment, by the third month, 9 of the subjects were able to move their knee joints and by the end of 6 months were able to lift the leg with an average knee extension force was approximately 30 N. Limb girth showed a progressive increase from the start of treatment, with an average increase of 41% over the 6 months.

The choice of muscle girth measurement although easier, includes non-muscle tissue and precludes direct comparison with other studies. The muscle response in terms of tension, appears to be more rapid that that of the more intensive rectangular biphasic pulse technique advocated by Kern, though no where near the 500 N typically achieved by indirect stimulation in similar cases [Petrofsky 1991]. However this may reflect differences in the state of degeneration of the muscle fibres of these particular individuals, as much as any advantage of the stimulation technique; that any
muscle response was achieved at all to 250μs pulses implies at least some fibres were still in reasonable condition, though “complete” denervation was confirmed by needle EMG recordings.

### 3.4.3 Functional Direct Electrical Stimulation Treatment

Attempts have been made to provide stimulation treatment with some functional outcome in cases of chronic muscle denervation. This, not only makes the treatment more purposeful, enhances patient motivation, provides cardiovascular exercise and other health benefits, but it is hoped, also increases quality and perhaps, independence of life for the individual. In these applications concentration is on maximising the contraction force and control of limb movement with measures to quantify the desired functional outcome.

Bicycle ergometry, stimulating the appropriate leg muscles to rotate the pedals of a bicycle against resistance, is used extensively for indirect stimulation muscle training with demonstrated benefits in terms of muscle bulk, perfusion and cardiovascular exercise [Baldi, Jackson et al. 1998]. It has also been developed for transcutaneous direct stimulation of denervated muscle, with motor assistance to compensate for the inability to selectively stimulate all the required muscles [Arndt, Eichhorn et al. 1987]. However this has not been widely adopted because of the complexity of the multi-channel system and is considered inferior to rising and walking functions for muscle strength development and cardiovascular exercise [Kern 1995].

Regular passive standing, with stimulation induced leg muscle contractions to maintain vertical posture, will assist the functioning of internal organs and it is claimed have a positive influence on the growth of bones and the flexibility of joints [Eichhorn, Arndt et al. 1987]. Far more effective as exercise and functionally is the transfer from sit to standing through stimulation induced contractions, however this has only become possible after prolonged conditioning of the muscles to develop the necessary strength (§3.4.2) [Kern, Hofer et al. 1999]. Quadriceps muscles are stimulated to produce isometric torque values measured at the knee of the order of 38Nm, though this appears low compared to the recommendation of 1Nm torque per kg of body weight for indirect FES [Taylor, Ewins et al. 1993]. However, standing has then been achieved and maintained with the upper body support of parallel bars, stimulating each leg in turn, as a preliminary training towards stimulated walking. However precise or energy efficient ambulation with direct transcutaneous stimulation is unlikely, unless techniques are developed for the selective contraction of the required muscles; even with the greater refinement of indirect stimulation, functional walking is not yet routinely clinically available.

These examples of functional stimulation have been applied to regions of complete denervation without any sensation limit to the stimulation intensity. In many cases of chronic partial limb denervation, direct stimulation may be used to restore functional use, supplementing voluntary
 movements or in conjunction with indirect stimulation. However given the long pulses required for transcutaneous stimulation, intensities may be limited by recruitment of functional sensory nerves and unwanted co-contraction of surrounding or antagonist muscles.

One of the few studies in this area is that by Valencic and Vodovnik et al [1986] who attempted to restore dorsiflexion and thereby aid gait, in 8 cases of 'dropped foot' resulting from unilateral traumatic sciatic nerve lesion at hip level and one case following spinal L1 fracture. Treatment was started 2-40 months after injury and "complete" tibialis anterior denervation was confirmed by needle EMG and SD curve testing. Plantaflexor muscles remained innervated in 3 cases but not under voluntary control. In order to deduce the optimum stimulation parameters, at each week of the treatment, the ankle angle was measured from stimulation with pulse widths of between 5 and 50ms. From this, 20ms at 25Hz was deduced as 'optimum' for the treatment, however this perhaps just reflected the best combination of pulse width, frequency and duty cycle, all of which were varied by maintaining the pulse pause constant at 20ms. An initial week of conventional physiotherapy alone produced no significant difference in the stimulated ankle angle. For the subsequent 3 weeks, stimulation treatment was applied concurrent with physiotherapy consisting of 3s contractions followed by 3s rest for 20 minutes twice a day, 5 days/week. Intensity of stimulation was kept at the same level for the particular individual for all treatment and testing, at the limit of their tolerance (5-40mA).

There was an improvement in dorsiflexion angle in all cases, greatest in those with higher intensities, with a mean of 15.8° and positive dorsiflexion in 5 cases of up to +10° flexion. With four cases, stimulation was applied to achieve successful dorsiflexion during gait, though no quantitative measurements of gait were made. The improvement in some cases was limited by the tolerable level of stimulation intensity or the recruitment of innervated antagonist muscles and the development of associated contractures. The authors suggest that the majority of improvement was due to increases in muscle strength but recognise the contribution of possible reduction of existing contractures, though this was not quantified.

There were no signs of reinnervation at the end of the treatment. The greatest improvement in dorsiflexion angle was in fact achieved in one case of over 3 years post denervation, without innervated plantaflexor muscles. It is somewhat surprising, given the experience in other studies, that muscle denervated for this period of time responded to pulses as short as 10ms and frequencies as high as 33Hz without prior conditioning with galvanic stimulation and without mention of fatigue; furthermore that such muscle strength development was possible with just 3 weeks of stimulation treatment. It is possible for the activity of surrounding musculature to preserve the contractile properties of denervated muscle, but it was stated that none of these cases had any volitional control over the ankle joint. It is unfortunate that no follow up studies have been
published, for this relatively common denervated condition which is frequently mis-referred clinically for the available indirect 'dropped foot' stimulators (§1).

### 3.4.4 Other Applications of Direct Stimulation

Direct muscle stimulation may also have clinical application to a number of conditions producing denervation like symptoms where the voluntary or indirect stimulation induced contractions are not possible or ineffectual (§2.3.6). However little work has been published to develop appropriate stimulation treatments for these conditions. LeFlohic (1994) has treated cases of GBS, and PPS, but without detailed reporting.

Muscle subject to inactivity due to disuse or immobilisation, undergoes some of the changes of denervated muscle, including a progressive atrophy and loss of contractile ability. For such cases, Patterned Neuromuscular Stimulation (PNMS) using an 80µs pulse width and pattern derived from the EMG signal of normal but fatigued muscle, has been shown to be more effective than a uniform frequency or random frequency pattern. It produced increases in muscle strength and endurance following severe muscle wasting of the hand due to rheumatoid arthritis [Oldham and Stanley 1989] but was less effective in treating quadriceps femoris muscle weakness in elderly subjects with osteoarthritis of the knee [Oldham, Howe et al. 1995].

However as disuse continues, muscle excitability decreases until contraction is only possible with the longer pulses widths of direct stimulation. It is possible that this applies to case 15 of the study by Mokrusch and Neundörfer [1994], a brachial plexus lesion, who experienced partial reinnervation during the initial 3 years post injury but no thereafter. During the stimulation treatment started 20 years post injury, hand flexion and extension became possible with some sensation, which was cited as evidence of reinnervation, but may have been the reversal of disuse atrophy following earlier reinnervation.

### 3.4.5 Summary of Clinical Applications of Stimulation of Denervated Muscle

If anything, the clinical studies to date give more cause for optimism than those in animals, with beneficial results obtained in terms of functional reinnervation, muscle tissue properties and restored function through FES. The treatment regimes for both acute and chronic cases have proved acceptable to patients and benefits suggestive of clinical value. The controversy over the effect of stimulation on nerve growth, although unresolved in its mechanisms, has at least been demonstrated to be beneficial to the overall aim of functional reinnervation, though so far widescale clinical application is still dissuaded.

For the treatment of acute injuries, continuous subcutaneous stimulation appears to offer real improvement in functional reinnervation, though this has yet to be confirmed in a wider clinical
§3.4 Clinical Stimulation of Denervated Muscle

The exact effect of the stimulation on the processes of nerve sprouting, growth and endplate formation remain to be determined, but it has at least been demonstrated not to be precluded, even if not actually enhanced. A means of in vivo monitoring of nerve growth and reinnervation would provide greater confidence in the application of the technique and especially in the timing of its commencement after the nerve injury, which as yet has not been immediate. This may also assist in determining whether similar benefits can be achieved with transcutaneous stimulation of appropriate parameters for cases where implantation is not feasible. The modelling of the electric currents induced in the tissue concurrent with biological processes will provide an important contribution to this.

For the treatment of chronic denervated muscle the utilisation of the change in electrical and contractile properties of the muscle fibres for tetanic contractions, has heralded a treatment technique with conclusive benefits and the prospects of functional standing for complete flaccid paraplegia. It is tempting to project the application of the sophisticated techniques developed for indirect FES for these cases, however, refined functional control will require the means of selective direct stimulation of individual muscles. This will also be essential in cases of chronic partial denervation, such as 'dropped foot' or brachial plexus, where arguably the restoration of a smaller functional goal may offer greater rewards in terms of independent living. The techniques of selective stimulation therefore deserve further investigation, such as accommodating waveforms, multiple electrodes fields and sensory fibre blocking through stimulation with higher frequency or other techniques [Eichhorn, Schubert et al. 1984; Rattay 1990]. Also the energy per pulse of the biphasic stimulation technique are more than ten times the recommended maximum (MED-GV, ÖNORM) and applications for amendment of the regulations have been made [Kern, Hofer et al. 1999] and will need to be accepted prior to its clinical adoption.

However it is the therapeutic benefits, in terms of prophylactic improvements to tissue properties against decubital ulcers and circulatory disorders, which may be the ultimate justification for the clinical adoption of stimulation treatment in cases of chronic denervation, rather than the functional benefits. There remains the need to establish with statistical significance, the improvements seen in tissue bulk and perfusion. In particular the need to quantify the change to resting or average blood flow, rather than just during the stimulation session, and to determine whether these are sufficient to have a preventative influence. Such evaluation means may also be used to determine the optimum stimulation parameters and treatment pattern for the therapeutic benefits, whereas studies to date have largely focused on maximising contraction force. There is also scope for evaluated comparison of stimulation pulse shapes other than rectangular, including sinusoidal, for which similar benefits have been shown. Evaluation monitoring through the initial treatment period, while the muscle is undergoing the property changes may also help optimise this process. The Strength-
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Duration curve (§2.4.4) has been demonstrated as a means of selecting the stimulation parameters initially and as the muscle excitability alters with treatment.

In determining treatment and interpreting results, the need for precise diagnosis of the muscle innervation has been shown, especially in cases of partial denervation. SD testing provides a ready means of differentiating flaccid from spastic paralysis, to ensure the appropriate stimulation treatment be applied, should it be of proved of clinical value. The earlier after nerve injury, that stimulation is commenced, the lesser the muscle fibre degeneration and the greater the benefit that will accrue, though the appropriate parameters and treatment pattern may differ with the end objective. For instance where reinnervation is expected, ensuring no detrimental effect on nerve growth is paramount while preserving fibre type or contraction speed for appropriate reinnervation.

For therapeutic rather than functional gain, consideration of work performed and fatigue resistance may be more applicable than maximising contraction force, and may allow more comfortable stimulation patterns, especially in cases of retained sensation or the elderly [Campbell and Meadows 1995]. Part of the optimisation of stimulation parameters, must be the consideration of the biochemical mechanisms operating during direct stimulation and consequently the possible causes and extent of damage, including cellular analysis, ischaemic effects of contraction and nutritional impairment. Considerable research has already been conducted into the effects during indirect stimulation, and warrants application of the knowledge to direct stimulation of denervated muscle.

The need is therefore for a holistic approach with a role for combination therapies, not least in the management of contractures and maintenance of soft tissue.

For conditions with denervation like symptoms, careful investigation into the potential contraindications, will be required as part of the research into the application of direct stimulation treatment. For instance with GBS and PPS, a major worry is that stimulation may exacerbate the underlying muscle and general fatigue. The retained and possibly hyper-sensitive sensory innervation of such conditions, may limit the tolerable intensity of stimulation and hence its effectiveness. It is also possible, that autonomic dysreflexia prompted by the stimulation may be more likely, leading to symptoms such hypertension, headaches, temperature disturbances or loss of bladder control. As with partial denervation, co-contraction of antagonist muscles will requiring monitoring for contracture formation.

Finally, or perhaps foremost, should treatment of denervated muscle become a clinical possibility, is consideration of the needs and aspiration of the users. For instance, surveying the opinions of the UK SCI population as a whole, highlighted that improved muscle bulk and cosmetic appearance ranked as highly as the ability to stand, though this did not differentiate the nature of the paralysis [Maxwell, Granat et al. 1999]. Also, the acceptability of the proposed treatment patterns have not been evaluated outside of research studies, for which subject compliance may not be typical of clinical practice.
3.5 Clinical Assessment of Stimulation Treatment

The primary aim of the treatment of chronic denervated muscle is to increase the tissue viability, enhance cosmetic appearance and where possible restore function (§2.3.7). The criteria for assessment of any such treatment must therefore reflect these aims and the appropriate evaluation measures may also be employed to optimise the treatment, for instance in terms of the stimulation parameters. Although the incidence of ulcers is dependent on a multitude of influencing factors, there is evidence of these including a minimum tissue thickness, circulation and tissue perfusion levels [Clark, Rowland et al. 1989; Livesley 1990; Negus 1995]. These parameters provide the basis of evaluation of many therapeutic stimulation studies and are also of relevance to cosmetic appearance. Assessments of functional value range from the degree of contraction force and limb movement to improvements in daily living tasks. When treatment is applied to muscle in the acute stage after nerve injury or to degenerative diseases, then the extent of muscle fibre innervation and the progress of any nerve regeneration is the measure of primary clinical interest, especially to monitor for any hindrance of it. Techniques for the assessment of innervation and nerve growth are discussed in §2.4. Considered here, are those evaluation measures applicable to the evaluation of stimulation treatment of chronically denervated muscle in a routine clinical environment, which is the focus of this study.

3.5.1 Muscle Thickness Measurement

By far the simplest measure of peripheral limb muscle bulk is circumferential girth, measured with a simple flexible tape measure and Petrofsky [1991] used this technique in evaluation of stimulation of denervated muscle. Apart from variability of measurement due to stretching of the tape and distortion of the tissue, the method suffers the obvious disadvantages of measuring total tissue bulk, without differentiating the muscle tissue or the particular muscle of interest. It is therefore subject to other factors influencing total body weight and composition, and is also only suitable for treatment of peripheral limbs.

Changes in muscle bulk are most easily determined in cross-section at particular locations. X-ray Computer Topography (CT) provides such an image from which muscle, fat, bone and other tissues are differentiable and individual muscles within muscle groups can be delineated allowing estimation of cross sectional areas. Kern and Hofer et al. [1999] have used this technique in the evaluation of stimulation of denervated muscle, by assessment of each of the quadriceps muscles Qualitative CT has been developed for the evaluation of FES bicycle ergometry training [Block, Steinbach et al. 1989]. CT has the advantages of clarity of interpretation and consistency of measurement location, as this can be determined from imaged bone landmarks. However, the technique suffers disadvantages of complexity, availability and cost of the equipment and
limitation of the frequency of measurement due to ionising radiation exposure. **Magnetic Resonance Imaging (MRI)** avoids the exposure limitations and provides much greater image contrast of soft tissues, but at greater cost and time for scanning. It is however unsuitable for those with heart pacemakes and other implanted metal objects, which also cause distortion in the CT image. MRI has also been used for evaluation of stimulation treatment [Mokrusch and Neundorfer 1994] and the diagnoses of denervation (§2.4.2). Resolution and accuracy of CT and MRI are dependent on the image size and 0.5mm is typical of clinical systems [Liang 1999].

Real time **Ultra-sound** imaging with a portable scanner is quick, convenient and non-invasive and avoids the major disadvantages of CT or MRI. However, this is at the expense of some of the ease of interpretation of the resulting image, and cross-sectional area can only be measured for small muscles or with a static scanner. Ultrasound has no established adverse biological effects at diagnostic power levels, is non-invasive and painless and therefore is particularly suitable for measurements of children or those with sensitive conditions [Schmidt and Volt 1993]. A-scan ultrasound offers perhaps the most accurate measure of tissue thickness, but requires considerable experience in the interpretation of the signal. The measurement signal is derived from the reflections of a single point source of ultrasound waves transmitted through the skin surface. Reflections and refractions occur at discontinuities of conductivity and therefore predominately at interphases between different media, such as tissue/bone, to a lesser extent intermediate fat/muscle boundaries, as well within the tissue layers). To avoid the air/tissue interface dominating, water based conductive gel is used to couple the source to the skin surface. With B scan ultrasound, the source is scanned across the skin surface or an array of sources is employed, with appropriate processing of the signal to produce a 2D image. The resolution of the image increases with the frequency of the ultrasound, but this also reduces the possible penetration depth. Identification of the boundaries between muscles within a muscle group is usually possible, allowing their individual thickness' to be determined using electronic callipers. Typical, systems employ a 5MHz source signal, allowing measurements to tissue depths of the order of 100mm with a resolution of 1mm [Foster, Pavlin et al. 1993]. The depth of tissue boundaries is calculated from the time for reflection and an estimation of the speed of sound in tissue. As an average value is employed by the device, this typically over-estimates the thickness of fat by 6% and under-estimates the thickness of muscle by 3% [Heckmatt, Pier et al. 1988] and is the major source of accuracy error in most systems [Liang 1999].

Ultrasound has been shown to be a reliable technique for measurement of quadriceps thickness. Repeat measurements showed a coefficient of variance of 8.3% [Schmidt and Volt 1993] and a reproducibility standard deviation of 2mm for fat and 3mm for muscle thickness [Heckmatt,Pier et al. 1988]. Measurement of cross sectional area demonstrated a high intra-rater reliability (p>0.05) and a significant (p<0.01) but consistent (8%) inter-rater effect between two operators [Oldham, Howe et
al. 1995]. The technique has been used for assessment of FES training [Taylor, Ewins et al. 1993], for measurement of facial soft tissue thickness [Liang 1999], for evaluation of muscle to subcutaneous fat ratios in children, particularly those with SMA [Heckmatt, Pier et al. 1988; Schmidt and Volt 1993] and as a predictor for skin diabetic foot lesions and sacral pressure sores [Clark, Rowland et al. 1989]. Degenerative tissue is characterised by increased echo-density, although this is not unique to denervated muscle [Schmidt and Volt 1993].

For repeated measures with each of the above techniques, it is necessary to standardise the location of the measurement for consistency. For measurement of the quadriceps muscle group, Block et al. [1989] used 100 and 175mm proximal to the tibial plateau. For single site measurements, the midpoint between trochanter and patella is typical [Petrofsky 1991; Oldham, Howe et al. 1995] [Heckmatt, Pier et al. 1988; Schmidt and Volt 1993] or 150mm proximal of the patella [Taylor, Ewins et al. 1993]. Measurements are typically taken with the knee extended and the subject seated or supine but without the thigh touching the supporting surface to avoid tissue distortion. Measurement has also been performed with the knee flexed to 90° [Schmidt and Volt 1993]. Distortion of the tissue due to pressure applied to the skin by the hand held scanning probe, is avoided by using a soft, but ultrasonically transparent, stand-off block [Clark, Rowland et al. 1989] or copious amounts of the coupling gel combined with care by the operator and monitoring of the image [Heckmatt, Pier et al. 1988; Schmidt and Volt 1993].

3.5.2 Muscle Structural Damage

Even given a positive effect on muscle atrophy, evaluation of damage to muscle fibres due to stimulation is of interest to optimise parameters and treatment patterns. Of particular interest is damage due to overuse or reperfusion arising from the type or pattern of contractions induced. Histological analysis and microscopy structural analysis are possible from muscle biopsy samples and have been used in some clinical studies [Neumayer, Happak et al. 1997; Williams 1996a]. However the frequency of measurement is obviously limited and non-invasive clinical measures have yet to be refined for application to stimulation studies.

Blood serum assays for creatine kinase (CK II and III) and myoglobin (Mb) are used to identify damage in cardiac muscle following an ischaemic event and to assess skeletal muscle damage, though carbonic anhydrase III (CAIII) is considered more suitable for acute events in skeletal muscle. Even though levels are raised by common exercise in normal muscle, condition specific increases occur following exercise with some neuro-muscular disorders [Dop Bär, Reijneveld et al. 1997]. Also dramatic increases in CK are observed following eccentric exercise muscle damage and revascularisation reperfusion damage, associated with capillary endothelium trauma, muscle fibre necrosis, oedema and tenderness. [Jones and Round 1997]. It is recognised that these techniques still require further development to differentiate normal from abnormal damage, especially arising from
stimulation treatment. Urine assay analysis may also be possible, although slightly easier to collect, research will be required to determine the optimum time of sample, especially given impaired urinary function in SCI patients.

### 3.5.3 Bone Mineral Density (BMD)

Immobilisation following SCI doubles the risk of bone fracture, primarily from low energy fractures of the lower extremities, with upper extremities protected by increased loading activity [Vestergaard 1998]. This is associated with a significant decrease in bone mineral density, (BMD) especially in high trabecular bone around the knees and ankles, where fracture incidence is highest. In the first year following injury, BMD decreases to 90% normal levels over most of the lower extremities, decreasing in the second year to approximately 80% and continues to decrease in the distal femur to 65% after 3 years. Conversely, BMD levels in the lumbar spine, remain approximately unchanged [Inman, Sharp et al. 1998]. Comparing paraplegic and tetraplegic SCI, upper limb BMD loss is greater in tetraplegics, whereas the greater loss in the lower limb is not significantly different. BMD loss is greater amongst ‘complete’ than incomplete SCI and greater with flaccid compared to spastic paralysis, though not observed in all studies [Demirel, Yilmaz et al. 1998].

Despite the decrease in BMD with SCI, only 25% may be classified as osteoporotic in the femoral neck, by having levels in excess of 2.5 standard deviations from normal. The fracture risk stabilises 3 years after SCI [Vestergaard 1998] and may reflect an adaptation of lifestyle, such that treatment of reduced BMD is of low priority, though perceived as high by persons with SCI. The condition is, however, of concern for FES for standing or walking, because of the risk of fractures from increased loading and from the risk of falling. Those classified as osteoporotic in the femoral neck are therefore typically excluded from participation. The increased risk of ankle fractures, may also be of concern in selecting candidates for FES ergometry.

BMD is determined by dual X-ray absorptiometry (DXA) and dual photon absorptiometry (DPA), with pDXA single x-ray absorptiometry (SXA) and radiographic absorptiometry (RA) used for peripheral location to a precision of 1-2%. Quantitative ultrasound scanning (QUS) of the calcaneus has been developed with high correlation to BMD measurement and significant advantages in the cost and portability of equipment and in the use of non-ionising radiation [Blake and Fogelman 1998; Geusens 1998; Ross 1998].

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2 Clinical practice at Salisbury District Hospital (SDH)
3.5.4 Cardiac Output

Artificially induced muscle contractions by electrical stimulation offer the potential for improved circulation and therefore a positive contribution towards conditions caused by its deficiency. General circulation as indicated by cardiac output and limb blood flow may be increased by enhanced venous return, especially in the lower limb, and any cardiovascular exercise component. Improved muscle perfusion is associated with the capacity for greater contraction force and endurance (§3.4). Skin perfusion can be enhanced by the heat generated from the underlying muscle contraction [Grant & Pearson 1938 quoted by Woodcock 1975 p229] and due to the direct effect of the stimulation on vaso-motor control. However, treatment and therefore muscle contractions, are typically limited to a portion of the day, and it is the effect on the resting or average blood flow which may be of clinical significance. Difference techniques may be required for measurement of blood flow at rest or during exercise or electrical stimulation.

Conventional techniques for the assessment of cardiac output are based on Fick and dilution methods, are invasive in terms of catheters or injections and require precise procedures for accurate results [Woodcock 1975]. Cardiac output can also be determined from the average stroke volume of individual heart contractions and the heart rate. One of these methods is impedance cardiography, by which changes in the electrical impedance of the thorax are measured and assumed to be caused predominately by blood flow, as the most conductive element of the body [Porter 1986]. Two circumferential electrodes are placed around the neck and two around the trunk below the level of the heart. An alternating current of known amplitude is passed between the outer electrode poles and the resulting voltage across the inner poles measured, typically with a bridge circuit. A high frequency current (100-250kHz) is used, as skin impedance is then much reduced and the risk of ventricular fibrillation negligible given the typical 4mA maximum current employed [Geddes 1969 quoted by Woodcock 1975]. The change in blood volume during each heart pulse, the stroke volume, is determined from the change in impedance assuming a uniform current density distribution and homogenous conductor of uniform cross section, which is only approximate for body segments. The value of blood resistivity varies with frequency, temperature, velocity of flow and with the haemocrit level [Woodcock 1975]. Many studies have used a resistivity of 150Ω/cm, but a value of 135Ω/cm has been suggested as an average in-vivo value corresponding to a range of haemocrit levels [Porter 1986]. Impedance changes are also attributed to changes in the quality of electrode contact with tissue swelling [Woodcock 1975]; movement and inspiration/expiration introduce artefacts into the measurement [Porter 1986].

Absolute calibration of impedance cardiography is difficult, and evaluation of its accuracy is largely by comparison with concurrent measurements by other established methods [Porter 1986]. The values obtained by impedance cardiography tend to be higher than other methods, attributed by
some to the additional flow from the right ventricle, but by Porter [1986], also to an excess value of blood resistivity. Correlation coefficients are therefore wide ranging (0.55-0.98) but comparison with electromagnetic flowmeter measurement is most appropriate and yields correlation coefficients 0.82-0.85 for cardiac output [Porter 1986]. Taylor et al. [1993] used the same impedance cardiograph to demonstrate that cardiac output is not significantly altered from normal, in those with paraplegia following spinal cord injury or by their participation in 3 months of electrical stimulation treatment of the quadriceps which greatly increased thigh blood flow.

3.5.5 Limb Blood Flow

For peripheral limbs, plethysmography is conventionally used to measure the change in volume of the limb arising from the blood flow into the limb segment. The volume is either measured directly, by the displacement of fluid or air from a surrounding chamber or inferred from weight changes, a circumferential strain-gauged cuff or from changes in electrical impedance or capacitance [Woodcock 1975; Porter and Swain 1986]. The displacement method is considered most accurate and used as a comparative benchmark, even though results are probably affected by hydrostatic pressure and it assumes all arterial flow is translated into tissue expansion. Flow is typically measured with proximal venous occlusion for at least 15s and is based on the assumptions that occlusion is instantaneous and complete and does affect arterial flow, which is the sole cause of tissue expansion. Occlusion methods are somewhat cumbersome, time consuming, and dependent on precisely controlled conditions for accuracy. They are therefore considered unsuitable for continuous or immediate measurements post trauma, surgery or exercise [Porter, Swain et al. 1985].

Alternatively, determination of pulsatile blood flow in peripheral limbs may be performed by measuring the change in tissue impedance in a similar manner to Impedance Cardiography (§3.5.4). The impedance measured is that of the blood in parallel with that of the tissue, and changes occur as blood perfuses through it, whereas other methods such as the ultrasonic doppler technique measures only arterial flow. Comparison of impedance plethysmography with electromagnetic flowmeter measurement yielded correlation coefficients of 0.91-0.96 for limb flow. Direct comparison of pulsatile and occluded flow measurements, is questionable given that the former is vascular expansion due to the unobstructed pulse pressure wave propagating down the limb, the latter due to the accumulation of fluid in an occluded limb However, pulsatile measurement is criticised for ignoring any steady arterial flow [Porter, Swain et al. 1985; Porter and Swain 1986].

Using Impedance plethysmography, considerable variation was observed in repeat measurements on a single occasion (2*SD as % of mean: 6.9%-45%, average 15.7%) [Porter 1986 p.96]. Peripheral blood flow with its many influencing factors, is in a constant state of fluctuation, particularly in the hand, where the skin flow dominates and plays a major role in thermoregulation [Porter and Swain 1986]. The blood flow ratio of concurrent measurements of both limbs of an individual has
provided greater discrimination of unilateral abnormalities, where ratios are outside the normal range of 0.66 -1.5 for forearm [Porter, Swain et al. 1987]. However Impedance plethysmography has significant benefit of simplicity and versatility, allowing measurement of cardiac output and bilateral limb blood flow with the same equipment and therefore concurrently. It is non-invasive, causes minimal disturbance to the patient and is not critically dependent on room environment or elaborate setting up procedures. However it is subject to low signal to noise ratio in cases low tissue impedance or low flow rate for which ultrasonic Doppler technique is considered more suitable, providing precise control of incidence angle is feasible [Porter and Swain 1986].

3.5.6 Muscle Tissue Perfusion

Vascular measurement of blood flow into muscles is difficult in cases of dual arterial supply and so indicator clearance methods are employed, typically using Xenon (133Xe) [Woodcock 1975]. A quantity is injected locally into the tissue of interest and the rate at which it is removed, measured by means of scintillation counters, which may be strapped to the limb for measurement during exercise. The method assumes the removal of the indicator is solely due to blood flow and that it is not metabolised, altered or stored by the tissue. Variation in measurement is introduced in the site of initial injection. The rate of removal is reduced during exercise or muscle contraction, attributed to ischaemia but greatly increased immediately post exercise. Lassen [1964] found this hyperaemic response is predominately in the initial minute and lasted not more than 3 minutes with prolonged response symptomatic of a pathological condition (Fig.3.5.1) [Woodcock 1975].

Kern [1995] used Thallium 210 scintigraphy to measure the long term effect of direct electrical stimulation on quadriceps muscle perfusion (§3.4.2). Measurements were relative to brain perfusion, on the assumption that this remains approximately constant over a year, though the method or difficulties of doing this were not alluded to. The effect of stimulation treatment has also been evaluated in terms of the capillary and micro-vessel density by histological analysis of tissue samples [Clemente and Barron 1993]. Radio labelled microspheres of 15μm diameter allow measurement of muscle blood flow on denervation and reinnervation [Eisenberg and Hood 1994].
§3.5 Clinical Assessment of Stimulation Treatment

3.5.7 Skin Perfusion

Skin blood flow has a fundamental role in body temperature regulation under sympathetic nervous system control and therefore highly dependent on the temperature of the environment. In the hand and particularly the finger, at times the majority of blood flow is through the skin [Porter and Swain 1986], whereas for other body segments, skin blood flow was not observed to significantly effect limb blood flow in normals [Woodcock 1975].

Skin perfusion has been measured by Xenon clearance, calorimetry, impedance plethysymography or photo-electrically. Xenon clearance may be monitored following intramuscular injection or epicutaneous application to the skin surface, though not if sweating occurs [Woodcock 1975, p.232]. Kern [1995] employed Xenon clearance in evaluating direct muscle stimulation (§3.4.2). Photoelectric methods measure the variation in opacity of tissue with blood flow through it. In particular, laser doppler measures flow to a depth of 1mm and is suitable for continuous, though very localised measurement, providing the probe orientation remains constant [Porter and Swain 1986].

Skin temperature has also been measured as an indicator of skin perfusion levels. This assumes that the body temperature is steady and in equilbrium with the surroundings, which necessitates at least 20 minutes for acclimatisation, no sweating and a stable environment. Skin temperature depends on the arterial and capillary blood flow, the capillary density and degree of vasoconstriction/dilation and therefore varies over the body. Eddy & Taylor [1931] measured average skin temp as 32.5°C with a reduction of 1-2°C in the upper extremities and 2-3°C in the lower and variations of 4-6°C over the hands, and 6-8°C over the feet [Woodcock 1975, p.64]. Localised variation also occurred due to arteries or veins making measurement at the skin surface with thermocouples or thermistors (thermometry), more variable.

Thermography infers the temperature of an object from its radiated energy, which depends on the object’s absolute surface temperature and its emissivity [Woodcock 1975, p.65]. Modern measurement is performed with semiconductor detectors sensitive to emitted radiation and array or scanning systems to produce a direct thermal image of the object, for display and analysis per computer graphical packages. Calibration is achieved by means of objects of known temperature and emissivity. Errors in sample measurement arise from estimation of skin emissivity poor image focusing onto the detector and local variation in the ambient temperature. There is also some question over whether the temperature recorded is in fact that of the skin layer or that of the underlying tissue radiating through the skin. Even so infra red thermography may provided a useful, non-invasive comparative study measure and has been employed in the evaluation of direct muscle stimulation [Taylor, Ewins et al. 1992; Kern 1995] (§3.4.2).
3.5.8 Joint Movement Range and Ease

Goniometers for measurement of joint range of motion vary from simple plastic protractor type to electronic units. The former are used typically and provide reasonable accuracy and consistency. The majority of inter-rater variation is due to differences in the technique of measurement alignment, but correlation coefficients of 0.8 or greater are achievable [LaStayo and Wheeler 1994].

3.5.9 Contraction Characteristics

The simplest assessment of muscle contraction strength is with respect to a standardised numerical grading scale, such as that of the MRC used by Williams [1996a];

MRC Classification of Motor Recovery
- M0 No contraction
- M1 Return of perceptible contraction in proximal muscles
- M2 Return of perceptible contraction in proximal and distal muscles
- M3 Return of function in proximal and distal muscles to such a degree that all important muscles are sufficiently powerful to act against gravity
- M4 All muscles act against strong resistance, and some independent movements are possible
- M5 Full recovery in all muscles

Additional intermediate levels are typically employed [Boonstra, Van Weerden et al. 1987];

- M4' .......muscles act against light resistance,
- M4 ......muscles act against 'normal' resistance,
- M4^+ ......muscles act against heavy resistance

Where movement against gravity is possible, strength may also be quantified in terms of the possible angular movement of a joint. More precise quantification of contraction strength is possible by measurement of the isometric force exerted, usually for a particular limb movement. Hand held dynamometers can provide reasonable results but care must be taken to isolate the contraction of the muscle of interest and an instrumented rig to achieve this is usually more accurate. For instance, measurement of quadriceps muscle strength may be achieved with subjects seated in an adjustable chair, to maintain knees and hips at 90° flexion, a webbing strap around the waist to prevent further hip flexion and upper body movement and force measurement at the angle [Oldham, Howe et al. 1995].

The capability to measure contraction force also allows determination of other contraction characteristics. During a sustained contraction, the force produced will decrease due to fatigue. This is usually quantified in terms of the ratio of initial to final force over a certain period of contraction or the time taken for the force to decrease by a proportion. This may be a maximal voluntary contraction (MVC), or a contraction induced by a set of standard stimulation parameters.
Clinical Assessment of Stimulation Treatment

[Binder-Macleod and Snyder-Mackler 1993]. The task of defining a standard is made more difficult when the muscle excitability varies between subjects and with the period of treatment, however is still valid as a comparative measure for the individual [Degens and Veerkamp 1994].

3.5.10 Functional Tests

When the stimulation treatment has a functional objective, then various standard tests have been developed to evaluate either a functional movement or completion of a relevant task in terms of both quality and time taken. For hand function this includes evaluation of the strength of different grips [Petterson, Smith et al. 1994; Williams 1996a], the completion of certain repetitive manipulative tasks, or the dynamics of movement with tracking tests [Wright 1998]. For the lower limb, such as cases of compensation for 'dropped foot', the quality of gait may be assessed simply by measuring the physiological cost index (PCI) over a set distance walk (§4.5.10). More sophisticated analysis of gait is possible with evaluation of ground reaction force and position tracking of joints.

3.5.11 Quality of Life Assessment

Several standardised questionnaires have been developed to allow quantifiable assessment of quality of life, [Wade 1992], although these will not necessarily reflect the priorities of life quality of the individual and are dependent on their subjective judgement. The health service quantifies the benefit of treatments in terms of added quality of life years (QUALYS) in order to justify its clinical application.
4. **Clinical Study Outline**

4.1 Study Hypothesis and Objective

The literature suggests that considerable benefits can be obtained from electrical stimulation of denervated muscle (§3.4), but that further research is necessary to investigate the physiological mechanism of its effects, to confirm its treatment efficacy and to develop the appropriate techniques for routine clinical application. In particular, for the treatment of acute peripheral nerve injuries, it remains necessary to establish the exact effect on nerve regeneration and muscle reinnervation. However the methods to monitor these, which are routinely available, (§2.4), infer the extent and changes in muscle fibre reinnervation, rather than measure nerve growth directly. Also, given the variability in the timing and success of nerve regeneration and reinnervation, the selection of individually matched controls is difficult and it is anticipated that any study will require a sizeable sample for statistical significance. In regard of these considerations and the clinical need and experience of a previous study at Salisbury District Hospital MPBE (§1), this study concentrated on treatment of chronically denervated muscle, when the effect on nerve regeneration is not of primary concern.

Clinical studies have demonstrated considerable benefits to chronically denervated muscle from the application of long pulse biphasic (LPB) stimulation waveforms, but latterly these have concentrated on the restoration of function, especially in the lower limbs of those with flaccid paraplegia (§3.4.2). The extent of the therapeutic value of the treatment to tissue properties and particularly to resting limb perfusion, which may in the long term be of greater clinical priority, remain to be quantified with a statistically significant sample size and the optimum stimulation parameters to achieve this, are yet to be confirmed. Also, there are few current attempts to address the difficulty of achieving therapeutic or functional benefits in cases of chronic partial denervation, such as 'dropped foot' or brachial plexus injury.

Before its adoption as a routine clinical treatment, it is necessary to establish the **hypothesis** that;

"transcutaneous biphasic rectangular stimulation can produce clinically significant therapeutic tissue property and appropriate functional benefits for chronically denervated muscle of peripheral limbs and that similar benefits can accrue though the treatment of partially denervated limbs with trapezoidal shaped pulses."


However prior to a formal clinical trial to rigorously test this hypothesis, it is necessary to develop suitable stimulation equipment and standardised, but condition specific, treatment protocols. The purpose of this work was to facilitate these and to provide further supportive evidence for the benefits of the treatment, through the following study objectives;

1. quantify the therapeutic tissue benefits, throughout the treatment period of transcutaneous biphasic rectangular stimulation of chronically denervated muscle in cases of complete limb flaccid paralysis

2. evaluate the effectiveness of trapezoidal shaped stimulation pulses in alleviating sensory and motor nerve recruitment and to quantify the therapeutic tissue benefits of such stimulation in cases of chronic partial limb denervation

3. to optimise the stimulation parameters with respect to the therapeutic benefits, both during the process of conditioning of the muscle and thereafter.

It was recognised that the study would be of an exploratory nature, particularly for the cases of partial limb denervation, and that the exact treatment regime would depend upon the condition and response of the individual. Some initial clinical investigations were therefore planned with a small number of subjects with the following preliminary objectives;

4. familiarity with the LPB stimulation technique

5. confirm and quantify the changes in muscle excitability using Strength-Duration testing

6. quantify changes to tissue properties in terms of muscle thickness, resting limb blood flow and skin temperature and confirm the likely treatment period for these to occur

7. evaluate the effectiveness of accommodating trapezoidal shaped pulses for the treatment of partial limb denervation and quantify changes to tissue properties as 6

8. investigate and quantify functional benefits of treatment where appropriate to the condition

9. confirm the suitability of the stimulation equipment and treatment protocol

10. confirm the suitability of the chosen measurements techniques and protocol for treatment evaluation

These preliminary investigations form the basis of this thesis and using the experience gained, a subsequent clinical study would seek to achieve the overall study objectives (1-3), with a restricted range of neurological condition, a more defined treatment protocol and sufficient number of subjects to be permit numerical statistical analysis.
4.2 Study Outline

A one year investigative study has been conducted at SDH MPBE with 5 subjects with peripheral limb denervation, commencing July 1998. Given the variability in condition and response expected, subjects acted as their own controls and are analysed on an individual case basis. The study was of an ABA design, with initial baseline measurements, against which measurements during the treatment period are compared, and a follow up period, without treatment, to confirm any changes observed. Given the experience of other studies for the time taken for tissue changes to occur [Taylor, Ewins et al. 1992], a 6 month treatment period was chosen, with equal follow-up period. Unlike some other studies, treatment was of a single limb, with the contralateral limb untreated to serve as control against measurement changes due to influences other than the treatment. The technique is limited by the possibility of treatment also having an effect on the contralateral limb, however the trend of changes in both limbs during the study were correlated to likely influencing factors (e.g. body weight, room temperature) in order to try to identify this.

Treatment consisted of twice daily stimulation of a single chronically denervated muscle or muscle group with long pulse biphasic pulses and surface electrodes. Stimulation parameters were chosen according to the muscle condition and were reviewed and adjusted regularly with the anticipated increase in muscle excitability. This was quantified by means of Strength-Duration testing to guide the choice of stimulation parameters and to aid the development of the standardised treatment protocols. The treatment was evaluated by qualitative and quantitative measurements, including muscle thickness, limb blood flow, skin perfusion and joint motion. These were performed at regular intervals throughout the treatment and follow-up periods. Subject participation was purely voluntary and unpaid, though travelling expenses were reimbursed by the generous donation of the INSPIRE foundation. Approval for the investigations was obtained from the Wiltshire medical research ethics committee and the agreed protocol appears in Appendix B.

4.3 Subject Selection

The number of subjects (5) was based on the feasibility of completing the schedule of evaluation visits specified in the protocol, given that all were conducted by the researcher and given the availability of the clinical space at Salisbury District Hospital MPBE. All subjects were selected from previous referrals to SDH MPBE for electrical stimulation treatment but which had proved unsuitable, probably due to lower motor neurone damage. To avoid possible effect on reinnervation and the variability of response that might be expected from degenerative disease denervation, subjects were sought with denervation arising from peripheral nerve injury, at least one year and preferably two years previously. The potential candidates attended for an initial assessment visit,

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1 INSPIRE Foundation for Integrated Spinal Rehabilitation, Salisbury District Hospital, Wiltshire, SP2 8BJ
which included evaluation of the extent of limb denervation, and the muscle contraction, skin reaction and other response to stimulation with various pulse widths and frequencies. An adverse response, was one of the possible contra-indications to participation in the study, others included active wounds or skin problems in the treatment area, excess muscle spasm, contractures or joint problems. Subjects were eligible for participation, given the absence of contra-indications and following their own written informed consent and that of their general practitioner and the medical consultant of the study (Appendix B).

For the later, larger study, maximum commonality of condition amongst subjects was intended to permit inter-subject comparison and evaluation of different stimulation parameters. This was not possible with the small sample size of this preliminary study, however it was at least desirable to compare the use of rectangular shaped pulses used in other studies (§3.4.2) for complete limb denervation with trapezoidal shaped pulses for cases of partial limb denervation. Cases of flaccid paraplegia from T12/L1 level SCI and stimulation of the quadriceps muscle were favoured as this would permit comparison with the previous studies and given the number of such referrals to SDH MPBE with the proximity of the Spinal Treatment Centre. For upper limb, brachial plexus injuries are also of clinical concern to those at SDH. Consideration was given to the feasibility and expense of subjects attending for evaluation visits at SDH.

The five selected subjects who commenced treatment separately, comprised three paraplegics 5-10 years post T12/L1 SCI (subjects LC and LD with near complete denervation apart from the toes and subject LE with more extensive innervation), subject LB with unilateral brachial plexus lesion, 23 years post injury with denervation of the triceps and wrist extensors and subject LR with unilateral loss of dorsiflexion (‘dropped foot’) following a spinal infarct 3 years previously (§6 for details). Subject LR, differs from the original study aim, in that the primary treatment objective was to restore the dorsiflexion muscle function but participated as a previously selected paraplegic candidate was unable to do so due to illness. However, as one of many such, lower motor neurone ‘dropped foot’ referrals to SDH, the condition is of considerable clinical interest and for which the accommodating stimulation waveforms under investigation are particularly appropriate. The triceps of subject LB in fact transpired to be partially innervated with some of the muscle fibres under voluntary control. Subject LD had to withdraw from treatment at week 17, due to an infected pressure sore following urinary tract infection. All other subjects completed the treatment and follow up periods, with some extension to the treatment period to compensate for weeks without treatment due to holiday, illness or recovery from skin reaction. For subject LR, the treatment period was extended to 12 months as the follow-up period to confirm tissue property measurement changes was of lesser significance to the functional outcome and given the likely dominating influence of still functioning plantarflexor and other surrounding muscles. The study subjects therefore represent 3 groups for which direct stimulation is applicable, with appropriate parameters; 1) complete limb denervation, 2) partial limb denervation, 3) disuse atrophy of innervated muscle
4.4 Treatment Protocol

4.4.1 Stimulation Equipment

To perform the daily stimulation treatment, subjects were each supplied with a portable, rechargeable stimulator unit which was custom designed for the project, given that no suitable alternative could be found. The LPSTIM10 unit (§5), is capable of producing a single channel stimulation output with a wide adjustment range of parameters, and in particular the long duration, biphasic pulse form, found to be of benefit in other studies (§3.4.2). The stimulation pattern is programmed into the unit from a personal computer (PC) connected to it during the clinical visit to the hospital. The PC link also permits monitoring of the stimulation output during use in the clinical setting and for Strength-Duration testing (§2.4.4). The unit maintains a record of the total duration and number of uses, which can be downloaded to the PC. The unit control available to the user allows adjustment of the stimulation intensity. Indication is provided during the stimulation output pulse and when the battery is in need of recharging. The stimulation output is inhibited and appropriate audio and visual warning provided, in the case of very low battery, excessive stimulation output or the detection of a fault.

Full instruction in the use of the stimulator was given to subjects, both verbally and written (Appendix J), who were required to demonstrate competent use, prior to participation in the study. This included adjustment of the stimulation intensity to achieve the desired level of contraction. As this depends on the skin impedance and may vary, indication of the absolute value of intensity was not provided on the unit, to avoid subjects setting it to a particular value irrespective of the muscle response. In particularly, most subjects observed an improvement in muscle response during the course of the treatment session as the skin impedance decreased, necessitating a reduction in the setting of the intensity control to avoid excessive current or contraction. However in two cases (LB, LR), where no contraction was visible initially, and sensation was impaired, such an indication was found necessary and provided by an externally connected meter and modified software (§5.7).

Commercially available Axelgaard PALS® reusable transcutaneous neurostimulation electrodes were employed for this study, as used routinely at SDH. These consist of a conductive wire mesh overlaying a layer of conductive gel, which self adheres to the skin surface. The gel is kept hydrated and clean by regular washing, which was found most effective after the treatment session, thereby removing any adhered dry skin. The PALS® Blue electrodes with approximately 1.5mm gel thickness are typically used for people with high skin sensitivity and were used as a

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2 available from Nidd Valley Medical Valley Ltd, Conyngham Hall, Knaresborough, N.Yorks HG5 9AY, UK
precautionary measure in this study, in sizes 50mm by 50mm (LB, LD) and 40mm by 90mm (LE, LR). The PALS® Flex electrodes, more typically used for indirect stimulation treatment, are available in larger sizes; the 130 by 80 mm oval size were used for subject LC and are more comparable with the electrode size used by [Kem, Hofer et al, 1999]. However the thinner gel layer of the PALS® Flex, allows the skin to more easily come into contact with the electrode mesh, and it is thought the fraying ends of some wires on the perimeter of these electrodes were responsible for the occurrence of some localised skin burns (§6.1.3). The oval electrode size was therefore abandoned in favour of the 75mm diameter round size PALS® Flex and were positioned away from the skin burns, which subsequently healed completely. These electrodes were not specifically designed for direct stimulation and the supplier accepts no responsibility for this application.

In addition to the LPSTIM10 long pulse stimulator unit, subject LB was also issued with a Microstim\(^3\) (MSTIM) unit for stimulation of innervated muscle. This produces a stimulation output of 300\(\mu\)s passively charge balanced pulses at a range of selectable frequencies and was used with 20Hz pulses and 20x40 mm PALS® Flex electrodes for treatment of the triceps where some fibres are innervated.

During the treatment period, subject LB regained voluntary control of at least some of the triceps muscle fibres and to encourage his voluntary exercising of these, he was issued with surface EMG equipment (§2.4.3). His normal stimulation electrodes in their normal position were connected to a BEAC\(^4\) pre-amplifier, and this in turn to a small portable interface unit, whose analogue meter indicated the amplitude of the integrated EMG signal after selectable gain amplification. The interface unit also permitted the 'raw' EMG and integrated envelope signal to be displayed on an oscilloscope or to be captured and stored by a PC based data acquisition package. In practice the EMG output was dominated by simultaneous recruitment of the biceps, unless the subject exercised caution to isolate the triceps recruitment. It is possible that with further training from a therapist, this may be possible providing the subject has the motivation. The EMG value was not pursued as an evaluation measure for this study, but the subject was encouraged to practice what voluntary recruitment of the triceps he could manage, as often as possible.

4.4.2 Stimulation Protocol

The stimulation treatments were performed twice daily by subjects in their own home, using the equipment described above. Treatment sessions were generally performed at the beginning and end of the day for convenience. Session duration was 5min for the first week, and gradually increased

\(^3\) produced by Salisbury District Hospital MPBE
\(^4\) BEAC Biomedical Division, Via E. Montale, 3 1-27040 Portalbera PV, Italy Tel:- 010 39 385 43378
Fax:- 010 39 385 48923
in approximately 5min increments each week up to 30min. This was to permit the skin, muscle fibres and the general body systems to adjust to the treatment, as gentle exercise is advocated for weak muscles and allows the increase in muscle perfusion necessary for development and endurance (§2, §3). When stimulation parameters were altered significantly and especially at the transition to tetanic contractions, the session duration was reduced once more, to allow adjustment to the increased metabolic demand and then progressively increased again to 30min. At times, subject LB performed treatment of the triceps with both the long pulse stimulator unit for the denervated fibres and a Microstim unit for the innervated fibres. Sessions consisted of up to twenty minutes with each unit, typically starting with the Microstim unit. Details of the session duration for each subject through the study are given with the results (§6).

The stimulation parameters for each subject were chosen according to their muscle excitability, which increased with treatment in the manner of other studies (§3.4.2). This was monitored by means of the Strength-Duration curve, determined at the regular evaluation visits, and guided the choice of pulse width (which progressively decreased) and pulse frequency (which progressively increased) (§6). Initially pulse widths of the order of 100ms at 1Hz or less were necessary to produce any contraction. Frequencies of 1Hz or less were used, so as not to overuse the muscle, and resulted in twitch contractions. Pulses were rectangular in shape, except in cases of partial limb denervation (LB, LE, LR), where trapezoidal shaped pulses were used with twitch contractions to minimise recruitment of the neighbouring innervated muscles. All pulses were of a symmetrical biphasic form (Fig.3.2.1) for charge balancing and to minimise the risk of skin damage (§3.2).

For lower limb subjects, the initial twitch contractions and isometric tetanic contractions were performed by the subject when semi-recumbent, usually on their bed, with a pillow or cushion placed beneath the knees to ensure they were slightly flexed. As contraction strength increased, isotonic contractions were possible. Given that protein synthesis and muscle development is greatest when loaded at the normal physiological length (§3.3), isotonic contractions against gravity were considered optimum for therapeutic benefit. For the SCI subjects (LC, LE) these were performed seated with the knees flexed at 90° and the lower legs able to swing freely. This provided a progressively increasing load against gravity as the lower leg was raised by the quadriceps contraction, and cushioning protected the heels on release. The level of stimulation intensity and therefore strength of contraction was limited to when localised autonomic skin dysreflexia in the form of sweating occurred (§6.1.3).

For subject LE, co-contraction of toe flexors, was of concern given existing mild ankle contracture. This was monitored and the subject encouraged to stand at least 30min each day. For stimulation of the dorsiflexor muscles of subject LR, initial isometric contractions were performed with the foot supported in the neutral position (90° flexion), whereas isotonic contractions were with the foot unsupported (approximately 40° flexion), with loading provided by gravity and the shortened
Achilles tendon. With concern over exacerbating the latter, intensity was maintained at the threshold of co-contraction of plantarflexor muscles and the subject similarly encouraged to stand and exercise with the Achilles tendon stretched each day. Treatment of the triceps and wrist extensors of subject LB was performed with the elbow flexed and the lower arm supported on a cushion on the lap. Isotonic contractions were not achieved, but considerable co-contraction of the biceps occurred.

The stimulation envelope and therefore the duration of tetanic contraction was based on that for direct and indirect muscle stimulation of other studies (§3.2), though the unit only produced rectangular shaped envelopes. Initially the envelope duration was restricted to 3s with an off period of 8-10s. This was gradually changed to 4s on and 8s off for the triceps and dorsiflexors and 8s on and 16s off for the quadriceps, (i.e. with the off period was maintained at double the on period).

In terms of skin care, subjects were instructed to wash the skin of the treated limb segment, before and after treatment, to minimise the risk of skin irritation and to ensure skin hydration, which notably improved contraction response. Contraction response was always notably better at the evaluation visits than at home and this was attributed to prior hydration of the skin by the application of a water based gel for approximately 15mins for the ultrasound tissue thickness measurement and then washed off (§4.5.6). Subject LR was therefore supplied with this gel for use in a like manner prior to treatment at home. The application of moisturising oils or creams to the skin is not generally advocated at electrode locations to ensure uniform electrode adherence and to minimise the risk of chemical reaction or transmission of substances into the skin. However moisturising agents were found essential by some subjects to control the skin drying due to the treatment (§6.1.3), but were applied at times separated from treatment sessions. Subjects LR and LE also varied the position of the electrodes slightly from week to week to allow skin recovery.

Electrodes were positioned to optimise the contraction response, achieved by placement at approximately either end of the muscle (§3.2). For the quadriceps muscle (LC, LD, LE), this was on the anterior aspect of the thigh, 50-80mm and 220-250mm proximal of the proximal patella border. For the tibialis anterior (LR), 40 x 90 mm electrodes were placed longitudinally over the muscle with 20mm separation or 50x50mm electrodes at approximately 200 and 300mm proximal of the lateral malleolus. For subject LB electrodes were positioned on the triceps at 70mm and 170mm proximal of the lateral humeral epicondyle and at approximately 80mm and 180mm distal for the wrist extensors on the dorsum forearm. These electrode positions were also maintained for the SD curve testing (§4.5.8), even though it is not necessarily optimum for indirect stimulation of any innervated fibres.

5 Aloe Vera water based gel (subject LR), Vaseline Intensive skin care cream (LC), Dipo Base (LE)
4.5 Evaluation Measurement Equipment and Protocol

To assess the effect of the stimulation treatment a number of evaluation measurements were performed at regular intervals throughout the treatment and follow-up periods. The selected measures reflect the clinical aims of the treatment, to enhance the tissue condition, viability, and cosmesis, in terms of muscle thickness, resting limb blood flow and skin perfusion and these were all measured quantitatively. Co-variant measurements of blood pressure, heart rate, body weight and room temperature were also made to help identify any non-stimulation induced changes. The subsidiary aim of improving muscle function was assessed qualitatively and where possible quantitatively, in terms of contraction response and appropriate functional measures. The muscle excitability was monitored for possible changes in the extent of innervation and to guide the selection of stimulation parameters as the muscle became more responsive. Sensory innervation was also monitored because changes may occur due to enhanced innervation or re-education, and is both desirable to subjects and may enhance skin condition.

The techniques used were chosen for being non-invasive and suitable for the frequency of measurement envisaged. These are well established methods, and the equipment has been used in other studies of direct electrical stimulation and therefore capable of measuring the magnitude of parameter change expected [Taylor, Ewins et al. 1992]. Of some importance to the logistics of the study, these methods were also apparently easily performed by the researcher alone with minimal training, in the routine conditions of the hospital environment, thereby avoiding excessive visit duration. Not least the equipment and consumable supplies were available at Salisbury. All measurements were performed by the researcher.

The evaluation measurements were performed at the initial assessment visit, the baseline visit at the commencement of treatment and then at regular intervals throughout the treatment and follow-up periods. During the first month, these were every week, during the second and third month, every two weeks, then monthly till the seventh month and thereafter at 6-8 week intervals until the end of the follow-up period. Some variability occurred in this schedule to accommodate individual subjects arrangements, illnesses and when reaction to the treatment required investigation. The visits for each subject were arranged at approximately the same time of day and followed a standard protocol, which lasted between 2 and 3 hours (Appendix D,E). Subjects changed into shorts and a short sleeved shirt to permit access for measurement and were seated, semi-recumbent on a therapy plinth and where appropriate on their wheelchair pressure relieving cushion. During a period of approximately 20min for acclimatisation to the room environment and the measurement position, the preceding weeks of treatment and any changes in medical condition were discussed. On occasions, sensory perception evaluation was performed during this interval (§4.5.2) and the skin condition photographed, but without touching the skin. The tissue property evaluation
measurements were then performed, followed by refreshments as required and then the stimulation assessment. To avoid influencing the measurements, subjects were requested not to eat, drink or perform vigorous exercise for 1 hour prior to the visit, nor to consume alcohol for 24 hours before hand (though in fact none of the subjects consume alcohol regularly). A request to refrain from smoking for 1 hour before the visit was inadvertently omitted, and it transpired that subject LB consistently smoked one cigarette immediately prior to the visit.

Details are given of evaluation measures in the approximate order which they were performed

4.5.1 Subject Observations

Subjects were issued with blank Observation Sheets (Appendix F) and encouraged to record the time and duration of treatment each day, the nature of the contraction, including fatigue, the intensity control setting or output current (LB, LR) and any observed effects. These were completed consistently by subjects LB, LD and LR, but not at all by LC or LE. A record of the duration and number of uses is maintained automatically by the stimulator (§5.6) and was noted and zeroed at each visit.

At the beginning of each evaluation visit, while the subject was acclimatising to the room environment, these observations were reviewed, and supplemented by questioning about the treatment; the nature of the contraction and limb movement, any delay in its start and fatigue, the co-contraction of other muscles, the effect on the skin, sensation and other effects. Subjects were also asked whether their exercise, diet, medical condition or medication had changed in any respect since the previous visit.

4.5.2 Sensory Perception

Sensory perception was measured at the beginning and end of treatment and follow-up periods. The standard static two point discrimination assessment (§2.5.4) was performed on the hands of subject LB on seven occasions during the study. Single point touch perception was assessed initially on other subjects using a single metal rod of 0.5mm diameter. Semmes-Weinstein Aesthesiometer monofilaments 6 (2.83, 4.31, 4.56, 6.65) were available in the latter part of the study but only used once on each subject due to lack of time during evaluation visits.

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6 Supplied to SDH by Neuro Corporation, Cleveland USA
4.5.3 Skin Temperature

Infra red thermography (§3.5.7) measurement of apparent skin temperature was made using an AGA Thermovision® 782 system consisting of germanium detector based camera, scanner unit and PC based graphical analysis package, BTERM (Fig.4.5.1). The latter displays an image of the measurement object with the temperature of each pixel represented according to a colour scale.

![AGA Thermovision System and BTERM Image on PC](n.b. tripod raised for measurement of subjects recumbent)

The spot temperature of individual pixels can be displayed and data analysis performed on selected areas of the image. Those used were in common with the routine clinical procedure at SDH; anterior aspect of the thigh, shin, dorsal aspect of the foot; lateral aspect of biceps and forearm with the elbow flexed at 90° and dorsum aspect of each hand. A non-absorptive thin foam cushion was placed between the upper limb and the body for these measurements to enhance contrast. For each defined area, the package calculated the minimum and maximum, mean and standard deviation of pixel temperatures, which were transferred manually to a spreadsheet for analysis calculations (§6.2). Typical distances between the object and detector unit were 1m for hands and feet and 2m otherwise, the latter giving an estimated pixel resolution 4mm. A macro adapter giving 0.5mm resolution was fitted for close-up examination of potential current concentration. Calibration of the system to within 2% was performed by the manufacturer on delivery. Calibration with the BTERM software at SDH in 1998 demonstrated agreement with thermocouple measurements within 0.3°C on black body sources.

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7 AGEMA Infred Systems Ltd, Arden Ho. West St. Leighton Buzzard BEDS LU7 7ND UK  
8 BTERM Version 1.1 ISOTEC Imaging Ltd. 15 Lon-y-Rhyd, Rhiwbina, CARDIFF CF4 6JS
Previous studies of denervated muscle stimulation have demonstrated changes in resting limb temperature asymmetry of the order of 1.5°C, using this equipment [Taylor, Ewins et al. 1992]. Standard values of asymmetry between limbs in normals have been recorded at SDH (Appendix G). Thermographic measurements were performed at the start of each evaluation visit to avoid influence from other measurement and skin examination. Subjects were measured seated, with legs extended except subject LB. The detector camera was positioned as near vertically above the limb segment as possible, using a tripod stand and trolley. Room temperature and relative humidity were not controlled but monitored using an RS thermometer with respective precision of 1% and 5%. Although a room with more stable, but not controlled, temperature was available elsewhere in the hospital, it was considered that measurement of all parameters in one location was preferable to avoid prolonging the visit duration with additional intervals for temperature and heart rate stabilisation in more than one location.

4.5.4 Skin Condition

Skin condition was assessed visually and by touch. Note was taken of skin dryness, clamminess, temperature to touch and any blemishes, sores or irritations, especially around the electrode sites. Photographs were taken of the treated and contralateral limbs, at the beginning and end of treatment and follow up periods and on intermediate occasions to record any usual skin condition.

4.5.5 Limb Segment Blood Flow

Limb blood flow was measured by electrical impedance plethysmography (§3.5.5) using an IFM Minnesota Impedance Cardiograph 304A (Fig.4.5.2), generating a 4mA constant current at 100kHz. This is the same equipment used at SDH MPBE for previous studies evaluating blood flow in normals [Porter 1986] following electrical stimulation treatment [Taylor, Ewins et al. 1993], including of denervated muscle [Taylor, Ewins et al. 1992].

The output signals from the Cardiograph unit (dZ/dt, AZ, Zo) are connected to the National Instruments (§5) DAQ 7000 analogue interface card of a PC for capture, display and analysis using a general purpose data acquisition software package written within the BME group using NI LabVIEW graphical programming language. Given the upper frequency component of dZ/dt in normals adults is 12Hz for adults and 33Hz in those with arterial obstruction [Filho, Brum et al. 1983], the sampling rate of 200Hz was felt adequate without generating excessively large data files.

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9 RS High Accuracy Thermo Hygro RS 204-072
10 Surcom Inc. 4180 Edmond Boulevard Minneaplos Minnesota 55406
Blood flow measurements were taken after the subject had been rested for 20-30 minutes in semi-recumbent position as used by Porter [1986]. The electrode pairs consist of lengths of stainless steel wire braiding mounted 4cm apart on a cloth backing strip. One such pair was placed around either end of the limb segment of both limbs and secured with crocodile clips to ensure skin contact over the complete limb circumference [Porter 1986]. Electrodes were placed to maximise the separation distance $L$ (measured between inner electrodes), whilst retaining them on one limb segment, given that a uniform cross section is assumed. The separation distance chosen for each subject was maintained approximately equal on each limb and for each measurement visit. Prior to that of the limb impedance, a sample or recording was made of the instrument calibration signal and stored using the PC analysis package. Two recordings were then made of the $dZ/dt$ signal from each limb with approximately two minutes between recordings, always starting with the left limb and then swapping the connections to the previously positioned electrodes on the right limb. Care was taken not to talk or excite subjects during the course of this procedure and they were asked to sit quietly without moving. Just prior to recording, subjects were asked to stop breathing after a small inhalation. A sample time of 6s (6-8 beats) was chosen, as for subject LR after this the $dZ/dt$ pulses became lengthen and distorted, coincident with a decrease in heart rate. This was extended to 10s on occasions for other subjects to reduce heart rate error. For each recording the associated value of baseline impedance $Z_0$, displayed on the instrument front panel and the electrode separation were noted. On some occasions, recordings were also taken after the period of stimulation.
The PC analysis package was used for display and measurement from the dZ/dt recordings, after software filtering to remove unwanted noise and interference, notably 50Hz. An 8 pole Bessel filter with 40Hz 'cut-off' (-3dB) frequency was used on all sample waveforms, as this sufficiently reduced the interference with minimal effect on the signal amplitude or timing. The filtered dZ/dt waveform is displayed and adjustable cross hairs allow the determination of dZ/dt_{max} and blood beat flow time (t_B) (equivalent to L_{VET}) The recorded calibration signal is used to determine the correct zero and scaling factor (\Omega/s/V) for the dZ/dt signal. The instantaneous heart rate is determined from the time of a complete number of beat cycles in the dZ/dt recording. On some occasions, heart rate was also measured simultaneous using a chest mounted Polar heart monitor, and found to be approximately equal, with both showing a declining heart rate during the sample period. This was always less than that recorded by the automated blood pressure cuff because of the error in estimation from the small sample time and therefore underestimates blood flow.

The measured values for dZ/dt_{max}, t_B, Zo, L and HR were entered into a spreadsheet for calculation of the average blood volume per beat (Eqn.4.5.1) and the average blood flow (Eqn.4.5.2) for each recording in the manner of Kubicek for pulsatile cardiac measurement [Kubicek, Karnegis et al. 1966]. As Porter [1986], a value of blood resistivity of 135\Omega/cm was used, and the flow duration (\tau in Fig.5.5.3) differs from the left ventricle ejection time (L_{VET}) of cardiac measurements.

Equation 5.5.1  \[ BV = \Delta V = \rho (L/Zo)^2 C (dZ/dt)_{max} t_B \]
- BV = beat volume (ml/min)
- \rho = blood resistivity 135 (\Omega cm)
- L = distance between inner electrodes (cm)
- Zo = mean body impedance (\Omega)
- (dZ/dt)_{max} derived from dZ/dt waveform (V)
- C = calibrarion scaling for dZ/dt (\Omega^{-1/V})
- t_B (\tau) = beat duration from dZ/dt waveform (s)

Figure 4.5.3 Signal Waveforms of Blood Flow Measurement [after Kubicek et al.1966]

Equation 5.5.2  \[ BF = \text{Beat Volume (BV)} \times \text{Heart Rate (HR)} \]

The same Impedance Cardiograph with electrodes on the thorax was used to measure cardiac output of subjects LC and LE on one occasion during the follow-up period, towards the end of the study, to obtain a value of L_{VET}. Blood pressure and heart rate were measured at intervals throughout each visit to obtain a reliable resting value and to monitor for any excessive changes arising from the stimulation using an automated inflation cuff\(^{11}\) on the 150mmHg setting.

\(^{11}\) A&D Co.Ltd. Tokyo, Japan - Digital Blood Pressure Monitor model UA767
4.5.6 Tissue Thickness and Limb Girth

Real time ultrasound measurement of muscle tissue thickness (§3.5.1), is particularly suitable for this project given the required regularity of repeat measures, avoiding ionising radiation and being quick and convenient to perform within the clinical space at Salisbury. A Dynamic Imaging System XLP B-scan linear array device was used. This operates at 2.5MHz with a hand held measurement probe, allowing imaging of tissue to a depth of approximately 50mm. This same instrument has been calibrated and used at SDH MPBE for evaluation of tissue thickness changes following stimulation [Taylor, Ewins et al. 1992; Taylor, Ewins et al. 1993].

Lower limbs were measured fully extended, upper limbs with the elbow at 90° flexion and the forearm supported anteriorly on a pillow. To avoid tissue distortion, the measured limb segment was unsupported as far as possible, for quadriceps, this was achieved by the subjects seated on their wheelchair cushion, though the thigh was supported proximally. Measurements were made on the limb segment at specific distances from readily identifiable anatomical landmarks, which approximated to the locations of proximal and distal electrodes and at the mid-point between. For the quadriceps (subjects LC, LD, LE), this was on the anterior surface of the thigh at 50, 150 and 200 or 250mm from the proximal patella border. For the tibialis anterior (subject LR), this on was anterior surface of the lower leg at 200 and 300mm from the lateral malleolus. For the triceps (subject LB), this was on lateral aspect of the supported upper arm at 50, 100, 150 and 200mm from the lateral epicondyle of the humerus. To avoid distorting the tissue, measurements are taken though a 3cm 'stand-off' block of Kitecho gel, which cushioned the tissue from the pressure applied to the scanner probe, but is transparent to the ultrasound signal. A water based transmission gel is generously applied to both sides of the block before positioning at the measurement site to ensure coupling. Care was taken to minimise measurement error due to an oblique signal path in the tissue by tilting the scanner probe about the perpendicular to the skin, to minimise the bone depth on the displayed image on the basis that the underlying bone is approximately parallel to the skin surface.

The instrument displays a real time image of the underlying tissues, which can be 'frozen' and relative distances measured by means of adjustable electronic cursors, with a resolution of 1mm. These were recorded at the time of measurement as unfortunately the image storage and camera facilities were not available to record the image and therefore Fig.4.5.4 shows a typical tissue image of the innervated quadriceps muscle of a SCI subject from a previous trial [Taylor, Ewins et al. 1993]. This clearly identifies the underlying bone, fat and boundaries of the rectus femoris and vastus intermedius muscles.

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12 Dynamic Imaging, 16 Young Sq. Brucefield Ind.Pk, Livingstone, GH54 9BX , UK Tel: 01506 415282
13 Aquasonic ©100 Hypoallergenic Parker Labs Inc. Orange NJ 07050 USA Tel. 201-676-5000
Unfortunately, the image quality obtained from the unit during this project was far inferior, with muscle boundaries often too indistinct to be identified. For the tibialis anterior muscle, located between the tibia and fibula, but without an underlying bone, thickness measurement was rendered highly unreliable. The variability in image quality was attributable to poor internal connections of the instrument due to age prohibited servicing. In the latter stages of the project a new Dynamic Imaging Concept MC 5MHz scanner unit became available, providing a far superior image with greater anatomical detail and cursor resolution of 0.1mm. Several concurrent measurements on different study subjects were made with both instruments and confirmed consistently equal results to within cursor resolution (+/-1mm), when image definition of the older machine was good. As image quality of the 2.5MHz unit became increasingly poor with diminished use, the 5MHz unit was used for the remainder of the study.

**Limb girth** was measured concurrent with tissue thickness at each of the measurement locations, using a simple tape measure with 1mm resolution and care was taken not to pull this tight during measurement. Because of difficulties in reliably finding the tape at SDH, a new one was procured in early 1999 and used for the rest of the study. **Body weight** was also measured to monitor for concurrent changes in limb or overall body composition. Wheelchair bound subjects (LC, LD, LE) were measured clothed in the Spinal Treatment Centre at SDH. Subjects LB and LR measured themselves unclothed at home with bathroom scales.

### 4.5.7 Joint Range of Movement

The passive and where appropriate voluntary (active), range of motion of both limb joints was measured with a protractor goniometer, to an estimated accuracy of +/-5°. Angles are defined with respect to 0° when limb segments are aligned diagonally across the joint. The severity of joint contractures was also assessed by a physiotherapist by passive movement. (subjects LC, LR).
4.5.8 Muscle Excitability

Muscle excitability was determined at most evaluation visits by recording of the Strength-Duration (SD) curve (§2.4.4) using the stimulator unit issued to the particular subject. Uni-polarity rectangular pulses at 0.67Hz were employed, with specific pulse widths, between 200ms and 0.3ms in descending order. Electrodes were positioned as for the stimulation treatment, typically at either end of the muscle, rather than over the motor point conventional for innervated muscle. The stimulation intensity was gradually increased until a minimal contraction was detected, which was assessed visually, because the weakness of the contraction during initial treatment made the palpation method difficult. The corresponding value of stimulation current displayed on the stimulator PC user interface monitor screen (§5.6) was noted for each pulse width, and later plotted using Excel Spreadsheet.

Each SD curve determination took approximately 15-20min, and a number of difficulties were encountered which, it is expected, decrease the reliability of the measurement, even though all were performed by the researcher. For several subjects, current flow through the tissue gradually increased over the course of 5-15min of stimulation, as skin impedance decreased, in a manner also noted by [Guttmann 1976]. It was therefore necessary to perform a limited period of treatment, prior to SD testing, but without fatiguing the muscle. The location and nature of the minimal contraction often varied as the pulse width was decreased, because of the variation in excitability of different fibres. This was particularly so, in the case LB, where some of the triceps fibres remain innervated. In the cases of partial limb denervation (LB, LE, LR), as the pulse width was decreased, the surrounding innervated muscles are recruited at smaller intensities than the denervated muscle of interest. The limb movement resulting from their contraction as the intensity was further increased, precluded reliable detection of the minimal contraction of the denervated muscle.

4.5.9 Contraction Response

At each visit the contraction response to the chosen stimulation parameters was evaluated subjectively by the researcher in terms of its strength, the location and proportion of the perceived muscle volume recruited and the extent of any fatigue. Contraction response was also recorded on video tape with the corresponding stimulation parameters. As isotonic contractions became possible, this extended to assessment of the limb movement. For subjects LC and LE, this was from a seated position with the knee swinging freely, the projected linear movement of the foot with respect to a scale on the ground was recorded during stimulation of the quadriceps with a variety of parameters. For subject LR, dorsiflexion angle was assessed. The contraction force and torque exerted by the limb movement, was not sufficient for measurement on the available rigs at SDH MPBE.
4.5.10 Functional Measures

For subject LR, where the purpose of the treatment was to compensate for absent dorsiflexion function, the Physiological Cost Index (PCI) was measured as an indication of the energy consumption of gait. As used for evaluation of indirect stimulation systems for 'dropped foot' [Burridge, Taylor et al. 1997], this involves the subject walking a set 10m distance at their normal pace, which is timed and the final heart rate measured by a chest worn Polar monitor with respect to a resting heart rate previously measured after at least 3min of silent seated rest. The mean PCI (Eqn.5.5.3) from 3 such walks is calculated.

Equation 4.5.3 \[ PCI \text{ (bt/m)} = \frac{\text{change in heart rate (bt/min)}}{\text{walking speed (m/min)}} \]

For subject LR in this study, PCI was only measured without stimulation.

4.5.11 Subject Questionnaire

Within the first week after completion of the treatment period, subjects were asked to complete a questionnaire (Appendix H). Subjects were requested to identify what changes, if any, they thought had occurred in a number of aspects, both during the stimulation session (Qu.19) and in their general condition from the start of the study (Qu.20). This was to compare any quantifiable changes in the evaluation measures to the subjects' own perception of treatment effects. Subjects were also questioned about their aspirations of benefits from the treatment, whether these had been fulfilled and whether they would like to continue with it, if it were available to them. At evaluation visits during the follow-up period, subjects were asked verbally about any perceived changes in their condition (Qu.20) with respect to during the treatment period and before its start. At the end of the follow-up period, subjects were once again asked about their expectations and overall opinion of the treatment.
5. **Stimulator Unit Development**

This chapter describes the development of a versatile stimulator unit for the direct electrical stimulation of denervated muscle by surface electrodes to achieve the research objectives outlined (§4). Its specification allows for a wide variation of stimulation parameters but with particular emphasis on the ability to generate long duration, biphasic stimulation pulses, which have proved of benefit in the recent studies (§3.4.2). The flexibility of output is required to allow investigation of the physiological effects of various stimulation patterns and to permit Strength-Duration curve and accommodation testing (§2.4.4).

5.1 **Stimulator Unit Specification**

As the stimulation evaluation study envisaged involves several months of operation away from clinical environment and personnel, the device is required to be portable and capable of safe 'stand-alone' operation by the user. It was therefore envisaged to be powered from internal rechargeable battery, which offers the additional advantage of inherent isolation from the mains supply. For use in the clinical environment the device was also required to interface with and operate under the control of a personal computer (PC). This was to permit operation of the device with stimulation parameters derived either directly 'on-line' from the PC when connected to it, or from those stored internally when operating independently from the PC. Controls on the stimulator unit accessible to the user were required to permit switching on/off, selection of the stimulation pattern mode (sets of parameters) and adjustment of stimulation intensity. The intensity control may alternatively be configured by the PC to control pulse width (PW) or inter-pulse interval (IPI). The stimulator was also required to monitor and store information on usage of the stimulator and from physiological transducers (e.g. gait detection foot switches) which can transferred to the PC.

From the review of previous studies and clinical experience at SDH, the following functional requirement specification for the unit and PC interface was compiled.

**Stimulation operation**

1.1) Two electrically isolated stimulation output channels, each with independently controllable stimulation parameters (defined as per Fig.3.2.1) over the following ranges

.1) Pulse amplitude 0-150mA, 0-100V(1kΩ), ripple variation <5%,
.2) Pulse width 1 - 1000ms, resolution 1ms for PW up to 100ms, 10ms thereafter
.3) Inter-pulse interval 1-5000ms resolution: 1ms for IPI 0-250ms, 20ms for IPI >250 non-regular inter-pulse intervals (e.g. for multiple frequency or dehabituation)
.4) Pulse train envelope 0-255s with 1s resolution on/off periods
.5) Session duration 1-30min with resolution 1min
.6) Pulse type monophasic or biphasic (with separate parameters for each impulse)
.7) Pulse shape rectangular, triangular, trapezoidal, sawtooth pulse shape, linearity 5%
.8) Pulse rise/fall time 0.1-1000ms with resolution 0.1ms<10ms, 1ms thereafter

1.2) Operational endurance up to 1hr/day 'Stand alone', mains free from internal supply
§5.1 Stimulator Unit Specification

1.3) PC programme and user interface to stimulator unit to allow 'on line' control of:
   1) stimulation parameters (as per 1.1)
   2) parameter to be controlled by operator control (default to intensity)
   3) limit of variation of parameter under operator control
   4) stimulator output indication parameter
   5) enable/disable of audio stimulation indication (PC operation only)
   6) transfer from stimulator and analysis of usage/transducer data
   7) definition of usage/transducer data to be stored by stimulator when in use
   8) definition and transfer to stimulator of stimulation pattern modes (up to 10) for 'stand alone use, each consisting of a set of the above parameters

1.4) non-volatile storage of stimulation parameters for up to 10 modes and usage/transducer data as defined by PC or selected mode

Operator Controls -
2.1) ON/OFF switch - disables unit and stimulation output
2.2) Variability control of stimulator parameter for each channel (default to intensity)
   - parameter selection and range of adjustment defined by PC or stored mode
   - to be inhibited when stimulation channel switched off
2.3) stimulation pattern mode selection (up to 10) for each channel

Indicators & Warnings
3.1) Visual indication of stimulation channel output related to pulse frequency, intensity, envelope
3.2) Audio indication as 3.1, enabled by PC, inhibited during 'stand alone' operation
3.3) Indication/display of stimulation parameter selected for external control
3.4) Audio and visual warning of the following, (prioritised and distinguishable)
   1) adverse stimulation output or fault condition
   2) initialisation of unit or reset in use whence no stimulation output
   3) stimulation intensity set too high at initialisation
   4) low battery warning - visual and audio prior to and after output inhibited
   5) end of treatment session - audio & visual

External Connections
4.1) Serial interface to PC (mains isolation provided externally)
4.2) Serial interface to other stimulators (e.g. Inter IC for transfer of transducer data)
4.3) Digital stimulation timing signal for synchronisation of multiple stimulators
4.4) Stimulation electrodes - 2 pairs
4.5) Transducer analogue signal inputs (4) and outputs (2)
4.6) Reference voltage output (5V) for transducers
4.7) External power supply input (>12V), mains isolated for stimulator operation
4.8) External battery charger input, using same connector as 4.4 to prevent stimulation operation

Safety
5.1) Conform with relevant sections of BS 5724 Parts 1 and 2.10 (nerve and muscle stimulators)
5.2) Patient isolation with isolated stimulation outputs
   - mains free 'stand alone' patient operation
   - mains isolation of PC RS232 interface provided externally
   - inhibition of stimulator output during battery charging
   - enabling of stimulation output with external supply operation inaccessible home user
5.3) Protection against spurious stimulation output during:
   - switch on and shut down
   - low battery / Vcc condition
   - micro-controller failure
5.4) Limit of maximum amplitude and rate of rise of output current
5.5) Monitor of output current and voltage to detect electrode peeling
5.6) Limit on duration of stimulation session in case of patient falling asleep
5.1 Stimulator Unit Specification

Packaging
6.1) Size <190x130x50 mm
6.2) Weight < 1kg
6.3) Cost <£500/unit
6.4) Portable & durable casing
6.5) Cosmetically acceptable appearance and ease of use of controls

The following additional requirements became apparent during the Failure Mode and Effects Analysis (FMEA) (Appendix M) into single fault failures as required by BS 5724 (Appendix L).

5.7) Limit or warn when pulse duty cycle exceeds 50% (i.e. \( \frac{PW}{PW+IPI} > 0.5 \))
5.8) Limit on the degree of asymmetry and therefore charge imbalance between biphasic impulses
5.9) Monitor and limit of the output current between pulses due to circuit failure
5.10) Protection against damage to operator or unit in case of output short or open circuit

5.2 Stimulator Unit Development and Design Outline

No suitable commercially manufactured device could be found, the majority being for stimulation of innervated muscle and do allow sufficient adjustment of parameters up to the levels required for denervated muscle. Those clinical models which do, were not considered suitable for ‘home based’ operation either in terms of portability or flexibility of pre-programming the stimulation pattern. Enquiries to centres involved in denervated muscle research studies revealed that custom made stimulators were used, but none were forth coming with a full specification or an offer of equipment for use in this study. Also, none of these units appear to meet all the specification requirements for this project without some adaptation and it was considered that the dependence upon another centre for technical support would be potentially time consuming and expensive.

It was therefore decided to produce an ‘in-house’ stimulator for the project drawing on the experience with existing stimulators in the department and having the advantage of potential commonality between stimulators for different purposes, especially in terms of the user interface, and embedded programmable controller. The Compustim10, is a four-channel unit that was modified for a preliminary investigation of denervated muscle simulation at SDH [Taylor, Ewins et al. 1992] but would require extensive modification to fulfil the full specification of this project. In particular, the controller module is of older technology and less suitable for expansion, however the output power stage was eventually adopted for modification for this project (§5.4).

In common with existing stimulators produced in the department, the function but not the physical layout of the stimulator unit may be partitioned into three modules (Fig 5.2.1). The unit is based around a programmable Micro-Controller module (MCM §5.5), whose embedded programme generates the stimulation pattern and control signals necessary for the Output Power module (OPM §5.4) to produce the corresponding stimulation output. The stimulation parameters are defined by the clinician using a Personal Computer based User Interface (PCUI §5.6), and downloaded into the stimulator when connected. The serial communication also permits transmission of other data
as defined in the specification. The MCM also receives information from the operator controls (INTENSITY and MODE SELECT) and performs the output monitoring and warning indication functions. The Power Supply module (PSM §5.3) supplies power to the other modules as required.

Monitoring of output current and voltage levels is included in the requirements for reasons of safety; to permit detection of failure of the stimulator, poor contact of the electrodes and breakdown of the tissue. Comparing the actual output with that desired and using the difference to dictate the output is known as closed loop feedback control. This permits more accurate control of the stimulation intensity throughout the long pulse widths of direct stimulation and the desired control of pulse rise and fall shape. It also compensates for differences in load impedance between stimulation sites and between patients. Closed loop control of the stimulation output was therefore incorporated into the unit specification, as it was deemed unlikely that output monitoring could be continuous throughout the pulse.

The effectiveness of muscle contraction induced by external stimulation is related to the current density in the tissue [Eichhorn, Schubert et al. 1984], and it is arguably most appropriate to control the stimulation output using current feedback. However, should the patient load impedance increase for instance due to deterioration in electrode contact, then as the feedback attempts to maintain the output current constant, the current density in the tissue will increase, perhaps to dangerous levels. Conversely maintaining the output voltage constant with voltage feedback may result in excessive current and tissue burns should the load impedance decrease or the electrodes is too close together. Whether output current or voltage is used for the feedback control, it is important to monitor both to detect adverse conditions.

The stimulator therefore monitors output current and voltage and has the option of either type of feedback. Voltage feedback was implemented for initial development, as it was previously found superior to current feedback in terms of output ripple variation [Andijani 1992], though probably a consequence of the characteristic of the sensing device. The closed loop control is implemented by

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**Figure 5.2.1**  
Functional Schematic of Stimulator
analogue circuitry in the OPM, as digital implementation in the MCM may not be sufficiently fast given the current consumption requirement limitation on controller frequency. The MCM does however receive the feedback signals, to retain this option and to perform the monitoring function.

Feasibility studies conducted into the choice of micro-controller device for the MCM and implementation of control software revealed the difficulty of achieving full independent control of two channels and it was decided to opt for a single channel unit for the initial clinical study. From these it would be concluded whether such flexibility of control, particularly of pulse rise and fall shape has clinical treatment value and should remain in the requirements for a future unit. Multiple channel stimulation can still be achieved by using additional single channel units with the option of synchronising outputs.

The completed unit is 170 x 150 x 60mm, weighs 1.2kg and contains two circuit boards, a rechargeable battery, interconnect wiring and connectors (Fig.5.2.2). The lower circuit board is constructed with prototype solderable strip-board and consists of the analogue circuitry of the OPM and PSM and all connections to the upper circuit board. The latter has the digital circuitry of the MCM and is constructed using Road-Runner® inter pin soldered wire connections. The high voltage components of the OPM are physically segregated from other circuitry to minimise their electrical interference effect, with the opto-isolator devices forming a division on the board. Experiments with electrostatic screening of the output transformer, inductor and blocking diodes demonstrated no beneficial effect on the output quality. Magnetic screening was not considered practical given size restraints, however there is no evidence of interference of the MCM operation.

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Figure 5.2.2 Subject Stimulation Equipment
5.3 Power Supply Module (PSM)

The function of this module is to provide power to the stimulator unit circuits either from the internal re-chargeable battery or a mains isolated external source, though the latter is only to be possible in the clinical environment. Appropriate buffering and smoothing is incorporated to accommodate any voltage drop due to current flow especially during generation of stimulation pulses. The supply voltages generated are;

- \( V_p \)  +12-14V pulse transformer primary supply
- \( V_e \)  +12V power stage supply
- \( V_{cc} \)  +5V micro-controller module supply
- \( V_{ref} \)  +5V reference supplies for external transducers

Warning is given for the loss of any supply and the unit rendered safe. Fuse protection is provided in the case of excess current flow due to component failure or misuse.

5.3.1 Internal Battery Supply and Charger

The battery capacity (>1Ahr) is based on a requirement for at least 1 hour operation per day at 50% stimulation duty cycle (100mA, 100V output) and assuming 12 hour over night charging of the battery. A Dryfit \(^2\) A500 12V 1.2AHr lead acid cell was selected as this provides the required capacity with the convenience of a compact (approximately 50x50x100mm), single package. With a maximum discharge current rating of 40A, the lead acid cell was also considered most suitable to supply the large peaks of current required by the OPM circuit. The battery gel electrode allows charging and discharging in any orientation without leakage, though venting of the unit casing is necessary.

A commercial Lawtronics \(^3\) SLA480MU mains powered battery charger is used which provides indication of continuing and completed charging conditions. This is connected to the battery, without requiring its removal from the unit, via the same external connector (S3-Fig.5.3.1) used for the stimulator electrodes. This prevents stimulator operation whilst charging and isolation of the circuit modules from the battery due to the absence of the interconnection link fitted in the electrode connector. The unit may also be powered from an external supply via the appropriate pins of connector S3.

5.3.2 Supply Voltage Regulation

All current from the battery to the stimulator passes through a 5A quick blow protection fuse (Fig.5.3.2), and the operator controlled \texttt{ON/OFF} switch, integral with the operator \texttt{STIMULATION INTENSITY} control which therefore inherently prevents stimulator output with the unit switched off (Fig.5.3.1).
The Vp (+12V) supply is derived directly from the battery and supplies only the OPM transformer primary current, which in normal operation may have a sub-pulse peak value of 20A and average value at 50% pulse duty cycle of 1A. Capacitor C9 supplies some of the current during sub-pulse conduction, but is only able to maintain voltage for short duration pulses. It also reduces oscillations at primary FET gate voltage at switch on (Fig 5.4.4) and so is mounted as close as possible to the transformer (Tr1) and FET (Q3) (Fig.5.4.2a), with its negative terminal adopted as the zero volt equipotential (single common ground point) for all the low voltage circuitry.

Ve supplies the remainder of the 12V circuitry of the OPM and Vcc with normal quiescent consumption up to 36mA, but dependent on stimulation pattern. C10 provides sub-pulse smoothing and diode D4 prevents it from discharging into the lower impedance primary circuit. The values of C9 and C10 (1000μF) are a compromise between their physical size and the acceptable voltage variation.

Vcc (+5V) is produced from the Ve supply by a constant voltage regulator (U9) and supplies the MCM and circuitry of the OPM. The 250mA capacity Maxim MAX 667 device is used because of its low quiescent power consumption (20μA), low voltage drop between input and output (150mV) and low drop-out voltage, (the minimum input voltage before the 5v output is effected). Capacitor C11 provides voltage smoothing and individual ‘de-coupling’ capacitors are fitted across the supply pins of each IC device in the circuit.

5.3.3 Power Supply Monitoring

The regulator U9, also includes a comparator monitor, the output of which (LBO) is set low, when its input (LBI) decreases below 1.225V. Resistors R42 and R43 are selected to generate this warning (PWDN) to the MCM when Ve falls below 7V, otherwise it is pulled high by R44. This indicates failure of Ve or that the battery is significantly depleted, such that the micro-controller should save data before Vcc is affected and corruption occurs. Vcc is monitored by the MCM Watchdog monitor (MCM/U7), which resets the controller if Vcc falls below 4.5V. Voltage Vp, scaled by potential divider (R45/R46) is supplied as an MCM analogue input (AnPwr) and monitored by the micro-controller at each stimulation pulse to warn of battery depletion. When Vp reaches a certain threshold, the stimulation output is inhibited with a continuous warning and this level is chosen to allow battery recharging overnight (§5.5).
Figure 5.3.1
Stimulator Unit Interconnect wiring diagram
Figure 5.3.2
Power Supply Module Circuit Diagram
§5.4 Stimulator Output Power Module

5.4 Output Power Module (OPM)

The function of this module is to produce the stimulation output pattern in response to the pulse amplitude demand and timing signals from the MCM, within the specified range of stimulation parameter values (§5.1). This is essentially a task of dc to dc conversion, from the low voltage demand signals into the high voltage stimulation output. It is also required to provide monitoring of the output current and voltage to the MCM.

5.4.1 Alternative Design Concepts for OPM

The feasibility of a number of alternative designs was considered to perform the OPM functions. A transformer is the conventional means of voltage conversion and provides inherent output isolation, however it is optimised for alternating currents waveforms.

a) Commercial dc-dc converter modules

The commercially available miniature dc-dc converters are of insufficient power rating for this application and unlikely to be suitable for the repeated pulse operation and fine control of pulse shape, especially if connected in parallel to increase output current.

b) Pulsed transformer technique

Current is passed directly through a transformer primary coil for the duration of the stimulation pulse and the output voltage is sustained so long as the primary current continues to increase, limited by flux saturation of the transformer core. However the size of transformer required to sustain the longer pulse widths for denervated stimulation would be probably be prohibitively large with typically used materials. The technique is also less amenable to fine control of pulse shape or amplitude control as is dependent upon the magnetising characteristic of the core. Demagnetising of the core between pulses would be essential to avoid saturation and limitation of pulse duty cycle, though this may be possible with bi-directional control of the primary current to generate biphasic pulses.

c) Switched Mode Power Supply (SWPS) techniques

This problem of transformer core magnetic saturation may be avoided by discontinuous pulses of current, allowing de-magnetisation in between. As the duration of continuous primary current is much reduced, then so is the core magnetic capacity required to avoid saturation and the transformer size, which is dictated by the frequency of the sub-pulses. The secondary current must be smoothed by a filter to produce a continuous dc output for stimulation. The frequency of primary current switching should be much greater than that of the stimulation pulses to minimise the output ripple variation, however as switching losses are proportional to the power of frequency, loss of efficiency and heatsink requirements can negate the advantages of
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frequency increases above a certain level. This ‘switch-mode’ technique is commonly used in power supplies and is essentially one of pulse width modulation (PWM), the output amplitude is determined by the duration of the primary current sub-pulses (§5.4.2). The maximum output value is limited to when the sub-pulse width equals the switching period and the primary current becomes continuous or by core saturation if this occurs earlier. The arrangement for producing a ‘step-up’ in voltage is known as a ‘Forward Converter’ [Mohan, Underland et al. 1989]. The primary current is required to be switched at a high rate for which Field Effect Transistor (FET) devices are typically used. However their switching characteristics introduce non-linearly and instability into the output control, which is only partly compensated for by closed loop output control (§5.4.4). The high frequency pulsed current can result in significant electro-magnetic interference (EMI).

d) Rectified Sine Wave Converter

The limitation imposed by core saturation with uni-polarity transformer primary current pulses can be avoided by using a symmetrical alternating current with zero average (d.c) value. The secondary current must then be rectified and smoothed in order to produce a d.c output for stimulation. This is most efficiently achieved by using sinusoidal primary current, as the single frequency allows optimisation of the transformer efficiency and minimises EMI. However, the advantage may be reduced because flow is continuous, albeit varying. A powerful dual polarity amplifier is required to supply the large transformer primary currents and its characteristics, including probable crossover distortion, may influence the stimulator output amplitude and quality.

e) Continuously Active High Voltage Rail

For both the forward and rectified sine-wave converters, where the primary switching waveform is modulated by the stimulation pulse pattern, there is an inherent compromise between a filter capable of producing a reasonably smooth output and its consequent limitation of the maximum rate of rise of the output pulse. This may be avoided if either circuit is employed to produce a constant, smoothed high voltage rail, from which the stimulation output pulse is obtained via a modulating switch or amplifier. This amplifier determines the pulse duration, rise/fall time and amplitude, under the control of the MCM and closed loop output feedback. The advantage this approach offers in terms of quality of output may be at the expense of reduced efficiency, though overall efficiency will be influenced by a number of factors. For instance, primary current is continuous, even without a stimulation output. The output controlling device must be rated for the higher voltages of the transformer secondary circuit and switching losses may be greater especially as it must accommodate any voltage difference between the rail and the output. A continuous active high voltage rail and large storage capacitors also have significant safety implications necessitating careful circuit monitoring. A compromise may therefore be to
vary the rail voltage according to the maximum selected amplitude. With an approximately constant or slowly varying rail voltage, advantage can be taken of the 'soft-start' design techniques for improve efficiency, component stress and EMI emissions [Hnatek 1981; Billings 1989]. The circuit is also more applicable for investigating the efficacy of pulse width rather than amplitude modulation of pulses to achieve the desired stimulation envelope.

Prototype circuits of the rectified sine-wave and forward converters were constructed for evaluation and highlighted their deficiencies as mentioned above. A comparison of primary current consumption revealed both circuits to be approximately 30% efficient. Although the sine-wave converter demonstrated superior smoothness and controllability at low output voltages, maximum output amplitude (70V) and pulse rise times were limited. This was attributed to the inadequacy of the amplifier supplying the primary current and further development would have been required to investigate performance with closed loop or digitally controlled gain. It was therefore decided to concentrate the limited development time available on the already proven forward converter design.

The Compustim 10 unit incorporates a forward converter power stage and the circuit has previously been reviewed [Andijani 1992]. The stimulation output has considerable ripple variation at the switching frequency and instability at low output voltages. These were largely attributed to coupling of the switching currents onto the feedback signal, and improvements were achieved by single point grounding and shielding. The design was adopted for this project and a number of modifications and component changes were incorporated to improve output ripple, controllability and accuracy, especially during long (>100ms) and trapezoidal pulses and high pulse duty cycles. Failure tolerance was also improved and single fault 'fail-safe' operation was demonstrated (§5.7).

The majority of applications of SMPS circuits are to provide a continuous output with 'soft-start' design techniques employed to limit output rise rate. However these were not evaluated for this application, as the requirement is to maximise the control over the output waveform.

The OPM consists of low voltage circuitry generating the variable duty cycle 100kHz switching waveform (§5.4.2) for the switch controlling the current through the transformer primary (§5.4.3), a filter to smooth the high voltage secondary output (§5.4.4) and an 'H-bridge' switching network to produce the biphasic stimulation output (§5.4.6) which is monitored and feedback to low voltage circuitry for closed loop control of the output (§5.4.5). This section concentrates on the modifications to the Compustim circuit as the basis of its operation is described elsewhere [Mohan, Underland et al. 1989].
Figure 5.4.1
Output Power Module Schematic
Figure 5.4.2a
Output Power Module Circuit Diagram - sheet 1/2
Figure 5.4.2b  Output Power Module Circuit Diagram - sheet 2/2
5.4.2 PWM Switching Waveform Generation

The sub-pulses of current through the transformer primary required for forward converter operation are achieved using a FET switch (§5.4.4) and the duration of the conduction period determines the level of output voltage. The control signal for this switch consists of a series of regular pulses, whose duration are proportional to the desired final output. Although this switching waveform may be generated directly by the MCM it is unlikely to be able to do this and the necessary closed loop control, without excessive power consumption due to high processor speed. The primary switching waveform is therefore produced with analogue circuitry by comparing a continuous demand signal of amplitude proportional to the desired final output, with that of a regular waveform at the sub-pulse switching frequency. In this circuit, a sawtooth shape was used, although triangular or sinusoidal waveforms were also evaluated. The comparator output is high, to close the primary current switch, whenever the demand signal amplitude exceeds that of the switching waveform. The proportion of time for which the switch is closed and when primary conduction occurs is referred to as delta (δ), the peak primary current during the sub-pulses and therefore the final output amplitude increase with δ.

![PWM Switching Waveform Generation and Primary Current](image)

**Figure 5.4.3** PWM Switching Waveform Generation and Primary Current

In this circuit (Fig.5.4.2.a), closed loop control of the output is achieved by the PWM comparison being performed on an error signal (V_{error}) from a differential amplifier (U1D), proportional to the difference between the demand signal from the MCM (V_{demand}) and a scaled version of the output voltage or current (V_{feedback}). The 100kHz sawtooth switching waveform is generated by a separate oscillator circuit based on a standard 555 timer device (U3) [Pippenger, Tobaben 1985]. External components determine the waveform frequency, with circuit layout chosen to minimise interconnection distance and parasitic capacitance. These functions are also available in a standard SMPS integrated circuit device [Andijani 1992], but this did not provide the level of control and fault monitoring required for this application.
This PWM circuitry is supplied by the regulated Vcc supply for direct compatibility with the MCM and for isolation from the variations in Vp and Ve during stimulation pulses and with battery depletion. If the supply voltage to the switching waveform generator circuit is allowed to decrease, then so does the maximum amplitude of the waveform, thereby increasing $t_{on}$ and the stimulator output for a given $V_{error}$ level. If $t_{on}$ increases such that $\delta = 1$, then primary conduction becomes continuous and the circuit acts like a pulsed transformer. In this condition, after an initial output peak, the transformer core becomes saturated and the secondary output collapses to zero as the power source is unable to supply the high primary current. The maximum voltage of the sawtooth waveform is 3.2V and the differential amplifier gain is adjusted so that with feedback, $V_{error}$ is just less than this at the maximum output level. However this will not altogether prevent $t_{on}$ increase and continuous primary conduction. As the battery charge level decreases, so does the sub-pulse peak primary current and the final output, the resulting decreased feedback, increases $V_{error}$ and $t_{on}$ for the same $V_{demand}$. The output level corresponds only to the peak primary current occurring during the sub-pulse, which depends upon the sub-pulse duration and the battery charge level. Therefore, with operation from a depleting battery supply and feedback, there is no unique correspondence between the demand from the MCM ($V_{demand}$) and the sub-pulse duration ($t_{on}$) or the final stimulator output level.

The maximum output level is therefore limited by the duration and amplitude of the primary current sub pulses but ultimately by saturation of the transformer core. The shape of the output stimulation pulse determines the point of maximum primary current and therefore of potential output collapse due to continuous conduction. The greater the demanded rate of rise of output, the greater the primary current flow to achieve it, and the lower the maximum output level before continuous conduction occurs. For instance, at the start of rectangular pulses the primary current has a rectangular form, due to the initial high current flow to charge up the capacitance of the output filter. Continuous primary conduction ($\delta = 1$) was avoided by limiting the value of $V_{error}$ and $\delta$ to 0.8, using the reverse breakdown conduction of a zener diode (D1) controlled by R5. The maximum output amplitude possible for rectangular pulses is thereby increased.

Continuous primary conduction ($\delta = 1$) can also arise from a number of the modes of failure of the sawtooth waveform generator which reduces its output level (Appendix M). Most significant are the failures causing the waveform output to be reduced to zero and thus below the level of the $V_{error}$ offset of UID (0.6V), when the demand is zero. This results in continuous primary conduction at all times, irrespective of the demanded pulse pattern and so the output must be monitored by the MCM during the off pulse period (§5.5.2). Although the stimulation output collapses in this instance, the switching FET power rating is exceeded with consequent device failure. To ensure reliable and instant detection of failure of the sawtooth waveform, its output is averaged by a high input impedance low pass filter (R18 and C6) of 1kHz corner frequency and monitored by
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 comparator U2A/B. Exceeding the **sawtooth waveform monitor** thresholds results in the PWM comparator output being clamped to 0V, thereby switching off the primary FET switch and reducing the primary and secondary current to zero.

The stimulation output can be similarly inhibited by the enable/disable (E/D) control from the MCM via transistors Q5 and Q6, for instance, following detection of a fault or spurious output or micro-controller reset (§5.5.2). Inverter Q5 is powered from the Ve supply to ensure the output is inhibited when Vcc fails. Resistor R25 is included to ensure the inhibiting clamp is still applied in the case of spurious micro-controller operation causing the control lines to ‘float’ in neither a high or low state.

5.4.3  **Primary Current Switching**

A controllable switch is required to produce the pulses of transformer primary current, and a transistor is the obvious choice because of its speed of operation and high current rating. A metal oxide semiconductor field effect transistor (MOSFET) is chosen in preference to a bipolar because of its ease of control without biasing, greater operating range at high power dissipation and the absence of secondary breakdown effects. However a bipolar may have a more linear switching characteristic.

The IRF530 MOSFET [Int.Rectifier 1993] (Q3) used in the circuit has a maximum continuous current rating of 14A (V_{drain}=10volt, T_{case}=25°C) and a pulsed current rating of 50A, providing the junction temperature is maintained below 175°C. Calculation of thermal conductivity predicted that, without any external heatsink attached, the device can tolerate an average current of 2A, and with the 21°C/W heatsink used in the circuit, a current of 3.3A continuously (Appendix N). This was demonstrated during fault testing of the circuit; a short circuit failure of the FET results in continuous primary current of 10A until ceased by failure of the circuit fuse (F1).

The switching operation of the FET is dominated by its gate input capacitance (Ciss=670pF@Vds=25V), which consists of that between the gate and source (Cgs) and that between gate and drain (Cgd), but varies considerably with drain-source voltage (Vds) [Clemente 1993; Pelly 1993]. The IF530, is an n-channel enhancement mode device, so the drain-source current flow (that through the transformer primary Ip) is determined by the magnitude of the positive gate voltage supply from the switching comparator. The gate threshold voltage (V_T = 3volts for IRF530) must be exceeded to establish the drain-source conducting channel and permit current flow. As the gate voltage is increased above the threshold, drain current increases and current also flows in to the gate to charge Cgs. Only when this is fully charged, at gate voltage of Vgsp (5-7volt for IRF530), is the drain–source channel established. However the drain voltage can only decrease at the rate at which Cgd is discharged by current flow into the gate, the so-called Miller effect. The
gate voltage is held almost constant (at $V_{gsp}$) during this period, and the charge flow is in fact greater than when $C_{gs}$ is charged. Only with $C_{gd}$ fully discharged and drain voltage at its minimum is the device fully switched on and acts as a resistive channel. A maximum gate voltage greater than $V_{gsp}$ is used to ensure the device remains fully switched on as drain conduction increases, and to increase the charging speed)[Clemente 1993; Pelly 1993]. When the transistor turns off at the end of the sub-pulses, then this process occurs in reverse with similar form to the gate voltage (Fig.5.4.4).

![Graph](image1.png)

**Figure 5.4.4** Primary Current MOSFET Switching Characteristic (not to scale)

![Graph](image2.png)

**Figure 5.4.5** Output Response to Linear Ramp Demand (not to scale)
The switching characteristic of the MOSFET is reflected in a non-linear open loop output response to a linearly ramped demand (Fig.5.4.5). The sub-pulse duration ($t_{on}$) of the switching waveform supplied to the gate increases as the demand amplitude increases. At low amplitudes, $t_{on}$ is insufficient for $V_t$ or $V_{gsp}$ to be reached and to fully charge $C_{gs}$, so minimal primary flow or final output occurs (ABC). Hence, after a delay compared to the demand, as $t_{on}$ progressively increases, so does the primary current and the final output voltage, but in a non-linear fashion (CD). A transition to a linear output response occurs (D) when $t_{on}$ is sufficient to fully discharge $C_{ds}$ allowing primary current to increase linearly and for the stimulation output to be proportional to $t_{on}$.

A high gain, high current capacity complementary push-pull gate drive circuit (Q1, Q2) was chosen to increase the rate of charging of the gate capacitance and thereby reduce the output voltage at which the transition occurs, to approximately 20V. This also serves to reduce the power dissipation in the MOSFET during the charging when both drain current and voltage are large. Increasing the closed loop voltage feedback gain by means of resistor R14 reduces the transition voltage level further. The initial delay until $V_t$ is reached can not be eliminated entirely but results in a step of only a few volts. However, because there is no unique relationship between $V_{demand}$ from the MCM and the stimulator output level ($V_o$) (§5.4.2), the FET switching characteristic cannot be compensated for by translating into a non-linear demand characteristic, as used in the Compustim 10B unit [Michael 1996].

With its load dominated by the secondary inductor, the transformer primary current ($I_p$) increases linearly during the sub-pulse (Fig.5.4.4), to 10mA for 100mA output current and up to 20A at the start of a rectangular pulse. However at the start of the sub-pulse, it is subject to considerable oscillation (~2MHz) of up to 5A, gradually decaying as the base level current increases, but extending beyond the period of MOSFET switch on. The amplitude and frequency of oscillation are affected by the output inductance and load resistance but particularly by the output capacitance, and is therefore attributed to its charging. Corresponding oscillations also occurred on the gate voltage and transformer secondary voltage. These were reduced by means of capacitor C9 connected across the transformer primary supply and mounted as close as possible to the transformer and Q3. Further oscillations, but of higher frequency (28MHz) are measured following transistor switch off on the primary current, drain voltage and output current, the amplitude of which was increased by reduction in the switch off time.

The decay in primary current is opposed by the magnetic flux stored in the transformer inductance until de-magnetised. The rise in drain voltage due to this does not occur until after these oscillations have decayed away and reaches a peak of 55V on the primary side and greater than 1000V on the secondary. This is blocked by diode D2, but the magnitude of the voltage necessitates a high current rating, heatsink mounting and limits the pulse duty cycle to 50% at
100mA output current, to avoid thermal runaway breakdown and component failure. A 'free-wheeling' diode across the transformer primary or a 'snubber' network connected to the FET drain is commonly employed to reduce this 'inductive kick' voltage peak. However these necessitated a very low reverse recovery time diode (<100ns) in order to switch fast enough, and although reducing the amplitude of the voltage peak, increased its duration. Alternative methods of de-magnetising the core include employing dual switching devices and diodes or the more usual, third transformer coil [Mohan, Underland et al. 1989]. However all these techniques involve returning current into the supply at potentially elevated voltages which is not suitable for the lead acid cell used, and therefore none were pursued further.

Resistor R8 serves to limit the amplitude of primary current, especially in failure case conditions and therefore protects the battery from short circuit. In normal operation it limits the high peak current at the start of pulses, and at high ton values, thereby avoiding output diode failure without greatly reducing the final stimulation output.

5.4.4 Secondary Output Circuit

During the MOSFET (Q3) on period (ton), the primary current increases linearly because of the inductive load, predominately that of the output filter. This changing current induces a flux into the transformer core and hence current flow in the secondary circuit. The series diode D2 permits circulation of the secondary current through the inductor to the load. At Q3 switch off, the primary current decays to zero opposed by the flux stored in the transformer inductance and causing a transitory peak in Q3 drain voltage. However diode D2 blocks any reverse current flow in the secondary winding with output current maintained by the magnetic flux in the output inductor (L1) through the shunt diode D3. The capacitor C7 maintains the output voltage approximately constant. The inductor current and stored magnetic flux change approximately linearly as the integral of the voltage across it and over a complete switching period has zero net value, so the input to output voltage ratio of the circuit is proportional to the switch duty ratio (δ) and the transformer ratio (N1/N2) [Mohan, Underland et al. 1989]. The capacitor C7 is alternately charging and discharging during the switching period corresponding to the variation in inductor current, the ripple component of which flows through the capacitor and the average component through the load. At small values of ton, the flux in the secondary inductor may decay to zero during toFF so the inductor current becomes discontinuous, and the current to the load is supplied entirely by the capacitor.

The capacitor voltage and therefore the stimulator output varies with this charging cycle but this is minimised with the filter 'cut-off' (-3dB) frequency (fc=1/(2πLC)) very much smaller than the switching frequency (fs). However, the charging and discharging periods of the capacitor C7, limits the minimum output pulse rise and fall times, and necessitates rapid discharge by the output clamp circuit for biphasic pulses (§5.4.6). With rectangular pulse shape, the initial charging of capacitor
C7 results in a peak in the output at the start of the pulse. With closed loop control of the output, this is compensated for by sense capacitor C8, which increases the initial feedback, thereby reducing the primary current, compared to purely resistive feedback. With the 11mH inductor of the Compustim 10 circuit, a value of $C7=680\text{nF}$ ($f_c=1.8\text{kHz}$) was found necessary to reduce the output ripple when operating with closed loop voltage feedback. Attempts to reduce the ripple by increasing the switching frequency from 100kHz, were not pursued as this would require re-optimisation of the transformer and consequent delay in the project.

5.4.5 Output Monitoring and Feedback Control

A signal proportional to the magnitude of the output is derived to permit closed loop control of the output and monitoring by the MCM to protect the patient and the unit in the case of adverse output. Both output current and voltage are monitored by U4 and U5 respectively, whose opto-isolation ensures the necessary isolation of the output from the low voltage circuitry when it controls more than one output channel. As it is the output voltage that is used for the closed loop control, its sensing device is located after that of the output current. The output current measurement therefore includes that through the voltage sensing path (approximately 10mA). Reversing the order of these sensing elements would result in an error in the voltage measurement (approximately 1.5V).

The opto-isolators consist of an input sense diode, whose current optically controls the current through the output transistor. However due to the temperature sensitivity of the device, its output varies over a period of continuous conduction in respect to pulse width and frequency and introducing an error of up to 10%. Input-output characteristics also vary considerably between devices, which had to be individually matched to standardise the circuit and calibration. Scaling resistors R13 and R14 are chosen to allow output monitoring up to 350mA and 150V respectively to accommodate short circuit and open circuit conditions, before device saturation occurs. Resistor R9 limits the output current to approximately 600mA when the output leads are shorted circuit, which U4 can withstand for several seconds at least, permitting detection by the MCM. R14 also determines the closed loop feedback gain, which is set to minimise non-linearity in output due to the MOSFET Q3 switching characteristic and zener diode D1 conduction. The monitor signals are buffered and available at connector S11 (pin 5 \text{Vomonitor}, pin6 Iomonitor) for external monitoring on an oscilloscope, though saturation of the buffer amplifiers (U1C,D) corresponds to approximately 270mA and 90V.

5.4.6 Biphasic Switching and Clamp of Stimulation Output

To achieve the biphasic output pulses, two impulses are generated in quick succession and an H-bridge arrangement of switches reverses the direction of current flow through the load between these pulses. The MCM provides the appropriate control signals to the switches (Fig.5.5.4) via opto-
§5.4 Stimulator Output Power Module

isolation to maintain isolation of the output. MOSFET based solid state switches (International Rectifier PVR3301 U7 & U8) are used as these can withstand up to 300V and are controllable even with the output terminals floating. However it was found that for output voltages greater than approximately 32V, the switches failed to remain closed for the duration of the pulse, unless the secondary 0V was connected either to the primary 0V, or to an oscilloscope (even battery powered) or to the operator. It is assumed that this provides the necessary path for leakage currents and pending further investigation, the secondary and primary 0V were connected by capacitor C12, of 0.1μF, the minimum value to obtain correct operation. Isolation of the secondary from the low voltage circuitry is no longer essential while only one channel is being controlled and because the device is inherently mains free during stimulation operation. The biphasic switch control circuitry is supplied from Vcc, so that in the case of its failure, which would also effect the MCM, the switches will open to inhibit any stimulation output. Power rating of the switch devices limits the stimulation output current to 150mA at 50% pulse duty cycle.

The large value of output capacitor (C7) limits the minimum fall time of a 100V stimulation output pulse to 3.5ms, which is typically within the period for the following second impulse. To ensure the biphasic pulse switching occurs without delay and only when the output is at zero, thereby maintaining impulse symmetry, any residual charge on C7 is discharged through resistors R10 and R12 via switch U6. A solid state opto-isolated controlled device is used as for the biphasic switching (PVR3301) with its two switches in parallel to reduce the current loading. However considerable difference in the speed and conducting resistance between the switches of the same device was consistently found and prevented effective current sharing, except in short circuit conditions. With a value of 100Ω for R10 and R12, the pulse fall time from 100V is reduced to approximately 0.7ms and so the minimum inter-impulse interval used is 1ms. The output clamp switch is controlled by a logic signal (O/Pclamp) from the MCM via Q7 and is held closed between biphasic impulses and after each pulse to allow discharge of the body capacitance. Inverter Q7 is supplied by Ve, so remains operational in the case of failure of Vcc and resistor R28 is included to operate the clamp switch, in the case of spurious, floating MCM signal.

With a patient equivalent 'dummy load' (0.5-5kΩ resistor in parallel with 100nF capacitor), the OPM circuit has been demonstrated to produce satisfactory biphasic output up to 95V (1kΩ load) and 150mA for pulse widths from 0.3ms to 3s at 50% pulse duty cycle, with controllability of pulse rise and fall times to 0.5ms, linearity for ramped demand within 10% and current ripple of 12.
5.5 Micro Controller Module (MCM)

The main functionality of the MCM is provided by the embedded software of its programmable micro-controller device, and also operates in conjunction with the User Interface programme of the Personal Computer (PCUI) (§5.6) via the serial data connection, to allow changes to the stimulation parameters. Following in this section are brief details of both the MCM circuit (§5.5.1) and the embedded controller software (§5.5.2). These were designed 'in-house' in the department in accordance with the core requirements specified by the author, who also performed the conceptual design and all verification and validation testing on the unit. Additional software requirements were introduced and incorporated as a result of the Failure Mode and Effects Analysis (Appendix M).

5.5.1 MCM Hardware Circuit

The MCM is a general-purpose micro-controller based circuit for the processing and synthesis of signals from various sources with stored data and was originally intended to form a generic controller module suitable for a wide range of stimulator applications. A number of 'state of the art' micro-controller devices were considered with the intention of fulfilling the specification with a single integrated circuit, however this introduced the difficulty of ensuring regular communication with the PC for transfer of stimulation and monitored parameters. Especially, as it was desired to maintain a common PC serial communication format with existing stimulators produced by the group, which transmit data asynchronously in blocks of 8 bytes and requires dedicated time periods of 20msec [Michael 1996]. Also, with the requirement for independent control of two stimulation channels, maintaining the amplitude demand to the OPM during long pulse rise or fall ramps may require the controller to operate at higher frequency and therefore increased current consumption or necessitate interrupting the stimulation pattern.

A number of alternative designs solutions were considered to avoid this compromise;

a) Separate controller devices for PC communication and stimulator output functions, with intervening Dual Ported Memory (RAM) device used for the transfer of data between them.

b) An autonomous external digital to analogue converter (DAC), capable of generating the ramped amplitude demands from rise time or rate information and avoiding the need for continual updating. Such as PWM control of an incremental DAC, however available devices or programmable logic arrays have high current consumption and discrete counter logic, many ICs.

c) Separate but simple micro-controllers for each channel connected in a bus structure to a master communication micro-controller with appropriate arbitration protocol.

d) Direct micro-controller generated OPM primary switching waveforms from the processor PWM output, however speed would have to be sufficient for the micro-controller to also perform the closed loop feedback summation with consequent increase in controller current consumption.
Given these complications of providing continuous independent amplitude control of two stimulation channels with trapezoidal shaped pulses, it was decided to construct a single channel unit to allow the initial clinical investigations to be performed (§4), which may establish whether these functions are indeed necessary for the clinical treatment. This resulted in a much reduced MCM specification for which the Arizona Microchip \(^5\) PIC 16C73 micro-controller was selected, because it provides many of the desired functions in a compact package (28pin) with low operating current consumption. With only a single channel to control, direct parallel output to an external DAC is possible and serial access to external memory is adequate. The completed single MCM board is a general purpose micro-controller circuit based around the PIC 16C73A device (U12) with external non-volatile Electrically Erasable Programmable Read Only Memory (EEPROM)(U13), serial RS232 communication, analogue and digital Input/Output connections (I/O), audio and visual indications and warnings and various supervisory features (Fig.5.5.1, 5.5.2).

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**Figure 5.5.1** Micro Controller Module Schematic
Figure 5.5.2  Micro Controller Module Circuit Diagram
§5.5 Stimulator Micro-Controller Module

Serial communication (RS232 standard 19k baud rate) to the PC and User Interface is accomplished by specially configured pins of the micro-controller device and line-driver device (U11) to boost signal levels. Other digital signals emanate from the 8 bit port RB of the micro-controller and are arranged into a data bus, with selectable 8 bit latches for input (U9) and output (U8 and U10). The timing signals (O/P Bph, Cph, Clmp) associated with the stimulation output are generated by the micro-controller and output to the OPM synchronised to the required analogue stimulation pulse demand ($V_{\text{DEMAND}}$). The Mode Selector switch position is read in (MODE 1-4) and output lines control the front panel indicator light emitting diodes (LEDs) and audio buzzer. Unallocated I/O (digital D05,6, DI4-7 analogue AI5-6, AO1) is also connected via connector P6/S6 and the OPM board to connector S11 for possible external monitoring or signal input.

Analogue outputs from the MCM are generated by a dual 8 bit digital to analogue converter (DAC) (U2) connected to the data bus and associated amplifiers (part U1). One channel provides the instantaneous stimulation intensity demand ($V_{\text{DEMAND}}$) to the OPM and therefore defines the stimulation pulse and envelope shape and timing. Signals proportional to the output current ($I_{\text{OF/B}}$) and voltage ($V_{\text{OF/B}}$) and the OPM sawtooth waveform ($V_{\text{STMON}}$) are feedback to the micro-controller analogue to digital converter (ADC) via an 8 to 1 channel analogue multiplexer (U3). The value of the front panel intensity control is also input to the controller by this means, with a 'pull down' resistor to DGND (OPM/R48) to ensure zero value in the case of loss of Vcc supply to the control potentiometer. From MCM software version R1, the analogue output channel B is the stimulation intensity envelope, for display to the user on an analogue meter connected to S11/pin8.

The PIC 16C73A micro-controller includes 4k (x14bit) of 'on board' Electrically Programmable Read Only Memory (EPROM), in which is stored the unit programme and the set of default stimulation parameters. User programmable, non volatile storage for up to 10 sets (modes) of stimulation parameters and the unit usage data is provided by 2k byte of Electrically Erasable Programmable Read Only Memory (EEPROM) (U3). Data transmission to this device is performed serially using the micro-controller device pins specially configured for such Inter-Integrated Circuit (I²C) communication.

The logic signals to select or control the various circuit devices at the appropriate times, are generated by U6 and U5 derived from signals from the micro-controller. This includes the E/D signal to enable or disable the stimulation output from the OPM. A Watchdog monitor (U7) resets the micro-controller in the event of the Vcc supply falling below 4.5V, the reset button being pressed or the micro-controller failing to provide the strobe signal within the specified 1200ms time interval, indicating the controller programme has stopped operating correctly. On reset the E/D signal is set low to disable the OPM stimulation output, and is only enabled again when the micro-controller successfully performs its initialisation routine.
The circuit operates from Vcc supply, with -5V generated by device U4 for the DAC and associated amplifiers. Separate Vcc and OV connections are provided for analogue (+5V, AGND) and digital (Vcc, Dgnd) circuits, with the Vcc regulator on the OPM board (OPM/U9) acting as the common ground point.

5.5.2 MCM Software Programme

The MCM software is operated by the PIC 16C73A micro-controller device (U12) and is stored within its programme memory. The programme has been written in the PIC mnemonic assembler language, compiled into machine code and tested using an in-circuit emulator system, before downloading into the device. The device is operated at 3.579MHz (derived from Crystal X1) to minimise current consumption, the machine cycle is therefore approximately 1.1µs. The programme is synchronised by means of regular interrupts generated by one of the device Timer-counters. The interval between interrupts is specified via the PCUI (§5.6), to allow flexibility in the stimulation pattern. As only one stimulation pulse is generated in each interrupt cycle, this allows stimulation frequencies of up to 182Hz.

Upon occurrence of an interrupt, the programme performs a sequence of operations, known as the interrupt service routine (ISR)(Fig.5.5.3), some of which is dependant on the status of a number of flag parameters which are set by appropriately by corresponding events. These flags also determine the priority given to performing the various programme tasks as follows;

1. safety monitoring and warning,
2. saving usage data to EEPROM and closing down,
3. generating stimulation pulse
4. serial communication to PC.

In addition, frequently performed tasks use subroutines such as;

- stim-fail - provides appropriate warning indication/buzzer and includes shut down
- RS232 - serial communication to PC
- analogue input - read in the value of an analogue channel and convert to digital
- analogue output - output a value and convert (using the DAC) an analogue channel
- digital input/output - using the port RB data bus and selected digital latch
- EEPROM - read or write to serial memory

At switch on, an initialisation routine is performed which configures the micro-controller registers and stack pointer, sets the stimulation output to zero, loads in the stimulation parameters of the default or selected mode, enables the stimulation output and produces a continuous warning if the intensity control is above zero.
Interrupt

- Check Timer Flag that interrupt did occur
- Send out strobe to Watchdog monitor
- Set RS232 flag
- Update session counters
- Set envelope and session flags as necessary
- Increment usage statistics block

Y Set fail-flag T
subroutine

N

Battery level low?

Y Set fail-flag T
subroutine

N

Finish Pulse flag set?

N

Return From Interrupt

Time for new pulse?

Y Set fail-flag R
subroutine

N

Session end flag set?

Y

Set fail-flag R
subroutine

N

Pulse envelope on?

Y Set fail-flag A
subroutine

N

lo(a) > threshold?

Y

Set fail-flag A
subroutine

N

Read in Intensity Control

Y Set fail-flag A
subroutine

N

Inten.rate > threshold?

Y

Set fail-flag S
subroutine

N

DAC value increment + wait in 16 bit counter delay loop

N

DAC value=Intensity?

Y

Set fail-flag S
subroutine

N

DAC value =Intensity + wait in 16 bit counter delay loop

DAC value =Intensity + wait in 16 bit counter delay loop

Y Set fail-flag B
subroutine

DAC value > max lo?

Y

Set fail-flag B
subroutine

DAC value decrement + wait in 16 bit counter delay loop

N

DAC value = zero?

Y

Enable 0/P B-ph and disable O/PCImp, 1ms delay

Set Finish pulse flag

Y

Enable 0/P clamp, disable O/P B-ph Intensity LED

Monophasic pulse?

Y

RFI

16 bit counter delay loop to time inter-impulse interval

Y

Set fail-flag B
subroutine

16 bit counter delay loop to time inter-impulse interval

Y

Set Finish pulse flag

RFI

Figure 5.5.3 MCM Controller Interrupt Service Routine (see Fig.5.5.4 for definitions)
Safety Monitoring and Warning

The stimulation output current (Io) and primary voltage (Vp) are monitored on a number of occasions during the generation of the stimulation pulse (Fig.5.5.3) corresponding to some of the defined points (Fig.5.5.4). This involves sampling the analogue input channels IoF/B and AnPwr respectively, by means of the analogue input sub-routine. The output current is monitored at a to check for any fault causing continuous stimulation output. The output current is also monitored at c and g to ensure the maximum specified value is not exceeded in each half of the biphasic pulse and then both are compared to ensure approximate pulse symmetry and therefore charge balancing. The output current is not sampled at b, because of the transient current peak that occurs with rectangular shaped pulses as the body capacitance is charged. Vp is monitored to warn of the impending (intermittent warning) or immediate (continuous warning) need for battery charging. Stimulation can continue during the former, but output is inhibited in the case of the latter. Thresholds typically correspond to 11.0V and 10.5V respectively, which permits the battery to be fully recharged in the typical, 12 hour overnight charging period. Although the battery voltage at both a and g are sampled, the former is used for monitoring as the latter is considerably lower because of the current flow during the pulse. A count of the duration of the current stimulation in seconds and minutes is maintained and monitored for the end of the specified session length.

The warning threshold of each of the monitored parameters is specified by the 'Fault Levels' User Interface screen (§5.6) and when exceeded, a corresponding warning fail-flag is set and the sub-routine 'stim_fail' is called. This sub-routine performs the following tasks;

I. sets the stimulation output to zero by clearing the analogue output (DAC) value
II. updates the usage statistic values (total usage time and number of uses)
III. saves the updated usage statistics to the EEPROM,
IV. operates the indicator and audio warnings according to the fail-flag set (Tab.5.5.1)
V. repetitive loop to strobe the watchdog monitor to prevent a micro-controller reset
Items II and III are included, as this sub-routine is also entered when the unit is switched off, when the declining primary voltage is detected.

<table>
<thead>
<tr>
<th>Fail flag</th>
<th>Warning Meaning</th>
<th>OPM output</th>
<th>LED Indicator warning</th>
<th>Audio warning</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>lo &gt; continuous current limit</td>
<td>Disabled</td>
<td>Fault (continuous)</td>
<td>Continuous</td>
</tr>
<tr>
<td>B</td>
<td>lo &gt; max. current limit</td>
<td>D</td>
<td>&quot; -</td>
<td>&quot; -</td>
</tr>
<tr>
<td>G</td>
<td></td>
<td>G 1 &gt; log 1 &gt; asymmetry limit</td>
<td>D</td>
<td>&quot; -</td>
</tr>
<tr>
<td>R</td>
<td>Intensity or Intensity rate &gt; limit</td>
<td>D</td>
<td>&quot; -</td>
<td>&quot; -</td>
</tr>
<tr>
<td>S</td>
<td>Tsession = session limit</td>
<td>D</td>
<td>Fault (flashing)</td>
<td>Intermittent</td>
</tr>
<tr>
<td>T1</td>
<td>Vp at a &lt; upper limit</td>
<td>Enabled</td>
<td>Battery low (flashing)</td>
<td>Intermittent</td>
</tr>
<tr>
<td>T2</td>
<td>Vp at a &lt; lower limit</td>
<td>D</td>
<td>Battery low (continuous)</td>
<td>Continuous</td>
</tr>
</tbody>
</table>

Table 5.5.1 Stimulator Operating and Failure Warnings

Stimulation Pulse Generation

At any moment, the instantaneous stimulation intensity required is output from the MCM to the OPM as an analogue value ($V_{demand}$) by DAC channel A and derived from an 8 bit value from the controller. The resolution of output intensity control is therefore approximately 1mA. Throughout the stimulation pulse, the intensity value output to the DAC is updated at regular intervals by a programme loop performed repeatedly. This loop incorporates a 16 bit software counter decremented to zero to produce a known delay (Fig.5.5.3). During the first pulse, the B-phase switches conduct, then the switching signals are reversed during the inter-impulse interval so C-phase conducts during the second pulse. The output clamp path is connected at the end of each pulse to discharge the output capacitance (OPM/C7) and reduce the voltage across the switches, before switching occurs. (§5.4.6). A 1ms switch settling time is also incorporated. The C-phase and output clamp remain connected during the pulse-off period to allow the body to discharge into the stimulator (Fig.5.5.4). On completion of the second pulse and clamp interval, the programme sets the 'finish-pulse flag' and returns from the ISR. On return from the ISR, if a pulse has not been produced in that interrupt interval, the programme sends out the RS232 communication initialisation byte to the PC and awaits communication with it. If this is not completed before the next interrupt, it is abandoned. An interrupt can occur during a long pulse, however in the initial steps of the ISR, the 'finish-pulse' flag is checked to confirm this and after incrementing the usage statistics and checking the session time, the programme continues with the pulse generation (Fig.5.5.3). The stimulation envelope is also controlled by means of a flag checked at the start of each ISR and counters incremented at each ISR. Currently only rectangular shaped envelopes are possible.

Serial communication to PC

Serial communication with the PC is in accordance with the RS232 standard and in common with other stimulator units developed in the group [Michael 1996]. Data is transmitted in blocks of 8 bytes, preceded by a command byte defining the data and type of transmission (TXD or RXD). The command byte is returned by the MCM before and after the data to confirm initialisation and the
end of the transmission. The returned command byte is verified but no parity or other checking is included, as credit is taken for the correct receipt of data being checked by means of the PCUI (§5.6). Communication is performed by the MCM subroutine RS232, which is entered when an ISR is not required to generate a pulse. This sends out an initialisation byte to inform the PCUI it is available for communication. When wanting to communicate, the PCUI sends out the command byte, which is returned by the MCM, followed by the data block in the appropriate direction and then the confirmatory command byte. Each data block requires a minimum of 20μs to complete transmission and some PCUI communications require transmission of two such data blocks (§5.6).

If an interrupt occurs during a transmission, then it is abandoned and repeated by the PCUI in a subsequent interrupt interval. Hence for interrupt/stimulation frequencies of greater than 34Hz, PCUI communication can no longer be sustained, but this was not a limitation in this application.

EEPROM data saving
Access to the non-volatile memory is performed serially by sub-routine 'EEPROM'. The stimulator usage statistics (total usage time and number of uses) are saved to the respective memory locations at switch off as described above. These locations are cleared when a TXD STATS command is sent from the PCUI. The EEPROM is also accessed for retrieving stimulation parameters on initialisation or saving parameters and fault levels following the corresponding PCUI TXD[P] commands.

5.6 Personal Computer User Interface software package (PCUI)

The PCUI is written in National Instruments LabVIEW 6 graphical programming language. This is orientated around a series of display screens, known as 'virtual instruments' (VI) as they mimic the appearance of conventional electronic instruments, with elements for input of operator variables (numerical dials, logical selectors and switches) and the display of output parameters (numerical, graphical and logical indicators). The programme coding is represented by a diagram of interconnections between these and other standard computational elements.

The PCUI consists of a series of nine screens, (example Fig. 5.6.1), each selected by means of the Mode Select menu and performing one of the functions of the interface as follows;

- **RXD-STIM** Displays the current stimulation parameters
- **RXD-Monitor** Displays the monitored parameters (output current, voltage and Vp)
- **RXD-Fault levels** Displays the current monitored parameters warning thresholds
- **RXD STATS** Displays the current session and cumulative usage statistics
- **TXD[T]-STIM** Enters stimulation parameters for temporary use, until switch off
- **TXD[P]-STIM** Enters stimulation parameters for permanent storage
- **TXD[T]-Fault levels** Enters monitored parameter thresholds for temporary use
- **TXD[P]-Fault levels** Enters monitored parameter thresholds for permanent storage
- **TXD STATS** Clears the current session and cumulative usage statistics
§5.6 Stimulator PC User Interface

Each of these modes involves communication with the stimulator MCM (§5.5.2), to either receive (RXD) or transmit (TXD) data. Transmitted data is either stored temporarily [T] in the microcontroller memory or permanently [P] in the EEPROM, only the latter is retained after the unit is switched off. Definition of the parameters available for each mode are given in Appendix K, each consists of one 8 byte block of data for transmission, except for the STIM modes, which have two such blocks. The appropriate Communication Status Indicators indicate successful communication, though it is assumed that parameters transmitted to the stimulator using a TXD mode, will be verified by the corresponding RXD mode. The programme includes calculation of the intensity at which 50% pulse duty cycle occurs for the specified stimulation parameters. This is displayed on all mode screens and acts as a guide to the clinician, to minimise the risk of excess current flow into the patient, however the stimulation intensity itself is not limited.

![Figure 5.6.1](image-url)

**Figure 5.6.1** PC User Interface Screen for Transmitting Stimulation Data TXD[T]-STIM
5.7 Unit Testing and Clinical Use

The completed unit design has been demonstrated to fulfil the majority of the specified requirements (§5.1) and be capable of producing a single channel of stimulation output under closed loop control within the following range of parameters:

1) Pulse amplitude 0-150mA, max, 0-95V (1kΩ load), ripple variation
2) Pulse width 0.3 - 450ms rectangular pulses, resolution
   Inter-impulse interval 1 - 25ms (i.e. between positive and negative impulses)
3) Inter-pulse interval 5.5ms - 20s, fixed frequency 0.05 - 182Hz
4) Pulse duty cycle 50% maximum at max intensity (PW/IPI+ PW)
5) Pulse train envelop 0-255s with 1s resolution on/off periods
6) Session duration 1-45min with resolution 1min
7) Pulse type monophasic or symmetric biphasic impulses
8) Pulse shape rectangular, triangular, trapezoidal pulse shape
9) Pulse rise/fall time 750mA/ms to 2.3mA/s +/- 10% (i.e. 0.04ms to 16s at 40mA)

Linear pulse rise/fall rate is maintained within 10% up to 90mA with slight differences in calibration between units because of the individual characteristics of the feedback devices. However during the initial 0-10mA region, the rate of increase is governed by the Q3 MOSFET switching characteristic and has a minimum 166mA/ms (Fig.5.4.5), when the output amplitude is also less controllable. With a patient equivalent 'dummy load' (0.5-5kΩ resistor in parallel with 100nF capacitor), pulse amplitude remains within 1% of the stable value after the initial peak, for the duration of even the longest pulses, providing the battery does not become depleted. However in patient use, output ripple is approximately 20% and the amplitude can decrease at the end of pulses (§5.7.2). With the battery low warning threshold at 10.5V, nearly 5 hours continuous operation has been demonstrated with 25ms pulses at 20Hz and 50mA output. In typical clinical use with twice daily 30-minute sessions twice a day, 7 days a week, battery recharging has only been necessary, at most once a week. Quiescent current consumption is typically 35mA.

Non-compliance with the original requirement specification is in terms of the single output channel, a single stored stimulation pattern mode with only symmetrical impulses, operator control of intensity only, absence of audio stimulation indication and that interfacing with transducer input data await definition. As the indication of stimulation output is implemented in a single LED indicator, it was considered inappropriate to relate this to intensity (requirement 3.1) given the difficulty of identifying this at very low levels in bright lighting conditions. The function was in fact provided by an external meter connected to S11, when found necessary (§5.7.2).

5.7.1 Failure Conditions and BS 5724 Compliance

Compliance with the requirements of BS 5724 for medical devices and the particular requirements of Part 2.10 for stimulation devices are detailed in Appendix L. This requires the unit to operate in a
fail-safe manner in the event of any single fault or failure mechanism. In this application 'fail-safe' is interpreted as inhibiting the stimulation output or reducing it to zero, with an unmistakable warning to the user, (continuous visual indication and audio warning). Short circuit and open circuit output conditions are not considered as failure conditions, the unit is rendered safe, but remains usable after resetting the warnings (i.e. without necessitating changing a fuse). As a result of a Failure Mode and Effects Analysis (FMEA) into all single fault and failure mechanisms, compliance with BS5724 has been demonstrated in each condition, taking credit for the safety features and monitors incorporated in to the unit (Appendix M). These also protect the user in case of misuse. Faults detected by the MCM result in a continuous red FAULT indicator and audio warning and inhibited stimulation output until the unit is switched off. The User Manual, instructs the user to do this and if the warning re-occurs on switching on again to inform the clinical team. The units were therefore considered safe to use in the clinical investigations. Suggestions for improvement of the design are given in §8.

5.7.2 Clinical Use

Six units for clinical use have been constructed and tested in accordance with a defined procedure. During the six months treatment period of the study, five of these units have been in daily use, including overseas, with no reports of failure, unexpected operation or battery replacement.

In the course of the clinical use, two modifications were incorporated into the MCM software. Software Version R1 enables a visual indication of the stimulation intensity envelope to be provided on an external meter connected to and mounted on S11. This was found necessary for treatment without visible contraction, which is usually used as the guide to the intensity for treatment. Software version R2 was produced for a particular subject, to initiate the stimulation envelope by an external switch connected to S11 for synchronisation with the gait cycle.

Of particular concern with stimulation with long pulse is to minimise the risk of tissue damage arising from net charge transfer. Although the symmetry of biphasic pulses was established with a 'dummy load' (of 0.3-3kΩ in parallel with 100nF), it was noted in clinical application that the current decreased over the course of the second impulse, though the resulting charge imbalance was less than 3%. At frequencies of greater than 30Hz, this effect occurred on both impulses. It is largely attributed to the electrodes, as also occurs when these are placed in contact separate from the skin. In the course of these investigations, it was noted that no discharge of the body in to the stimulator occurred after monophasic pulses, despite the clamp circuit and one phase of the biphasic switch pairs remaining closed. Also noted, was that for inter-impulse intervals of less than 1ms, the incomplete discharge of the output capacitor OPM/C7, results in its discharge into the patient.
§ 5.7  Stimulator Unit Testing and Clinical Use

Figure 5.7.1  LPSTIM10 Unit in Use for stimulation of Tibialis Anterior of Subject LR
(with rear mounted stimulation current display meter)

1. RoadRunner - available from Farnell Components Ltd. Canal Rd, Leeds, LS12 2TU, UK
2. Manufactured by Sonnenschein, available from CMP Batteries Ltd, 14 Gunnels Wood Park,
   Stevenage, Herts, SG1 2BH UK. Telephone +44(0)1483 359090
3. Lawtronics Ltd. Unit 8, Enterprise Way, Edenbridge, Kent TN8 6HF, UK.
4. International Rectifier, Hurst Green, Oxted, Surrey, RH8 9BB UK. Tel. +44(0)0883 714234
5. Arizona Microchip Technology Ltd, Unit 3, The Courtyard, Meadow Bank, Furlong Road,
   Bourne End, Bucks SL8 5AJ UK. TEL.+44(0)1628 850177
6. National Instruments Corp.(UK) Ltd. 21 Kingfisher Court, Hambridge Rd. Newbury, Berks,
   RG14 5SJ UK.Tel.+44(0)1635 523545
6.

STUDY RESULTS

6.1 General Study Observations

Some general comments are made about observations from the study treatment before detailing those for each subject individually. The 3 SCI subjects are presented first with treatment of the quadriceps; LC and LD with near complete bilateral denervation, for whom rectangular shaped stimulation pulses were employed and LE with greater residual innervation and for whom trapezoidal shaped pulses were used initially. Following is subject LB with partial arm denervation arising from unilateral brachial plexus lesion, for whom the triceps was treated. Finally, subject LR with unilateral lower motor neurone damage 'dropped foot' condition but otherwise normal lower limb innervation, and for whom the desired treatment outcome is largely functional. Measurements of subject LD have not been analysed, as treatment was interrupted by illness and periods in hospital leading to cessation of treatment at week 17, however comments on the response to treatment are given.

6.1.1 Subject Compliance and Motivation

The stimulator unit usage data log and observation of the tissue indicated that all subjects completed treatment according to the protocol on the selected muscle only, some with breaks due to skin problems and illness, as detailed. All found the stimulation equipment and protocol convenient and did not suggest any changes; setting up took between 2 and 5min. Similarly all have attended SDH regularly for the evaluation measurements.

From subject comments during the evaluation visits and from the questionnaire at the end of the treatment period, all the subjects remain enthusiastic about the treatment, and consider it to have been of overall benefit. Not least was the psychological benefit all felt from participating in an activity which brought visible movement to their paralysed limb or muscle and which they considered was improving their condition, when no other treatment was available to them. In particular, subject LB benefited from restoration of voluntary control of part of the triceps, although not functional use. The subject also reported increased ease of motion of passive wrist and finger joints with a release of muscle tightness and increased sensory perception of the upper arm, which 'feels more normal'. Subject LC also reported greater sensation in the lower limbs and abdomen from the start of treatment, with the highly important benefit of the ability to reliably detect full bowel.

All subjects (though to a lesser extent LR) said they would like to continue with the treatment and stated that the 6 months period was too short. Subject expectation from the treatment is realistic;
improvement in tissue bulk and/or temperature being the primary objectives, with restored function remaining an ultimate hope for LC and LD through standing and for LB some voluntary arm movement. Functional restoration had always been the primary objective for subject LR. Subject LE primarily hoped for increased sensation, even though it was explained that further reinnervation is highly unlikely.

6.1.2 Contraction Response

Treatment started with low frequency (0.5Hz) twitch contractions with rectangular pulses of 100-150ms width (unless trapezoidal pulses are used), though no visible contraction occurred initially with subject LR. The muscle response, effect of electrode position and sensation were found to alter in the first weeks of treatment, so attempts at their rigorous optimisation at this stage are not thought worthwhile. The strength and endurance of contraction and excitability of the muscle (in terms of pulse width) progressively increased allowing a reduction in pulse width and increase in frequency and session length. Except for subject LR, once reasonable twitch contractions with 40ms were achieved (LB-wk6, LC,LD-wk7, LE-wk8), then tetanic contractions at 10Hz were performed. Initially these were localised to between the electrodes (especially distal), with more peripheral areas of the muscle ‘quivering’ in non fused contraction (e.g. vastus medialis of the quadriceps). In these cases, the twitch contractions are continued until the tetanic response improved. Progression to smoother tetanic contractions at 10-20Hz was possible for all subjects, eventually; (LB-wk6, LC-wk7,LD-wk10, LE-wk12, LR-wk44).

Trapezoidal (almost triangular) shaped pulses with gradual increase in stimulation intensity were used with subjects LB, LE and LR, to reduce and sometimes eliminated recruitment of innervated muscle in the same limb. This was possible providing the ramp rate was less than approximately 0.67mA/ms (i.e. ramp duration greater than 50ms at typical treatment intensities). These long ramp times result in pulse widths of up to 400ms, and the two impulses of the biphasic pulses produce distinct ‘double-let’ contractions. Recruitment of functioning sensory fibres was also reduced but not eliminated with these pulses. Muscle fibre excitability altered with the trapezoidal pulses, in a similar manner as with rectangular pulses and tetanic contractions were achieved in a similar timescale for LE, compared to LC and LD. However, with the shorter pulse periods required for tetanic contractions, the ramp possible shows no appreciable reduction in motor nerve recruitment over rectangular pulses.

For most subjects, the contraction response took time to develop at the start of each session and was associated with a gradual increase in the output current, through a decrease in apparent skin impedance. This process occurred faster with tetanic contractions (LD) and response was immediate with the 0.3ms Microstim unit (§4.4.1) used by subject LB. The delay was also reduced by washing or wetting of the skin prior to treatment and keeping the electrodes clean and hydrated.
It was not usually observed to a great extent at evaluation visits as the skin was hydrated by the water based ultrasound gel (§4.5.6), which is then washed off prior to stimulation, except with subject LR when the epidermis became hardened to a thin shiny film. Due to their condition, all of the subjects suffer from varying degrees of dryness and coldness of the skin in the treatment area resulting in high skin impedance. With subject LB, the muscle response decreased to almost nothing following sun-tanning. Consequent peeling of the dry skin and stimulation on the fresh skin produced a markedly greater contraction response, which in turn diminished after about 2 weeks. Skin hydration was therefore monitored carefully, and moisturising agents used with caution (§4.4.2).

As expected the denervated muscle response was largely indifferent to electrode polarity, however, that of the co-contracted innervated muscle varied, and with subject LB appeared to respond more to positive going pulses. The level of sensation to the stimulation was reduced when only monophasic negative pulses were employed with subjects LB and LE.

### 6.1.3 Skin Reaction to Stimulation

Although the reaction of the skin to stimulation treatment varied between individuals and from day to day, it typically consisted of mild to moderate erythema, concentrated around the electrodes (Figure 6.1.1), which usually dispersed within one or two hours of the treatment session. Erythema was less severe with the larger area electrodes used by subject LC and generally decreased with isometric contractions as pulse width was reduced, (though skin dryness and hardening became a problem with some subjects LE and LR, as described later). At higher stimulation intensities, and especially with isotonic contractions when the tissue is stretched thinner, erythema was greater and very localised sweating occurred adjacent to the electrode and sometimes spreading to between the electrodes. This was of the form of a dampness of the skin or small area of visible liquid rather than beads of sweat. Typically this was accompanied by 'goose-pimples' on the skin surface, but again localised to between the electrodes. On these occasions, there were no symptoms of general autonomic dysreflexia, such as raised blood pressure, heart rate, or other observation of the subject.

Of particular concern was the isolated occurrence of what were assumed to be localised burns from excessive current density. With subject LC, this took the form of about 10 small dark red marks of approximately 1mm diameter in a semi-regular grid pattern at approximately 3-5mm spacing, located beneath the distal patella (positive) electrode and to a less extent beneath the proximal electrode following stimulation with 100ms pulses at 2.5Hz. At first glance, these had the appearance of small surface scabs, but on closer inspection were thought to extend deeper into the tissue, and the uniform colour was not the same as a 'normal' wound scar. These occurred at one particular stimulation session, though not the first with these parameters, and full recovery was made within 7 days without stimulation. Although not observed by researcher, subject LD reported
a similar occurrence but to a lesser degree with only a few such scars, which healed within 2 days. On one occasion, close inspection of the electrode sites of subject LB upper and lower arm revealed tiny ‘pin-prick’ size scabs with a similar regular pattern, when stimulating with 400ms triangular pulses using PALS® Flex electrodes (§4.4.1). Concurrent with this, was more severe skin damage at about six dispersed locations beneath the electrodes on the lower arm, where tissue thickness is minimal. One scar was up to 4mm diameter, indented and located over an underlying bone towards the wrist, beneath the distal (positive) electrode (Figure 6.1.2). These took about 20 weeks to heal completely, and stimulation was continued with electrodes at slightly different locations.

Similarly, but more severe ‘cigarette like burn’ scars occurred around the periphery of the oval shaped PALS® Flex electrodes (§4.4.1) used by subject LC and which exactly corresponded to where the conductive mesh of the electrode protrudes from the underlying gel layer (Figure 6.1.2). The electrodes themselves also had a burnt appearance at these locations, mainly on the proximal edge of the proximal electrode, where tissue bulk is greater, but also on the extreme medial edge of the distal electrode. At the time of occurrence, the subject reported diminished contraction response, the electrodes became hot around the edges and the stimulator unit current limit warning was activated (set at 75mA). This shape of electrodes was withdrawn from further use and the supplier informed. After a week without treatment (wk 13), it was resumed using smaller electrodes positioned away from the damage sites, which were completed healed after approximately 15 weeks. This perhaps confirms the origin of skin damage on this and other subjects as due to excess current density, but not necessarily its cause, as only in this case is it clearly attributable to the electrodes.

Subject LR suffers intermittent skin problems with dryness and inflamed pores on both lower legs. This was generally exacerbated by the stimulation, especially at the beginning of the study, when long pulses were applied. In particular, after the first 2 weeks of stimulation with 400ms triangular shaped pulses, subject LR developed approximately five inflamed and enlarged pimples (approximately 1mm diameter) capped by a small scab, beneath the proximal (negative) electrode (Figure 6.1.2). Some were concentrated together, but with non regular spacing in an area of approximately 200mm² where thermography showed the greatest temperature rise (+5°C). Thermographic imaging of the skin to 0.5mm resolution using a macro lens, did not reveal any local ‘hot spots’ on the skin after removal of electrodes following stimulation, with and without the skin immediately covered by cling film to retain the generated heat. However whilst viewing the upper surface of the electrodes during stimulation, ‘cold spots’ of approximately 0.5 to 1mm diameter were observed momentarily with temperatures of 26.6°C compared to the surrounding 28.5°C. The skin reaction lessened as the study continued with altered stimulation parameters and careful skin care, so no further investigation into the phenomenon was conducted.
Figure 6.1.1  
Erthyma arising from long pulse biphasic stimulation treatment  
a) Subject LB, b) Subject LD, c) Subject LE
Figure 6.1.2 Skin damage at stimulation electrode sites on subjects a) LB, b) LC, c) LR
Excess stimulation current can occur if intensity control and therefore output voltage remain constant, due to the decrease in skin impedance as the treatment session progressed. With this experience of skin damage, subjects were asked to monitor their contraction and skin response during the treatment session more carefully, and to reduce the intensity setting if these became excessive. For subjects LB (forearm) and LR, stimulating without any muscle contraction response to monitor, an indicator display of stimulation current was provided (§5.7). The stimulator unit current limit was set at a level just below that when localised skin dysreflexia was observed, in terms of sweating or goose pimples. With these precautions, no further incidents of skin damage occurred and no investigation were conducted to confirm whether the 'burn' damage was due to current concentration in sweat pores, activated by the stimulation.

It must be emphasised that the electrodes used in this study were not specifically designed or recommended by the manufacturers for this application. The suppliers, Nidd Valley (§4.4.12) co-operated in this investigation but do not accept any responsibility or their use in this application.

6.1.4 Adverse Stimulation Effects

Apart from the manageable skin reaction, no other adverse effects of the treatment were observed or reported by any of subjects. There was no evidence of generalised autonomic dysreflexia induced during the treatment session; blood pressure was increased in the case of subject LR, and on occasions with LE but by no more than routine exercise and this did not prompt any complications. For the other subjects, blood pressure was unchanged or decreased slightly, attributed to their relaxed state during the treatment. None of the subjects reported any adverse sensory disturbance during the treatment period and none were adverse to the sensation of the stimulation, tolerance of which generally increased with continued treatment.

6.2 Measurement Data Analysis

For the analysis of the evaluation measurements collected, subjects were treated on an individual case basis because of the variability in their neurological condition and other factors such as age, weight and lifestyle. Even amongst those with common T12/L1 SCI (subjects LC, LD, LE), inter-subject comparison must take into account differences in the extent of motor and sensory innervation, muscle atrophy and skin condition. Given the small number of subjects and high inter-subject variability, no statistical sample analysis was performed. As muscle on only one limb of each subject was treated, the contralateral limb served as a control to compensate for changes to the measured parameters arising from effects other than the stimulation treatment, such as systematic body changes from dietary, hormonal or seasonal variations, and the changes in the measurement environment. However, both the absolute value of measurements of each limb and the asymmetry between them are evaluated, to investigate any differential limb effect and because it is possible for the treatment to have also had an effect on the contralateral limb.
The trends of measured and asymmetry values throughout the treatment and follow-up periods are evaluated and plotted in terms of the study week number for the individual subject, with respect to the value at the baseline visit at the start of the treatment (week 0). Measurements were also performed on some subjects at the initial assessment visit, which preceded the baseline visit by 4 weeks (subjects LB and LE) or 10 weeks (subject LC); though the later is stated as 4 weeks for commonality of presentation. However these measurement values may be expected to differ from those at baseline because of the familiarisation of the subject and the researcher on that initial occasion. Similarly measurement values at week 1 may differ from baseline due to some reaction to the treatment even without strong muscle response. Nevertheless, confirmation of baseline values is sought from these neighbouring measurements.

Skin temperature and blood flow measurement values are obtained by manual processing of the recorded signal, in terms of defining analysis areas and determining waveform shape respectively (§4.5). For consistency, this data extraction process for each subject was performed by one individual usually over one or two consecutive days. The processor was not made aware of which limb received treatment and therefore was less likely to bias the results, however for skin temperatures of subject LB, the effected limb is quite obvious from its diminished size.

Limb segments are defined proximally to distal as follows:

- Upper limb: Arm, Forearm, Hand
- Lower limb: Thigh, Leg, Foot

### 6.2.1 Skin Temperature Measurement

Skin temperatures were evaluated for each limb segment separately, as absolute limb values and their ratio. For all or part of the limbs of some subjects there was very poor contrast between the skin temperature and the background making exact determination of limb segment area unreliable, especially on warmer days. For subject LB with unilateral injury and to a lesser extent in other subjects, the limbs responded differently to the variation in measurement room environment during the course of the study. Skin temperatures are therefore plotted separately for each limb and correlated to room temperature and relative humidity. Correlation is also given for the absolute asymmetry between limbs. Inconsistencies in this correlation may reflect insufficient acclimatisation by the subject, though a minimum of 15min was allowed.

To assess the repeatability of the measurement and processing technique, 5 images were captured on one occasion in successive seconds, with the subject (LR) and equipment in the same position. These were each processed twice by the same operator with approximately one hour interval between. The standard deviation of the 10 values is 0.11°C for both limbs and two standard deviations represent 0.9% of the mean value.
6.2.2 Limb Segment Blood Flow Measurement

In processing the recorded dZ/dt waveform to extract values for the beat pulse duration (t_b) and magnitude (dZ/dt_max) (§4.5.5), some variation in the pulse shape was found, rendering determination of t_b more difficult. This was largely due to variations in the waveform at frequencies below that of the filter cut-off, which distorted the expected shape (Fig.6.2.1). The beat duration (t_b), was defined as the zero crossing before the beat pulse to the minimum after it. (§4.5.5). Although, typically this minimum for a particular individual was quite consistent (approximately 0.2), a second minimum often occurred (between 0.3 and 0.34s i.e.approximately equal to L_{VET}) and was sometimes of greater magnitude. Conversely, for some pulses, there was an unmistakable minimum immediately after the peak (e.g.0.15s). Porter (1986) also reported t_b values less than L_{VET} for finger blood flow and used a value of t_b derived from the impedance waveform. Whereas, Taylor et al. [1993] used the value of L_{VET} derived from concurrent cardiac output measurements in place of t_b for lower limb blood flow measurements, and found this to vary little over the course of 3 months. As much of the uncertainty appeared due to low frequency variation in the dZ/dt trace (Fig.6.2.1), and allowed some interpretation of t_b value, the limb blood flow values presented are with t_b equal to a constant value (approximately 0.2s) equal to the mean value for that subject. In fact, compared with t_b derived from the waveform, this did not greatly alter the trend of averaged blood flow values (Fig.6.6.4).

Two impedance measurements were taken on each limb at each evaluation visit, always starting with the left limb. Averaging the calculated blood flow values for each limb produced considerable variation between study weeks. Attempts were made to determine whether this was due to a measurement or analysis artefact masking any underlying trend in the value, or whether this is natural variation of the manner observed by Porter (1986). The first and second measurements of each limb are therefore shown separately together with their mean for each subject. Differences between first and second values are typically less than 10% of the mean value. Those weeks showing greater difference, did not necessarily correspond to when the averaged blood flow values were 'out of trend', and setting t_b equal to a constant value did not greatly alter the differences (Fig.6.6.4). Neither between study weeks or between limbs was their any apparent consistency to the polarity of measurement difference, for instance as would occur if the first measurement were always greater than the second. This was further investigated by performing up to six repeated measurements of the same limb on one occasion at approximately 2min intervals for subjects LC (wk 47-Fig.6.6.2) and LE (wk 50-Fig.6.6.3). Values for t_b are taken from the dZ/dt waveform, as is the heart rate (instantaneous HR = number of complete beat cycles/corresponding time interval).

1 Personal communication; Medical Physics and Biomedical Engineering Salisbury District Hospital §4.4
Figure 6.2.1  Examples of Thigh Blood Flow $dZ/dt$ waveform from Minnesota Cardiograph
Subject LE wk 12, 1st and 2nd measurements on Left (contralateral) and Right (treatment)
Figure 6.2.2.a  Subject LC Thigh Blood Flow (Recumbent) - repeated measurements

Figure 6.2.2.b  Subject LC Thigh Blood Flow (Supine) - repeated measurements

Figure 6.2.2.c  Subject LC Cardiac Output (Supine) - repeated measurements
Figure 6.2.3.a  Subject LE Thigh Blood Flow (Recumbent) - repeated measurements

Figure 6.2.3.b  Subject LE Thigh Blood Flow (Supine) - repeated measurements

Figure 6.2.3.c  Subject LE Cardiac Output (Supine) - repeated measurements
Subject LC showed a gradual increase in beat volume (BV) and blood flow (BF) on the second and subsequent measurements over the first (Fig. 6.2.2.a). The increase is more pronounced with subject LE, but returned to initial values at the third or fourth measurement (Fig. 6.2.3.a). Expressing twice the standard deviation of these values as a percentage of their respective mean and averaging for both limbs is 13.9% for LC and 22% for LE. Porter [1986.p96] reported such 2*StDev values of between 6.9% and 45% (average 15.7%) for 10 concurrent measurements on 10 different subjects and values of between 7.4% and 37.7% (average 20.7%) for measurements repeated on 10 subjects taken at different times on the same day.

Porter [1986] also reported considerable variability in blood flow when measured in a recumbent position. Repeated measurements taken in the supine position showed similar trend to when recumbent for subjects LC and LE, and variability was little changed (Fig. 6.2.2/3b). However the shape of the dZ/dt waveform beat pulse was far more repeatable, with consistent values of $t_8$ of 0.2s for LC and 0.21s for LE, the latter being slightly greater than the 0.19s when recumbent. The dZ/dt waveform was similarly very repeatable during cardiac measurement of LC and LE supine, providing consistent values of $L_{vet}$ of 0.31s and 0.34s respectively (Fig.6.2.2/3c). Apart from a low initial low with subject LC, cardiac output recorded was reasonably constant, even after a 10 minute interval for LC, with 2*SD/mean variation of 5.9% for LC and 4.6 % for LE. The change in stroke volume with repeated measures was compensated for by a reciprocal change in heart rate, though these were of the opposite sense for LC and LE. Measurement of cardiac output recumbent produced a less regular dZ/dt waveform.

When recording the impedance signal waveforms, subjects were asked to hold their breath for a period of 6 or 10 seconds, after a small inhalation. Typically, (especially subjects LC and LR), during this period the calculated beat volume increased (by up to 30%) and the instantaneous heart rate decreased (by up to 20%) as determined from the interval between pulses and confirmed by a chest worn monitor. Such changes were also recorded with subject LE but of inconsistent direction, and did not result in significant change in, for instance cardiac output (Fig.6.2.2c). When measurements were taken surreptitiously with the subject quiet, but breathing normally, up to 6% variation in heart rate and beat volume occurred but without consistent trend in either direction. Hence for subject LR breath holding produced blood flow values of approximately 10% less than that without breath-holding in both limbs. After exercise by subject LR, the pattern of change was altered and after an initial decline, heart rate recovered during the measurement period.

Determination of $t_8$ and therefore blood flow values was particularly difficult for the contralateral right arm of subject LB, because the very low mean impedance ($Z_0$) of approximately 200 resulted in very small dZ/dt amplitude and a low signal to noise ratio. Blood flow values for this subject were similarly reduced on some occasions, but generally there was no significant correlation between variation in mean impedance values and measured blood flow. The influence of the
measurement environment is evaluated by correlation of blood flow values with room temperature and relative humidity. This showed some significance with relative humidity, but only of one limb and not with all subjects.

Blood flow was also measured after a typical period of stimulation for subjects LE and LR. For subject LE thigh blood flow showed an appreciable increase of perhaps 72% in the treated limb and 22% in the contralateral limb (§6.5.6). Whereas, for subject LR, neither stimulation nor walking exercise produced appreciable change in leg blood flows.

### 6.2.3 Tissue Thickness Measurement

The poor quality of the ultrasound image for the majority of the study, precluded consistent identification and measurement of intermediate tissue boundaries and those shown for subjects LC and LE are presumed to be that between quadriceps muscles and superficial subcutaneous fat. The bone was more clearly identifiable, but at least some of the apparent variability in its depth may be attributed to misinterpretation of the image. The quality of the ultrasound image with the old (2.5MHz) instrument varied considerably from week to week, and those with particularly poor quality are mentioned. Such ambiguity was avoided with the clearer images of the new (5MHz) scanner unit (§4.5.6). Tissue thickness values obtained when both units provided good images, were in agreement to within 1 or 2mm, but greater difference occurred where interfaces were less well defined in the image of the old unit. For subject LR, measurement of the tibialis anterior muscle thickness, necessitates identification of non bone tissue boundaries and this was only possible reliably by using the new scanner unit and therefore are not presented. Tissue thickness and limb girth measurements are presented with body weight, which altered in all subjects during the treatment period.

The tape used for girth measurements was changed at the start of 1999 and may account for some of the measurement variation. Measurements of the quadriceps of subjects LC, LD and LE are made with them seated on their wheelchair cushion, and contact with this may contribute to variability in the measurements at locations 200mm and 250mm proximal of the patella.

### 6.2.4 Correlation Significance Levels

Detailed are correlation coefficients of significance for the sample sizes of interest in this study.

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<th>17</th>
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<th>19</th>
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</table>

Table 6.2.1 Pearson Correlation Coefficients for 2 Sided Distribution [Powell 1982].
6.3 Subject LC Results

6.3.1 Subject Profile

Subject LC (male) was aged 32 at the start of the study and involved in a motor cycle accident 5 years previously resulting in T12/L1 level spinal cord injury but initially with some retained lower limb muscle control and sensation. Unfortunately, nine days after the accident, transfer into a wheelchair resulted in complete lower limb paralysis and loss of all sensation in the legs, bladder and bowel. There had been little change in his condition since this, with occasional pains and soreness in the hips and discernment of touch, though not identification of exact location. The left leg was particularly cold to touch with ulcer like discoloration of the foot since injury, though no active sore. The subject reports the left limb took time to heat up at night, whereas the right leg became very warm. Tissue wasting of the leg was visibly appreciable but not of the thigh. There was no motor response to stimulation with 0.3ms pulse stimulation in any of the main muscles of either limb. Occasional involuntary foot movements occur from mild extensor spasms, especially on the right. Sensation was felt when stimulation was applied to the quadriceps. The subject had not received any active therapy since initial rehabilitation, but performed knee flexing exercises every day and stoods in a standing frame for approximately 30 min, 3 to 4 times per week.

6.3.2 Contraction Response to Direct Stimulation

At the initial assessment visit, response to quadriceps stimulation was approximately the same in each leg with good twitch contractions possible from pulse widths of 95ms necessitating intensities in excess of 120mA but without overflow into other muscles of the leg. The stimulation did however initiate some spasm of the abdominal muscles, which caused the subject no apparent adverse effect. Threshold contractions were achieved with pulse widths down to 20ms (Fig.6.3.1). The left quadriceps were chosen for treatment because of the greater potential benefit to limb temperature, even though the contraction response was slightly inferior.

Treatment started 10 weeks after the initial assessment using 50mm square PALS® Blue electrodes (§4.4.1) on the anterior of the quadriceps, centred at 70mm and 270mm proximal to the proximal patella border. Rectangular shaped pulses were used throughout the study, as there was no co-contraction or excess sensation to alleviate. Initial response occurred in vastus medialis, which appeared warmer on the thermography. The strong muscle contraction and absence of fatigue allowed an increase in session length and frequency to 2.5Hz by week 4, equivalent to the ‘shaking contraction’ treatment used by Kern et al. (§3.4.2). It was these stimulation parameters which resulted in the regular pattern of current burns (§6.1.3), necessitating a week without treatment. Treatment was resumed in week 6 when the scars had almost disappeared, with 1Hz twitch
contractions and using larger PALS® Flex oval shaped electrodes (80mm x 130mm) positioned away from the damaged areas. This size of electrode is more akin to the size used by Kern et al., but required a greater stimulation current than the smaller PALS® Blue electrodes (e.g. 52mA cf. 40mA) to achieve a contraction of comparable strength, however a greater proportion of the quadriceps were recruited.

At week 7, the response to stimulation at 40ms was sufficient to allow isometric tetanic contractions at 10Hz throughout the muscle, without significant fatigue, and allowing a progressive increase in session length over succeeding weeks to 30min at week 11. Unfortunately a later replacement set of electrodes resulted in the skin burns described previously (§6.1.3), necessitating another week without treatment. This resumed (wk13) with 75mm diameter PALS® Flex electrodes positioned away from the areas of skin damage, once more at approximately 70mm and 270mm proximal of the patella. A pulse width of 20ms and frequency of 20Hz was used, which avoided the unfused contraction at the proximal electrode at 10Hz.

By week 21, the strength of contraction was sufficient to permit isotonic contractions when seated with the knee flexed at 90° and the leg able to swing freely; the distal electrode was positioned more proximally so not over patella tendon. At the limit of skin dysrelexia (§6.3.4), approximately 85mA, the foot swung out by approximately 20mm with respect to a scale on the ground and continued to increase in subsequent weeks. Treatment was halted during weeks 23 and 24, due to a period of nosebleeds, jaw pain and feeling hot, but these were not attributed to the treatment and did not reoccur when treatment restarted. At week 25, the duration of isotonic contraction was extended from 4s to 8s, akin to that used for training of innervated muscle (§3.2.4), though some fatigue occurred during the session and leg movement decreased if the stimulation intensity was kept constant. The amount of anterior movement of the foot during contractions varied with the pulse width for a given intensity and frequency (Tab.6.3.1). A pulse width of 40ms at 20Hz is recommended by Kern et al. (§3.4.2) for maximising contraction strength, with 2s contractions at 4s intervals, in sets of 8-10, separated by a 2min rest period. This stimulation pattern was adopted from week 28, for the remainder of the treatment period, initially with 5 sets of 10 contractions, though fatiguing was still found to occur. Unfortunately treatment was stopped for weeks 29-31 due to influenza, which resulted in some body weight loss. When treatment was resumed for a further 2 weeks, the amount of foot movement for each pulse width was less than that achieved in week 28, however measurement was preceded by 2 sets of the 10 contractions.

The treatment period was ended at week 33, after 26 weeks of actual treatment, including 20 weeks with tetanic contractions, of which 7 had been isotonic. During the follow-up period, the muscle continued to respond to stimulation with tetanic isometric contractions, but the amount of foot movement for the given parameters continued to decline and the rate of fatigue increased. The
smaller foot movement in week 37 compared to week 47 may be due to prior fatigue with other periods of stimulation.

<table>
<thead>
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<th>Pulse Width (ms)</th>
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Table 6.3.1 LC Isotonic Contraction Response to Stimulation Pulse Width at 20Hz and 86mA

**SD Curve Measurement**

Comparison of SD curves (Fig 6.3.1.a) between study weeks is hindered by differences in Rheobase. However, those with equal Rheobase values (wks 0&4, 7&9, 33&47) show an apparent shift to the left (decrease in intensity for given pulse width), which may be interpreted as increased excitability with treatment. This is also indicated by the declining Chronaxie values, as treatment progressed and the rise during follow-up. The shift in values from week 7 corresponds to the use of the larger size of electrodes and different form of muscle recruitment from thereafter. Given this and with the exception of week 2, Rheobase values decreased during the treatment period.

The SD curves at the beginning of the study are almost identical for both limbs (Fig 6.3.1.b). Both curves show a decrease in Rheobase and increase in excitability, but to a greater extent for the treated limb. Considering Chronaxie values, both limbs had equal values after the treatment which is greater than that before treatment and perhaps illustrates the disadvantage of a single value characterisation of the curve, especially when Rheobase differs. A simpler indication of the increase in muscle excitability is that by the end of the treatment period, the muscle responded to pulse widths of 0.5ms (though not with tetanic contractions), and this was maintained throughout the 14 week follow-up period, whereas prior to treatment, the minimum pulse width was 10ms.

**6.3.3 Sensation and Sensory Perception**

Prior to the study, sensation was limited to the groin area and upper leg but was not specific. During the stimulation session, including at the initial assessment visit, the subject reported sensation which spread progressively down both legs and into the abdomen, including a burning sensation in the upper leg and tightness in the feet. This was sustained for some time after the stimulation and the subject reported the lower leg and foot felt warm for days after the initial session. With isotonic contractions, the subject reported feeling a surge of blood flowing into the leg and tinkling into the calf and foot. Aching of the hips and knees, was no longer felt by the subject on the left after the first few days of treatment and returned during the follow-up period. By week 4, the subject reported increased level of sensation in the abdomen, including feelings of
hunger and being able to reliably predict full bowel, which had not been possible previously and which continued into the follow-up period, though gradually diminished. During the follow-up period, the subject reported ‘pins and needles’ sensation, whenever either leg was touched or moved, which was not present before starting the treatment and which is desirable to the subject. However, sensory perception assessment revealed that reliable location discrimination of touch was not possible at any time during the study.

6.3.4 Skin Response and Condition

Skin reaction to the stimulation was minimal from the start of treatment, with mild erythema, which was lessened by use of the larger PALS® Flex electrodes. However the treatment did result in some dryness of skin at the electrode sites, necessitating the use of moisturising cream (§4.4.2), applied approximately 30min after the treatment session. At higher intensities (>85mA) at tetanic frequencies (20Hz) erythema occurred between the electrodes accompanied by slight localised sweating and occasional ‘goose pimples’, but without appreciable change to blood pressure or heart rate. The subject was instructed to maintain the stimulation intensity just below this level, however with treatment sessions of 30min a slight skin discoloration persisted between some sessions but did not progressively worsen. In particular, with isotonic contractions, the distal electrode was positioned proximal of the patella tendons to avoid excess erythema of these tissues. Initially with these contractions, ‘goose pimpling’ occurred with intensities of approximately 65mA, but sweating not till 85mA, the limit for treatment. This segregation was attributed to stretching of the skin when seated affecting the skin dysreflexia. After 2 weeks of isotonic treatment, skin reaction had diminished to mild erythema lasting approximately 15minutes after treatment. The skin response to the 40ms, 20Hz stimulation was no different from that of other treatment patterns. During the follow-up period, the subject reported goose pimples on the left leg around the knee, as per the right leg. The subject considered skin condition over the left quadriceps had improved slightly as a result of the treatment, though was reasonable before the study, as indicated by the successful healing of induced localised skin damage.

6.3.5 Skin Temperature Measurement

The measured skin temperatures showed a significant (p<0.05) correlation with room temperature for most segments of both limbs and greatest on the contralateral limb. Also a significant (p<0.1) correlation with relative humidity on the treatment limb (Fig.6.3.2). Increases in skin temperature at weeks 4, 7 and 28 appear due to environment changes. In the higher room temperatures at the start study, asymmetry of skin temperature between limbs was minimal in all segments. However, at lower temperatures, the lower limb segments were appreciably colder on the left as experienced by the subject.
Neither the isometric or isotonic contraction treatment overcame the fluctuations in room temperature affecting skin temperature, though in weeks 18 and 21 are contrary to them. During the first month of the follow-up period, skin temperatures of all segments of both limbs rose without a rise in room temperature. However during the remaining 10 weeks of follow-up only the right leg followed the room temperature increase, whereas the left actually decreased in the shin and foot. Therefore, the measurements do not substantiate the subject's opinion that treatment had improved the temperature of the treated limb.

6.3.6 Blood Flow Measurement

Blood pressure and heart rate show some variation over the course of the study and with room environment changes; heart rate was raised for weeks 21 and 25 (Fig.6.3.3). Blood flow measured in the thigh showed considerable variation in both limbs and there is no discernible significant differential effect of the stimulation on the treated limb (Fig.6.3.4). There is some negative correlation to relative humidity especially of the contralateral (p<0.1), however for a given relative humidity, blood flows in both limbs appear higher in the later stages of the treatment period than without treatment.

Cardiac Output

Cardiac output was measured on one occasion at week 47. For the six repetitive measurements (Fig.6.2.2.c), the average cardiac output was 4.2 l/min and average stroke volume 71.4ml, which lie within the range for normals specified by Porter [1986]. On the same occasion average thigh blood flow was approximately 75ml/min, and therefore constituted approximately 1.8% of cardiac output. If a value of $t_g$ equal to $L_{vot}$ (0.34s) is used as per Taylor [1993], this implies a thigh blood flow of 128ml/min or 3% of cardiac output.

6.3.7 Tissue Thickness and Limb Girth

To the subject and the researcher, the treated limb segment appeared to thin during the treatment period, especially just proximal of the knee. This was reflected in the thigh girth measurements (Fig.6.3.5) but is not easily discernible from those of tissue thickness (Fig.6.3.6). Both measurements were affected to a greater extent by the weight loss with influenza in weeks 29 to 31, and which coincided with the period of isotonic contraction treatment.

Girth measurements of the treated limb closest to the knee show an initial slight decline at the start of treatment, are relatively stable during the period of isometric contractions but decline further from the start of isotonic contractions (wk21), which continues during the period of infection with recovery during the follow-up period. However measurement values from the right limb show a greater degree of variability and decline. Some of the variability in the proximal thigh measurement values may be due to the distortion of the underlying cushion and at week 21, the change in tape
measure used. At 250mm from the patella there is no trend of change in the treatment limb, but at 200mm it appears to increase during the period of isometric contractions and thereafter decrease, though this also occurred in the contralateral limb. Proximal measurements of both limb appear to show a progressive decline following the infection, till the end of the follow-up period.

On the occasions when the ultrasound image was clear the image was noticeably different for the contralateral limb, compared with the treated limb, with greater echogenity and less pronounced layer structure as reported for denervated muscle [Schmidt, Volt 1993]. This made identification of tissue interfaces more difficult and may account for the greater variability of the contralateral limb measurements and some of the 'out of trend' values. The old and new instruments showed agreement to within 1mm in most bone depth measurements. If the initial increase in both limbs is due to probable operator familiarisation, and discounting those values when image quality was poor, then the treated limb shows no appreciable change in bone depth or interpreted muscle thickness, except for a marked decline at 150mm during the period of body weight loss and some increase at 200mm during isometric treatment, followed by a decline with isotonic treatment.

### 6.3.8 Joint Range of Motion

Prior to treatment, knee joints appeared swollen and mis-shapened due to numerous motor cycle accidents and emphasised by the muscle atrophy, however range of motion was maintained by passive exercising by the subject. By week two, the subject reported the knee joint on the treated side, no longer ‘cracked’ when flexed, whereas the contralateral limb continued to do so. Joint range of motion was measured from the start of isotonic contractions (wk21) (Tab.6.3.2). After a couple of weeks of isotonic contractions, the subject commented that the knee flexor muscles felt ‘tight’, but measured joint angles suggest only a marginal decrease on knee extension, which was also measured in the follow-up period. Therefore, although perceived by the subject, there were no discernible changes in measured joint mobility during the treatment period. Changes during the follow-up period may have arisen from the subject not performing standing exercises; decrease in left ankle extension, increase in right ankle flexion and increase in right knee flexion.

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Table 6.3.2 Subject LC Lower Limb Joint Range of Motion (°)- passive.
Figure 6.3.1  Subject LC Strength Duration Curve and Chronaxie Values

Table 6.3.3  Subject LC Treatment Stimulation Parameters

(n/c -no change, isoM - isometric, isoT - isotonic contractions, parameter definition see Fig. 3.2.1)
Figure 6.3.2  Subject LC Lower Limb Mean Skin Temperatures
Figure 6.3.3. Subject LC Blood Pressure and Heart Rate Variation

Figure 6.3.4. Subject LC Thigh Blood Flow

Figure 6.3.5. Subject LC Thigh Girth at locations proximal of patella border
Figure 6.3.6  Subject LC Quadriceps Tissue Thickness at locations proximal to patella border (poor image quality for week numbers 2, 11, 21, 28)
6.4 Subject LD Results

6.4.1 Subject Profile

Subject LD (male) was aged 42 years at the start of the study, with 'complete' T12/L1 level SCI from accidental trauma 10 years previously. His condition was therefore comparable with that of subject LC though with a greater extent of innervation of the toe flexor muscles of both limbs, which were recruited by 0.3ms stimulation, even at upper leg level. These muscles are also subject to occasional involuntary recruitment, initially single twitch contractions, which can progressively built up to causing foot and toe movement, especially on the right. Voluntary hip control was retained. The subject reported no sensory perception to touch in the lower limbs but intermittent 'root' pains in the top of the left leg. Muscle atrophy was uniform over both limbs and moderately severe. Skin condition was reasonable, though a sacral sore which developed one year previously, had not healed. From 11 weeks prior to the start of treatment, the subject received laser treatment for the sore on Thursday mornings; evaluation visits were therefore arranged for Wednesday afternoons. The sore prevented use of the callipers for standing exercise, but otherwise the subject maintains an active lifestyle as a wheelchair user.

6.4.2 Contraction Response to Direct Stimulation

At the initial assessment visit, the response to long pulse stimulation of the quadriceps was greater than the other subjects, with twitch response to pulse width of 3ms on the right and 10ms on the left, where an unfused tetany was also obtained from 10ms, 10Hz stimulation. The right quadriceps was chosen for treatment because of the greater excitability in terms of minimum pulse width, and the lower sensation threshold. As no adverse sensation or co-contraction occurred, rectangular shaped pulses were employed for treatment and trapezoidal pulses produced a smaller contraction response. Treatment commenced with a pulse width of 100ms at 0.5Hz, with contraction initiated in vastus medialis, and possibly sartorius, just proximal of the patella and spreading throughout the quadriceps as intensity was increased, with tightening of the patella tendons palpable. PALS® Blue 50mm square electrodes were used and the optimum positions found to be at 50mm and 240mm proximal of the patella. The strength of contractions built up over a period of 2-3min and the lack of fatigue permitted an increase in frequency (1Hz) and session length up to 25mins in week 6. Contraction of toe flexors occurred intermittently during treatment, but not synchronised to it.

The increase in muscle excitability is reflected in the shift of the Strength Duration curve and decrease in Chronaxie (Fig.6.4.1). By week 7, this was sufficient to allow treatment with 40ms pulses at 25Hz, which produced a shaking of the whole leg, but only contraction of the quadriceps. Sessions consisted of two periods of 10min continuous stimulation separated by a 5min rest. Skin
erythema was minimal, but during week 9, small pinhead marks were observed by the subject at the electrode sites (§6.1.3). These diminished by the next day and stimulation was continued with the electrodes in a new position. At week 10, the frequency was increased to 10Hz with 40ms, achieving tetanic contraction, without clonus. Intensity was kept low initially and recruitment restricted to mainly rectus femoris, rather than the whole of the quadriceps with longer pulse widths. The limited fatigue permitted an increase in intensity and session length to 20min. Isotonic contractions with the lower leg swinging freely produced foot displacement of approximately 20mm.

Unfortunately treatment was interrupted in weeks 2, 5, and 9 for hospitalisation due to urinary tract infection. From week 12, treatment, was limited to the morning due to subjects deteriorating condition following cross infection of the sacral sore and by week 17 this necessitated intensive hospital care and stimulation treatment was ceased. After release from hospital, at week 22 tetanic contractions of the quadriceps were still possible with 40ms pulses at 10Hz, though concentrated in vastus medialis, without adverse skin or other reaction. Treatment was continued on an occasional basis for a further month with twitch contractions, but no further measurements were recorded.

6.4.3 Sensation and Sensory Perception

The subject reported considerable sensation of the stimulation at the initial assessment visit, with 'pins and needles' on the right and a muscle contraction sensation on the right. At the start of treatment, 5 weeks later, no such sensation from the stimulation occurred however 'root' pains were initiated on the right, where not present previously. Tetanic contractions brought an initial surging sensation, which diminished during treatment.

6.4.4 Skin Response and Condition

Skin response to stimulation was variable, at its most severe consisted of an initial intense 'salmon pink' colour, which as treatment continued, diminished in area and darken to red after about 5min. Sometimes this extended between the electrodes, but typically was limited to about 20mm around the electrodes (Fig.6.1.1), greater at the distal patella electrode, where it also remained longer after treatment, but dispersed within one hour. Tetanic contractions made little difference to the response, but the subject reported the knee feeling warmer at night.
Figure 6.4.1  Subject LD Strength Duration Curve and Chronaxie Values

Table 6.4.1  Subject LD Treatment Stimulation Parameters
(n/c -no change, isoM – isometric, parameter definition see Fig. 3.2.1)
6.5 Subject LE Results

6.5.1 Subject Profile

Subject LE (male) was aged 30 years at the start of the study and sustained a T12/L1 level SCI 6 years previously. Voluntary twitch control of left vastus medialis was retained and stimulation with 0.3ms pulses revealed innervation of other left quadriceps, also some hamstrings, plantaflexors and toe flexors on both limbs. Toe flexors were subject to occasional mild spasm. Sensation was limited to the lateral thigh and pelvic area, with considerable 'root pains' in the hips, for which the subject took medication. He usually stood in a support frame for 30min, 2 to 3 times a week and goes out to office work each day by wheelchair. For the 5 months prior to the study, the subject had been using a passive bicycle egometry trainer 2 or 3 times a week, but stopped this for the duration of the study. Skin of the lower limbs is pale and dry. The subject is a light smoker (typically 1.5 hours prior to the appointment). Stimulation treatment was usually performed in the morning, approximately 6 hours prior to the evaluation visit in the afternoon.

6.5.2 Contraction Response to Direct Stimulation

At the initial assessment, twitch contractions were obtained in both quadriceps from stimulation pulse widths down to 1ms at relatively low intensity (Fig.6.5.1). Given the greater motor and sensory innervation of the left lower limb, the right was selected for treatment, with potentially greater therapeutic need. PALS® Blue 50mm square electrodes were placed at 50mm and 220mm proximal of the patella, with the proximal electrode positioned lateral of the thigh centreline to minimise sensory recruitment. Despite this, contraction was initiated in vastus medialis and spread to rectus femoris as intensity was increased. To eliminate co-contraction of toe flexors, trapezoidal shaped pulses were used, with ramp of approximately 50ms and overall pulse width of 220ms initially, increasing to 75ms and 310 respectively as intensity increased in subsequent weeks. It was not possible to reduce ramp rate without co-contraction, as occurred when treatment transferred to rectangular pulses in week 8. However, this did not appear to worsen the existing Achilles tendon shortening and more frequent standing was advised as a precautionary measure.

Tetanic contractions of rectus femoris became possible at week 8, treatment continued for a further 4 weeks with twitch contractions because of unfused tetany on the medial periphery. Isotonic contraction treatment, was commenced in week 12, with 40ms pulses at 10Hz for one week, and 20ms at 20Hz thereafter, with the absence of fatigue allowing a progressive increase in session length to 30min. At week 17 the electrode size was changed to 40mm by 90mm in order to recruit more muscle fibres and to alleviate the skin drying. At week 24, treatment with isotonic contractions was commenced with the subject seated and with the leg swinging freely.
Displacement of the foot increased with pulse width and 27ms at 17Hz was chosen producing almost as much movement (50mm) as 40ms. Fatigue was compensated for by the increasing current as skin impedance decreased, but 25min was found to be the limit of endurance. For instance, at week 28, 60mA stimulation produced 90mm foot displacement and after 25min, current had increased to 68mA with displacement decreased to 60mm. The muscle recovered somewhat from a few minutes rest, but the subject seemed unwilling to do this during the treatment session. The treatment period ended at week 31, and during this it is estimated there were at most 10 days without stimulation. During the follow-up period, the isotonic contraction response in terms of foot displacement diminished to about a third at wk40, and fatigue occurred in about half the time.

SD Curve Measurement

Chronaxie as determined from the Strength-Duration curve (Fig.6.5.1), decreased to approximately half its pre-treatment value during the first two weeks or treatment, but thereafter remained stable at approximately 12ms. This was reduced at week 14 with the increase in Rheobase. By the end of the treatment period, Chronaxie had returned to its pre-treatment value. Comparison of SD curves, for week 0 and 2, shows a shift in the curve indicating increased excitability, but variation in Rheobase hinders comparison of curves for other weeks. However the proximal electrode position was changed at week 4 and the electrode size at week 17. Also noticeable are the curve 'kinks' at weeks 10 and 31, resulting from slight changes in the location of minimum contraction.

6.5.3 Sensation and Sensory Perception

The subject reported no change in resting sensation of the lower limbs as a result of the treatment, and monofilament assessment showed no touch perception over either limb up to mid thigh level. Neither were the subject's 'root pains' affected by the treatment. Sensations of the stimulation during the treatment session altered from a 'tinkling' at the beginning of the study, to a 'sense of being touched' with tetanic contractions. Apparent sensation on the medial thigh necessitated a lateral distal electrode location and perhaps limited the stimulation intensity used by the subject during treatment.

6.5.4 Skin Response and Condition

Erythema extended for approximately 30mm around each electrode and lasted for 1 to 2 hours after treatment. This was greater with tetanic contractions (Fig.6.1.1), and when isotonic, the stretched tissue around the patella tendons, became moderately warm to touch. At higher intensities erythema expanded throughout the inter-electrode area, with localised sweating and 'goose pimples' when excessive, but these ceased within minutes of intensity being reduced. Blood pressure or heart rate were sometimes raised by treatment as with other exercise or stimulants, but not consistently so and there was no evidence of generalised autonomic dysreflexia.
The delay before contractions started at the beginning of each session lengthened and by week 10, the skin at the distal, patella electrode had become dried and flaked, necessitating a change of electrode position proximally. These two distal positions (50mm and 80mm proximal of the patella) were then used alternately on a 2-4 week cycle, and treated with moisturising agents in between (§4.4.2). At weeks 17, 24 and 30 during the period of tetanic treatment, 2-4 red skin marks (approximately 1.5mm diameter) were observed at the distal electrode position, though the subject did not report occurrence at any one treatment session. Skin reaction was less severe with the larger electrodes.

### 6.5.5 Skin Temperature Measurement

The leg and foot of both limbs of subject LE were very cold to touch and barely discernible against the background on the thermographic image, precluding exact determination of the limb outline. The mean skin temperatures of all segments of both lower limbs show a highly significant correlation (p<0.01) to changes in room temperature but not to relative humidity (Fig.6.5.2). However all segments also showed a decreased mean temperature in weeks 1 and 28 compared to the previous measurement, despite a relative increase in room temperature. Given that the latter visit was late February, this may be due to lack of sufficient subject acclimatisation. Thigh skin temperature asymmetry between limbs was reversed from week 24 to 28 during the period of isotonic treatment, when previously the right limb had been consistently colder. During this period the treated limb leg and foot segments also became marginally warmer than those of the contralateral limb, as during the initial period of twitch contractions. A 15min session of isotonic treatment in week 40 produced an appreciable change in mean skin temperature compared to the contralateral limb (Tab.6.5.1).

| Mean skin temperature asymmetry (°C) (treatment limb - contralateral) |
|-----------------------------|-----------------|----------------|
| Before treatment | After treatment | Change |
| THIGH           | -0.8            | +1.8       | +2.6 |
| LEG             | +0.6            | +1.6       | +1.0 |
| FOOT            | -0.7            | +1.5       | +2.2 |
| Room temp (°C)  | 24.7            | 24.2       | -0.5 |

Table 6.5.1 Subject LE Mean Skin Temperature Asymmetry Change with Treatment (wk40).

### 6.5.6 Blood Flow Measurement

The subjects' blood pressure and heart rate varied considerably during the study period (Fig.6.5.3), though the extreme values do not coincide with those of thigh blood flow (Fig.6.5.4). Correlation of thigh blood flow to the room environment is not significant for the study period as a whole, but for weeks 0 to 17, greater correlation is apparent between the treatment limb and asymmetry to
relative humidity. From week 17, for the remainder of the treatment period and the initial nine weeks of follow-up period, treatment thigh blood flow exceeds that of the contralateral limb (by up to 50%) whereas it had not consistently done so earlier in the study. This occurred within the period of tetanic contraction treatment.

Thigh blood flow measurements of the treated limb following a 15min treatment session of isotonic contractions were found to increase by up to 72% after 15mins or after 10min, 49%, when that of the contralateral limb was increased by 22% (Tab.6.5.2). It is therefore possible that blood flow measurements for this subject may also be influenced by the treatment performed in the morning prior to the evaluation visit. However this would not account for the continued elevated values in treatment limb during the follow-up period. Blood pressure was also raised by stimulation treatment on some occasions, but only to levels equivalent to those of other exertion.

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Table 6.5.2 Subject LE Thigh Blood Flow Change with 15min Treatment session (Wk40)

Cardiac Output

Cardiac Output was measured in week 50, yielding an average value of 2.7 l/min and an average stroke volume of 42ml/min (Fig.6.2.2.c). These are at the bottom of the range of normal values specified by Porter [1986]. On the same occasion average thigh blood flow was approximately 90ml/min, and therefore constituted approximately 3.3% of cardiac output. If a value of $t_b$ equal to $L_{vet}(0.31s)$ is used as per Taylor [1993], this implies a thigh blood flow of 150ml/min or 5.6% of cardiac output.

6.5.7 Tissue Thickness and Limb Girth

Thigh girth measurements show an increase in both limbs over the study period, particularly in the contralateral limb and from week 17, with stabilisation during the follow-up period (Fig.6.5.5). Body weight increased by 2.2kg (3.8%) during the treatment period, continuing a trend of the foregoing year.

The tissue thickness measurements show sporadic variation, some of which are attributable to the poor ultrasound image quality (Fig.6.5.6). Measurements at all locations suggest an increase in bone depth during the treatment period, perhaps reflecting the increase in body weight, though greater on the treatment limb. However, interpreting the intermediate layer (1) shown as that between superficial fat and muscle, the quadriceps muscle thickness only shows an appreciable change of the treated thigh at 250mm from the patella, particularly during the period of isotonic
treatment. The measurement as taken, implies an increase from 11mm to 19mm (72%). Given the variability in measurement and the over estimation at week 31 at other locations, the increase might more conservatively be estimated as 13mm to 16mm (23%). However the changes earlier in the study, with a dramatic decrease in thickness at week 17, imply that measurements at this location are subject to other influences, possibly that of the underlying support cushion, though such changes were less on the contralateral limb.

### 6.5.8 Joint Range of Motion

The subject reported no change in ease or range of motion of lower limb joints, however the researcher perceived a decrease in ease of motion of the ankle of the treated limb during the period of tetanic treatment. This is reflected in the measured range of motion (Tab.6.5.3), with a decrease in the ankle flexion and knee extension range, and some recovery during follow-up period. Conversely ankle extension and knee flexion increased. Variation in measurements of the contralateral limb, may reflect changes or illustrate high intra-rater measurement variability.

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Table 6.5.3 Subject LE Lower Limb Joint Range of Motion (°)- passive
Figure 6.5.1  Subject LE Strength Duration Curve and Chronaxie Values

Table 6.5.4  Subject LE Treatment Stimulation Parameters

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(n/c - no change, isoM - isometric, isoT - isotonic contractions, parameter definition see Fig. 3.2.1)
Figure 6.5.2  Subject LE Lower Limb Mean Skin Temperatures
Figure 6.5.3. Subject LE Blood Pressure and Heart Rate Variation

Figure 6.5.4. Subject LE Thigh Blood Flow

Figure 6.5.5. Subject LE Thigh Girth at locations proximal of patella border
Figure 6.5.6  Subject LE Quadriceps Tissue Thickness at locations proximal to patella border  (poor image quality for week numbers 10, 14, 21, 24, 28)
6.6 Subject LB Results

6.6.1 Subject Profile

Subject LB (male) was aged 40 at the start of the study and had suffered a unilateral left brachial plexus lesion 23 years previously in a motor cycle accident. From initially having no voluntary movement or sensation, biceps function was restored within one year and finger flexor movement returned after approximately two years. Twice weekly physiotherapy was continued for 3 years post injury, including electrical stimulation for wrist extension. No subsequent treatment was received for the affected arm, which he makes use of it for certain daily tasks and otherwise enjoys a normal active life. At commencement of the study he had voluntary control of deltoid, biceps and finger flexors, though movement of the latter was minimal due to their almost fully flexed resting position. Investigation with 0.3ms pulse width stimulation confirmed these muscles as innervated but produced no response from finger and wrist extensors, or triceps with up to 80mA. From this, it was deduced that the radial nerve had the principle motor impairment. Sensation throughout the limb was limited to an awareness of touch without point discrimination and an aching sensation in cold weather. The left limb is severely atrophied with very little tissue except in the biceps and a mottled red appearance to the skin. Conversely, the contralateral limb, is visually proportionately larger in bulk, fully functional and with typical 2 point hand discrimination ability. The subject works for very long hours at a computer, smokes moderately and always had a cigarette immediately prior to the evaluation visit. He felt he had 'nothing to loose' from receiving the treatment, "any improvement, however slight would be a bonus and any degradation, would not be a problem".

6.6.2 Contraction Response to Direct Stimulation

At the initial assessment, stimulation with pulse widths of 200ms produced minimal contraction of triceps and barely detectable contraction of wrist extensor muscles, though difficult to identify due to considerable co-contraction of surrounding muscles, notably biceps and interestingly, brachioradialis, which is normally innervated by the radial nerve. Treatment of the biceps commenced with twitch contractions at 0.5Hz. PALS® Blue 50x50mm electrodes were used and their optimum position was found to be centred at 70mm and 170mm proximal to the lateral epicondyle of the humerus on the posterior aspect, respectively, over the belly of the medial head and between the long and lateral heads of the triceps. By the end of the first week, slight voluntary contraction of a very small area of the triceps medial head was possible, which the subject performed during the '10s off period of the stimulation. This innervation of at least part of the triceps accounts for the shape of the Strength-Duration curve and low Chronaxie value (Fig.6.6.1). Initially, decreasing the rate of rise of the pulse and therefore increasing its width appeared to
reduce the response of the triceps, perhaps due to fatigue, without diminishing the co-contraction. However by the second week, perhaps due to increased sensory tolerance, 300ms pulses with approximately 55ms rise time, reduced the violent jerk of the biceps to a ripple propagating up the arm into the deltoids and produced a more sustained triceps contraction. This treatment continued until week 6 when tetanic contractions at 10Hz with smaller pulse widths could be sustained. Although some contraction was possible with pulse widths of 0.3ms, the area of muscle contracted was greater with 10ms and this was chosen with the intention of continuing the conditioning of these other fibres. The intensity was set at below the level of biceps co-contraction, however during a treatment session this usually built up from a clonus to a fused contraction. Although no fatigue of the triceps was apparent, it would take 2 to 3 minutes for the contraction to build up, even after prior washing of the skin, and the strength of contraction varied from day to day.

Given that at least part of the triceps muscle was obviously innervated, with some under voluntary control, the evaluation measurements were no longer able to assess the effects of the stimulation treatment alone. At week 12, it was therefore decided to extend the treatment to the wrist extensor muscles. The subject was supplied with a Microstim unit (MSTIM) and PALS® Flex electrodes (33x54mm) (§4.4.1) for stimulation of the triceps with 0.3ms pulses at tetanic frequencies. The LPSTIM10 unit (LPS) was programmed with almost triangular shaped pulses of 450ms for galvanic stimulation of the wrist extensors to minimise co-contraction of finger flexors and brachioradialis. However, there was no visible or palpable contraction in the wrist extensors during treatment. The LPSTIM10 unit was also used on the triceps in order to stimulate the long and lateral heads whose fibres only flickered with the Microstim unit. To encourage voluntary contraction, the subject was issued with a biofeedback unit displaying the magnitude of the integrated EMG (§4.4.1), however it was found that with the lack of arm tissue and without training to isolate triceps contraction, the response was dominated by the biceps.

Due to localised current burn on the lower arm (§6.1.3), the LPSTIM10 was withdrawn for two weeks for inspection and treatment continued on the upper arm only with voluntary contractions (wk15) and with the Microstim unit (wk16). Thereafter treatment of the triceps continued with long pulse twitch contractions and short pulse tetanic contractions as before. The former usually increased in strength over the course of 10 minutes, whereas the latter started straight away. Treatment continued with the same parameters and progressively longer sessions up to 30 minutes, but using only one type of stimulation at each session. The extent of voluntary contraction and response to short pulse stimulation increased in the medial head of the triceps but not in lateral and long heads. The last month of the treatment period therefore concentrated on developing these muscle fibres using tetanic contraction with 20ms pulse widths from the LPSTIM10 unit and treatment of the wrist extensors ceased. The subject found it increasing difficult to perform the treatment in the morning due to work commitments, so the evening session was extended to 45min. However this also meant
the subject was not able, or insufficiently motivated to practice the voluntary contraction, which required increasing concentration to perform as it produced no sensation of contraction.

By the end the treatment period (wk 29), 22 weeks of tetanic contractions had been performed. The medial, long and lateral heads of the triceps all responded to the stimulation with fused contraction though mainly in the medial head. Although the majority of the muscle tissue was recruited, there was no appreciable increase in its small size, and no detectable force was generated. This may be because the intensities required to produce notable muscle bulging in the triceps (30-35mA) also recruited the biceps forcibly. The 10 weeks of galvanic stimulation of the wrist extensors had produced no detectable contraction.

By the end of the follow-up period (wk50), the triceps still responded to stimulation at 20Hz with tetanic contractions. Voluntary contraction of part of the triceps was still possible and the subject commented that it did not require so much thought to do so.

**SD Curve Measurement**

The SD curve recorded at the start of the study resembles that of innervated muscle (Fig.6.6.1). In succeeding weeks, as more of the muscle responded to the stimulation, the curve shifted to the right, developed a 'kink' and Chronaxie increased. The 'kink' may reflect the difficulties of measurement as much as a differentiation of fibre innervation. With the smaller pulse widths, the location of minimum contraction shifted proximally and it became increasing difficult to discern the triceps contraction amidst the far greater biceps response, which necessitated restraining the arm. The curve for the end of the treatment period with the 'kink' at greater pulse width may be interpreted as reflecting greater excitability in a greater proportion of denervated fibres, which was then lost with the cessation of treatment when the Chronaxie increased.

**6.6.3 Sensation and Sensory Perception**

To quote the subject; "after the very first 'evaluation' session at Salisbury using long pulses my left arm felt very much more 'alive' than during the extensive period (20 odd years) without any stimulation". He also commented this effect lasted the 4 weeks until the next session. During the treatment period the subject perceived an increase in touch sensitivity in the upper arm, which diminished somewhat during the follow-up period, though he still felt the upper arm had 'more normal touch' at the end of the study compared to its start. The evaluation assessment showed high sensitivity to touch in the treatment limb hand (2.83 monofilament) with a perceived improvement in the ability to reliably identify touch of the first, second fingers and palm. However this may also reflect greater area of exposure of the palmer surface of the hand as the fingers became less flexed at rest. There was no ability to discriminate two point touch at any time. Perhaps most noticeable to the subject was that the limb did not ache in cold weather is previously.
6.6.4 Skin Response and Condition

As a result of the stimulation, the subject experienced at most a moderate uniform erythema beneath the electrodes, which lasted about an hour afterwards (Fig.6.1.1). This was more consistent with tetanic compared to twitch contraction but was less severe with the 0.3ms pulses of the Microstim unit compared to longer pulse widths. The skin was dry rather than oily and this was increased at the electrode sites. The electrodes tended to dry out quickly and is thought to be due to adhering dry skin.

From week 2, the treated arm appeared a more blotchy red colour, which persisted through the treatment period, though comparison was hindered by sun-tanning. The subject considered that skin condition had improved slightly as a result of treatment.

6.6.5 Skin Temperature Measurement

Skin temperatures of the treated limb remained below those of the contralateral limb throughout the study, except in the arm, where asymmetry values approach those of normals (Appendix G). Skin temperature measurements of all segments of both arms, show significant correlation to room temperature, (treatment limb p<0.1, contralateral limb p<0.01) (Fig.6.6.2). However in the segments without voluntary control (forearm and hand), the decrease in skin temperature with decreasing room temperature was greater in the affected arm than the contralateral arm, notably in week 25, probably reflecting the diminished or denervated vasomotor function. There was also some correlation with relative humidity, but only significant (p<0.01) for the contralateral limb.

It is therefore difficult to discriminate any effect of the stimulation on skin temperature, however those of the forearm and hand follow a similar trend which in some respects corresponds to the variation of the treatment pattern. For instance, the decline in skin temperature at week 4 is greater than expected for the room temperature change, and coincides with when skin peeling following sun-tanning precluded effective stimulation treatment. Similarly, the commencement of tetanic contractions with the long pulse stimulation from week 8, coincided with a rise in skin temperature despite decreasing room temperature. These levels were sustained whilst this stimulation continued until week 12, but declined thereafter when tetanic stimulation was provided by 0.3ms pulses in conjunction with longer pulse twitch contractions, though from week 14 to 15 there was no stimulation treatment all. However, the resumption of long pulse tetanic stimulation from week 25 to 29 failed to reverse the decline in skin temperature with room temperature, which continued into the follow-up period. The long pulse twitch contraction treatment applied to the forearm between weeks 12 and 25 (except week 15) shows no obvious effect on skin temperature.
6.6.6 Blood Flow Measurement

Blood pressure and heart rate showed no consistent or significant change over study period (Fig.6.6.3). A typical stimulation treatment session produced no significant change in blood pressure or heart rate and on occasions these decreased with the subject rested.

Blood flow was measured in the arm, with electrodes as proximal and distal as possible but separation distance was low at 90mm. The measurements imply that blood flow in the affected limb is comparable with that in the contralateral limb (Fig.6.6.4), despite considerable differences in tissue bulk and level of activity. This may be a measurement artefact, rising from the very low baseline impedance of the affected arm (typically <20Ω) and consequently small dZ/dt peaks which rendered waveform analysis very difficult. The right arm also showed a greater variability between the first and second measurements of each session, though not for weeks 10 and 18, when the values are apparently 'out of trend'. Blood flow in the contralateral limb shows greater correlation with room environment, which is significant against relative humidity (p<0.05).

Blood flow in the treated limb is seen to rise during weeks 6 to 12 and 25 to 29, which coincides with the periods of long pulse tetanic treatment. Conversely, blood flow declined during the period of treatment short pulse tetanic and long pulse twitch stimulation (weeks 12-25). However during weeks 25-29, contralateral limb blood flow also increased coincident with decreasing relative humidity, which may account for at least some of the changes in the treated limb.

6.6.7 Tissue Thickness and Limb Girth

The variation in measured limb girth of the contralateral limb when body weight did not change, illustrate the expected reproducibility of the measurement (Fig.6.6.5). The variation during the initial weeks of treatment may reflect the inexperience of the researcher. Given this level of reproducability, the measurements do not indicate any noticeable change in limb girth of the treated limb period of the study, except perhaps a slight decrease, thereby confirming the observations of the researcher. However, the triceps muscle heads were each more discernible, but perhaps still not of sufficient bulk to affect the measurements.

Similarly the ultrasound tissue thickness measurements show an unexpectedly high degree of variability in the contralateral limb (Fig.6.6.6), perhaps attributable to variation in the arm position, muscle tension and orientation of the probe during measurement. The severity of muscle atrophy of the treated limb, made standardisation of probe orientation particularly difficult. Only the tissue thickness to the bone is presented, as intermediate interfaces could not be reliably identified. The measurements suggest a decrease in tissue thickness from week 18, especially proximally. Changes do not appear to correlate to the type of stimulation treatment, though session length was
progressively increased. The greater changes in the contralateral limb suggest a non treatment effect.

6.6.8 Joint Range of Motion

The tightly flexed fingers at the start of the study, became visibly and to examination, more relaxed by week 6 of treatment, requiring less force to extend, an effect also noticed by the subject after 1 week. The wrist movement also became easier. The measurements of range of motion (Tab.6.6.1) show improvements in wrist extension and flexion, but also considerable variability of values including of the contralateral limb, perhaps attributable to operator inexperience with the technique. The measurements show no obvious change in the elbow range of motion. The subject considered the improvements in joint motion and muscle tightness, diminished without the treatment, as the measurements also suggest. However he expressed the desire to persevere with the finger extension with passive exercising.

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Table 6.6.1  Subject LB Upper Limb Joint Range of motion (°). (*wk29 post treatment measmt)

6.6.9 Additional Subject Comments

The subject considered the main benefit of the treatment had been the return of voluntary contraction to at least part of the triceps. Although the treatment encouraged his voluntary exercising, he lacked the motivation to perform it consistently without the discipline of a treatment regime and he would have liked to have continued with the treatment to determine the extent of returned function possible.
**Figure 6.6.1** Subject LB Strength Duration Curve and Chronaxie Values

**Table 6.6.2** Subject LB Treatment Stimulation Parameters
(n/c - no change, isoM - isometric, parameter definition see Fig. 3.2.1)
Figure 6.6.2  Subject LB Upper Limb Mean Skin Temperatures
Figure 6.6.3. Subject LB Blood Pressure and Heart Rate Variation

Figure 6.6.4.a. Subject LB Arm Blood Flow (tB=0.2s constant)

Figure 6.6.4.b. Subject LB Arm Blood Flow (tB from dZ/dt ware form)
Figure 6.6.5. Subject LB Arm Girth @ locations proximal of lateral epicondyle of humerus

Figure 6.6.6. Subject LB Triceps Tissue Thickness @ locations proximal of lateral epicondyle of humerus
6.7 Subject LR Results

6.7.1 Subject Profile

Subject LR was aged 59 at the start of the study and suffered a spinal infarct 3 years previously, initially resulting in near complete lower limb paralysis. Motor function returned, except for dorsiflexion of the left foot, which previous attempts at electrical peroneal nerve stimulation revealed to be lower motor neurone damage. In order to compensate for the consequent 'dropped foot', the subject walked with pronounced knee flexion and a stick, which was tiring and used a wheelchair for long distances. However she prefers this to the traditional rigid ankle-foot orthosis. The Achilles tendon had become shortened but not contractured, and the subject experienced occasion spasms in the calf muscles, at night and when using the orthosis. At the start of the study, the left tibialis anterior was severely atrophied, but otherwise both lower limbs were in proportion with the large body size. Both lower limbs had impaired sensation, especially in the toes and heel. The left limb appeared cooler and redder than the contralateral limb. The subject remains active and performs weekly swimming exercise.

At the start of the study, the subject was taking Aspirin (75ml) and other medication related to thyroid, hernia and cholesterol conditions, which continued throughout the study. The stimulation treatment was found to raise an existing high blood pressure. This was reduced by medication prescribed by the subjects GP (daily 2.5mg Bendrofloazile) and taken from week 2 of the study. The subject stopped smoking 5 years previously and commenced a weight reduction diet at the start of the study. Slight oedema and inflammation continued on the anterior contralateral leg just distal of the patella as a result of a fall 3 months previously. Although, it was anticipated that these factors and the surrounding musculature, would influence the tissue property evaluation measures, the objective of the treatment was primarily directed at restoring dorsiflexion function, which was also assessed. Left voluntary foot eversion control was retained.

6.7.2 Contraction Response to Direct Stimulation

At the initial assessment, stimulation with 200ms rectangular pulses and electrodes on the anterior left leg produced no detectable tibialis anterior contraction, but co-contraction of the plantaflexors and upper leg muscle spasms. The latter were attributed to a reflex response, as occurred after a slight delay. Use of trapezoidal stimulation pulses with a ramp in excess of 100ms, minimised calf contraction but not quadriceps response. However, 8 months later, at the start of treatment, the quadriceps response only occurred at higher intensities and the treatment was started below this threshold with pulse ramp rates of 0.67mA/ms to minimise plantaflexor contraction. Treatment was performed with the subject seated and the knee slightly flexed by supporting on a pillow to prevent
plantaflexor spasm. PALS® Blue electrodes (40 x 90mm) were positioned longitudinally over the tibialis anterior from beneath the tibial condyle, with approximately 20mm between them and as anteriorly as possible without being over the tibia (Fig. 5.7.1). However to avoid the ensuing skin reaction (Fig. 6.1.2), 50mm square electrodes were used in subsequent weeks and their position was altered slightly. By week 4, contraction of tibialis anterior was noticeable at its centre when the foot was held in dorsiflexion and no fatigue was apparent after 30min of 0.5Hz stimulation. This contraction increased in area and strength as the intensity was gradually increased and by week 6, the flexor tendons of the largest toe were visibly tensioned across the foot dorsal surface. The square electrodes were continued with, because of the flexibility of position, although the contraction was greater with the larger electrodes. By week 12 foot dorsiflexion and inversion of approximately 5mm was possible with the long trapezoidal pulses of up to 50mA. However ramp rate could not be reduced without plantaflexor recruitment and tetanic stimulation (40ms, 10Hz) produced only plantaflexion response.

As the epidermis became dehydrated (§6.1.3) contraction response diminished and took an increasing proportion of the treatment session (10-15min) for the current to build up to the level for effective contraction. Pulse width and ramp rate were therefore reduced at week 16 to minimise skin reaction, even though plantaflexion limited intensity to 29mA. Increasing the frequency to 4Hz (wk18) produced a semi-fused tibialis anterior contraction. Although intensity was initially limited by subject tolerance to 20mA, this subsequently increased, probably resulting in plantaflexion recruitment and accounting for the greater foot movement. These parameters also reduced the skin reaction, allowing the epidermis to rehydrate and the use of the larger (40x90mm) electrodes, which more selectively recruited the tibialis anterior at lower intensities.

Attempts to reduce the pulse width and increase the frequency reduced the tibialis anterior activity, such that only a small range of intensity (16-20mA) existed when dorsiflexion occurred before foot movement was dominated by plantaflexor recruitment. On occasions, the subject also reported plantaflexor spasm and a ‘tight’ feeling in the limb after treatment. By week 28, the epidermis had become hardened once more. After 9 weeks of treatment with 5.5Hz stimulation, 70ms pulse width, 8s on, 16s off contraction envelope and session duration of up to 30min, dorsiflexion was minimal and contraction force could only be felt with the foot passively held at 90° dorsiflexion. Contraction with long trapezoidal pulses soon fatigued. It was therefore concluded that the tibialis anterior contraction force was still insufficient to overcome the shortened Achilles’ tendon in order to produce dorsiflexion. Passive stretching exercise of the Achilles’ tendon for 10min each day, failed to alter the response and steps were taken to produce a brace to hold the foot at 90° dorsiflexion during the night, but not completed within this study.

At week 44, a better contraction response was obtained with the subject standing, which allowed the electrodes to be placed more centrally over tibialis anterior, without risk of thin tissue over the
tibia. The patient was also able to tolerate intensities up to 25mA in this position and plantaflexor contraction was minimal. Visible contraction of tibialis anterior was obtained from stimulation with 30ms pulses at 16Hz, although no dorsiflexion was detected. Treatment with these parameters and 1s on, 4s off contraction cycle continued in this form for the remainder of the study, with minimal dorsiflexion and inversion, but taking up to 25min for the contraction to develop, which was continued for 15min.

An attempt was made (wk 28) to provide dorsiflexion during gait using ramped long pulse stimulation, with the pulse width adjusted to the swing phase and initiated by a hand held switch operated by the subject. However dorsiflexion was not sufficient to allow gait pattern to be altered. Further investigation awaited greater dorsiflexion and was not repeated within the study period.

**SD Curve Measurement**

Determination of Strength-Duration curve at smaller pulse widths was precluded by the dominance of the plantaflexion movement. The curves illustrate an increase in excitability associated with a decrease in Chronaxie (Fig. 6.7.1), however analysis is hindered by variation in Rheobase.

**PCI measurement**

The subject reported a perceived improvement in gait during the treatment period. Physiological cost index was measured on 3 occasions during the study without stimulation, though for week 33 it was measured pre and post a treatment session. The attempt to provide dorsiflexion during gait was not practised sufficiently to justify PCI measurement and awaits its greater efficacy. The measurements show a considerable improvement in PCI (39%), though predominately due to a decrease in heart rate change and not an increase in walking speed and therefore this is probably due to the improved blood pressure rather than the stimulation treatment.

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**Table 6.7.1** Subject LR Physiological Cost Index Measurements

**6.7.3 Sensation and Sensory Perception**

Sensation of stimulation included sharp pulses, a *drawing* sensation between the electrodes and a *tingling* when the toe flexor muscles were first activated. The subject was generally less tolerant of higher frequencies, which produced a *gripping* sensation, though tolerance increased with
continued treatment. The subject reported no increase in sensory perception during the study and this was only assessed with the monofilaments on one occasion (wk 24), showing a perception of the 4.31 filament over most of the foot but worse in some areas of the left.

6.7.4 Skin Response and Condition

Prior to the study, the subject experienced occasional skin ailments including mild dermatitis of the hands and usually used moisturising agents daily over the whole body. Intermittently, during the course of the study, the skin of both lower limbs developed inflamed pimples, dryness and a thin hardened 'glazed' surface film, but these were exacerbated at the electrode locations. Stimulation with long pulses and twitch contractions particularly aggravated the skin, in terms of inflamed pimples rather than the uniform erythema of other subjects. Electrode position was rotated to allow recovery between sessions and water based Aloe Vera gel was found aid this. Reaction was less with shorter pulses and higher frequencies however skin hardening was not avoided. This hardened layer as with suntanning (wk 38) diminished tibialis anterior contraction response necessitating higher stimulation intensities and delaying the start of contraction by up to 25min, such that session length was extended by 15min.

6.7.5 Skin Temperature Measurement

Mean skin temperature in both lower limbs correlate with room temperature (p<0.05) and therefore was reduced for the majority of the study during the winter months (Fig.6.7.2). Leg skin temperatures were lower on the treatment limb and showed an initial increase in asymmetry, though this coincided with inflammation of the contralateral leg. Otherwise, measurements show no obvious change in asymmetry during the study, except in the foot where determination of segment area was particularly unreliable.

6.7.6 Blood Flow Measurement

As a result of prescribed medication, the subjects' blood pressure declined over the study (Fig.6.7.3), but also showed some variation. In week 24 systolic blood pressure was raised above the neighbouring measurements; in the preceding week the subject had been diagnosed as dehydrated and instructed to drink more liquid. The subject was very active on the morning preceding the visit of week 28 and heart rate was raised.

Leg blood flow measurements also show considerable variability (Fig.6.7.4), however this is not consistent in both limbs and does not correlate with room environment changes and correlation with diastolic pressure is only significant (p<0.05) on the contralatera limb. Initial fluctuation in the contralateral limb may be due to the affect of trauma oedema. Mean impedance values show no significant correlation to blood flow values, however low values on both limbs in week 4 made
waveform analysis difficult and accounts for the low blood flow of the contralateral limb and high measurement variability of the treated limb. Blood flow of the contralateral limb shows an increasing trend up to week 24 and then a marked decline. The treated limb appears to show a consistent increase in leg blood flow initially but this is not sustained, however values during the period of treatment with twitch contractions (wks 0-18) are greater than those subsequently with fused contractions.

Leg blood flow in either limb showed no consistent change immediately after a treatment session compared with before. Blood pressure and heart rate during the stimulation session were raised, but by no more than routine walking.

### 6.7.7 Tissue Thickness and Limb Girth

Leg girth measurements (Fig. 6.3.5) show some variability, especially proximally, which probably reflect varying degrees of oedema. There is a decreasing trend in the girth of the treatment leg over the study, in parallel with that of body weight, however there is a marked decline from week 22, not long after the commencement of treatment with tetanic contractions, and increase towards the end of the period. Given the small size of tibialis anterior, the effect of treatment on girth is more likely to be on limb oedema than muscle bulk. Reliable tissue thickness measurement was not possible, because of the difficulties of identifying the tibialis anterior boundary, without a directly underlying bone.

### 6.7.8 Joint Range of Motion

In the subjects' opinion, the ankle on the treated limb has increased in ease of motion. The range of motion measurements (Tab.6.7.2), although demonstrating variability, shows consistent change only for the contralateral limb. Certainly the decrease in dorsiflexion of the treated limb feared as a consequence of plantaflexion is not confirmed and the 'active' value, representing the resting angle is unchanged. Inconsistent week 0 values are probably due to operator inexperience.

<table>
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<tr>
<th>Week No.</th>
<th>EXTENSION (Plantaflexion)</th>
<th>FLEXION (Dorsiflexion)</th>
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Table 6.7.2 Subject LR Ankle Range of Motion (°)
Figure 6.7.1  Subject LR Strength Duration Curve and Chronaxie Values

Table 6.7.3  Subject LR Treatment Stimulation Parameters
(n/c - no change, isoM – isometric, parameter definition see Fig. 3.2.1)
Figure 6.7.2  Subject LR Lower Limb Mean Skin Temperatures
Figure 6.7.3. Subject LR Blood Pressure and Heart Rate Variation

Figure 6.7.4. Subject LR Leg Blood Flow

Figure 6.7.5. Subject LR Leg Girth at locations proximal of lateral malleolus
7. DISCUSSION OF STUDY RESULTS

7.1 Muscle Excitability and Strength Duration Curve

The study confirmed the findings of Kern, Hofer et al. [1999] and Mokrusch and Neundörfer [1994] (§3.4.2) that there is a progressive increase in muscle excitability with continued treatment, in terms of a decrease in minimum pulse width needed to cause muscle contraction. For instance, for subject LC, before treatment the minimum pulse width required for quadriceps contraction was 10ms and by the end of the treatment this had decreased to 0.5ms, albeit at a greater intensity. This is not merely due to a decrease in apparent skin impedance allowing greater current flow, which on the contrary, typically increased as a result of the drying effect of stimulation with the electrodes used. Rather the initial treatment with low frequency twitch contractions appears to have had a conditioning effect on the muscle fibres, increasing their responsiveness. The few histological studies performed following this type of treatment [Mokrusch, Engelhardt et al. 1990, Neumayer, Happak et al. 1997] do show improvements in muscle fibre structure (§3.). It is possible its effects are both electrical (increasing the fibre membrane excitability) and mechanical (perhaps in releasing adhesion between fibres of the muscle and tendons). This was reflected in a decrease in Chronaxie during the treatment period and subsequent increase in the follow-up period. The major reduction in Chronaxie for subjects LC, LD and LE (from between 20 and 30ms to 13 and 10ms) occurred during this initial period of treatment with low frequency twitch contractions with little further change with tetanic contractions. This would account for the observations of a previous study [Taylor, Ewins et al., 1992] that, although the initial treatment with twitch contractions produced no change in tissue property measures, it made possible the later tetanic contractions which did.

The increased excitability is seen in the Strength-Duration (SD) curve (§2.4.4) for those with near complete muscle denervation (subjects LC, LD and LE), as a shift of the curve downwards and to the left as the threshold intensity is decreased especially at smaller pulse widths. These changes can only speculatively be related to fibre changes. Changes in mechanical properties and membrane electrical resistance may be expected to effect the response at all pulse widths evenly, whereas improvements in the contractile propagation process may effect smaller pulse widths proportionately more. However that, the Rheobase values was observed to vary (including increases) during the treatment period implies other factors are involved. The intensity was measured in terms of current (mA) and the limit of voltage of the unit was not reached until the smallest pulse widths. This negates the simple explanation of increased threshold intensity as due to increases in skin resistance, which occurred due to hardening of the skin beneath the electrodes. However it is possible that this disrupted the current path or added capacitance, necessitating the greater current.
§7.1 Discussion - Muscle Excitability

However, Chronaxie did not provide a direct guide to selection of stimulation parameters, largely because the threshold of minimum contraction applied only to a portion of the muscle and therefore the intensities required to contract the whole muscle at this pulse width were considerably higher. Also the SD curve and Chronaxie are determined for twitch contractions and do not indicate the muscle response at the higher frequencies required for tetanic contractions. For instance, a twitch response down to 3ms was obtained at the start of treatment from subject LC, but tetanic contractions could not be sustained over the whole muscle until at least 7 weeks later. It is probable that during this period of treatment the necessary changes in muscle structure and metabolism occur, with the increase in capillarisation and perfusion observed by others [Brown, Cotter et al. 1976]. Nevertheless, tetanic contractions were not possible with Chronaxie values of greater than 10 to 15ms.

For subjects with partial limb denervation (LB and LR) determination of the SD curve was severely hindered by co-contraction of the antagonist muscles, which caused limb movement and in stretching the muscle of interest and its tendons, could give a false impression of its contraction. Hence for subject LR, SD curve analysis was not as effective. However those for LB may reflect those of a partially innervated or partially conditioned muscle. It is possible to interpret the pronounced 'kink' in the curve (§6.6.2) as the transition between fibres 'conditioned' by voluntary control and less responsive ones, especially given that the kink shifted to longer pulses in the manner of a re-innervated muscle (Fig.2.4.2). Given the time since injury, it is unlikely that re-innervation had occurred. It is more likely, (with the apparent innervation of the more distal brachioradialis) that the majority of the remaining contractile fibres are innervated but have severely deteriorated over years of disuse. This is possibly similar to one case treated by and Mokrusch and Neundörfer [1994] (§3.4.1). It would account for the rapid return of voluntary control of some fibres and response to 0.3ms pulse widths after conditioning with longer pulses. Treatment failed to produce any detectable contraction in the very severely atrophed wrist extensor muscles of subject LB, perhaps confirming its denervation, which after 23 years has resulted in severe atrophy.

7.2 Contraction Strength

As the muscle excitability increased, so did the strength of contraction for a given pulse width, as assessed visually in terms of muscle belly displacement. However, each time the treatment pulse width was decreased, the contraction response was reduced initially and then increased progressively over subsequent weeks, both in perceived strength and area. For instance, with subject LR, muscle contraction was only visible after 4 weeks of treatment as a slight flicker which then spread. This may reflect a conditioning of the contractile structures of the fibres as much as an increase in their size with the addition of new myofibrils. With isotonic contractions (subjects LC and LE ), contraction strength was assessed by means of limb movement. Subjects LB and LR did
not develop isotonic contraction strength sufficient to overcome the co-contraction of innervated antagonist or associated shortened tendons. For subject LB, although the visible bulk of triceps recruited during contractions increased, the resting tissue bulk did not, despite 23 weeks of tetanic treatment, perhaps due the limited number of still active fibres. With subject LR, 26 weeks of 6Hz stimulation was ineffectual in developing sufficient contraction strength for the desired dorsiflexion. The 16Hz stimulation possible after 44 weeks, appeared more effective and selective, but was also hindered by elevated skin impedance. For subjects LC and LE, quadriceps stimulation produced leg movement of up to 14° with the knee at 90°flexion and therefore against minimal gravity component but not approaching the full extension achieved in other studies (§3.4.2). This is perhaps because isotonic contractions were only performed for a limited period, intensity and fibre recruited was limited by the electrodes used or possibility the stimulation pattern used. For instance the session length (30min) was longer than most other studies and may led to overuse damage.

Full knee extension contraction was achieved in other studies after 6 months [Mokrusch and Neundörfer 1994, Petrovsky, 1991] or 8 months [Kern, 1995] of treatment, though only Kern describes an initial period of conditioning treatment with twitch contractions. In this study, tetanic contractions were performed by subject LC for 20 weeks and subject LE for 19 weeks, of which 7 and 10 weeks respectively were with isotonic contractions. The period of treatment is therefore considerably less and for subject LC was interrupted by illness on several occasions. For subject LE, limb movement continued to increase, though not dramatically; for subject LC it declined over the last 5 weeks, although this included the periods of illness.

Kern et al. [1999] used large conductive rubber electrodes inside wetted towelling sleeves, with which the strength and area of contraction are considerably greater than observed in this study. Perhaps these electrodes permit the use of far greater stimulation intensities (>150mA) without the tissue damage of smaller electrodes, though at the expense of considerable inconvenience of application. The larger size of self adhering electrodes used temporarily with subject LC, indeed produced a more distributed contraction and reduced erythema. However, in this study, stimulation intensity was restricted to the level of localised dysreflexive sweating, largely due to the unconfirmed possibility that the skin burns experienced were due to current concentration in sweat pores. These occurred with pulse widths of 100ms or greater, when any charge imbalance between the pulses would be greatest. Investigation of this showed a pulse asymmetry of less than 3%, due to the progressively diminishing amplitude of the second pulse, an effect apparently associated with the electrodes, which retain a charge when isolated (§5.7.2). The electrodes used in this study do appear to have introduced problems not reported by others, albeit with greater convenience. However smaller electrodes are required for treatment of smaller muscles and further investigation

1 Presentation and communication at Vienna 6th International FES Workshop Sept 22-25 1998
of the suitability of size, shape and materials is required, as well as the chemistry occurring at the skin interface, for instance Guttmann [1976] suggested salt solution to avoid burns.

The contraction response and effectiveness of the treatment in this study was affected considerably by skin impedance, to which the type of electrodes used may or may not contribute. After about two weeks of treatment, the contraction did not commence immediately at the start of the session, but took several minutes to build up as the current also increased (§6.1.2). The delay was less with tetanic contractions and large electrodes except in those with an existing dry skin condition (LE and LR). For instance, with subject LR whose epidermis hardened, current increased from 4mA to 20mA over 15min, with an apparent impedance change from approximately 16kΩ to 3.5kΩ. This change may be a result of the erythema around the electrodes, a charging effect of the electrodes or a limitation of the stimulator, though the output voltage was not at its maximum value. No such delay was apparent with the equipment used by Kern et al. The delay in start of contraction was lengthened to 25min when the duration of contraction was shortened to 1s, presumably its effect takes longer to accumulate.

The amount of limb movement from isotonic contractions, increased with pulse width and Kern, Hofer et al.[1999] recommend the use of 40ms at 20Hz with 2s on, 2s off contraction cycle in sets of 6-8 contractions. This 80% pulse duty cycle, raised concern over the possible detrimental effect of near continuous current, and so a 50% duty cycle with 20ms at 20Hz or 27ms at 17Hz was employed in this study. Kern's stimulation pattern was attempted with subject LC at the end of the treatment period, but because of illness only performed for 2 weeks and produced no noticeable difference in evaluation measures. However, limb movement was considerably less with 2s contraction duration compared with the 8s used previously, when movement and current progressively increased during the contraction, despite a rectangular stimulation envelope.

In addition to the pulse width, there was concern during the study as to the most appropriate contraction duration and duty cycle. The original intention was to base the treatment pattern on that recommended by others who had demonstrated beneficial results. Initially a contraction duration of 3 or 4s was used, based on that of Kern [1995], but with a rest period of 8s rather than 5s. Later, contraction duration was extended to 8s, with 16s rest as this provided a more sustained contraction, given the electrode effects noted above and comparable with the 10s on, 30s off used by Mokrusch and Neundörfer [1994]. For subject LR, a contraction duration of 1s was adopted latterly as being more akin to the normal physiological recruitment during gait and therefore less likely to induce overuse damage, However once again this lengthened the delay before start of contractions. Given that muscle perfusion in normal adults may be elevated for up to 2min following exercise (Fig.3.5.1), it is unlikely that full reperfusion can occur with any of these stimulation patterns between contractions, especially given diminished circulation of denervated muscle.
Continuous, 24 hour stimulation of innervated muscle for cardiomyoplasty, can be tolerated and damage minimised by use of 2.5Hz [Lexell et al. 1997], however this does not necessarily apply to denervated muscle, with its altered metabolism. With subject LE, fatigue of isotonic contraction had reduced limb movement to 67% of its initial value after 25mins when the subject usually ended the session. Fatigue was similar with subject LC but more pronounced with 2s on, 2s off pattern even with a 10min rest in between, though this could also have been the after effects of influenza. Treatment sessions lasted for up to 30minutes, twice a day; the same as employed by Kern in 1995, and less than typically employed for innervated muscle. However, others have seen benefit from far less treatment time, for instance, 6min treatment per lower limb muscle per day [Mokrusch and Neundörfer 1994].

Without the use of an appropriate non-invasive measure, it was not possible to determine whether the treatment patterns employed resulted in muscle cellular damage, and further optimisation of stimulation parameters necessitates a reliable means. However there was no obvious evidence of damage and muscle contractile ability was retained, whereas excess damage is said to lead to its complete loss [Herbison, Jaweed et al.1983]. The decrease in thigh girth of subject LC immediately proximal to the knee, especially during isometric contractions, is explicable as a toning of the muscle tissue and tendons, and that more proximally as due to general body weight loss due to infection. Conversely, for subject LE measurements show an increase in thigh girth and tissue thickness concurrent with increased body weight. With subject LR, the apparent failure or delay of muscle development of tibialis anterior may be attributed to eccentric work damage from co-contraction of the plantaflexors. However this is the normal manner of working of the muscle during the gait cycle from heel strike to prevent 'foot slap' [Soderberg and Knutson 1995] and the lack of response appears to be related to skin impedance, but has continued to improve very gradually.

7.3 Evaluation Measures

Each of the treatment evaluation measures performed was subject to considerable variation, some of which can be attributed to measurement artefacts and operator clinical inexperience. This degree of variation masked any small effect of the treatment that occurred. Only with subject LE, for whom treatment continued the longest and most consistently, was there any noticeable change in the measures. This suggests the lack of change in other subjects, apart perhaps from LB, is due to insufficient treatment period, rather than some overall detrimental treatment effect. Other studies only cite the change in evaluation measures after a longer treatment period and therefore comparisons are difficult.

7.3.1 Resting Skin Temperature

The measured mean skin temperatures all show a strong correlation with room environment, and it is apparent that this is the major cause of change in values which could have been avoided by
conducting measurements in an environment where temperature and humidity were controlled. Contrast of the leg and foot with respect to the background may also be enhanced by using a frozen towel behind the limb\(^2\), and would improve the reliability of determining the segment area. However the environmental changes did highlight the differential deficiencies of vaso-motor control of some subjects, resulting in an increase in asymmetry between limbs in lower room temperatures. Asymmetry values were typically in excess of those of normals.

There was no consistent treatment effect on skin temperatures observable across all subjects. With subjects LE and LR there was a dramatic decrease in mean skin temperatures during the first week of treatment despite an increase in room temperature, indicating perhaps an initial negative reaction of the treatment, though this may also be due to relative humidity related blood flow changes. For subject LC, room temperature also decreased at week 1 therefore masking any such effect, however skin temperatures did increase during the initial follow-up period without change in room temperature.

Amongst other studies, only that of Taylor (1992) cited a change in resting skin temperature of \(+3^\circ\text{C}\) after 8 weeks of forearm stimulation (§3.4.2). This is corresponds to subject LB, who indeed did experience a similar increase in mean skin measurements during the period of treatment with long pulse tetanic contractions, both relative to the contralateral, and in absolute values, despite decreasing room temperatures. Kern et al. [1995] observed an increase in skin temperature of \(1.6^\circ\text{C}\) immediately after treatment, which was sustained for up to an hour but only in the thigh. In contrast, the increase in skin temperature observed after treatment of subject LE (Tab.6.5.1) also occurred distally, but the reversed asymmetry was not observed at other evaluation visits, five hours after treatment.

7.3.2 Resting Limb Blood Flow

Again, blood flow measurements exhibit some correlation with environmental conditions, however at least some of the variation in values obtained is attributable to many other factors and has been observed by others (§3.5.5). Of the two measurements taken of each limb on each occasion, the majority show close agreement and no consistent repeat measure effect. However it is apparent that subjects holding their breath during the measurement initiates a physiological response, contributing to variability in repeat measurements and may result in an underestimate of blood flow of the order of 10\%. The \(dZ/dt\) waveform and repeatability of measurements was more consistent with the subject supine rather than recumbent, except for measurement of arm blood flow.

In other studies using impedance plethysmography to determine peripheral blood flow in normals; the average of 111 forearm measurements was approximately 155 ml/min (91-282) and the average

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\(^2\) Advice from Burns Unit, Salisbury District Hospital
§7.4 Discussion

Evaluation Measures

of 84 lower leg measurements was approximately 235 ml/min (60-639) over all ages [Porter, Swain et al. 1985]. No significant difference in blood flow was observed between those below or above 50 years unless expressed relative to stroke volume, representing a larger proportion as cardiac output declined with age. At the start of this study, the approximate arm blood flow for subject LB was 45ml/min. Although comparison is most appropriate in terms of per unit volume or weight of tissue values are expectedly low for the affected arm, but surprising low for the contralateral limb, though attributable to measurement artefacts (§6.6.6). For subject LR, leg blood flows, were approximately 115ml/min throughout the study, which may be reduced from normal by the limited mobility of the subject and oedema.

Taylor, Ewins et. al.[1993] also observed considerable variation in impedance plethysmography measurement of thigh blood flow in 19 normals (average 324, SD 150 ml/min = 7.1% mean cardiac output) but were able to identify a significant difference amongst another 20 with bilateral spastic paraplegia following SCI (average 214, SD 153 ml/min = 5.4% cardiac output). In a further group of 7 SCI subjects, thigh blood flow was increased (from a mean of 167 ml/min SD 70ml/min = 5.1% mean cardiac output) to the levels in normals by 3 months of stimulation of the quadriceps muscle. The figures in the Taylor study use $L_{VET}$ from concurrent measurement of cardiac output for the beat flow duration ($t_B$) whereas Porter derived it from the $dZ/dt$ waveform, which is typically lower. In this study approximate mean values at the start of treatment for the SCI subjects are 110 (183) ml/min for subject LE and 95 (128) ml/min for subjects LC, where figures in parenthesis are with $t_B$ equal to $L_{VET}$ and represent 6.8% and 3.8% respectively of cardiac output measured in the follow-up period. The larger blood flow value for subject LE may reflect his greater level of innervation, however that it already constitutes a near normal proportion of cardiac output may account for the lack of great increase with treatment, with cardiac output being near the lowest level specified for normals by Porter [1986] whereas the converse applies to subject LC.

Amidst the variability of measurement there is some detectable change, which may be attributable to the treatment. Thigh blood flow measurement values of subject LC increased in both limbs over the treatment period as a whole, by up to 31% (95 to 125ml/min). That flow levels were approximately equal in both limbs throughout the study may indicate a non treatment cause. However, the subject reported considerable sensation in both limbs during the treatment session and Kern (1995) also reported a contralateral limb perfusion increase amongst spastic paraplegics. For subject LE, blood flow asymmetry was reversed in favour of the treated limb towards the end of the treatment period even though absolute values did not increase greatly from at the start. With subject LB, a blood flow increase estimated at 10% occurred during the period of tetanic treatment with long pulse stimulation. There was no discernible trend of change in blood flow measurements.

Subject LE also showed a progressive increase in thigh blood flow with treatment of up to 42% at 15min afterwards, with still increasing trend. Therefore, the effect of twice daily stimulation
treatment on the averaged daily blood flow is greater than that indicated by the resting value. For instance, if blood flow remained elevated at these levels for one hour (as observed for skin temperature by Kern, Hofer et al.[1999], it would constitute a 3.5% increase in average flow. It is possible that a beneficial effect on skin condition and viability may accrue from even short but regular periods of elevated blood flow and skin temperature.

The difficulties encountered in interpreting the impedance waveform and surprising results on occasions, questions the use of the technique adopted for blood flow measurement in this application. Certainly, measurement supine and with concurrent cardiac output measurement is recommended to improve consistency. Concurrent measurement with another method of pulsatile blood flow, such a doppler ultrasound, may help with interpretation of the waveform and variability of values.

7.3.3 Tissue Thickness and Limb Girth

The difficulty and variability of measurement of tissue thickness was largely due to the poor image quality of the original ultrasound scanner. However contributing to this, was that measurements were taken from images at the time of capture rather than storing them for later processing on a single occasion which would allow the tissue interfaces to be identified and changes in thickness followed with greater consistency. The method of limb support during measurement requires improvement; measurement of the arm were not performed in a consistent position or with the subject sufficiently relaxed, and the lower limb was measured with the subject seated on their wheelchair cushion, which distorted the proximal thigh, especially for girth measurements. The latter may be improved by a supine position. Given the variability of thickness values, concurrent measurement of limb girth and body weight were essential for interpreting results, especially for contralateral limb changes, although they are also prone to measurement errors and artefacts.

Determination of quadriceps thickness relies upon the correct identification of the intermediate tissue interface between the subcutaneous fat and the rectus femoris. Those identified from the image have been shown. However, the most consistently identified interface, yields values of the ratio of muscle to fat at mid thigh of 1.4 for subject LE and 2.3 for subject LC. Taylor found that amongst adult spastic paraplegic SCI subjects, the thigh muscle/fat ratio at mid thigh was 0.9, with subcutaneous fat thickness remaining approximately constant at 15.9mm following injury out of a total tissue thickness of 30.4mm. Overall tissue thickness was reduced in these denervated subjects at 20mm (LE) and 26mm (LC) and this would suggest, that at least for subject LC, the second interface identified is more suitable, giving mid thigh ration of 1.0. Muscle/fat ratios amongst patients with muscle atrophy due to SMA have been found to reduce from 2.0 to 1.0 [Schmidt and Voit 1993].
Only with subject LE was there an appreciable increase in muscle thickness, which may be due to treatment and coincides with longer treatment period. Intermediate interfaces were not consistently identified on subject LB, the decrease in tissue thickness of the triceps and arm girth may be due to a toning of the tissues and tendons with muscle contractions. Similarly for decreases in limb girth occurring adjacent to the knee of subject LC, who reported a greater firmness to the thigh tissue and discernible muscle during contractions.

7.3.4 Range of motion

All subjects reported their limbs felt easier to move as a result of treatment. Subject LB in particular, experienced an appreciable decrease in resting finger flexion and therefore improved range of motion of fingers and wrist of the treated hand. With subjects LE and LR, the concern was that co-contraction of the innervated plantaflexors and toe flexors would exacerbate existing tendon shortening. Ankle range of motion was unchanged for subject LR but decreased in flexion for subject LE by up to 20°, which was not prevented by regular, though not daily standing. However the ankle of the treated limb did not appear less easier to move.

7.3.5 Sensory Perception

For most of the treated limbs, sensory perception was too poor to be assessed by the evaluation measures. However all subjects reported some sensation of the stimulation and subjects LB and LC increased sensory perception in the treated arm and abdomen respectively. The sensation as much as the limb movement was considered of benefit by the subjects, and enhanced motivation to perform the treatment.

7.4 Clinical Significance of Study

Since the start of the study, researchers in Vienna [Kern, Hofer et al. 1999] have developed the long pulse biphasic technique to demonstrate functional standing for cases of chronic complete lower limb flaccid paraplegia and hope to continue towards ambulation. Stimulation, with quite different parameters is being employed transcutaneously and subcutaneously to enhance functional reinnervation in acute cases of brachial plexus and other peripheral nerve injuries. Both techniques appear to provide tangible function benefits, but it remains to be seen, whether these justify their adoption as routine clinical treatments.

The focus of this study was on the therapeutic benefits of stimulation to chronically denervated muscle, together with the possible functional benefits to cases of partial limb denervation. As originally envisaged, further studies with a larger number of subjects are still necessary to establish the therapeutic value of direct stimulation of chronically denervated muscle and its clinical
treatment viability. However this study has confirmed some of the findings of other studies of its potential benefits and highlighted some concerns for these future investigations (§8.2).

In particular the use of nerve accommodation using trapezoidal pulses for partial limb denervation has been shown to increase muscle excitability of denervated muscle. However accommodation cannot be achieved at tetanic frequencies because of the limitation of rise time and therefore it is likely that functional stimulation will probably require a combined approach with other techniques to avoid or block the recruited nerve fibres. The value of 0.67mA/ms as the maximum rise rate to achieve accommodation applied with intensities of up to approximately 40mA, and therefore is of the same order of magnitude as that suggested by LeFlohic [1994] (0.2mA/ms = 20% of 100ms) or Stephens [1973] (0.3mA/ms = 30x Rheobase of 10mA/s) (§2.4.4).

In addition to the intended application of direct LPB stimulation for complete and partial chronic denervation, the study also included application to chronic disuse atrophy of innervated muscle and therefore highlighting another potential treatment group. It is interesting that if reinnervation occurred within the expected 2 years after injury, why it was not apparent earlier. The subject had adapted to manage without triceps function and therefore any fibres that were reinnervated did not receive loaded exercise and have become disused. It is speculation, as to whether functional use could have been restored, had stimulation treatment been applied much earlier, either before or after reinnervation, but the evidence cited in this work does suggest this. Certainly it is apparent that without the prompting of a treatment programme, the subject lacks the motivation to perform daily voluntary exercises with no functional outcome and it is probable that a refinement of the EMG based bio-feedback technique would be very suitable for this subject.

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3 Also observed by LeFlohic – personal communication September 1999
8. CONCLUSIONS AND FURTHER WORK

8.1 Study Conclusions

The review of existing studies revealed that direct stimulation of complete lower limb denervation is being developed successfully towards functional standing. However the therapeutic benefits to tissue properties remain to be fully quantified and the application to partial limb denervation yet to be fully explored. The preliminary clinical investigations conducted in this study were not envisaged to fully test the hypothesis of the therapeutic benefits of long pulse biphasic stimulation to chronically denervated muscle, but to confirm the efficacy of the particular technique and the equipment developed.

The study has confirmed the findings of others that such stimulation treatment can restore the contractile ability of chronically denervated muscle through a progressive increase in muscle excitability, allowing a transition from twitch to tetanic isometric and then to isotonic contractions. This was demonstrated for three distinct treatment groups, near complete limb denervation (using rectangular shaped pulses), partial limb denervation (initially using trapezoidal pulses) and innervated muscle subject to long term disuse. However unlike other studies, functional use of this contractile ability was not demonstrated, either because of limitation in the technique adopted, or more probably, insufficient duration of the treatment period. In particular, difficulties of selectively stimulating a denervated muscle amidst surrounding innervated muscle were encountered and this limited the development of the muscle towards a functional contraction, even with prolonged treatment and as experienced in other studies. Trapezoidal shaped pulses were successful in selective recruitment of denervated muscle, but the intensity rise rate required for nerve accommodation precludes progression to tetanic frequencies. This highlights the need for a more sophisticated stimulation technique or other combinational therapy to allow selective treatment in cases of partial denervation.

The study was similarly inconclusive with regard to the therapeutic benefit of the treatment. The evaluation measures are suggestive of selective improvements in each of the measures, skin temperature, limb blood flow, tissue thickness and joint mobility. It is noteworthy, that the subject experiencing greatest benefit, had the longest and least disrupted treatment period, suggesting that its limited duration was the primary reason for the lack of significant changes. However, given that the changes observed in a previous study at SDH with shorter treatment period were not repeated, suggests other influencing factors, such as the length of period of denervation. Also apparent is the considerable variability in the evaluation measures, which may have masked any change or trend which occurred below this threshold. For the skin temperature and tissue thickness measurements,
much of the variability can be attributed to measurement artefacts. Whereas for limb blood flow, measurement technique artefacts are likely to be a contribution but not the sole cause of its variability, which has been shown to be naturally high and therefore highlighting its disadvantage as an evaluation measure in this application.

Of the subjects themselves, those with near complete limb denervation, are convinced of the value of the treatment. Although the psychological effect of activity in an otherwise long dormant limb may be temporary, subjects were obviously more aware and taking greater care of their denervated limb than they had done previously. The sensations induced in the limb, the visibility of its movement and the act of participating in some exercise, enhanced motivation for attention to and in some cases use of the limb, for instance in passive frame standing. These factors can therefore act as a prophylaxis, quite apart from any measured improvements to tissue quality. In addition, some subjects cited increases in sensory perception and the relief of joint and other aches as definite, desirable benefits of the treatment and all wished to continue with it. Only in the case of partial denervation when the treatment was directly aimed at a functional outcome (that of restoring dorsiflexion), though not achieved, was it perceived not to be worthwhile continuing with the present technique alone. However it is probable that the restoration of contractile ability, loading and stretching of tendons and joint may prove to be a positive contribution to the eventual treatment option.

These investigations were originally intended as a forerunner to further clinical investigations and as such, have highlighted a number of limitations to be addressed in regard to the stimulation technique, the equipment, the study design and the evaluation measures chosen.

8.2. Suggested Considerations for Future Investigations

8.2.1 Stimulation Technique Considerations

1) All the subjects experienced some skin reaction, such that careful attention to the skin and electrodes was required. In particular, for a number of subjects, the skin became dehydrated and, in extremes, hardened, which delayed and diminished contraction response. Moisturising agents were required to counter this but raised concern over their suitability and possible tissue absorption.

2) Larger electrodes, appear to reduce skin reaction and recruit greater muscle area but necessitate greater stimulation current to achieve the same perceived contraction strength.

3) Stimulation intensity was restricted to the level of localised dysreflexive sweating and the unconfirmed possibility that the skin burns experienced were due to current concentration in sweat pores. The large conductive rubber electrodes inside wetted towelling sleeves used
by Kern, Hofer et al. [1999] permit greater current and strength of contraction at the expense of inconvenience of application.

4) Because of the delay in the start of contractions at the start of sessions, longer contraction duration and session lengths were used than in other studies and raise the concern over possible muscle damage, although none was observed. A rest interval of 10min within sessions and of 1 or 2 days per week may therefore be advisable.

8.2.2 Stimulator Unit Improvements

1) Multiple mode selection to permit concurrent treatment with a number of sets of stimulation parameters, for instance in the transition from twitch to tetanic contractions, allowing continued conditioning of less responsive fibres and gradual sensory accommodation to a change in parameters.

2) Multiple channel output to permit simultaneous stimulation of the same muscle group, with superimposed fields to improve selectively, or of multiple muscle groups for therapeutic or functional purposes. Possible simultaneous high frequency blocking waveforms.

3) Ramped stimulation envelope to permit a gradual increase in contraction strength during isotonic training, avoiding the current jerky movement.

4) Integral indicator of stimulation output current.

5) Pulse width range extension to 10µs and 300ms for Strength Duration curve testing.

6) Improvement in Output Power Module efficiency to permit more compact unit for functional use.

7) Improvement of User Interface ease of use, display of stimulation output pulse shape and automation of pulse selection and intensity recording for Strength Duration curve testing.

8) Incorporate interface with foot switches to control stimulation for gait assistance.

8.2.3 Study Design Improvements

1) Extend treatment period to 12 months preceded by a pre-treatment period of at least 3 months for collection of at least 4 reliable baseline evaluation measurements. Follow-up period should also be at least 3 months.

2) Evaluation measurement visits may be less often (probably once a month after the initial month) but of longer duration to allow more regular inclusion of all measures and for instance, post stimulation treatment measurement of skin temperature and blood flow until stabilised to determine effect on peak and average values, rather than just resting.
3) Evaluation measures should be performed in a temperature and humidity controlled environment with sufficient time allowed for acclimatisation with the subject in the supine measurement position.

4) Infra red thermography measurement would be improved by use of a frozen towel as background to enhance the contrast for very cool limbs.

5) Limb blood flow measurement should be performed with the subject supine. Repeat measures should be performed with at least 5 minutes interval between If Impedance Plethesmography is to be used, concurrent measurement of cardiac measurement is recommended to guide the choice of beat duration and correlation with another measurement technique to account for variability.

6) Tissue thickness measurements should be repeated three times at each occasion. Adequate limb support should be provided without causing tissue distortion.

7) Measurement 'raw data' (ultrasound and thermograph images and blood flow waveforms) should be stored to permit comparison for consistency of interpretation. Ideally, processing should be performed or repeated at one single occasion for final results.

8) Subjects should be advised not to perform treatment on the day.

8.3 Further Work

In addition to continuing the investigation of the therapeutic value of direct stimulation, the following are also suggested as in need of investigation.

1) Investigate the therapeutic efficacy of treating multiple muscle groups of each limb.

2) Development of suitable means of assessing muscle damage effects of stimulation to assist in the optimisation of stimulation parameters and treatment patterns.

3) Investigation into the optimisation of electrode design, in terms of dimensions and materials, including the possibility of current concentration in sweat pores, charging effects and chemical interchange with the skin.

4) Investigation of methods of minimising co-contraction of innervated antagonist or adjacent muscles, for instance to permit functional stimulation for 'dropped foot' compensation.

5) Further experience of the Strength-Duration curve as a diagnostic tool and to guide stimulation parameter selection.
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Chapman Hill.


This Appendix has been intentionally omitted
1. Study Title

Investigation of Long Pulse Biphasic electrical stimulation of long term denervated muscle in humans to evaluate therapeutic and functional benefits

2. Investigators

This study is being conducted by the University of Surrey Biomedical Engineering Group in conjunction with Salisbury District Hospital (SDH) Medical Physics and Biomedical Engineering Department (MPBE).

The investigators involved in the study are;

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Physiotherapy and other staff of Salisbury District Hospital will also be involved

3. Research Background

In conditions where the nerve to the muscle (lower motor neurone) is no longer completely functional the muscle is said to be denervated, voluntary control of contraction and therefore the muscle function is lost or impaired. This may be caused by direct injury of the nerve, compression or infection and can occur at the spinal nerve roots, plexi or more peripherally. Typically, muscle wasting occurs, especially of the contractile elements, together with changes in the muscle fibre membrane, which if prolonged can hinder successful re-innervation. Muscle capillary density and blood flow are also reduced, such that if re-innervation does not occur, for instance in cases of complete limb denervation, the limb may be more susceptible to poor skin condition, infection, prolonged wound healing or sores in addition to poor cosmetic appearance and diminished personal esteem of the patient.

These effects may be less pronounced in cases of partial denervation, but re-innervation may still be hindered by muscle atrophy and so the greater potential for restoring useful muscle function may be lost. However partial function may be restored in such cases surgically by the transfer of tendons from an innervated muscle and control either voluntarily or by electrical stimulation.

It is therefore desirable to seek to minimise or at least partially reverse the changes occurring following denervation, either to increase the chances of successful re-innervation and restoration of muscle function or where this is unlikely, to improve the tissue bulk and perfusion for preventative and cosmetic reasons.
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It has been postulated whether such improvements may be achieved by externally initiated contraction of the muscle. Indirect electrical stimulation of innervated muscle via its nerve in patients with spinal cord injuries has been shown to restore the reduction of muscle bulk (typically 50%) and limb blood flow (typically 45%) to near normal values over a period of 3 months. [Taylor, Ewins et al. 1992]. Contraction of denervated muscle is possible by electrical stimulation of the muscle fibres themselves, known as 'direct stimulation', but requires greater intensities and pulse widths than indirect stimulation.

Conventional electrical stimulation therapy for denervated muscle consisted of long duration (>150ms) 'galvanic' pulses producing twitch type contractions. The frequency of these single polarity, monophasic pulses was limited to approximately 1 per second because of fatiguing of the muscle and by the potential damage to skin and electrodes because of the lack of charge balance [Eichhorn, Schubert et al. 1984]. The lack of available equipment for regular unsupervised treatment precluded improvement in the muscle contractile strength and therefore produced little therapeutic benefit such that the technique has largely been abandoned as a therapy [Boonstra, Van Weerden et al. 1987; Taylor, Ewins et al. 1992].

Use of balanced, alternate polarity, Biphasic pulses with no net charge transfer to the tissue can allow pulse widths of approximately 20-30ms and frequencies sufficient to achieve tetanic contraction of the muscle. Depending on the period of denervation, it may be necessary to commence with twitch contractions from pulse widths of up to 150ms, with a progressive reduction and transition to tetanic contractions as the contractile mechanism of the muscle fibres is restored, which may take 3-4 months [Kern, et al. 1995]. Treatment with this Long Pulse Biphasic (LPB) stimulation for up to 30 minutes each day for 8 months or longer in recent studies have demonstrated sustained improvements in muscle contraction force and bulk and limb blood flow in lower and upper limb ([Kern 1995],[Mokrusch, Neundorfer 1994],[Taylor, Ewins et al. 1992],[Petrofsky 1991],[Eichhorn, Schubert et al. 1984]). All were long term, greater than 1 year post injury and most were complete lesion cases. However, some state that improvements were dependent upon achieving tetanic contractions [Kern, et al. 1995].

Electrical stimulation in some animal studies indicated a detrimental effect on muscle re-innervation [Brown, Holland et al. 1979], but employed significantly different stimulation parameters to those in studies on human muscle. Re-innervation was shown not to be inhibited by long pulse stimulation treatment [Mokrusch, Neundorfer 1994] and indeed some current unpublished research indicates that it may be enhanced by different stimulation parameters, and may therefore also be advocated for acute cases before excess muscle atrophy occurs.

Other studies have concentrated on restoration of the function of denervated muscles, so as to maintain standing [Eichhorn, Arndt et al. 1987] or foot dorsiflexion [Valencic, Vodovnik et al. 1986]. In many of these incomplete lesion cases, treatment was hindered by recruitment of functioning sensory fibres. Gradually increasing the stimulation intensity using trapezoidal shaped pulses, is known to allow accommodation of surrounding nerves [LeFlohic, et al. 1994] and may alleviate excess sensation of stimulation and adverse recruitment of neighbouring functioning muscles.
4. Study Objectives and Hypothesis

The objective is to investigate the effects of electrical stimulation of long term (greater than 1 year) denervated muscle in humans using Long Pulse, Biphasic pulses and surface electrodes in respect of:

a) quantitative evaluation of therapeutic benefits (in terms of muscle bulk, limb blood flow, skin temperature),

b) optimisation of stimulation parameters including any progressive reduction in pulse width,

c) evaluation of trapezoidal pulse shape and variation of the rate of increase and decrease of stimulation intensity for reducing stimulation sensation and recruitment of neighbouring muscles in cases of partial denervation (sensory or sensory and motor),

d) eventually to evaluate possible functional benefits (contraction strength, restored muscle function, improvements in Activities of daily living).

The hypothesis that therapeutic and functional benefits may accrue from such treatment is based on favourable results from previous studies [section 3]. However, it is known from these that the response does vary between individuals and benefits are not guaranteed.

5. The treatment

The treatment under evaluation consists of twice per day sessions, of electrical stimulation with biphasic pulses of a suitable denervated muscle, using surface electrodes and a battery powered stimulator unit at the subjects home. Subjects will commence with five minute sessions, but this will be increased during the trial, up to a maximum of 30 minutes and reviewed at each hospital visit. The stimulation pulse width is expected to be progressively reduced during the treatment period (initially up to 150ms) allowing a transition from the single twitch to fused, tetanic contractions, necessary for therapeutic improvements. This is expected to be completed within 3-4 months [section 3] and the pulse width and frequency found to produce the most effective contraction will be used for the remainder of the 6 month treatment period. Stimulation intensity will be adjusted by the subject to achieve a reasonable and tolerable strength of muscle contraction, though initially and after the transition to tetanic contractions, it will be progressively increased from a lower value to avoid overloading of muscles, tendons and joints. Rectangular shaped pulses will be used, unless trapezoidal shaped pulses are required to minimise stimulation of sensory nerves or neighbouring muscles.

6. Evaluation Measurements

Monitoring and evaluation of the treatment will occur at regular visits by subjects to Salisbury District Hospital MPBE Department during the treatment and follow up periods. The measurement techniques are all well established, non-invasive and cause minimal discomfort to the subject. Standard equipment is to be used [Section 12] which has been checked for compliance with the relevant sections of the Medical Equipment Standard (BS5724 Part 2).

To allow quantitative evaluation of the treatment, the following measurements will be made on the limb of the muscle undergoing treatment and the contralateral where appropriate to the subject’s condition, as a control. These parameters are known to decrease with denervation in common with other forms of muscle immobilisation. Measurements a), c) and d) were used to evaluate the effect of stimulation training of innervated and denervated muscle of spinal cord injured patients and showed significant increases [Taylor, Ewins et al. 1992]. This is of particular
therapeutic benefit where a complete or near complete limb is impaired. In cases of partial limb denervation, these changes may be smaller but any increase in \( f \) of greater value to the subject;

a) **muscle thickness** using linear array ultrasound on the selected muscle beneath the electrodes and at standard anatomically identifiable locations in-between. Measured prior to stimulation at each hospital visit. Limb is to be fully extended passively (if possible) and supported away from the muscle being measured. The thickness of surrounding muscles and other tissue will also be obtained where possible, to evaluate the selectivity of the stimulation, and which may account for changes in the other parameters.

b) **limb girth** measurement at the same time and locations as muscle thickness using a standard measuring tape to the mm.

c) **limb blood flow** using electrical impedance plethysmography, measured prior to and following stimulation treatment at each hospital visit.

d) **skin temperature** using Infra-red thermography at set angle of projection, measured prior to and following stimulation treatment at each hospital visit.

e) **muscle innervation/ stimulation sensitivity** using Strength-Duration curve determination for pulse widths from 0.1 to 300ms prior to stimulation treatment at each visit.

f) **force generated** by muscle contraction (where appropriate) using hand held dynamometer on appropriate part of limb, measured prior to and after stimulation treatment at each visit.

The following are measured to monitor for fluctuations which may affect baseline comparison and for the occurrence of autonomic dysreflexia as a result of treatment, which if severe may prevent its continuation;

g) **blood pressure** using standard automated cuff, at regular intervals throughout each hospital visit, including prior to, during and after stimulation treatment.

h) **heart rate** by same method and at the same times as blood pressure.

i) **body weight** at the beginning and end of treatment and follow-up periods.

The following assessments will also be performed subjectively, as a means of evaluating the treatment and to monitor for any adverse effects which may be alleviated by change of electrode type, position or stimulation parameters;

j) **limb examination** for sores, wounds, oedema, swelling and where appropriate, range of motion of relevant joints by a suitably qualified therapist including assessment for contractures, or abnormalities of movement.

k) **skin condition** including colour and hydration, from the judgement of investigator and comments from subject. **Video recording and photographs** will be taken of the limb providing the subject has given prior consent.

l) **skin reaction** to the stimulation electrodes.

m) **sensory assessment** - subjects will be asked to quantify the sensation of a given level of stimulation in terms of its nature/duration and intensity (0-10 scale).

n) **nature and strength of contraction** by video recording and photographs of the limb undergoing stimulation treatment, providing the subject has given prior consent.

o) **general observations** at hospital visits and daily by the subject, such as, ease and motivation for performing the treatment, ease of doing relevant daily living activities, limb and body temperature, neurological and autonomic effects (eg: sweating, breathlessness, disruption of bladder control).
The stimulation equipment [section 12] has been checked by SDH MPBE department for compliance with the relevant sections of the medical equipment standards (BS5724 Part 2) and correct operation will be confirmed by the investigators at each visit to the hospital. Mains isolation is ensured by internal battery power source, and when under the control of the computer, connection is optically isolated.

In common with all forms of electrical stimulation, excessive current through the heart is potentially fatal. The risk of this occurrence will be minimised by careful instruction of the correct stimulation technique, including strict instruction never to place electrodes across the heart or allow stimulator use or application by untrained persons. The subject and/or carer will have to demonstrate understanding and competent use of the stimulation equipment, which will be monitored at the measurement visits. This will also minimise the risk of excess loading of muscle, tendons or joints from incorrectly positioned electrodes or excess intensity of stimulation.

Controversy exists regarding the effect of electrical stimulation on nerve re-growth and therefore the potential detrimental effect on muscle re-innervation. Subjects for this study will be at least 1 year post denervation, after which re-innervation is very unlikely to occur.

Localised erythema (reddening of the skin) at the site of electrodes is normal with electrical stimulation and dissipates within 1-2 hours. Greater reaction will be identified at hospital visits or by the subject and may be alleviated by electrode position and type, but excess will preclude participation. Skin damage can arise from excess intensity or duration of stimulation. The risk of this from electrodes peeling from the skin is minimised by using a constant voltage output. The risk from incorrect use by the subject, or from an equipment fault, is minimised by monitoring of the output and duration of treatment session and automatic shut down of stimulation output with a warning to the operator.

The sensation of stimulation can be mildly discomforting at first, but is soon accustomed to, and may be alleviated by electrode position or stimulation parameters. Some autonomic response to the stimulation is possible which will be monitored for at the hospital visits. Subjects will be instructed to look out for any adverse reaction to the treatment, and to contact the investigators for advice whenever necessary.

The evaluation measurement techniques are all well established, non-invasive, and without known hazard. The measurement visits will last approximately two hours and subjects will be instructed to take necessary precautions against pressure related injuries during these and the daily stimulation sessions.

Subjects will be warned of the discipline required in performing the daily stimulation treatment and attending the hospital for visits. Also not to expect any dramatic benefits from the treatment. Subjects are free to withdraw from the study at any time without needing to give a reason.
8. Study design

a) Study type
The trial is a one year pilot case study with 5 subjects and no control group, consisting of a treatment period and subsequent follow up period without treatment. The study will be mostly of an exploratory nature as the exact treatment (stimulation parameters) will vary between individuals, dependent on the condition and the duration of denervation, and will be based on that of previous studies. Measurements will be taken throughout the trial period to quantify the effects of treatment but these will be evaluated on an individual case basis.

b) Trial duration
Providing subject compliance, the treatment period will last for 6 months, as evidence from previous studies [Taylor, Ewins et al. 1992] suggests that changes in the evaluation measurements will stabilise within this period or at least the trend of any change will be well established. The follow-up period without stimulation treatment will also be for 6 months. Funding for the trial cannot support continuation of treatment beyond the trial period, however this may be possible if additional funding is available.

c) Sample size
Subject numbers are not intended to permit statistical analysis of results, but rather an indication of the effect of the treatment, its clinical feasibility and some optimisation of stimulation parameters. If findings are favourable, the study may be expanded to evaluate the effectiveness of the treatment over a range of neuro-muscular conditions.

d) Treatment Controls
Subjects with a stable long term condition will be selected and serve as their own controls; with all receiving the treatment. The effectiveness of the treatment will be determined by evaluation measurements [section 6] taken at regular intervals throughout the trial. Measurements prior to treatment will be used as baseline levels for comparison and it is assumed subjects condition sufficiently stable not to justify an extended baseline measurement period, especially as contra-lateral measurements will monitor for fluctuations in baseline levels during the treatment period. Measurements during the follow-up period, without treatment will serve to confirm positive effects of the treatment.

e) Analysis of Evaluation Measurement Data
The measurements taken at the initial assessment visit are to assist in the selection of subjects. The baseline value for each parameter will be that obtained at the baseline measurement visit.

The values of the measured parameters and the percentage change from the baseline values will be presented with respect to time (for treatment and follow-up periods) for each subject of the treatment limb and contra-lateral. Comparison between subjects may not be appropriate because of differences in condition and stimulation parameters, especially in the duration of treatment with tetanic contractions, which are thought to be required to produce beneficial effect [section 3]. However with this caveat, the average percentage change for all subjects in each parameter may be similarly presented together with the corresponding variance. The data will therefore also give an indication of the variability in between subjects.

Comparison with contralateral measurements may assist in the interpretation of results, but may be influenced by other factors, especially if the extent of denervation and therefore daily muscle activity differs. It is also possible that these may be altered by some autonomic or neurological mechanism as a result of the stimulation.
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9. Subject Selection

The trial is to be conducted on 5 subjects, to be selected from previous referrals to Salisbury District Hospital MPBE or Spinal Treatment Centre, who have shown evidence of denervated muscle. To avoid any potential hindrance to nerve re-growth, these are to be at least one year post injury. Subjects will be sought with a denervated muscle that can be selectively stimulated with an acceptable level of recruitment of any neighbouring innervated muscle and/or sensory nerve fibres and easily accessible for evaluation measurement; a complete lesion of the lower limb and stimulation treatment of the quadriceps muscle group being the most suitable. To allow intersubject comparison, maximum commonality of condition and stimulated muscle is desirable. Subjects should be well adjusted to their medical condition, show comprehension of the trial format, treatment and limitations and indicate sufficient commitment for participation. Priority will be given to those candidates living closest to Salisbury to minimise travelling inconvenience and cost where consistent with the other considerations.

Prior to any participation in the trial, the approval of the subject’s GP/consultant will be obtained. The medical history of each subject will also be reviewed by the medical consultant for the trial.

The main reasons for exclusion of candidates are:

a) objection from the subject’s GP/consultant or trial consultant,
b) excess or large variation in heart rate and/or blood pressure or history thereof,
c) heart pacemaker or other implanted device which may be affected by electric fields,
d) other electrical stimulation device or therapy,
e) involvement in other research studies which will affect the results of this trial,
f) pregnancy,
g) local active pressure sores or wounds or less than 1 year post local surgery,
h) tissue oedema or broken skin in the vicinity of the selected muscle,
i) joint contractures, swelling or other skeletal or muscular abnormalities in the limb of interest affecting range of motion,
j) expected re-innervation (injury less than 1 year),
k) age, less than 20 years or greater than 60 years, approximately, unless commitment to trial can be reasonably given and other medical complications are unlikely to arise,
l) absence of muscle suitable for stimulation and accessible for evaluation measurement
m) intolerance to stimulation (eg. sensation, skin reaction to stimulation electrodes, joint swelling, unacceptable autonomic effect such as headaches, or excessive blood pressure)
n) adverse recruitment of neighbouring muscles especially if causing unreasonable movement, spasm or pain,
o) unsuitable disposition such as nervous of stimulation treatment, lack of commitment for duration of trial or excessively optimistic expectations of the benefits from it,
p) unsuitable lifestyle or home environment to ensure regularity of treatment and measurement visits,
q) inability of subject or carer to demonstrate competent use of the stimulation equipment or comprehension of the required treatment routine.
10. Outline Plan of Trial

a) Information Sheet
Candidate subjects and their GP/consultant will each receive an information sheet explaining
the reasons for the trial and the requirements on participating subjects.

b) Initial Assessment Visit
With their GP/consultants approval, candidates will be invited individually to attend without
obligation, an initial assessment visit at SDH MPBE Department to evaluate their suitability
for participation in the trial. This will last up to 3 hours and be conducted by a hospital
Clinical Scientist, the university investigators and a suitably qualified therapist.

Subjects will be requested to refrain from alcohol for 24 hours and from food and drink and
vigorous exercise for 1 hour prior to the visit and to wear suitable clothing (eg: shorts and
short sleeved top). A chaperon will be provided for female subjects if necessary. Precautions
against pressure induced tissue damage will be taken and subjects instructed to bring with
them any custom made equipment.

The visit will commence with an explanation of the format of the trial and stimulation
treatment with respect to the Consent Checklist to ensure the subject understands the
requirements of their participation. The subject will be asked to provide written consent if
willing to participate. In addition to the review by the medical consultant for the trial, an
external examination [6.j]] will be performed by suitably qualified therapist with regard to
the exclusion criteria for participation [9.j].

To identify a muscle or muscle group suitable for treatment and evaluation measurements,
the standard electro-therapy technique of Strength-Duration testing [6.e]] will be used to
explore the extent of denervation of the limb. Optimum stimulation parameters and electrode
position will be determined for each candidate denervated muscles, with regard to strength of
contraction, recruitment of neighbouring muscles, sensation or other responses. The most
appropriate muscle or muscle group, if any, for treatment and assessment will then be
selected and stimulated with the chosen parameters for a period equivalent to that to be used
during the initial week of the trial (5minutes). Subject tolerance and compliance to this will
be assessed including regular blood pressure and heart rate measurements [6.g,h]] and
external-examination [6.j]] with special regard to skin and other possible reactions. Subjects
will be encouraged to comment on the sensation of stimulation and report any noticeable
effects.

Evaluation measurements [6.a-h]] will be performed at the specified times during the visit to
ensure their feasibility for the subject, allow them to become accustomed to the procedures
and provide additional confirmation of baseline values.

c) Baseline Measurement Visit
For each of the selected subjects willing to participate in the trial, a second visit to SDH
MPBE will be arranged at least a week later for baseline values of evaluation measurements
to be obtained. This will be conducted by a university investigator under the supervision of
qualified MPBE staff and last up to 3 hours.
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The format of the visit will be similar to the initial assessment with a check for contra-indications to stimulation including blood pressure and heart rate measurements and an external examination. A period of stimulation treatment equivalent to that to be used during the initial week of the trial (5 minutes) will be performed after confirming the previously identified electrode positions on the selected muscle as optimum for the chosen stimulation parameters. Evaluation measurements [6a)-i)] and assessments [6k)-o)] will be performed at the specified times and after the stimulation, an external examination to check for skin or other reaction. Subjects will be encouraged to comment on the sensation of stimulation and report any noticeable effects.

Positioning of electrodes, connection to the stimulator and adjustment of stimulation intensity to achieve the required level of contraction will be demonstrated to and practised by the subject and/or carer. Full instruction in the use of the equipment will be given with reference to the User Instruction Manual; including all controls and indicator lamps and that the unit should be switched off and the researcher contacted in the case of failure, whether indicated or not. Warning will also be given of the potential risk from misuse of the unit and the necessity of keeping it out of the reach of children. Connection of the stimulator unit to the battery re-charging unit will also be demonstrated.

The required daily stimulation treatment routine will be discussed with the subject including timetabling and environment, to ensure they can realistically undertake participation. The format of subsequent regular measurement visits will be explained and dates provisionally agreed. The subject will then take home a stimulator unit programmed with their treatment parameters, battery charger and leads, supplies of electrodes, an User Instruction Manual for the equipment and treatment Observation Sheet.

d) Stimulation Treatment

At home, subjects will be required to perform the stimulation treatment of the selected muscle twice a day as demonstrated at the hospital visit. These sessions should be of the duration and times agreed with each subject at the previous measurement visit and any variation from this should be recorded on the Observation Sheet. They will also be encouraged to note down any observations regarding the stimulation, such as the comparative level of sensation, ease of obtaining a contraction and therapeutic or functional effects arising from the treatment, such as limb sensation, temperature, skin condition or colour, or ease of doing daily living tasks. Subjects will be instructed to examine themselves for swelling, skin reaction and be for aware for autonomic responses and, that in the case of any adverse reaction, to cease treatment and contact the investigators immediately or seek other medical assistance.

e) Measurement Visits

Each subject will be required to re-visit MPBE department at Salisbury for repeat measurements of those taken during the baseline measurement visit. These will occur at one week intervals for the first month, at two week intervals for the second and third months and at 4 week intervals thereafter. The total number of visits to MPBE Salisbury by each patient will therefore be 13 over 6 months and 19 over 12 months. The higher frequency of visits may be maintained if measurements indicate a continued rapid change. Visits will last about 2 hours and be conducted by one of the university investigators under the supervision of
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qualified MPBE staff. Ideally they will all be arranged at the same time of day for each individual subject.

Subject stimulation technique, parameters, electrodes position, treatment session duration and skin or other reaction will be reviewed at each occasion and the stimulator re-programmed accordingly. As the subject becomes more accustomed to the stimulation, the duration of the daily treatment session may be increased up to a maximum of 30 minutes with subject tolerance of this confirmed during the visit. If tetanic contractions become possible, the session duration may be decreased and then progressively increased again to allow the subject to become accustomed to this form of contraction.

The treatment may have to be ceased if adverse reaction to the stimulation is observed, such as excessive heart rate or blood pressure. Adverse skin reaction may be avoided by changing the type of electrodes or stimulation parameters, but if persistent this may also preclude continuation of the treatment.

11. Subject records  

Measurement data, video recordings and photographs of subjects will be kept confidential, referenced only by a subject identification code the details of which will be kept separately from the records. This and other subject information will be accessible only to the investigators. It may be made available to the subject’s GP/consultant on request, but will be anonymous if presented in publicly in reports, journal articles or conference proceedings. Additional written consent will be obtained from subjects to allow video recordings and photographs to be taken and if these are permitted to be presented publicly. Where the anonymity of the subject cannot be preserved in such material then these will be stored separately from other records.

12. Equipment for Trial  

a) Stimulation Equipment  

1) LPSTIM10 Long Pulse Stimulator Unit manufactured at University of Surrey to BS5724 Part 2 guidelines  
• self contained, portable unit (150x170x55mm), powered by an internal battery,  
• single channel bi-phasic stimulation output in accordance with stored set of parameters;  
  • stimulation intensity 0-100mA, 0-100V,  
  • pulse width 1-500 ms ( both positive and negative impulses)  
  • pulse rise time 0.5 - 250ms (linearly increasing)  
  • inter-pulse interval 30ms- 12s  
  • variable pulse repetition pattern  
  • maximum treatment time limit of 30 minutes  
• internal monitoring inhibits output in case of excess output, electrodes not connected, low battery level or detected circuit failure  
• operator controls for ON/OFF, stimulation intensity and mode selection  
• indication of ON state, stimulation output pulse , output inhibited , battery level low  
• external connection to stimulation electrodes or battery re-charging unit (mutually exclusive) , Personal computer, and Control Signals  

2) Re-charging unit - mains powered for re-charging stimulator unit battery in situ.  

3) Stimulation Electrodes - standard surface stimulation electrodes
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4) Opto-isolator interface unit for connection of Stimulator unit to PC
5) Personal Computer (PC) with LabVIEW user interface programme to allow
   • control of stimulation parameters ‘on-line’ during stimulation
   • downloading of parameters into stimulator unit for independent operation
   • Strength-Duration measurement, controlling pulse width and monitoring intensity

b) Evaluation Measurement Equipment [section 6]
   a) Muscle thickness
      Dynamic Imaging System XLF Linear Array 3.5 MHz Ultrasound scanner, producing a
cross-sectional image of the underlying tissues which may be printed. Measurement
through non-absorptive gel pad to prevent tissue deformation. Non-allergenic, water based
gel used on skin to provide good ultrasound signal transmission into tissue.
   b) Muscle girth measured with standard flexible measuring tape to nearest mm.
   c) Limb Blood flow
      Minnesota Electrical Impedance Cardiograph [Porter, Swain et al. 1985; Porter, Swain
1986] and 2 pairs of circumferential stainless steel electrodes, mounted 4 cm apart on
webbing straps which are placed at either end of the body segment of interest. The
equipment passes a 100kHz, 4mA signal between the two outer electrodes. The rate of
change of electrical impedance measured between the inner electrodes is proportional to
the pulsatile blood flow, from which actual blood flow can be calculated.
   d) Skin Temperature
      Thermovision 780 SW Scanner System - Infra-red video camera and PC based image
display of temperature of objects within field of view, following calibration against an
object of known temperature,
   e) Muscle sensitivity/innervation
      Strength-Duration testing is a standard electro-therapy technique in which the muscle of
interest is stimulated with single pulses of widths; 0.1, 0.3, 1.0, 3.0, 10, 30, 100 and
300ms, whilst the corresponding intensity required for each to obtain a minimum
contraction response is recorded. The stimulation pulses and intensity measurement will
be achieved using the LPSTM10 Stimulator unit.
   f) force generated
      Hand held Dynamometer held against the limb of interest at a suitable position
   g) skin condition & nature of contraction
      standard portable video camera, tripod, VHS recorder, photographic camera
   m) body weight - standard scales or sling harness scales as appropriate
   n.o) heart rate and blood pressure - standard portable, combined automated monitor

13. Resources

a) University will manufacture, test and maintain stimulation equipment
b) SDH will supply measurement equipment and any associated consumables
c) Travelling costs of subjects will be met by the Inspire Foundation, who have provided £1500.
University of Surrey Biomedical Engineering Group
in conjunction with
Salisbury District Hospital Medical Physics and Biomedical Engineering Department.

DENERVATED MUSCLE STIMULATION TRIAL

Research Protocol

14. References


Electrical stimulation is now used quite extensively for the toning of muscles to enhance cosmetic appearance and strength. It can also be used to restore muscle function, such as raising the foot during walking, grasping of the hand, control of breathing and internal organs. This treatment involves stimulation of the nerve controlling the muscle with an electric field from electrodes applied to the skin surface or implanted near the nerve and is used by people who have damage to their brain or spinal cord (typically T12 and above).

In conditions where the nerve to the muscle is no longer functional the muscle is said to be denervated. Typically muscle wasting occurs and there is a reduction in blood flow. Recent studies have shown that these effects can be at least partially restored by electrical stimulation of the muscle fibres themselves, known as 'direct stimulation'. However, this requires greater intensities and pulse widths than stimulation via the nerve and careful application of the stimulation current to ensure there is no skin damage.

The purpose of this study is to quantify the effects of using Long Pulse Biphasic (LPB) electrical stimulation on the tissue quality of long term denervated muscle. We will also evaluate the effectiveness of variation of stimulation pulse shape at minimising the sensation of stimulation and later, investigate the possibility of producing functional muscle use. The initial trial will be conducted on 5 volunteer subjects over 12 months, progressing with additional volunteers if results appear beneficial. Volunteers must have lower motor neurone nerve damage due to peripheral nerve lesion, low level spinal cord lesion or a brachial plexus lesion and be at least 1 year post injury.

If you agree to participate in this study, you will be asked to attend an initial assessment visit at Salisbury to evaluate your response to electrical stimulation and to reveal any adverse muscular action, pain or skin reaction. Given satisfactory responses and your willingness (together with that of your GP or Consultant) to continue with the trial, a second visit to the hospital will be arranged at which you will be supplied with electrodes and a portable battery powered stimulator unit. You will be required to apply the electrodes to the skin and perform the stimulation on yourself twice a day, initially for periods of five minutes at a time and increasing to up to 30 minutes according to your tolerance. The strength of muscle contraction is determined by the intensity of the stimulation which will be under your control. You will receive full instruction in how to use the equipment, to position the electrodes and to identify the required level of muscle contraction. We will also discuss how best to arrange the stimulation time into your daily routine. You will also be supplied with a battery re-charging unit and be shown how to use this as necessary between treatment sessions.

In order to evaluate the effectiveness of the treatment, you will be asked to make regular visits to Salisbury Hospital lasting about 2 hours, initially at 1-2 week intervals, and extending to 4 weeks as the trial continues. Non-invasive measurements will be taken of muscle depth (using ultrasound), limb blood flow (by electrical impedance plethysmography), skin temperature (by Infra-red thermography), heart rate and blood pressure and contraction force if appropriate.
Prior to these visits, you will be requested not to drink alcohol for 24 hours beforehand or take food, drink or vigorous exercise for 1 hour beforehand, as these will affect the measurements. With your permission, stimulation of the muscle undergoing treatment will be recorded on video or photographed and these will be kept confidentially. The stimulation parameters programmed into your stimulator may also be changed at these occasions as the muscle strength develops. You will be asked to use the stimulator for 6 months and then to stop the stimulation treatment but continue to visit the hospital for measurements at monthly intervals for up to a further 6 months.

Provided the operating instructions are adhered to, there is minimal risk from the equipment which automatically protects against excessive output intensity. The measurements to be taken are all non-invasive and are well established techniques. The sensation of stimulation can be somewhat discomforting at first but one soon becomes accustomed to it. Some temporary reddening of the skin usually occurs beneath the electrodes. Excessive discomfort or skin reaction, if not alleviated by different electrodes or stimulation parameters, may preclude participation in the trial. This will be monitored regularly at the hospital visits.

You are free to decline to participate in the trial or withdraw from it at any time without needing to give a reason and without penalty or affecting future medical treatment. Equally the organisers reserve the right to decline or withdraw the treatment if it proves unsuitable, but this will usually be explained. Participants will be asked to inform the researchers of any activity or other medical treatment which may affect the results of the trial and this will be discussed at the initial visit. All personal information and correspondence associated with the trial will be held in strict confidence, available only to your GP or Consultant but not publicly. Results and measurement data of the trial will only be presented anonymously and video or photographs only with your permission.

The initial assessment visit will provide opportunity for discussion and explanation of the trial without obligation. For ease of access to muscles, please bring or wear shorts and short sleeved top (for example Tee shirt or Crop Top), also any special cushions or such like you use for pressure relief. Please feel free to bring a friend, family member or carer if you wish to. A chaperon may be provided if required. No payment can be made for participation in the trial, but your travelling expenses can be reimbursed. If you would like any further information in the meantime please contact either;

Paul Taylor
Salisbury District Hospital, Medical Physics and Biomedical Engineering Department
Tel: 01722 336262 ext 4065

Dr David Ewins or Alan Woodcock
University of Surrey, Biomedical Engineering Group, Guildford GU2 5XH
Tel: 01483 259683
1. Subject Assessment Visit

Objectives: 1) assess suitability of subject for participation in trial including,
2) identification of suitable denervated muscle or muscle group for stimulation
treatment

Location: Salisbury District Hospital (SDH)
Medical Physics and Biomedical Engineering (MPBE) Department,

Duration: up to 3 hours

Conducted by: a qualified Medical Physicist,
university investigators,
qualified therapist as required,
subject chaperon provided if necessary

Environment: comfortable temperature (~25°C) and humidity for examination

Subject position: supine or seated with the limb extended,
but will depend upon the individuals condition

Precautions: subject should;
not consume alcohol during the 24 hours before visit
not consume food or drink or take vigorous exercise for 1 hour before visit
bring/wear shorts and short sleeved top (eg; tee shirt or crop top)
bring any cushions or other custom devices for pressure relief

Procedure: (refer to Subject Assessment Form)

a) Consent check list - review of the trial, stimulation technique, medical exclusion criteria
b) Consent form if subject willing to proceed with participation,
c) heart rate & blood pressure measurement at approximately 15 minute intervals thereafter
including prior to, during and after stimulation
d) limb examination for skin condition, sores, wounds, oedema and where appropriate,
range of motion measurement of relevant joints by suitably qualified therapist including
assessment for contractures, swelling and abnormalities of movement.
e) skin temperature measurement at rest using Infra-red thermography
f) limb blood flow measurement at rest using electrical impedance plethysmography

g) demonstration of experience of stimulation on subject muscle known to be innervated,
preferably on contralateral limb with 300μs pulses and
sensory assessment subjects will be asked to quantify the sensation of a given level of
stimulation intensity in terms of its nature/duration and severity (scale of 1-10)
h) extent of denervation of the limb is to be explored from the response of muscles to
stimulation with pulse widths between 100μs (to which only innervated muscle responds)
and 300ms.

Having identified candidate denervated muscles for treatment (those only responding to
longer pulses width, an iterative process may be required to establish the following (i) & (j)
DENERVATED MUSCLE STIMULATION TRIAL

Evaluation Measurement Procedure

i) **Optimum electrode position** will be determined for the candidate denervated muscles when stimulating with pulse widths of 300ms, to maximise contraction response and minimise recruitment of neighbouring innervated muscles, pain or skin reaction. The latter may be alleviated by an alternative electrode type. Positioning may have to altered if different parameters are to be use for treatment (especially for tetanic contraction) and once established, will be recorded with respect to anatomical landmarks for future reference.

j) **Optimum stimulation parameters**, by determining for each candidate muscle the minimum pulse width possible to achieve a reasonable contraction and the frequency and intensity tolerable to the subject. This exploration will be performed with extreme caution at avoid damage to muscle, tendons or joints, especially if tetanic contractions are possible though these may not be advisable for initial treatment. If recruitment of neighbouring innervated muscles, pain or skin reaction remain excessive with reasonable stimulation intensity, then the effectiveness of alleviating with progressively longer rise and fall times to the stimulation pulses (trapezoidal shaped) will be evaluated.

k) **Selection of the most suitable muscle or muscle group for stimulation treatment and evaluation measurement for each subject** will be made.

l) **Muscle thickness** measured using linear array ultrasound scanner on the selected muscle beneath the stimulation electrodes and at anatomically identifiable locations in-between on treatment limb and contralateral.

m) **Limb girth** measured at these same locations on the selected muscle and at positions of electrical impedance electrodes on treatment limb and contralateral using standard measuring tape.

n) **Force generated** by stimulation of selected muscle with the optimum parameters, (if tetanic contraction obtained) using hand held dynamometer suitably positioned against the limb.

o) **Period of stimulation** (5 minutes) of the selected muscle with the corresponding parameters will be performed to evaluate patient tolerance of the treatment. Fatigue of any contraction obtained will be assessed and the stimulation repetition envelope may be adjusted accordingly.

  - **Nature of contraction** will be recorded on video tape, if the subject has provided consent.

p) **Skin reaction** to the stimulation electrodes will be monitored during these tests and if excessive may be alleviated by change of electrode type, position or stimulation parameters. However any alteration will require repetition of SD curve measurement and re-optimisation of the parameters.

q) **Sensory assessment** subjects will be asked to quantify the sensation of stimulation of the selected muscle with a given level of intensity, in terms of its nature /duration and severity (scale of 1-10) and beginning and end of the stimulation period.

r) **Review interview** to summarise the findings to subject and assess patient compliance to treatment including subjects own observations. Where suitable for the trial, to discuss suitable times for the stimulation and measurement visits in the subjects daily routine and any prohibitive activities or medication. Confirm participation if known and arrange date for baseline visit.
Evaluation Measurement Procedure

2. Baseline Measurement Visit

**Objectives:**
1) obtain baseline values of evaluation measurements
2) confirm stimulation parameters and electrode positions for subject
3) instruct and demonstrate use of stimulation equipment and issue to subject
4) discuss arrangements for daily stimulation treatment and observing response

**Location:** Salisbury District Hospital (SDH)
Medical Physics and Biomedical Engineering (MPBE) Department,

**Duration:** up to 3 hours

**Conducted by:** a qualified Medical Physicist,
university investigators,
qualified therapist as required,
subject chaperon provided if necessary

**Environment:** comfortable temperature (~25°C) and humidity for examination

**Subject position:** supine or seated with the limb extended, dependent on subjects condition

**Precautions:** subject should;
- not consume alcohol during the 24 hours before visit
- not consume food or drink or take vigorous exercise for 1 hour before visit
- bring/wear shorts and short sleeved top (eg; tee shirt or crop top)
- bring any cushions or other custom devices for pressure relief
- not have food or fluid intake until at least after item (f)

**Procedure:** (refer to Evaluation Measurement Form)

- **a)** body weight measurement using standard scales or sling balance as appropriate
- **b)** heart rate & blood pressure measurement at approximately 15 minute intervals thereafter
  including prior to, during and after stimulation
- **c)** limb examination for skin condition, sores, wounds, oedema and where appropriate,
  range of motion measurement of relevant joints by suitably qualified therapist including
  assessment for contractures, swelling and abnormalities of movement.
- **d)** skin colour may be recorded on video or with photographs for comparative evaluation if
  the subject has provided prior consent
- **e)** skin temperature measurement at rest using Infra-red thermography on treatment limb and
  contra-lateral or other limb
- **f)** limb blood flow measurement at rest using electrical impedance plethysmography on
  treatment limb and contra-lateral or other limb
- **g)** muscle thickness measured using linear array ultrasound scanner at the previously
  identified locations on the selected muscle on treatment limb and contralateral.
- **h)** limb girth using standard measuring tape, at these same locations on the selected muscle
  and at positions of electrical impedance electrodes on treatment limb and contralateral.
- **i)** sensory assessment subjects will be asked to quantify the sensation of
  stimulation on an innervated muscle (eg: on contralateral) with 0.3ms pulses and a given
  level of intensity, in terms of its nature /duration and severity (scale of 1-10).
- **j)** electrode position identified previously will be confirmed as optimum in respect of
  maximum contraction response and minimum recruitment of neighbouring innervated
  muscles and sensation for the stimulation parameters previously identified as optimum.
DENERVATED MUSCLE STIMULATION TRIAL

Evaluation Measurement Procedure

k) Strength-Duration curve measurement of the selected denervated muscle to provide an indication of the sensitivity of the muscle fibre membrane. The muscle is stimulated with single pulses of widths of 0.1, 0.3, 1.0, 3.0, 10, 30, 100 and 300ms, whilst the corresponding intensity required for each to obtain a minimum contraction response is measured using the stimulator itself under the control of the computer.

l) stimulation parameters for treatment will be altered if SD measurement indicates altered sensitivity (minimum pulse width).

m) force generated by stimulation of selected muscle with the optimum parameters, (if tetanic contraction obtained) using hand held dynamometer suitably positioned against the limb.

n) period of stimulation (5minutes) of the selected muscle, using the parameters identified as optimum: Fatigue of any contraction obtained will be assessed and the stimulation repetition envelope may be adjusted accordingly.

o) nature of contraction will be recorded on video tape, if the subject has provided consent.

p) sensory assessment subjects will be asked to quantify the sensation of stimulation of the selected muscle with a given level of intensity, in terms of its nature, duration and severity (scale of 1-10) at the beginning and end of the stimulation period.

At the end of the period, stimulation will be ceased and electrodes removed to allow

q) skin temperature as per (e). Measurements will then be repeated at approximately 10 minute intervals during r) to v) until stable value reached, with care to ensure the same angle of projection

r) limb blood flow measurement as per (f),

s) observation review of the effects of stimulation treatment including comments by subject with regard to neurological and autonomic effects (eg: sweating, bladder control)

t) demonstration of stimulation technique and equipment. Positioning of electrodes, connection to the stimulator and adjustment of stimulation intensity to achieve the required level of contraction will be demonstrated to and practised by the subject. Full instruction in the procedures and precautions of using the equipment will be given with reference to the User Instruction Manual. Connection of the stimulator unit to the battery re-charging unit will also be demonstrated. The subject or carer will have to demonstrate understanding and competent use of the equipment before it is issued to them. Subjects will also be instructed to examine their skin a few hours after the visit and before and after each treatment session for adverse reaction and to contact one of the research team should any occur.

u) review of daily stimulation routine, session duration. The suitability of the timetabling and of the environment for the treatment will be discussed, to ensure they can realistically undertake participation. The programme of evaluation measurement visits will be outlined and dates provisionally agreed.

v) issue of equipment to subject-a stimulator unit programmed with their optimum treatment parameters, supplies of electrodes and leads, battery charger and leads, a User Instruction Manual for the equipment and copies of the Subject Observation Sheet.
3. Evaluation Measurement Visits

**Objectives:**
1) monitor for adverse effects of treatment
2) obtain values of evaluation measurements
3) review optimum stimulation parameters and electrode positions for subject
4) confirm competent stimulation technique and use of equipment by subject
5) review Subject Observation Sheet and the effects of the treatment noticed

**Location:** Salisbury District Hospital (SDH) Medical Physics and Biomedical Engineering (MPBE) Department,

**Frequency of Visits:**
- 1 week intervals for the 1st month,
- 2 week intervals for the 2nd and 3rd months,
- 4 week intervals thereafter, unless measurements indicate a continued rapid change necessitating maintaining the high frequency of visits or transition to tetanic contractions occurs.

**Time of Day:** Ideally at the same time of day for each individual subject.

**Duration:** approximately 2 hours

**Conducted by:** a qualified Medical Physicist, university investigators, qualified therapist as required, subject chaperon provided if necessary

**Environment:** comfortable temperature (~25°C) and humidity for examination

**Subject position:** supine or seated with the limb extended, but will depend upon the individual's condition

**Precautions:** subject should;
- not consume alcohol during the 24 hours before visit
- not consume food or drink or take vigorous exercise for 1 hour before visit
- not perform the stimulation treatment session on the day of the visit
- bring their stimulator, electrodes and any broken equipment with them
- bring/wear shorts and short sleeved top (e.g., tee shirt or crop top)
- bring any cushions or other custom devices for pressure relief
- not have food or fluid intake until at least after item (f)

**Procedure:** (refer to Evaluation Measurement Form)
After a review of the daily treatment with the subject, the procedure will be as per 2(a)-(v), with the amendments as described below

a) **body weight** will only be measured at baseline measurement visit and end on treatment period if this is difficult

1) **Adjustment of stimulation parameters**
Denervated muscle is expected to become more sensitive to stimulation and respond to progressively smaller pulse widths during the initial months of treatment and will be indicated by the Strength-Duration test. As this occurs, the stimulator unit will be reprogrammed with smaller pulse width and where appropriate, increased frequency. Eventually this may permit tetanic contractions to be achieved and to which the subject may have to become accustomed, with a gradual increase in contraction strength (stimulation intensity) over a period of a few days/weeks according to their tolerance. If not already employed, it may also be necessary to introduce trapezoidal shaped stimulation pulses to
DENERVATED MUSCLE STIMULATION TRIAL

Evaluation Measurement Procedure

alleviate pain or recruitment of neighbouring innervated muscles. The effectiveness of variation in the rate of increase/decrease in intensity of each pulse at achieving this can also be investigated. As tetanic contractions become possible, the frequency of measurement visits may be increased again to monitor for the greater tissue changes expected and to ensure the subjects technique provides sufficient contraction strength without causing excessive recruitment of neighbouring muscles, abnormal limb motion or joint loading.

n) period of stimulation will be of the duration being used by the subject during the preceding week unless altered by the investigators;

Adjustment of treatment session duration
As the subject becomes more accustomed to the stimulation, the duration of the daily treatment session (and the limit programmed into the unit) may be increased up to a maximum of 30 minutes. This will be reviewed at each visit in conjunction with the stimulation parameters and subject tolerance to any change evaluated during the period of stimulation of the visit. If tetanic contractions become possible, the session duration may be decreased and then progressively increased again to allow the subject to become accustomed to this form of contraction.

o & s) Monitoring for adverse reaction
The treatment may have to be ceased if adverse reaction to the stimulation is observed, such as excessive heart rate or blood pressure. Adverse skin reaction may be avoided by changing the type of electrodes or stimulation parameters, but if persistent this may also preclude continuation of the treatment.

p) sensory assessment
If a subject develops sensation from the stimulation after previously having none, then quantifiable measurement of sensation may be introduced, such as Von Fray hairs.

t) Subject stimulation technique
The patient will be asked to apply the electrodes and adjust the level of contraction, so that their technique can be monitored and corresponding stimulation intensity will be recorded for reference. Initially this will be conducted with the subjects current stimulation parameters and will be repeated if the parameters are altered to accommodate changes in the muscle sensitivity, see (3b).

v) issue stimulation equipment
Subjects will be issued with replacements for any items of equipment found to be faulty or broken.
### Evaluation Measurement Form

**STORE SEPARATELY from Subject Personal Details**

<table>
<thead>
<tr>
<th>Subject code</th>
<th>Week No</th>
<th>Conducted by</th>
<th>Date</th>
<th>Time</th>
<th>Finish</th>
</tr>
</thead>
</table>

**Subject Observations from treatment** (page 2 for examination details)

- **Completed treatment routine**
  - Yes/No
  - Obs.

- **Skin reaction - excess**
  - Yes/No

- **Skin condition/warmth**

- **Sensation**

- **Contraction/fatigue**

- **Other m.recruitment**

- **Headaches/dizziness/breathlessness**

- **Change in ADL/mobility**

- **Other/general**

**Replacement Equipment:**
- Stimulator Unit...
- Electrodes...
- Leads...
- Charger...

**Expenses**
- £
- Receipt No.

**Medical condition/medication change**
- Yes/No
- GP aware:

**Non-prescription medication/lotions**

**Body weight**
- Kg

**Precautions for measurement**
- Pressure relieving device: Yes/No

**Last eating/drinking**
- time

**Alcohol in last 24hrs**
- time

**Last stimulation session**
- Last exercise

**Change in exercise pattern**
- Yes/No

**Change in diet pattern**
- Yes/No
## Evaluation Measurement Form

**DENERVATED MUSCLE STIMULATION TRIAL**

<table>
<thead>
<tr>
<th>Examination</th>
<th>Treatment Limb</th>
<th>Contralateral</th>
</tr>
</thead>
<tbody>
<tr>
<td>skin temperature (including from thermography)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>skin condition/feel to touch (dry/clamy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>subject sensation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rashes/sores</td>
<td></td>
<td></td>
</tr>
<tr>
<td>wounds/surgery</td>
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<tr>
<td>tissue oedema</td>
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<tr>
<td>joint swelling</td>
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<tr>
<td>joint movement/contractures</td>
<td></td>
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<tr>
<td>muscle bulk</td>
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<tr>
<td>muscle spasm/voluntary control</td>
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</table>

**KEEP INFORMATION CONFIDENTIAL**
### Evaluation Measurement Form

**Skin temperature**  seated / reclined / lying ........................................ for .......... mins.

<table>
<thead>
<tr>
<th>Time</th>
<th>Room Tmp.</th>
<th>Rel. H</th>
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<thead>
<tr>
<th>Treatment Limb</th>
<th>Contralateral</th>
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<tbody>
<tr>
<td>ext</td>
<td>area</td>
</tr>
<tr>
<td>pixels</td>
<td>min</td>
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<tr>
<td>mean</td>
<td>SD</td>
</tr>
<tr>
<td>SD</td>
<td>diff</td>
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</table>

**Photograph No.** Flash Yes / no

<table>
<thead>
<tr>
<th>Time</th>
<th>Bid Pres.</th>
<th>HR</th>
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**Limb Blood Flow**  seated / reclined / lying ........................................ for .......... mins.

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<tr>
<th>Time</th>
<th>Room Tmp.</th>
<th>Rel. H</th>
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<td>ext</td>
<td>area</td>
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<tr>
<td>d/cm</td>
<td>Zo lΩ</td>
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<td>HR</td>
<td>LVet</td>
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<td>SV/ BF</td>
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**Muscle thickness**  seated / reclined / lying ........................................

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<th>time</th>
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<thead>
<tr>
<th>Location</th>
<th>muscle thickness</th>
<th>limb girth</th>
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**Skin Sensitivity** Two Point Discrimination  Yes/No Other

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**Limb Blood Flow**  seated / reclined / lying ........................................ at rest for .......... mins

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<th>Time</th>
<th>Room Tmp.</th>
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University of Surrey Biomedical Engineering Group
in conjunction with
Salisbury District Hospital Medical Physics and Biomedical Engineering Department.

DENERVATED MUSCLE STIMULATION TRIAL

Evaluation Measurement Form

Refreshments provided Yes / No ............................................................................................

Subject Stimulation Treatment Demonstration - parameters as programmed for treatment

Intensity: Threshold ............... mA Treatment ............. mA,

Contraction nature................................................................................................................

Comments............................................................................................................................

Strength duration Curve (stimulation intensity required for minimum discernable contraction) state contraction location

<table>
<thead>
<tr>
<th>pulse width (ms)</th>
<th>100/1/1</th>
<th>Treatment limb</th>
<th>Intensity (mA/V)</th>
<th>Contralateral limb</th>
<th>Intensity (mA/V)</th>
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<td>1.0</td>
<td>1 / 240</td>
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<tr>
<td>3.0</td>
<td>9 / 91</td>
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<tr>
<td>10</td>
<td>20 / 144</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>60 / 144</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>120 / 144</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>200 / 144</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200</td>
<td>237 / 244</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Review of parameters & electrode position

Unit used............ electrodes used...

<table>
<thead>
<tr>
<th>stimulation parameters</th>
<th>Lo / Vo / IN</th>
<th>Zo</th>
<th>muscle contraction</th>
<th>other muscle recruitment</th>
<th>sensation</th>
</tr>
</thead>
</table>

KEEP INFORMATION CONFIDENTIAL
## Appendix E Evaluation Measurement Form

University of Surrey Biomedical Engineering Group
in conjunction with
Salisbury District Hospital Medical Physics and Biomedical Engineering Department.

**DENERVATED MUSCLE STIMULATION TRIAL**

### Evaluation Measurement Form

<table>
<thead>
<tr>
<th>Stimulation parameters</th>
<th>10/100/1000</th>
<th>Zo</th>
<th>Muscle contraction</th>
<th>Other muscles</th>
<th>Recruitment</th>
<th>Sensation</th>
</tr>
</thead>
</table>

**Force generated (N)** measured at...

**Stimulation for a period of** minutes **Intensity** mA

**Contraction nature**

**Fatigue**

**Other muscles**

**Skin reaction**

**Sensation**

**Other**

**Time** | **Bid Pres.** | **HR**
---|---|---
/ | / | / |

**Video. Yes/no**

**Photographs No.**

**KEEP INFORMATION CONFIDENTIAL**
## Evaluation Measurement Form

### DENERVATED MUSCLE STIMULATION TRIAL

### Skin temperature

<table>
<thead>
<tr>
<th>Treatment Limb</th>
<th>Contralateral</th>
</tr>
</thead>
<tbody>
<tr>
<td>ext area</td>
<td>ext area</td>
</tr>
<tr>
<td>pixels</td>
<td>pixels</td>
</tr>
<tr>
<td>min</td>
<td>min</td>
</tr>
<tr>
<td>max</td>
<td>max</td>
</tr>
<tr>
<td>mean</td>
<td>mean</td>
</tr>
<tr>
<td>SD</td>
<td>SD</td>
</tr>
<tr>
<td>diff</td>
<td>diff</td>
</tr>
</tbody>
</table>

### Photograph No

- Flash: Yes / no

### Limb Blood Flow

- Seated / reclined / lying: at rest for ___ mins

### Stimulation parameters

- Change: Yes / No
- Intensity: mA
- Pulse ramp: ms
- Pulse width: ms
- Frequency / i/p: Hz
- Inter-impulse interval: ms

### Electrode position

- Change: Yes / No

### Session length

- am: ___ min
- pm: ___ min

### Stimulator Programming

- TXD [P] STIM enter parameters:
  - Transfer
  - Fault levels
- Switch OFF unit
- Switch ON unit
- RXD STIM: Fill out table opposite
- RXD Fault levels: Fill out table
- RXD STATS: Check cleared

### Observation sheet

- Date: ____________
- Comments

---

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Page 6
**Subject Observation Sheet**

Use the stimulator each day at the times and for the period agreed. Fill out this sheet at each session. Any serious adverse effects, **STOP THE STIMULATION**, contact the research team or seek medical advice.

In case of **EMERGENCY**, contact your GP or emergency services, try to inform the research team.

<table>
<thead>
<tr>
<th>DATE</th>
<th>TIME</th>
<th>SESSION LENGTH</th>
<th>OBSERVATIONS</th>
</tr>
</thead>
</table>

Please bring this observation sheet with you to your next hospital visit.

Contact the research team at any time

Alan Woodcock, Dr David Ewins (01483) 259683, Paul Taylor (01722) 336262 ext 4065
<table>
<thead>
<tr>
<th>Thermographic Assessment: Significance Levels</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin Temperature Asymmetry of Limb Segments</td>
<td></td>
</tr>
<tr>
<td>Lower Limbs, supplied by SDH MPBE</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lower Limbs</th>
<th>Mean Temp Difference (°)</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mid anterior thigh</td>
<td>0.23</td>
<td>0.19</td>
</tr>
<tr>
<td>Mid posterior thigh</td>
<td>0.17</td>
<td>0.16</td>
</tr>
<tr>
<td>Mid patella</td>
<td>0.28</td>
<td>0.22</td>
</tr>
<tr>
<td>Mid tibia</td>
<td>0.26</td>
<td>0.17</td>
</tr>
<tr>
<td>Calf</td>
<td>0.23</td>
<td>0.18</td>
</tr>
<tr>
<td>Dorsum</td>
<td>0.35</td>
<td>0.25</td>
</tr>
<tr>
<td>Plantar</td>
<td>0.35</td>
<td>0.25</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Upper Limbs and Back: Females</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Forearm</td>
<td>0.98</td>
</tr>
<tr>
<td>Elbow</td>
<td>0.82</td>
</tr>
<tr>
<td>Upper arm</td>
<td>0.78</td>
</tr>
<tr>
<td>Shoulder</td>
<td>0.74</td>
</tr>
<tr>
<td>Neck</td>
<td>0.38</td>
</tr>
<tr>
<td>Upper Thoracic</td>
<td>0.24</td>
</tr>
<tr>
<td>Lower Thoracic</td>
<td>0.32</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Upper Limbs and Back: Males</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Forearm</td>
<td>0.72</td>
</tr>
<tr>
<td>Elbow</td>
<td>0.70</td>
</tr>
<tr>
<td>Upper arm</td>
<td>0.58</td>
</tr>
<tr>
<td>Shoulder</td>
<td>0.64</td>
</tr>
<tr>
<td>Neck</td>
<td>0.30</td>
</tr>
<tr>
<td>Upper Thoracic</td>
<td>0.24</td>
</tr>
<tr>
<td>Lower thoracic</td>
<td>0.20</td>
</tr>
</tbody>
</table>
Subject Questionnaire -post treatment

<table>
<thead>
<tr>
<th>Subject code</th>
<th>Week no</th>
<th>Today's Date</th>
<th>Date stopped treatment</th>
<th>Week no</th>
</tr>
</thead>
</table>

This questionnaire is to help us evaluate the effectiveness of the trial. Please answer the questions honestly, do not try to be 'kind' to the researchers in your reply. The information will remain confidential. Your response will not prejudice your future treatment in any way and there will also be opportunity for discussion as required.

- Please answer all the questions; write 'N/A' (Not Applicable) or 'none' rather than leave a blank
- For questions with a choice of reply please tick the desired response. (eg: Yes ☐ No ☐)
- For other questions with a box, please enter a number according to the specified scale.
- Use the spaces provided for details as requested and any additional comments or suggestions, (if necessary, continue on the reverse side of the page, including the question number)

1) **Before you started the trial, what were your expectations of the benefits of the treatment?**
   ........................................................................................................................................
   ........................................................................................................................................
   ........................................................................................................................................

2) **Were you sorry to have to stop the treatment?**
   Yes ☐ No ☐

3) **Do you feel the duration of the trial was:**
   - too short ☐
   - long enough ☐
   - too long ☐

   Please explain your answer ..................................................................................................
   ........................................................................................................................................
   ........................................................................................................................................

4) **On the whole, do you feel the treatment was of benefit to you?**
   Yes ☐ No ☐

5) **What was the single most significant outcome (good or bad) of your participation in the trial?**
   ........................................................................................................................................
   ........................................................................................................................................
   ........................................................................................................................................

**KEEP INFORMATION CONFIDENTIAL**
Subject Questionnaire - post treatment

6) How convenient did you find performing the treatment?
Please use this scale to rate the following aspects of use and then specify the detail or comments:

<table>
<thead>
<tr>
<th>Convenience Level</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>very convenient</td>
<td>5</td>
</tr>
<tr>
<td>convenient</td>
<td>4</td>
</tr>
<tr>
<td>acceptable</td>
<td>3</td>
</tr>
<tr>
<td>inconvenient</td>
<td>2</td>
</tr>
<tr>
<td>very inconvenient</td>
<td>1</td>
</tr>
</tbody>
</table>

- a) positioning of the limb
- b) positioning of the electrodes
- c) care of electrodes (washing etc)
- d) skin care at electrode positions
- e) duration of treatment session
- f) time of day of sessions
- g) the controls of the stimulator
- h) adjustment of stimulation level
- i) connections of the stimulator
- j) recharging the stimulator
- k) in general / overall

other comments

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University of Surrey Biomedical Engineering Group

in conjunction with
Salisbury District Hospital Medical Physics and Biomedical Engineering Department.

DENERVATED MUSCLE STIMULATION TRIAL

**Subject Questionnaire -post treatment**

7) Is the current treatment procedure convenient enough for you
to continue with it on a long term basis if necessary?  
   Yes [ ]  No [ ]  
   If No, how would the procedure have to be modified to enable you to do so?  

8) Which type and size of electrodes did you find most effective or prefer to use?  
<table>
<thead>
<tr>
<th>Type</th>
<th>Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pals Blue Gel</td>
<td>5 x 5 cm square [ ] 3.3 x 5.4 cm [ ]</td>
</tr>
<tr>
<td>Grey Pals Flex</td>
<td>4 x 9 cm rectangular [ ] 7.5 cm round [ ]</td>
</tr>
<tr>
<td></td>
<td>8 x 14 cm oval [ ]</td>
</tr>
</tbody>
</table>

9) How often did you wash the electrodes?  

10) How often did you wash the skin in the area of treatment?  

11) Did you use any creams or ointment on your skin in the area of treatment?  
   Yes [ ]  No [ ]  
   If Yes, please specify what and when used.  

12) Typically, how long did it take you to get set up prior to the treatment session?  

13) Typically, how long did it take you to remove the equipment after the session?  

14) Did you have any reliability problems using the stimulation equipment at home?  
   Yes [ ]  No [ ]  
   If Yes, please specify:  

---

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Appendix H
Post Treatment Period Questionnaire

University of Surrey Biomedical Engineering Group
in conjunction with
Salisbury District Hospital Medical Physics and Biomedical Engineering Department.
DENERVATED MUSCLE STIMULATION TRIAL

Subject Questionnaire -post treatment

15) Did you use the stimulator at locations other than your own home? Yes ☐ No ☐
If Yes, please specify where and if you experienced any additional problems in using it there:

__________________________________________________________________________________________________________________________________________________

16) Do you have any suggestions for improvement of the stimulation equipment?
__________________________________________________________________________________________________________________________________________________

17) How adequate was the information provided to you about the treatment and participation in the trial?
Please use this scale to rate the following aspects of the explanation given to you,
very good 5 good 4 adequate 3 less than adequate 2 poor 1
and make additional comments or suggestions for improvements in the space provided

a) the purpose of trial ☐
__________________________________________________________________________________________________________________________________________________
b) the format of the trial ☐
__________________________________________________________________________________________________________________________________________________
d) the treatment procedure ☐
__________________________________________________________________________________________________________________________________________________
e) use of the stimulation equipment ☐
__________________________________________________________________________________________________________________________________________________
f) stimulator instruction manual ☐
__________________________________________________________________________________________________________________________________________________

18) What additional information or explanation would you like to have had before or during the trial?
__________________________________________________________________________________________________________________________________________________

__________________________________________________________________________________________________________________________________________________

__________________________________________________________________________________________________________________________________________________

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Subject Questionnaire - post treatment

19) **During a typical treatment session**, whilst using the stimulator what effects did you experience?

Please use this scale to rate the following aspects and then specify the details of the effect,

- very severe 5
- severe 4
- moderate 3
- slight 2
- none noticeable 1

If the effect varied from one session to the next, please use the scale to describe the largest and smallest effects and how often these occurred. Similarly, specify if the effect varied over the course of the trial, perhaps as the stimulation parameters were altered. Please also indicate how long any effect continued after the treatment and comment on whether you thought the effect was of benefit.

a) skin reaction at the electrode sites □

b) temperature of the treated limb □

c) sensation of the stimulation (eg: pins & needles, burning feeling, etc) □

d) sensitivity of the treated limb (eg: touch sensitivity, numbness, etc) □

e) sensation/sensitivity of other areas □

f) contraction of other muscles □

---

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Subject Questionnaire -post treatment

19) Remember this question refers to effects during a treatment session whilst using the stimulator.

   g) muscle tightness
      □

   h) muscle spasms
      □

   i) swelling of joints or tissue
      □

   j) ease of motion of joints
      □

   k) bladder/bowel function
      □

   l) headaches
      □

   m) nosebleeds
      □

   n) body temperature or sweating
      □

   o) other effects, please specify
      □
20) Comparing your general condition (without stimulation) before starting the trial and at the end, has this been affected by participating in the trial?

Please use this scale to rate the following aspects and then specify the details and any comments:


a) skin condition at the electrode sites
b) skin condition of the treated limb
c) cosmetic appearance of the limb
d) temperature of the treated limb
e) body temperature or sweating
f) sensations in the treated limb
g) sensitivity of the treated limb
h) sensation/sensitivity in other areas
i) any voluntary muscle control

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20) Remember, this question refers to any effect on your general condition (without stimulation), comparing before and after the trial

j) muscle spasms - severity

k) muscle spasms - frequency

l) muscle tone or tightness

m) swelling of tissue

n) swelling of joints

p) ease of motion of joints

q) ease of movement of limb

r) mobility

s) bladder function

u) bowel function

v) nose bleeds

w) headaches

x) energy levels or tiredness

y) appetite, eating patterns
Appendix H

Post Treatment Period Questionnaire H-9

University of Surrey Biomedical Engineering Group
in conjunction with
Salisbury District Hospital Medical Physics and Biomedical Engineering Department.
DENERVATED MUSCLE STIMULATION TRIAL

Subject Questionnaire -post treatment

20) z) sleep patterns

aa) other effects on your general condition?, (eg: changes to the opposite, untreated limb)

21) In what manner and how often do you use/exercise the limb in addition to the stimulation treatment?
(specify if formal physio or other therapy)

22) Does the stimulation treatment help with this use/exercise?
Yes [ ] No [ ]
If Yes, please specify how:

23) Would you like to continue to use the stimulator as a routine treatment on a long term basis?
Yes [ ] No [ ]

24) If Yes, what benefits would you expect to receive from the treatment?

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The PCUI consists of a series of nine screens, (example Fig. 5.6.1), each selected by means of the Mode Select menu and performing one of the functions of the interface, with parameters of each screen as follows. Pulse parameters as defined in Figure 3.4.1.

**RXD-STIM**

Displays the current stimulation parameters

<table>
<thead>
<tr>
<th>Screen</th>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>RX BANK A</td>
<td>AN1</td>
<td>Pulse step size</td>
</tr>
<tr>
<td></td>
<td>AN2</td>
<td>MSB of ramp delay</td>
</tr>
<tr>
<td></td>
<td>AN3</td>
<td>LSB of ramp delay</td>
</tr>
<tr>
<td></td>
<td>AN4</td>
<td>MSB of max pulse time</td>
</tr>
<tr>
<td></td>
<td>AN5</td>
<td>LSB of max pulse time (150=500\mu s)</td>
</tr>
<tr>
<td></td>
<td>AN6</td>
<td>IRQ time</td>
</tr>
<tr>
<td></td>
<td>AN7</td>
<td>IPI count (multiples of IRQ)</td>
</tr>
<tr>
<td></td>
<td>AN8</td>
<td>Inter-inter pulse interval (100\mu s)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSR&gt;50% yellow</td>
<td>Indicates pulse width (PW) greater than IPI</td>
</tr>
<tr>
<td>Max Intensity</td>
<td>The intensity value at which PW greater than IPI</td>
</tr>
</tbody>
</table>

**TX BANK B**

<table>
<thead>
<tr>
<th>Screen</th>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AN1</td>
<td>Intermittent per second</td>
<td>Number of ISQ's per second, determined by BKA-AN6</td>
</tr>
<tr>
<td>AN2</td>
<td>ON Time (seconds)</td>
<td>Stimulation envelope ON and OFF durations</td>
</tr>
<tr>
<td>AN3</td>
<td>OFF Time (seconds)</td>
<td>In seconds</td>
</tr>
<tr>
<td>AN4</td>
<td>Session Time (minutes)</td>
<td>Duration limit of each stimulation session</td>
</tr>
<tr>
<td>AN5</td>
<td>Current Pot Value [not used in TXD]</td>
<td>Stimulation envelope ON and OFF durations</td>
</tr>
<tr>
<td></td>
<td>Max</td>
<td>Scaling by 1</td>
</tr>
<tr>
<td></td>
<td>Half</td>
<td>Scaling by 0.5</td>
</tr>
<tr>
<td></td>
<td>Quarter</td>
<td>Scaling by 0.25</td>
</tr>
<tr>
<td>AN7</td>
<td>Max. current before Fail Mode</td>
<td>Value of stimulation current when Fail warning occurs and current is reduced to zero</td>
</tr>
<tr>
<td>AN8</td>
<td>T/F</td>
<td>Stimulation pulse type:</td>
</tr>
<tr>
<td></td>
<td>b0</td>
<td>Biphasic/mono</td>
</tr>
<tr>
<td></td>
<td>green</td>
<td>Biphasic</td>
</tr>
<tr>
<td></td>
<td>red</td>
<td>Monophasic</td>
</tr>
<tr>
<td></td>
<td>b1</td>
<td>Envelope</td>
</tr>
<tr>
<td></td>
<td>green</td>
<td>Envelope enable</td>
</tr>
<tr>
<td></td>
<td>red</td>
<td>Disabled — continuous pulse train</td>
</tr>
<tr>
<td></td>
<td>b2</td>
<td>External</td>
</tr>
<tr>
<td></td>
<td>b3</td>
<td>Not used</td>
</tr>
</tbody>
</table>

**RXD-Monitor**

Displays the monitored parameters (output current, voltage and Vp)

<table>
<thead>
<tr>
<th>Screen</th>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>RX BANK A</td>
<td>AN1</td>
<td>BAT_A</td>
</tr>
<tr>
<td></td>
<td>AN2</td>
<td>BAT_G</td>
</tr>
<tr>
<td></td>
<td>AN3</td>
<td>CUR_A</td>
</tr>
<tr>
<td></td>
<td>AN4</td>
<td>CUR_B</td>
</tr>
<tr>
<td></td>
<td>AN5</td>
<td>OVT_C</td>
</tr>
<tr>
<td></td>
<td>AN6</td>
<td>OVT_G</td>
</tr>
<tr>
<td></td>
<td>AN7</td>
<td>CUR_C</td>
</tr>
<tr>
<td></td>
<td>AN8</td>
<td>CUR_G</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Digital value 200 = ~11 V</td>
</tr>
<tr>
<td></td>
<td>188 = 10.5 V</td>
</tr>
<tr>
<td></td>
<td>Digital value approximately</td>
</tr>
<tr>
<td></td>
<td>Equal to Io (mA) up to 100mA</td>
</tr>
<tr>
<td></td>
<td>Digital value approx. equal to</td>
</tr>
<tr>
<td></td>
<td>Twice Vo (V) up to 100V</td>
</tr>
<tr>
<td></td>
<td>Digital value scaling as B, C</td>
</tr>
</tbody>
</table>

### Appendix K - PC User Interface Display Screen Parameters

The PCUI consists of a series of nine screens, selected by means of the Mode Select menu and performing one of the functions of the interface, with parameters of each screen as follows. Pulse parameters as defined in Figure 3.4.1.
RXD-Fault levels Displays the current monitored parameters warning thresholds

RXBANK A

AN1 Intermittent Battery Warning \{ warning thresholds with digital value
AN2 Continuous Battery Warning \} scaling as per monitor
AN3 Warning ON time (IRQ’s) \} values set the audible warning duty cycle
AN4 Warning OFF time (IRQ’s) \{ (typical values 1:40)
AN5 Max Current at Pulse B start \} max permitted Io (mA) between pulses
AN6 C:G Current Band \} max permitted difference in Io between end of pulses measured at C and G
AN7 Max Intensity (rate test) \} max intensity value before warning occurs
AN8 Intensity Rate (rate test) \} max change in intensity allowed per IRQ before warning occurs

RXD STATS Displays the current session and cumulative usage statistics

RXBANK A

AN1 LSB Session Use [seconds] \} Duration of stimulator use during this session
AN2 MSB Session use [seconds] \} in seconds
AN3 Session Use [minutes] \} in minutes
AN4 Not used [0]
AN5 LSB Use [minutes] \} Duration of stimulator use since count last zeroed
AN6 MSB Use [minutes] \} in minutes
AN7 LSB Use [count] \} Number of times stimulator switched on since count last zeroed
AN8 MSB Use [count] \} count last zeroed

TXD[T]-STIM Enters stimulation parameters for temporary use, until switch off
Parameters as RXD STIM

TXD[P]-STIM Enters stimulation parameters for permanent storage
Parameters as RXD STIM

TXD[T]-Fault levels Enters monitored parameter thresholds for temporary use
Parameters as RXD Fault levels

TXD[P]-Fault levels Enters monitored parameter thresholds for permanent storage
Parameters as RXD Fault levels

TXD STATS Clears the current session and cumulative usage statistics
Parameters as RXD STATS
<table>
<thead>
<tr>
<th>Item</th>
<th>BS5724 subpart 2 REQUIREMENT</th>
<th>REQUIRED TESTING</th>
<th>MEANS OF COMPLIANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sec.4</td>
<td>MECHANICAL HAZARDS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>Mechanical strength</td>
<td>following testing- equipmt-no safety hazard, no live parts exposed, insulation/air clearances not reduced decorative layer damage, surface/invisbl cracks ignored</td>
<td></td>
</tr>
<tr>
<td>21 a)</td>
<td>Inward force</td>
<td>45N over 25x25mm over any part of enclosure</td>
<td>current box probably unsuitable? x</td>
</tr>
<tr>
<td>21 b)</td>
<td>Impact force (device specified in appG)</td>
<td>3 blows 20mm dia h.spherical 0.5±/-0.5J all displays, lamps knobs if protode &gt;10mm, &gt;4cm²</td>
<td></td>
</tr>
<tr>
<td>21 c)</td>
<td>Carrying handles &amp; grips</td>
<td>loading to 4x equipment weight</td>
<td>attachment straps/ velco? x</td>
</tr>
<tr>
<td>21.1</td>
<td>Not used</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21.2</td>
<td>Not used</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21.3</td>
<td>Parts to support &amp;/or immobilised patients minimise risk physical injury/accident loosening Clause28 applies if breakdown= safety hazard</td>
<td>supporting parts for adults135kg* clause 28 safety factor applied gradually, sustained for 1min--equipmt shall be in equilibrium &amp; sustain no damage</td>
<td>failure sudden loss of limb support FES potent patient collapse, TES limb weight usually supported by other means or 'fall' cushioned</td>
</tr>
<tr>
<td>21.4</td>
<td>Not used</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21.5</td>
<td>Hand held-equipmt-1m free fall to hard surface shall not present safety hazard</td>
<td>1m free fall from 3 different starting attitudes onto 50mm block of &gt;700kg.m² over rigid concrete base</td>
<td>present box may shatter x</td>
</tr>
<tr>
<td>21.6</td>
<td>Portable equipmt- rough handling</td>
<td>drop test as 21.5 from 5cm for weight&lt;10kg</td>
<td>present box probably survive</td>
</tr>
<tr>
<td>22</td>
<td>Moving Parts</td>
<td>no moving parts</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>Surfaces, corners &amp; edges- rough/sharp</td>
<td>avoidance of safety hazard checked by inspection</td>
<td>smooth outer surface to enclosure+connectors</td>
</tr>
<tr>
<td>24.1-</td>
<td>Stability in Normal use</td>
<td>safe operation + transport in any attitude</td>
<td></td>
</tr>
<tr>
<td>24.6</td>
<td>Grips + handling devices for equipmt&gt;20kg</td>
<td>or</td>
<td>N/A -equipmt weight&lt;20kg</td>
</tr>
<tr>
<td>25</td>
<td>Expelled parts</td>
<td>N/A -no expelled parts</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>Vibration &amp; noise - not used</td>
<td></td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>Pneumatic &amp; hydraulic power- no reqmt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>Suspended masses</td>
<td></td>
<td>N/A no suspended parts (cables, attachment of unit to patient</td>
</tr>
<tr>
<td>Sec.5</td>
<td>UNWANTED/EXCESSIVE RADIATION</td>
<td></td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>X-radiation</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>Alpha, beta, gamma, neutron,particle radiation</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>Microwave radiation</td>
<td>N/A</td>
<td>e</td>
</tr>
<tr>
<td></td>
<td>Light radiation</td>
<td></td>
<td>N/A</td>
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<tr>
<td>---</td>
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<td>------</td>
</tr>
<tr>
<td>33</td>
<td>Infra-red radiation</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>34</td>
<td>Ultra-violet radiation</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>35</td>
<td>Acoustical energy (including ultra sonic)</td>
<td>under consideration</td>
<td>some noise from transformer-not significant</td>
</tr>
<tr>
<td>36*</td>
<td>ElectroMagnetic Compatibility (EMC) operation in presence of simulated shortwave therapy unit (27.12MHz)</td>
<td>change in (max,min+intermed) output params&lt;10%</td>
<td>no i/p filters included-may be necessary is o/p filter sufficient?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T1a)test signal applied across o/p terminals (each ch in trn b)</td>
<td>each o/p terminal-to enclosure/earth</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T2 test signal applied across mains input</td>
<td>N/A-no mains except during re-charging during PC operation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T3 test signal applied to remote control cable sending end radiated field test-under consideration</td>
<td></td>
</tr>
<tr>
<td>Sec.6</td>
<td>EXPLOSIONS IN MEDICAL ROOMS</td>
<td></td>
<td>N/A -non AP,APG no anaesthetic mixture involv battery-ga dischage on charging-if flammable then 39.2c, 39.2, 40.2/3/5 may apply</td>
</tr>
<tr>
<td>Sec.7</td>
<td>TEMPERATURE &amp; OTHER HAZARDS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>Excessive Temperatures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>42.1</td>
<td>Safety function parts-allowable max.temps in normal use &amp; conditions</td>
<td>Windings/core laminations -class E (enamel) 120°C Rubber, PVC Int.+Ext.wiring insulation &lt; marked Tmax Battery temp shall not cause safety hazard Accessible parts in continuous/short period operator contact:in Normal Use - metal 55/60°C -moulded material 75/85°C Parts having brief patient contact in normal use 50°C</td>
<td>N/A-rated for normal current, fault current momentary Battery operating temp -30 to +50°C heat generated by internal components(FET &amp; diode) no direct thermal conduction to accessible components- enclosure temp. unlikely to rise excessively, especially if vented-measure?</td>
</tr>
<tr>
<td>42.2</td>
<td>Equipment parts-allowable max.temps in normal use &amp; conditions</td>
<td>Appliance input pins hot/other conions 155/65°C External conductor terminals 85°C-ref 57.3 Air adjacent to switches,thermostats w/o spefd Tmax 55°C Rubber/PVC int+ext wiring insuln w-60, w/o flexing-75°C Rubber where deterioration effect safety (60/75°C) Cord sheaths used as supplementary insulation &lt;60°C Non-wire insulation- PTFE? &lt;290°C -thermoplastic (so as to avoid cracking, fire etc) Electrolytic capacitors (w/o tc marking) &lt;65°C</td>
<td>- not connected to heat generating components - only mains input? -enclosure temp should be &lt;55?, only on/off sw -within temp rating for normal optn - rubber not used elsewhere? -inputs cable - low level signals -circuit board-esp. nr FET/diode -enclosure-not in direct contact as air clearance - rating?</td>
</tr>
<tr>
<td>42.3</td>
<td>Applied parts - not intended to supply heat</td>
<td>surface temp &lt;41°C</td>
<td>electrodes - heat only from poor skin contact - enclosure may be in continuous patient contact</td>
</tr>
<tr>
<td>42.4</td>
<td>Not Used</td>
<td></td>
<td></td>
</tr>
<tr>
<td>42.5</td>
<td>Guards - to prevent contact with hot surfaces</td>
<td>N/A - no hot surfaces or guards</td>
<td></td>
</tr>
<tr>
<td>43</td>
<td>Fire hazard - should not occur following mechanical strength tests of 21</td>
<td>no fire hazard, though hot components may be exposed</td>
<td></td>
</tr>
<tr>
<td>44</td>
<td><strong>Overflow, leakage, humidity, ingress, sterilization</strong></td>
<td>poss. battery electrolyte leakage - only when re-charging - not mounted on patient sealing against liquid ingress not necessary?</td>
<td></td>
</tr>
<tr>
<td>44.1</td>
<td>Construct sufficient protection against hazard</td>
<td>N/A - no liquid reservoir/storage chamber</td>
<td></td>
</tr>
<tr>
<td>44.2</td>
<td>Overflow of reservoir/storage chamber</td>
<td>N/A - no liquid involved in use</td>
<td></td>
</tr>
<tr>
<td>44.3</td>
<td>Spillage</td>
<td>N/A - over charging may cause leakage</td>
<td></td>
</tr>
<tr>
<td>44.4</td>
<td>Leakage-rechargeable batteries exempt</td>
<td>possible sweating of patient</td>
<td></td>
</tr>
<tr>
<td>44.5</td>
<td>Humidity-proofed against normal use humidity</td>
<td>no degree of protection designed - possible sweating of patient/coffee spillage?</td>
<td></td>
</tr>
<tr>
<td>44.6</td>
<td>Ingress of liquids</td>
<td>electrodes - no need to sterilize?/cleanable? - instructions</td>
<td></td>
</tr>
<tr>
<td>44.7</td>
<td>Cleaning, sterilization, disinfection patient contact parts-specif of cleaning procd</td>
<td>parts should withstd specif/standard (134°C) cleaning</td>
<td></td>
</tr>
<tr>
<td>45</td>
<td><strong>Pressure vessels/parts subject to pressure</strong></td>
<td>re-chargeable battery fitted with pressure relief value to vent gas build up on charging</td>
<td></td>
</tr>
<tr>
<td>45.1</td>
<td>Not used</td>
<td>nospec pressure pressurisation testing not poss</td>
<td></td>
</tr>
<tr>
<td>45.2</td>
<td>testing</td>
<td>located on battery</td>
<td></td>
</tr>
<tr>
<td>45.7</td>
<td>Pressure relief device requirements</td>
<td>visual inspection on removing enclosure cover</td>
<td></td>
</tr>
<tr>
<td>45.7a</td>
<td>- proximity to vessel being protected</td>
<td>not adjustable</td>
<td></td>
</tr>
<tr>
<td>45.7b</td>
<td>- accessible for inspectn, maintenence, repair</td>
<td>contained within unit enclosure</td>
<td></td>
</tr>
<tr>
<td>45.7c</td>
<td>- not capable of adjustmt/inhibiting w/o tool</td>
<td>shield reqd to prevent discharge onto circuit</td>
<td></td>
</tr>
<tr>
<td>45.7d</td>
<td>- discharge directed away from personnel</td>
<td>max. working pressure not specif or testable</td>
<td></td>
</tr>
<tr>
<td>45.7e</td>
<td>- discharge will not cause safety hazard</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>45.7f</td>
<td>- max. working pressure not exceed by &gt;10%</td>
<td>not speed by manufacturer or testable</td>
<td></td>
</tr>
<tr>
<td>45.7h</td>
<td>- 100,000 min. operating cycle life</td>
<td></td>
<td></td>
</tr>
<tr>
<td>46</td>
<td><strong>Human Errors</strong></td>
<td>Io/Vo monitor will inhibit output+give warning switch off to reset or rqmt-uC to try periodically?</td>
<td></td>
</tr>
<tr>
<td>46.101*</td>
<td>open &amp; short circuit electrodes</td>
<td>max. output selected, each pair terminals, 10 mins o/c then 5 mins s/c then unit shall comply with all rqmts of stdndrd</td>
<td></td>
</tr>
<tr>
<td>47</td>
<td>Electrostatic discharges</td>
<td>Not used</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>Materials of applied pts contacting patient</td>
<td>Not used</td>
<td></td>
</tr>
<tr>
<td>49</td>
<td>Interruption of power supply</td>
<td>N/A</td>
<td>Internal supply depletion causes no hazard</td>
</tr>
<tr>
<td>50</td>
<td>DATA ACCURACY-HAZARDOUS O/P</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50.1</td>
<td>o/p intensity control-continuous or increments of not &lt;1V/1mA from min&lt;2% max value</td>
<td>checked with least favourable load impedance as specified in accompanying documents</td>
<td>resolution may be only 2V-depends on min rise time reqd.</td>
</tr>
<tr>
<td>50.2</td>
<td>Pulse duration, freq., intensity-variation+/-30% from indicated/specd with load range specified</td>
<td>measurement accuracy +/-10%</td>
<td>intensity not indicated only directn of incr (6.3c) pw,freq,inten range defined by mode-control by uC no display/monitoring of parameter accuracy</td>
</tr>
<tr>
<td>51</td>
<td>Hazardous/incorrect output protection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>51.1</td>
<td>Intentional exceeding safety limits interlock, selection, audible warning required to achieve output exceeding safety limit</td>
<td>o/p continuous upto maximum</td>
<td>o/p continuous upto maximum monitors inhibit above certain safety level but may be patient dependent as pain level</td>
</tr>
<tr>
<td>51.2</td>
<td>Indication parameters relevant to safety -preindication of hazardous output</td>
<td></td>
<td>stimulation intensity indicated, but not prior excess indicated by patient contraction/pain level</td>
</tr>
<tr>
<td>51.3</td>
<td>Reliability of components</td>
<td>not used</td>
<td></td>
</tr>
<tr>
<td>51.4</td>
<td>Accidental selection of excessive/incorrect o/p when high &amp; low setting eg interlock</td>
<td>o/p variation continuous upto maximum monitors inhibit above certain safety level</td>
<td></td>
</tr>
<tr>
<td>51.101</td>
<td>Supply fluctuations of +/-10%</td>
<td>resulting variation in output amplitude, pulse width, frequency. +/-10% measurement check</td>
<td>internally p/w, amplitude decreas. with batt depletion, o/p inhibited before p/w/frequency effected loss of PC control-stim o/p continues as stored</td>
</tr>
<tr>
<td>51.102</td>
<td>Output interlock-for o/p&gt;10mA/VRms to prevent o/p unless amplitude control set to min also following temporary mains interruption</td>
<td>functional check</td>
<td>o/p inhibited during initialization (at power up or following reset) till amplitude control set to min. internally powered, voltage monitored</td>
</tr>
<tr>
<td>51.103 *</td>
<td>Output indicator -normal+single fault conditions if o/p</td>
<td>R&lt;sub&gt;2&lt;/sub</td>
<td>=1kΩ</td>
</tr>
<tr>
<td>51 * 104a</td>
<td>Limitation of o/p parameters-therapeutic eqmt pw&gt;100ms-I&lt;sub&gt;o&lt;/sub&gt;=&lt;80mAmps (R&lt;sub&gt;2&lt;/sub&gt;=500Ω) pw&lt;100ms-pulse energy&lt;300mJ, &amp;I&lt;sub&gt;o&lt;/sub&gt;&lt;50mA(&lt;400Hz),80mA,100mA&gt;1500Hz Open circuit Vo&lt;500V peak Limits apply separately to simultaneous output circuits supplying same applied part</td>
<td>I&lt;sub&gt;o&lt;/sub&gt;max=160mA into(R&lt;sub&gt;2&lt;/sub&gt;=500Ω)-battery limited for pw 2ms-3s, freq upto 250Hz? μC monitors I&lt;sub&gt;o&lt;/sub&gt;+Vo to detect load reduction &amp; excess I&lt;sub&gt;o&lt;/sub&gt; Freq.of output variable</td>
<td>Open circuit Vomax=150V Each stim. output supplied by single circuit</td>
</tr>
</tbody>
</table>

Sec.9 ABNORMAL OPERN & FAULT CONDNS-
<p>| 52.1 | no Single fault Condition (SFC) to cause safety hazard during normal operation of equipment | no SFC (of 52.5) to cause safety hazard 52.4 (52.4) N/A to components where SFC power dissipation &lt;15W |
| 52.2 | Not used |
| 52.3 | Not used |
| 52.4 <strong>Safety Hazards</strong> - to be avoided in SFC | during testing of 52.5 |
| 52.4.1 | emission flames, gas, metal in hazardous quant | after testing &amp; cooling to room temp |
|  | - deformation of enclosure to impair compliance | - dielectric tests |
|  | - temperature of test environ + supply cord &lt;175 | - supp/reinn insulation-ball pressure test perfmd at 25 |
|  |  | - thermal cutouts, overcurrent devices to be re-tested |
| 52.4.2 | leakage current limits (19.3) &amp; |  - batt. emission minimal, fuse prevents fire in unit |
|  | - insulation voltage limits (16a5) for SFC |  - heat generated not sufficient, applied force(21) |
| 52.4.3 | starting, interrupting or locking movements involving masses in proximity to patient | failure may result in zero output &amp; sudden loss of stimulation support of patient limb-cushioning |
| 52.5 <strong>Single Fault Conditions</strong> - specific tests | tested 1 at a time, clearances &lt; reqmts to be short circuit |
| 52.5.1 Mains supply transformer overload | tests as per 57.9 |
| 52.5.2 | Thermostats | N/A - only mains in re-charger &amp; PC-reqd? |
| 52.5.3 | Double Insulation | N/A |
| 52.5.4 Protective Earth Conductor - interruption | N/A |
| 52.5.5 | Impairment to cooling | vents may be necessary for diode heat dissptn |
| 52.5.6 | Locking of moving parts | N/A - no moving parts |
| 52.5.7.8 | Motor capacitors &amp; operation | N/A - no motor components |
| 52.5.9 | Failure of components (1 at a time) | FMEA - no SFC result in hazard |
| 52.5.10 | Overload (short time/interruption) | N/A |
|  | g) short time/intermittent operation | test required include internal |
| 53 | Environmental Tests - ref 4.10, 10 | tests as per 4.10, 10 |
| Sec 10 | CONSTRUCTIONAL REQUIREMENTS |
| 54.55 | Not Used |
| 56 | Components &amp; general assembly |
| 56.1 | General a), c), e) not used |
| 56.1b Rating marking on all cmpnts mains/applied pt or indicative wrt reference documentation - ratings commensurate with conditions of use | checked by inspection |
|  | all cmpnts &amp; ratings identifiable from layout and circuit diagrams |
|  | circuit operation demonstrated in normal &amp; SFC |</p>
<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
<th>Verification</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>56.1d</td>
<td>Fixing cmpnts to prevent hazardous movement</td>
<td>checked by inspection</td>
<td>cmpnts securely mounted except FET &amp; diode heatsinks allow movement but not hazardous</td>
</tr>
<tr>
<td>56.1f</td>
<td>Fixing/insulated conductors &amp; connectors-no safety hazard from single end detachmnt (SFC)</td>
<td>checked by inspection</td>
<td>no component/wiring SFC results in safety hazard</td>
</tr>
<tr>
<td>56.2</td>
<td>Not Used</td>
<td></td>
<td></td>
</tr>
<tr>
<td>56.3</td>
<td>Connectors-excl.mains (see 57.2/5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>56.3a</td>
<td>Incorrect hazardous insertion not possible insulation reqmts as per I7g</td>
<td></td>
<td></td>
</tr>
<tr>
<td>56.3b</td>
<td>Connections between parts of equipment, accessible metal parts cannot become live</td>
<td></td>
<td></td>
</tr>
<tr>
<td>56.4</td>
<td>Connection of capacitor- not permitted between live parts+non PE accessible metal parts -mains pt+PE-amp-except comply IEC 384-14 -mains pt-non PE amp if cap.case basic insuln -contacts of thermal cut-outs</td>
<td>checked by inspection</td>
<td>no capacitive connection to accessible metal parts in stimulator -need to check re-charger - enclosure earthed</td>
</tr>
<tr>
<td>56.5</td>
<td>Protective devices-mains disconnection not to be achieved by short circuit-overcurrent trip</td>
<td>checked by inspection</td>
<td>no mains in stimulator -need to check re-charger</td>
</tr>
<tr>
<td>56.6</td>
<td>Temperature &amp; overload devices -thermal safety devices reqd-satisfy sec.9,57.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>56.7</td>
<td>Internal Electrical Power Source</td>
<td></td>
<td></td>
</tr>
<tr>
<td>56.7a</td>
<td>Housing-vented if gases escape on charging - short circuit hazard prevented</td>
<td></td>
<td></td>
</tr>
<tr>
<td>56.7b</td>
<td>Connection - prevention of hazard from incorrect polarity connection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>56.8</td>
<td>Indicators- unless otherwise apparent, for - equipment energised - non-luminous heaters on (if safety hazard) - output exists - if inadvertent/prolonged operation is hazardous - charging mode of internal power source</td>
<td>visible from position of normal use, colours as 6.7:- - red - danger requiring immediate action - yellow- caution, attention required - green - ready for action</td>
<td>indicators provided on front panel</td>
</tr>
<tr>
<td>56.9</td>
<td>Pre-set controls - not used</td>
<td></td>
<td></td>
</tr>
<tr>
<td>56.10</td>
<td>Actuating parts of controls</td>
<td></td>
<td></td>
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<tr>
<td>-------</td>
<td>-----------------------------</td>
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<td></td>
</tr>
<tr>
<td>a)</td>
<td>Electric shock protection of accessible parts</td>
<td>compliance with 16c</td>
<td>see 16c</td>
</tr>
<tr>
<td>b)</td>
<td>Fixing, prevention of mal-adjustment</td>
<td>fixing to be tested by application of: control knobs secured to shaft by covered thread portion requiring a tool to undo needs to be tested by application of force</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- cannot work loose during normal use</td>
<td>-torque1Nm &gt;2sec 10 times each direction (dia&lt;23mm)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- control position always corresponds to on/off, scale or other marking</td>
<td>-axial force of 60N 1min(electrical components)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- if removable- incorrect connection prevent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c)</td>
<td>Limitation of movement- prevent control change max-min if hazardous/wiring damage</td>
<td>force to be applied as per 56.10b)</td>
<td>intensity control mode selector-no stop-but under operating procedures- only altered with zero intensity/off?</td>
</tr>
<tr>
<td>56.11</td>
<td>hand/foot operated controls-cord connected</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a)</td>
<td>Operating voltage &lt; 25vac/60vdc mains isold</td>
<td>if fitted foot/other switches operated from 5v</td>
<td></td>
</tr>
<tr>
<td>b)</td>
<td>Mechanical strength</td>
<td>hand held- comply with 21.5 no hand controls envisaged at present foot operated - 1350N 1min - without hazard foot switches are established in use</td>
<td></td>
</tr>
<tr>
<td>c)</td>
<td>Inadvertent position- shall not change setting</td>
<td>all possible positions to be tested for any safety hazard</td>
<td>foot switches already well tested?</td>
</tr>
<tr>
<td>d)</td>
<td>Entry of liquids- foot switches to be drip proof</td>
<td>check as per 44.6 tested?</td>
<td></td>
</tr>
<tr>
<td>e)</td>
<td>flexible connection cords - at entry point</td>
<td>compliance with 57.4</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>57</th>
<th>Mains Parts</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>57.1</td>
<td>Isolation from supply mains</td>
<td>normal mains switch fitted to re-charger</td>
</tr>
<tr>
<td>57.2</td>
<td>Mains connectors-auxiliary outlets</td>
<td>no auxiliary mains outlets</td>
</tr>
<tr>
<td>57.3</td>
<td>Power supply cord-</td>
<td>single mains connection from single cord &amp; plug external dc via same unit connector - cannot be connected simultaneously with mains normal mains cord used</td>
</tr>
<tr>
<td>a)</td>
<td>application</td>
<td>units 1-4Kg</td>
</tr>
<tr>
<td>b)</td>
<td>types c) conductor area d) preparation</td>
<td>axial pull 1 sec, 60N , 25 times w/o jerking torque 1min 0.25Nm</td>
</tr>
<tr>
<td>57.4a</td>
<td>power cord anchorage</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- to provide strain relief- within unit</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- be insulating</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- secure cord other than direct screw contact</td>
<td></td>
</tr>
</tbody>
</table>
STIMULATOR FAILURE MODE AND EFFECT ANALYSIS

Following is an analysis of the single fault failure modes of the stimulator unit with respect to the effect on the output to the patient and any hazard thereby arising. The relevant circuit fault monitor, its action and the resultant output state are specified. The unit is thereby shown to be rendered safe to the user in all single fault conditions. Dual fault failures are not included because of their lower probably of occurrence. An associated audio and visual warning also occurs upon detection of a fault (section 3.2.3) but these are not included in this analysis.

Components numbers referred to are those of the output Power Module

Abbreviations:

- \( \text{av.} \text{I}_{\text{prim}} \): average primary current during fault condition without monitor action
- \( \text{fault durn} \): the period for which the fault has an effect on the stimulator output:
  - on -the output is only effected during the stimulation pulse
  - cont -the fault condition output is continuous
- \( \text{mon, M} \): monitor
- \( \text{V}_{\text{ST}} \): sawtooth waveform monitor
- \( \text{V}_{\text{ccM}} \): monitor of Vcc supply by MAX1232 -activated at Vcc=4.5v
- \( \text{V}_{\text{eM}} \): monitor of Ve supply -activated at Ve=7v (PWDN)
- \( \text{V}_{\text{pM}} \): continuous monitoring of Vp (ANALOGUE PWR)
- \( \text{wdog} \): Watchdog monitor in Microcontroller module
- \( \text{V}_{\text{o}} \): output voltage
- \( \text{Io} \): output current
- \( \text{Ip} \): transformer primary current
- \( \text{I}_{\text{sec}} \): transformer secondary current
- \( \text{V}_{\text{ST}} \): Sawtooth waveform voltage
- \( \text{V}_{\text{com}} \): PWM comparator output voltage
- \( \text{I}_{\text{clamp}} \): current through output clamp path (U6)
- \( \text{MCM} \): MicroController Module
- \( \text{OPM} \): Output Power Module
- \( \mu \text{C} \): MicroController device (16C73) part of MCM
- \( \text{DAC} \): Digital to Analogue converter in MCM
- \( \text{FET} \): Field Effect Transistor (T3 switching primary current)
- \( \text{E/D} \): Enable/Disable signal from MCM to OPM
- \( \text{O/P CLMP} \): Output Clamp signal from MCM to OPM
- \( \text{o/c} \): open circuit (\( \infty \Omega \) connection)
- \( \text{s/c} \): short circuit (0\( \Omega \) connection)
- \( \text{o/p} \): output (usually the stimulation output to patient)
- \( \text{i/p} \): input
- \( \text{incr.} \): increase
- \( \text{decr.} \): decrease
- \( \text{norm/nrm} \): normal
- \( \text{rect.spulse} \): rectangular subpulse shape to primary current waveform
- \( \text{intermit} \): intermittent
- \( \text{swtchg} \): switching ..referring to switching of primary current by FET
- \( \text{conectr} \): connector
- \( \text{s.probe} \): oscilloscope probe connection
- \( \text{connection} \):
<table>
<thead>
<tr>
<th>N.</th>
<th>Circuit element</th>
<th>failure mode -cause(s)</th>
<th>failure effect (without monitor action)</th>
<th>av.</th>
<th>fault</th>
<th>Mon-itor</th>
<th>monitor action</th>
<th>resultant output state (after monitor action)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>output terminals</td>
<td>short circuit</td>
<td>Io=600mA-limited by R9 zener limits ton</td>
<td>1A*</td>
<td>on</td>
<td>Io-int</td>
<td>Vo &amp; V_GATE clamped to 0V if V_DEM&gt;0</td>
<td>momentary high Io &amp; Ip Vo sudden decre.</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>open circuit</td>
<td>maxV_DEM-core satu/ed end ton-Ip, VSEC,D2 prw incr</td>
<td>1A*</td>
<td>on</td>
<td>Io-int</td>
<td>Vo &amp; V_GATE clamped if V_DEM&gt;0 &amp; Vo/Io mon (µC) operational by R25/27 if MCM E/D floating</td>
<td>Io=0, Vo incr. 150v max, until zeroed by mon</td>
</tr>
<tr>
<td>3</td>
<td>V_DEMAND</td>
<td>floating -R2 /wire/connct o/c MCM o/p fault µC fault</td>
<td>zener limits ton incr. continuous max output</td>
<td>2.3A</td>
<td>cont</td>
<td>Is&gt;10</td>
<td>Io-int</td>
<td>V_GATE clamped till µC restarted</td>
</tr>
<tr>
<td>4</td>
<td>V_DEMAND</td>
<td>spurious value µC fault MCM DAC/op-osc fault</td>
<td>zener limits ton incr possible cont. output</td>
<td>2.3A</td>
<td>cont?</td>
<td>wdog</td>
<td>Io-int</td>
<td>V_GATE clamped till µC restarted if R25/27 if MCM E/D floating</td>
</tr>
<tr>
<td>5</td>
<td>V_DEMAND</td>
<td>zero value D6 s/c MCM o/p fault µC fault</td>
<td>Ip=Vo=Io=0</td>
<td>0A</td>
<td>on</td>
<td>Io-int</td>
<td>if µC optnl &amp; V_DEM&gt;0-zero o/p detectd - warning+shut dwn</td>
<td>output zeroed by fault</td>
</tr>
<tr>
<td>6</td>
<td>V_FEEDBACK (Vo fb)</td>
<td>loss of U4 failure R11,8 failure R14, R1 failure</td>
<td>V_ERROR &amp; ton increase limited by zener D1 norm max*</td>
<td>on</td>
<td>wdog</td>
<td>V_GATE clamped till µC restarted</td>
<td>momentary jump in Vo to max.then zeroed</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>V.Feedback (Vo fb)</td>
<td>error U4,R11,R14,R1 value change</td>
<td>V error ton incr limit by zener D1 norm</td>
<td>on</td>
<td>Io-int</td>
<td>V_GATE clamped if Vo significantly differs from expected</td>
<td>output suddenly zeroed possible</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>differential</td>
<td>V_ERR saturated</td>
<td>as per V_DEMAND floating</td>
<td>2.3A</td>
<td>cont</td>
<td>Is/lin</td>
<td>Vo &amp; V_GATE clamped if V_DEM&gt;0</td>
<td>momentary max. o/p</td>
</tr>
<tr>
<td>9</td>
<td>amp. U1d</td>
<td>V_ERR floating</td>
<td>FET off-Ip,Vo,Lo=0</td>
<td>0A</td>
<td>on</td>
<td>Io-int</td>
<td>Vo &amp; V_GATE clamped if V_DEM&gt;0</td>
<td>spurious output</td>
</tr>
<tr>
<td>10</td>
<td>Zener D1</td>
<td>short circuit</td>
<td>V_ERROR &amp; ton=0</td>
<td>0A</td>
<td>on</td>
<td>Io-int</td>
<td>Vo &amp; V_GATE clamped if V_DEM&gt;0</td>
<td>output suddenly zeroed</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>open circuit</td>
<td>no ton limit,if V_ERR&gt;3.2v Ip cont-no switch in pulse</td>
<td>2.3A</td>
<td>on</td>
<td>lb-g=</td>
<td>Vo &amp; V_GATE clamped if V_e&gt;100v</td>
<td>whence o/p collapses to zero after initial peak</td>
</tr>
<tr>
<td>12</td>
<td>V_SAWTOOTH generator</td>
<td>V_ST const&gt;2.9v</td>
<td>V_Tymparator = Vgate=0</td>
<td>0A</td>
<td>on</td>
<td>V_ST</td>
<td>V_ST mon. clamps V_GATE to 0v V_DEM zeroed, warning given</td>
<td>o/p suddenly zeroed</td>
</tr>
<tr>
<td>13</td>
<td></td>
<td>V_ST const&lt;1.5v R16-o/c R17 s/c</td>
<td>no o/p&gt;30v, 30-60v normal Vo&gt;60v collapse- Ip cont</td>
<td>1A</td>
<td>on</td>
<td>V_ST</td>
<td>V_ST mon. clamps V_GATE to 0v V_DEM zeroed, warning given</td>
<td>o/p suddenly zeroed</td>
</tr>
<tr>
<td>N.</td>
<td>Circuit element</td>
<td>failure mode -cause(s)</td>
<td>failure effect (without monitor action)</td>
<td>av. I&lt;sub&gt;T&lt;/sub&gt;</td>
<td>fault duration</td>
<td>Monitor -itor</td>
<td>monitor action</td>
<td>resultant output state (after monitor action)</td>
</tr>
<tr>
<td>----</td>
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<td>---------------------------------------------</td>
</tr>
<tr>
<td>14</td>
<td>( V_{SAWTOOTH} ) generator</td>
<td>( V_{ST} ) const ( \sim ) 0v C5 s/c</td>
<td>1kHz Ip switching- ( V_o ) spikes of ( V_o=20v ) Ip=7A thereafter ( V_{COMP} )-( V_{GATE} )=Ve Ip continuous ( V_o ) collapse</td>
<td>7A</td>
<td>cont</td>
<td>( V_{ST} ) lo-int</td>
<td>( V_{ST} ) mon. clamps ( V_{GATE} ) to 0v ( V_{DEM} ) zeroed, warning given</td>
<td>momentary o/p peak &amp; Ip=10A-till zeroed by mntr</td>
</tr>
<tr>
<td>15</td>
<td>&quot;</td>
<td>200kHz ( V_{ST} ) T4 s/c,C5 o/c</td>
<td>normal circuit operation slight reduction in ( V_o )</td>
<td>norm</td>
<td>on</td>
<td>lo-int</td>
<td>( V_o ) decr.probably not detectable by ( V_o ) mon.</td>
<td>slight reduction in ( V_o ) zeroed if detected by mon.</td>
</tr>
<tr>
<td>16</td>
<td>&quot;</td>
<td>( &gt;300kHz ) ( V_{ST} ) C4 s/c,R15 s/c</td>
<td>primary switching- ( V_o=46v ) Ip=10Acontinuous</td>
<td>10A</td>
<td>cont</td>
<td>( V_{ST} ) lo-int</td>
<td>( V_{ST} ) mon. clamps ( V_{GATE} ) to 0v ( V_{DEM} ) zeroed, warning given</td>
<td>momentary change to cont.46v o/p &amp; Ip=7A</td>
</tr>
<tr>
<td>17</td>
<td>&quot;</td>
<td>floating o/p</td>
<td>o/p spike at start of pulse (Ip=12A) thereafter zero</td>
<td>0.2A</td>
<td>on</td>
<td>( V_{ST} ) lo-int</td>
<td>( V_{ST} ) mon. clamps ( V_{GATE} ) to 0v ( V_{DEM} ) zeroed, warning given</td>
<td>momentary o/p spike till zeroed by monitor</td>
</tr>
<tr>
<td>18</td>
<td>( V_{SAWTOOTH} ) generator monitor</td>
<td>spurious operation U2,U1 failure Res.failure</td>
<td>( V_{GATE} ) clamped to 0v Ip=( V_o ),Io=0</td>
<td>0A</td>
<td>on</td>
<td>lo-int</td>
<td>( V_o )&amp;( V_{GATE} ) clamped if ( V_{DEM} &gt;0 )</td>
<td>o/p suddenly zeroed with failure by monitor</td>
</tr>
<tr>
<td>19</td>
<td>&quot;</td>
<td>threshold error resistor fail /value change</td>
<td>monitor in-op/incorrect thrshld. o/p normal ( V_{ST} ) genr fault not detectable</td>
<td>norm</td>
<td>on</td>
<td>---</td>
<td>none</td>
<td>o/p normal. 2nd fault in ( V_{ST} ) generator not detectable</td>
</tr>
<tr>
<td>20</td>
<td>En/Disable circuit</td>
<td>spurious operation -T5 o/c MCM o/p ( 0V/0V )o/c MCM o/p device or ( \mu C ) fault</td>
<td>( V_{GATE} ) clamped - ( V_o ),Io=0 if E/D signal floating- then ( V_{GATE} ) clamped by R25</td>
<td>0A</td>
<td>on</td>
<td>lo-int</td>
<td>if ( \mu C ) optnl &amp;( V_{DEM} &gt;0 )-zero o/p detected- warn+shut down</td>
<td>output zeroed by fault</td>
</tr>
<tr>
<td>21</td>
<td>&quot;</td>
<td>inoperative T5 s/c MCM device flt E/D o/p ( &gt;3V )</td>
<td>normal output operation 2nd fault- no o/p inhibition E/D not direct from ( \mu C ) not inoperative due to ( \mu C ) fault</td>
<td>norm</td>
<td>on</td>
<td>---</td>
<td>none</td>
<td>output normal</td>
</tr>
<tr>
<td>22</td>
<td>comparator U2d</td>
<td>( V_{COMP} ) floating R6 o/c</td>
<td>during pulse -no switching Ip=( V_o )=0</td>
<td>0A</td>
<td>on</td>
<td>lo-int</td>
<td>( V_o )&amp;( V_{GATE} ) clamped if ( V_{DEM} &gt;0 )</td>
<td>o/p suddenly zeroed with failure</td>
</tr>
<tr>
<td>23</td>
<td>&quot;</td>
<td>( V_{COMP}=0V ) cont U2,T1,T6 s/c</td>
<td>( V_{Gate}=0V ) no fet switching Ip=Io=0</td>
<td>0A</td>
<td>cont</td>
<td>lo-int</td>
<td>( V_o )&amp;( V_{GATE} ) clamped if ( V_{DEM} &gt;0 ) but already at 0v</td>
<td>o/p suddenly zeroed with failure</td>
</tr>
<tr>
<td>24</td>
<td>&quot;</td>
<td>( V_{COMP}=Ve ) cont U2,o/c, T1 s/c</td>
<td>FET on &amp; Ip continuous no switching -Io=0</td>
<td>11A</td>
<td>cont</td>
<td>lo-int</td>
<td>( V_o )&amp;( V_{GATE} ) clamped if ( V_{DEM} &gt;0 ) unit operation ceased emptily</td>
<td>momentary max o/p spike then zero as no switching</td>
</tr>
<tr>
<td>N.*</td>
<td>Circuit element</td>
<td>failure mode -cause(s)</td>
<td>failure effect (without monitor action)</td>
<td>av. ( I_{primary} )</td>
<td>fault</td>
<td>Mon -itor</td>
<td>monitor action</td>
<td>resultant output state (after monitor action)</td>
</tr>
<tr>
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<td>---------------------------------------------</td>
</tr>
<tr>
<td>25</td>
<td>comparator U2d</td>
<td>( V_{COMP} ) rise time incr. - Q1 o/c</td>
<td>( I_{GATE} ) suppl by comparator samll decr. ( I_{o/p, V_o, I_o} )</td>
<td>norm</td>
<td>on</td>
<td>Io-int</td>
<td>decr. probably only detectable at large ( V_o ) values</td>
<td>Vo decr. eg 100v to 90v</td>
</tr>
<tr>
<td>26</td>
<td>&quot;</td>
<td>( V_{COMP} ) fall time incr. - Q2 o/c</td>
<td>( I_{GATE} ) sourced by comparator samll decr. ( I_{o/p, V_o, I_o} )</td>
<td>norm</td>
<td>on</td>
<td>Io-int</td>
<td>incr. probably only detectable at large ( V_o ) values</td>
<td>Vo decr. eg 100v to 104v incr. ripple(-swtchg&gt;100K)</td>
</tr>
<tr>
<td>27</td>
<td>gate res.R7</td>
<td>o/c( \theta_{GATE} ) floating</td>
<td>FET off cont-( I_o, V_o, I_o=0 )</td>
<td>0A</td>
<td>on</td>
<td>Io-int</td>
<td>( V_o &amp; V_{GATE} ) clamped if ( V_{DEM}&gt;0 )</td>
<td>o/p suddenly zeroed</td>
</tr>
<tr>
<td>28</td>
<td>&quot;</td>
<td>s/c ( \theta_{GATE} ) normal</td>
<td>negligible change in o/p</td>
<td>norm</td>
<td>on</td>
<td>---</td>
<td>not detectable</td>
<td>negligible change</td>
</tr>
<tr>
<td>29</td>
<td>FET Q3</td>
<td>o/c-drain-source</td>
<td>no switching ( I_p=I_o=V_o=0 )</td>
<td>0A</td>
<td>on</td>
<td>Io-int</td>
<td>( V_o &amp; V_{GATE} ) clamped if ( V_{DEM}&gt;0 )</td>
<td>o/p suddenly zeroed</td>
</tr>
<tr>
<td>30</td>
<td>&quot;</td>
<td>s/c-drain-source</td>
<td>( I_p ) cont( I_o=0 ) no switching</td>
<td>11A</td>
<td>on</td>
<td>Io-int</td>
<td>( V_o &amp; V_{GATE} ) clamped if ( V_{DEM}&gt;0 )</td>
<td>unit operation ceased emptly</td>
</tr>
<tr>
<td>31</td>
<td>Transformer</td>
<td>primary o/c</td>
<td>( I_p, V_o, I_o=0 )</td>
<td>0A</td>
<td>on</td>
<td>Io-int</td>
<td>( V_o &amp; V_{GATE} ) clamped if ( V_{DEM}&gt;0 )</td>
<td>o/p suddenly zeroed</td>
</tr>
<tr>
<td>32</td>
<td>Tr1</td>
<td>primary s/c</td>
<td>( \theta ) incr. - rect. pulses no transfmr action ( V_o, I_o=0 )</td>
<td>1A*</td>
<td>on</td>
<td>Io-int</td>
<td>( V_o &amp; V_{GATE} ) clamped if ( V_{DEM}&gt;0 )</td>
<td>o/p suddenly zeroed</td>
</tr>
<tr>
<td>33</td>
<td>&quot;</td>
<td>secondary o/c</td>
<td>( \theta ) intermit. spikes 10-700( \mu )s upto 20A - Isec, ( I_o, V_o=0 )</td>
<td>&lt;1A</td>
<td>on</td>
<td>Io-int</td>
<td>( V_o &amp; V_{GATE} ) clamped if ( V_{DEM}&gt;0 )</td>
<td>o/p suddenly reduced</td>
</tr>
<tr>
<td>34</td>
<td>&quot;</td>
<td>secondary s/c</td>
<td>( \theta ) incr. - rect. pulses no transfmr action ( V_o, I_o=0 )</td>
<td>1A*</td>
<td>on</td>
<td>Io-int</td>
<td>( V_o &amp; V_{GATE} ) clamped if ( V_{DEM}&gt;0 )</td>
<td>o/p suddenly reduced</td>
</tr>
<tr>
<td>35</td>
<td>D2 secndy series diode</td>
<td>o/c -as per Tr1 secondary o/c</td>
<td>danger of h.v arcing from Tr secndy to near by 0V</td>
<td>&lt;1A</td>
<td>on</td>
<td>Io-int</td>
<td>( V_o &amp; V_{GATE} ) clamped if ( V_{DEM}&gt;0 )</td>
<td>o/p suddenly reduced</td>
</tr>
<tr>
<td>36</td>
<td>&quot;</td>
<td>s/c-no blocking of neg.sw spike</td>
<td>latches to cont.( I_p ) state o/p pulse peak( \text{at} ) ( \text{spt} ) then 0</td>
<td>&gt;4A</td>
<td>on</td>
<td>Io-int</td>
<td>( V_o &amp; V_{GATE} ) clamped if ( V_{DEM}&gt;0 ) if Q3 fails( \text{ceases unit operatr} )</td>
<td>momentary max o/p spike then zero as no swtch o</td>
</tr>
<tr>
<td>37</td>
<td>D3 secndy shunt diode</td>
<td>o/c-no toFF Isec</td>
<td>( \theta ) limited to 30V s.probe on o/p( /I_p ) cont</td>
<td>&gt;1A</td>
<td>on</td>
<td>Io-int</td>
<td>( V_o &amp; V_{GATE} ) clmpd if ( V_o ) not 30V</td>
<td>change in o/p upto 30v</td>
</tr>
<tr>
<td>38</td>
<td>&quot;</td>
<td>s/c o/p bypassed</td>
<td>( V_o=0 ), ( \theta ) incr.-rect.pulses</td>
<td>1A*</td>
<td>on</td>
<td>Io-int</td>
<td>( V_o &amp; V_{GATE} ) clmpd if ( V_{DEM}&gt;0 )</td>
<td>o/p suddenly zeroed</td>
</tr>
<tr>
<td>39</td>
<td>L1 o/p inductor</td>
<td>o/c-o/p isolated</td>
<td>Isec in D2&amp;D3, ( \theta ) incr rise s.probe on o/p( /I_p ) cont</td>
<td>1A*</td>
<td>on</td>
<td>Io-int</td>
<td>( V_o &amp; V_{GATE} ) clamped if ( V_{DEM}&gt;0 ) unit operation ceased emptly</td>
<td>o/p suddenly zeroed</td>
</tr>
<tr>
<td>40</td>
<td>&quot;</td>
<td>s/c-no sec. flux storage</td>
<td>( \theta ) incr.amplitude+ripple av ( \text{qip incr.-rect.subpulses} )</td>
<td>norm</td>
<td>on</td>
<td>Io-int</td>
<td>incr. probably only detectable at large ( V_o ) values</td>
<td>Vo incr. eg 100v to 112v incr. ripple</td>
</tr>
<tr>
<td>41</td>
<td>C7 output</td>
<td>o/c-o/p o/p filter</td>
<td>( \text{norm o/p &amp; ripple upto 30v} )</td>
<td>norm</td>
<td>on</td>
<td>Io-int</td>
<td>detected if mon.samples ripple</td>
<td>( \text{norm o/p, ripple up to 30v} )</td>
</tr>
<tr>
<td>42</td>
<td>filter cap.</td>
<td>s/c o/p bypassed</td>
<td>( V_o=0 ), ( \theta ) incr.-rect. pulse</td>
<td>1A*</td>
<td>on</td>
<td>Io-int</td>
<td>( V_o &amp; V_{GATE} ) clamped if ( V_{DEM}&gt;0 )</td>
<td>o/p suddenly reduced</td>
</tr>
<tr>
<td>43</td>
<td>R9 output</td>
<td>o/c-output o/c</td>
<td>( V_o=I_o=0 ), ( \theta ) cont.</td>
<td>&gt;4A</td>
<td>on</td>
<td>Io-int</td>
<td>( V_o &amp; V_{GATE} ) clamped if ( V_{DEM}&gt;0 )</td>
<td>o/p suddenly reduced</td>
</tr>
<tr>
<td>44</td>
<td>limit resist.</td>
<td>s/c-decR.( R_{LOAD} )</td>
<td>o/p Is/c limit removed</td>
<td>norm</td>
<td>on</td>
<td>Io-int</td>
<td>probably not detectable</td>
<td>Vo,( I_o ) small increase</td>
</tr>
<tr>
<td>N.</td>
<td>Circuit element</td>
<td>failure mode (cause(s))</td>
<td>failure effect (without monitor action)</td>
<td>av. (I_{\text{inj}})</td>
<td>fault</td>
<td>Mon. -itor</td>
<td>monitor action</td>
<td>resultant output state (after monitor action)</td>
</tr>
<tr>
<td>----</td>
<td>----------------</td>
<td>-------------------------</td>
<td>---------------------------------------</td>
<td>----------------</td>
<td>-------</td>
<td>---------</td>
<td>----------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>45</td>
<td>Io mon</td>
<td>(I_{o} f/b = 5v) U4 failure, R13 o/c</td>
<td>Io mon in-operative (I_{o} f/b) signal false max</td>
<td>norm</td>
<td>on</td>
<td>Io-int</td>
<td>(V_{GATE}) clamped if (V_{DEM} &gt; 0)</td>
<td>o/p suddenly zeroed even though normal</td>
</tr>
<tr>
<td>46</td>
<td>&quot;</td>
<td>(I_{o} f/b = 0) or 5v U4 failure R10 s/c R13 s/c wire/connector o/c</td>
<td>Io mon in-operative (I_{o} f/b) signal false zero small change in Io - otherwise o/p normal</td>
<td>norm</td>
<td>on</td>
<td>Io-int</td>
<td>(V_{GATE}) clamped if (V_{DEM} &gt; 0)</td>
<td>o/p suddenly zeroed even though normal</td>
</tr>
<tr>
<td>47</td>
<td>&quot;</td>
<td>(f/b) signal error U4 failure R13 value change R10 o/c</td>
<td>Io mon value error o/p normal</td>
<td>norm</td>
<td>on</td>
<td>Io-int</td>
<td>(V_{GATE}) may be clamped if Io signal significantly differs from that demanded</td>
<td>o/p normal may be zeroed by monitor</td>
</tr>
<tr>
<td>48</td>
<td>O/p clamp circuit</td>
<td>excess (I_{CLAMP}) R10+R12 s/c</td>
<td>if subsequent U6 switch fail s/c as 48), o/c as 49)</td>
<td>norm</td>
<td>on</td>
<td>---</td>
<td>see 48), 49)</td>
<td>o/p may be suddenly zeroed with failure</td>
</tr>
<tr>
<td>49</td>
<td>&quot;</td>
<td>on continuously U6 failure Q8,Q9,Q7 fail R28,R29 s/c (\mu C) fault</td>
<td>(V_{o}I_{o}) decr.&lt;1/10 Io passes thru U6 switches, if max.-device failure after 40s to high impedance - inoperative clamp(see 50)</td>
<td>&lt;norm</td>
<td>on</td>
<td>Io-int</td>
<td>(V_{GATE}) clamped if (V_{DEM} &gt; 0)</td>
<td>o/p suddenly zeroed with failure,</td>
</tr>
<tr>
<td>50</td>
<td>&quot;</td>
<td>in-operative U6 failure (eg 48) Q8,Q9,Q7 failure R29,12,47+48 o/c (\mu C) fault</td>
<td>(V_{o}) not clmpd to 0v btwn impulses -distrt rise shape potential U7&amp;U8 failure if switched with large (V_{o}) (see 50)</td>
<td>norm</td>
<td>on</td>
<td>---</td>
<td>none - unless subsequent failure</td>
<td>normal</td>
</tr>
<tr>
<td>51</td>
<td>biphasic switching</td>
<td>all switches o/c U7&amp;U8 failure R34-9,Q10-13 MCM/wire failure (\mu C) failure (V_{cc}) failure</td>
<td>o/p terminals isolated at max(V_{DEM})-core saturated at end (t_{ON})-1p, (V_{sec},D2) pwr incr.</td>
<td>1A*</td>
<td>on</td>
<td>Io-int</td>
<td>(V_{GATE}) clmpd if (V_{DEM} &gt; 0) heatsink dissipates D2 power Ip zeroed</td>
<td>o/p zero</td>
</tr>
</tbody>
</table>

Note: \(\mu C\) - Microcontroller
\(V_{GATE}\) - Gate voltage
\(V_{DEM}\) - Demands
\(t_{ON}\) - On time
\(V_{sec}\) - Secondary voltage
\(D2\) - Diode
\(Ip\) - Input power
<table>
<thead>
<tr>
<th>Circuit element</th>
<th>Failure Mode</th>
<th>Cause(s)</th>
<th>Failure Effect</th>
<th>Monitor Action</th>
<th>Resultant Output State</th>
</tr>
</thead>
<tbody>
<tr>
<td>52</td>
<td>mistimed switching Q10-13,U7,8 delay MCM o/p device</td>
<td>µC fault</td>
<td>distorted output impulses psble loss charge balance most likely µC s/w fault not detectible by wdog mon</td>
<td>mon detects distortion</td>
<td>o/p suddenly zeroed if mon detects fault</td>
</tr>
<tr>
<td>53</td>
<td>partial swtchng 1ph U7&amp;U8 failure</td>
<td></td>
<td>assymetric phases loss of charge balance/patient</td>
<td>Vo&amp;V_GATE clamped if VDEM&gt;0</td>
<td>o/p suddenly zeroed by monitor</td>
</tr>
<tr>
<td>54</td>
<td>any 1 switch o/c any 1 switch s/c causes see 48</td>
<td></td>
<td>loss of 1 phase-0/p s/c (1-decr. stim durn loss of charge balance)</td>
<td>Vo&amp;V_GATE clamped if VDEM&gt;0</td>
<td>o/p suddenly zeroed by monitor</td>
</tr>
<tr>
<td>55</td>
<td>&gt;2 switches s/c causes see 49</td>
<td></td>
<td>o/p s/c - Vo, Io=0 high Ip, Isec (see1)</td>
<td>Io-int</td>
<td>o/p zeroed by fault</td>
</tr>
<tr>
<td>56</td>
<td>MCM µC s/w fault</td>
<td></td>
<td>loss/spurious o/p signals to OPM (see other items)</td>
<td>V_GATE clamped till µC restarted o/p zero till inten reduced to 0</td>
<td>o/p suddenly zeroed</td>
</tr>
<tr>
<td>57</td>
<td>µC spurious reset</td>
<td></td>
<td>V_GATE clamped, VDEM zeroed o/p suddenly zeroed</td>
<td>---</td>
<td>o/p suddenly zeroed</td>
</tr>
<tr>
<td>58</td>
<td>Vcc supply over voltage &gt;5v U9 failure</td>
<td></td>
<td>&gt;6v-µcircuit failure poss fitg/max VDEM (5,6)</td>
<td>wdog</td>
<td>o/p zeroed by monitor</td>
</tr>
<tr>
<td>59</td>
<td>undervoltage &lt;4.5v U9 failure, s/c to 0v wire o/c Vce decr./failure</td>
<td></td>
<td>psbl spurious MCM optn V_ST decr-1cont-0/p colps &gt;1v-biph switches o/c - patient o/p isolated</td>
<td>?</td>
<td>o/p zeroed by monitor or by fault</td>
</tr>
<tr>
<td>60</td>
<td>under voltage/fairl D4,C10 fault batt fault/depletin s/c to 0v-D4 fairl wire o/c</td>
<td></td>
<td>&gt;7v Q3 partly on-Vo decr &gt;4.5v Vcc decr.(see 53) safe o/p demonstratd to 0v =0v Q3 off, Ip=Io=Vo=0</td>
<td>?</td>
<td>o/p decr gradually by µC o/p zeroed by monitor or by fault</td>
</tr>
<tr>
<td>N.</td>
<td>Circuit element</td>
<td>failure mode(s)</td>
<td>failure effect (without monitor action)</td>
<td>av. ( I_{primary} )</td>
<td>fault dur.</td>
</tr>
<tr>
<td>----</td>
<td>----------------</td>
<td>-----------------</td>
<td>-----------------------------------------</td>
<td>-----------------</td>
<td>-----------</td>
</tr>
<tr>
<td>61</td>
<td>Vp supply</td>
<td>undervoltage/fail batt depletn/failr wire, fuse o/c s/c to 0V</td>
<td>( V_{e}, I_{p}, V_{o} ) decr. -as 54</td>
<td>( 0A )</td>
<td>on</td>
</tr>
<tr>
<td>62</td>
<td>Ext Supply</td>
<td>not for patient use</td>
<td>( V_{DEM} = I_{o} = V_{o} = 0 )</td>
<td>( 0A )</td>
<td>on</td>
</tr>
<tr>
<td>63</td>
<td>intensity control</td>
<td>intensity = zero VR1 s/c to 0V wiper disconcted R48 s/c</td>
<td>( V_{DEM}, V_{o}, I_{o} ) sudden change to max</td>
<td>( \text{norm} )</td>
<td>( \text{max} )</td>
</tr>
<tr>
<td>64</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>65</td>
<td>mode select switch</td>
<td>spurious /floating i/p (ant of 4)</td>
<td>incorrect mode selection (presently unused)</td>
<td>( \text{norm} )</td>
<td>( \text{s/w} )</td>
</tr>
<tr>
<td>66</td>
<td>RS232</td>
<td>communication fail wire disconnection MCM U11 failr PC failure uC s/w fault</td>
<td>no response to user commands o/p continuous under unit control</td>
<td>( \text{norm} )</td>
<td>( \text{PC} )</td>
</tr>
<tr>
<td>67</td>
<td>Electrodes</td>
<td>Peeling off skin</td>
<td>( I_{o} ) decr. ( I_{o} ) density incr. potential skin damage</td>
<td>( \text{norm} )</td>
<td>( \text{Io-int} )</td>
</tr>
<tr>
<td>68</td>
<td>&quot;</td>
<td>Too close/touching</td>
<td>( I_{o} ) /density too high</td>
<td>( \text{norm} )</td>
<td>( \text{Io-int} )</td>
</tr>
</tbody>
</table>
From IRF530 data sheet following method of Clemente, (1993)

(Hexfet, power MOSFET Designers Manual Vol.3 p137 - International Rectifier,

Maximum Junction temperature $T_{\text{MAX}} = 175 \, ^\circ\text{C}$

$R_{\text{DS(on)}} = 0.16\, \Omega \text{ (max)} @ V_{\text{GS}} = 10\, \text{V}, \, I_D = 8.4\, \text{A}$

$= 0.43\, \Omega \text{ @ } T_1 = 175 \, ^\circ\text{C}$ figure 4 of data sheet

Thermal Resistance $R_\theta$ ($^\circ\text{C/W}$)

$J=$ device junction, $C=$device case, $S=$heatsink, $A=$ambient

$R_{\theta JA} = R_{\theta JC} + R_{\theta CS} + R_{\theta SA} = (T_{\text{MAX}} - T_A)/ I_D^2 R_{\text{DS(on)}}$

$I_D_{\text{MAX}} = \sqrt{(T_{\text{MAX}} - T_A)/ R_{\theta JA} R_{\text{DS(on)}}}$

With no heatsink fitted:

$R_{\theta JAMAX} = 62\, ^\circ\text{C/W}$

$I_D_{\text{MAX}} = \sqrt{(175-45)/ 62.0.43} = 2.2\, \text{A}$

With $21\, ^\circ\text{C/W}$ heatsink fitted:

$R_{\theta JA} = 1.7 + 0.5 + 21 = 23.2\, ^\circ\text{C/W}$

$I_D_{\text{MAX}} = \sqrt{(175-45)/ 23.2.0.43} = 3.6\, \text{A}$