Electrotherapy and Tissue Repair

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[Abstract]
Electrotherapy is one form of intervention that has the capacity to influence the processes associated with tissue repair. Some modalities are more effective at achieving this than others, and there are differences in they type of tissue that respond to the different modalities. Numerous electrotherapy modalities have significant clinical effects, but not primarily on tissue repair, and they are excluded from this review for this reason.

Evidence for the relationship between electrotherapy and tissue repair is continuously updated and thus, this is the story is it is at the moment – the current state of the art. It is fully expected that this will change – maybe next month, maybe next year – and therefore the latter section of this paper considers some of the emerging issues
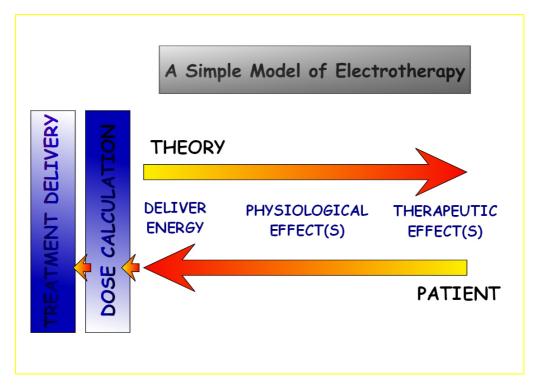[Abstract ends]

Capacity for Electrotherapy to Influence Tissue Repair

It is evident from published research that some electrotherapy modalities have the capacity to influence the repair process in what might be considered to be a 'direct' mode of action. These primarily include ultrasound, pulsed shortwave therapy and therapeutic laser. Full information on these and other interventions can be found in standard texts, review papers and various online resources (e.g. www.electrotherapy.org). Modalities such as interferential therapy, TENS and other neuromuscular electrical stimulation (NMES) do not appear to have a direct effect on tissue repair, though research in these areas continues and the evidence may change in future.

Basic Electrotherapy mode of action

Model of Electrotherapy

Electrotherapy modalities follow a very straightforward model that is presented below. In principle, the model (Figure 1) identifies that the delivery of energy from a machine or device is the start point of the intervention. The energy entry to the tissues results in a change in one or more physiological events. Some are very specific whilst others are multifaceted. The capacity of the energy to influence physiological events is key to the processes. The physiological shift that results from the energy delivery is used in practice to generate what is commonly referred to as therapeutic effects.

Figure 1 : A simple model of Electrotherapy

The clinical application of the model is best achieved by what appears to be a reversal of this process. Start with the patient and their problems, identified from the clinical assessment. Once the problems are known, the treatment priorities can be established and the rationale for the treatment determined. Knowing what it is that is intended to be achieved generates the target for the intervention. Moving one step back through the model, the question then arises – 'if that is the intended outcome or therapeutic effect, which physiological process(es) need to be stimulated, modified or affected in order for the outcome to be achieved?' Once the physiological changes are established, one further step back through the model will enable the determination of the most appropriate modality that can be used to achieve this effect, based on the best available evidence. If for example, the patient presents with a chronic hamstring muscle tear, with pain, disturbed movement patterns and functional difficulty, then what needs to be changed, stimulated or activated in order to get a clinically beneficial outcome? Once this is decided, it is a matter of deciding from the evidence which modality, if any, is

best able to achieve these results? If there is no electrotherapy modality capable of stimulating this / these physiological change(s) in the tissue in question, then electrotherapy has no place in the management of this particular patient.

The effects of electrotherapy appear to be modality dependent. This is a critical decision, in that some modalities have a limited sub set of effects which are fundamentally different from another modality.

Having identified the modality that is best able to achieve the effects required, the next clinical stage is to make a 'dose' selection. Not only is it critical to apply the right modality, but it needs to be applied at the appropriate 'dose' in order for maximal benefit to be achieved. There is a substantial and growing body of evidence that the same modality can be applied at different doses and the results will not be the same. An obvious example might be Laser Therapy. Applied at low dose, laser has effects that are harnessed by therapists when treating a variety of open wounds and musculoskeletal tissue problems. Applied at a higher dose, the same light energy is used by the surgeon as a means to ablate tissue. The energy form might be the same, but the dose is different and the outcome is easily distinguished.

One might argue that this is an extreme example, which in some ways it is, but the point is that the effects of the therapy are both modality and dose dependent. There are 'therapeutic windows' in electrotherapy (as there are in almost all therapeutic interventions) and in order to achieve the 'best' outcome, it is essential to get as close to this window as one possibly can.

This fundamental model used to explain electrotherapy could be applied to many interventions – drug therapy, manual therapy, exercise therapy. All involve the use of an intervention in order to achieve a physiological shift or change. It is this change that is the therapeutic tool. The treatment is just a tool to stimulate the physiological change. Electrotherapy is therefore little different from manual therapy or anything else in the treatment realm. It is a tool that when applied at the right time at the right dose and for the right reason has the capacity to be beneficial. Applied inappropriately, it is not at all surprising that is has the capacity to achieve nothing or in fact to make things worse. The skilful practitioner uses the available evidence combined with experience to make the best possible decision taking into account the psycho-social and holistic components of the problem – it is not a simple reductionist solution.

Therapeutic windows

Windows of opportunity are topical in many areas of medical practice and are not a new phenomenon at all. It has long been recognised that the 'amount' of a treatment is a critical parameter. This is no less true for electrotherapy than for other interventions. There are literally hundreds of research papers that

illustrate that the same modality applied at a different 'dose' will produce a different outcome.

Given the research evidence, there appear to be several aspects to this issue. Using a very straightforward model, there is substantial evidence for example that there is an **'amplitude' or 'strength' window**. An energy delivered at a particular amplitude has a beneficial effect whilst the same energy at a lower amplitude may have no demonstrable effect. The laser example above is a simple extension of this case – one level will produce a distinct cellular response whilst a higher dose can be considered to be destructive. Karu (1987) demonstrated and reported these principles related to laser energy and the research produced since has served to reinforce the concept (Vinck 2003). Further examples of amplitude windows can be easily seen in the work of Hill et al 2002, Reher et al 2002, Miller & Gies 1998, Cleary 1987, Pereira et al 2002).

Along similar lines, **'frequency windows'** are also apparent. A modality applied at a specific frequency (pulsing regieme) might have a measurable benefit, whilst the same modality applied using a different pulsing profile may not appear to achieve equivalent results. Examples can be found in many papers including Martin et al 1991, Young & Dyson 1990, Sontag 2000)

Electrical stimulation frequency windows have been proposed and there is clinical and laboratory evidence to suggest that there are frequency dependent responses in clinical practice. TENS applied at frequency X appears to have a different outcome to TENS applied at frequency Y in an equivalent patient population. Studies by Han et al 1991 and Palmer et al 1999 illustrate the point.

Assuming that there are likely to be more than two variables to the real world model, some complex further work needs to be invoked. There is almost certainly an energy or time based window (e.g. Hill et al 2002) and then another factor based on treatment frequency (number of sessions a week or treatment intervals). Work continues in our and other research units to identify the more and less critical parameters for each modality across a range of clinical presentations.

One research style which has proved to be helpful in this context is to test a treatment on non injured subjects in the laboratory using a variety of doses, and then to take the same protocol out into the clinical environment and repeat the testing procedure with real patients with particular clinical problems. Preliminary results indicate that there are distinct differences between the responses on 'normal' and 'injured' tissues at equivalent doses and further work is essential to maximise our understanding of these behaviours. (Al Mandil and Watson in press)

Modality Specific Information

General Issues – overlap effects and differences in absorption

The three main modalities under consideration in this paper essentially have very similar, if not identical effects. Whilst there are some (relatively minor) differences in the research findings, it appears that the majority of the therapeutic effects of ultrasound, pulsed shortwave and laser overlap for the majority. The logical query at his point is why might it be necessary to ever employ more than one of them? The essential difference between the modalities is that although they all have essentially similar effects, these outcomes are not primarily achieved in the same tissues – different forms of energy are preferentially absorbed by different types of tissue. The dominant effects of the modality are achieved in the tissue in which the energy is best absorbed, hence knowing the relative absorption of the different energies in the various tissues will enable the practitioner to discriminate between modality use in a clinical decision making process. It is appreciated that not all modalities will be available to all therapists in all circumstances, but in the 'ideal world' the availability of all three modalities would offer maximal flexibility and thus effectiveness.

Ultrasound

Therapeutic ultrasound is one of the more established and most widely used of the electrophysical agents (Pope 1995, Robertson 2002, Robertson and Baker 2001). The energy output of the machine is a sound wave which, whether audible or not, is a mechanical wave form, and in the case of therapeutic ultrasound, it is most often applied with frequencies between 1 and 3 MHz. The ultrasound treatment 'head' is the source of this energy, and the ultrasound machine as such provides the necessary circuitry to generate the sound energy.

Not all tissues will absorb US equally, and thus the effectiveness of the modality will be influenced by the type of tissue being treated. The listed set of effects of ultrasound are best achieved in the tissues that do absorb the energy most efficiently. These are the dense collagenous tissues – such as ligament, tendon, fascia, capsule and scar tissue. Although not an exclusive list, these represent the tissues for which US appears to be most effective, and would be consistent with the associated background physics. Clearly ultrasound can have an effect in other types of tissue (e.g. muscle), but it would be less effective if used to treat an acute muscle tear than it would be if used to treat an acute ligament tear – the nature of the tissue is a critical element in the clinical decision making process (Watson 2000, ter Haar 99, Nussbaum 1998, Frizzel & Dunn 1982). Recent (animal) studies have clearly demonstrated this phenomena with no significant effect being demonstrated immediately following muscle contusion injury (Wilkin et al 2004, Markert et al 2005) whilst benefits are achieved following ligament injury (Sparrow et al 2005, Takakura et al 2002).

Ultrasound Modes

Ultrasound can be used in THERMAL or NON THERMAL modes. In thermal mode, it will be most effective in heating the dense collagenous tissues and will require a higher intensity, preferably in continuous mode to achieve this effect. In the non thermal application, lower energy levels, preferably in pulsed mode are applied in order to achieve cell 'up regulation' without heating. The primary non thermal effects involve enhancement of the tissue repair process by optimising the normal inflammatory, proliferative and remodelling events. (Nussbaum 1997, 1998, Watson 2000)

Many papers have concentrated on the thermal effectiveness of ultrasound, and much as it can be used effectively in this way when an appropriate dose is selected (continuous mode >0.5 W cm^{-2}), the focus of this paper will be on the non thermal effects on tissue repair and recovery from injury. Both Nussbaum (1998) and ter Haar (1999) have provided some useful review material with regards the thermal effects of ultrasound. Leonard et al (2004) provide evidence that the deep tissue temperature changes achieved with therapeutic ultrasound are or limited therapeutic value. Comparative studies on the thermal effects of ultrasound have been reported by several authors (e.g. Draper et al 1993, 1995a,b,c, Meakins and Watson 2006) with some interesting, and potentially useful results. Finally, Merrick et al (2003) demonstrated that different ultrasound machines delivering apparently the same treatment energy give rise to different amounts of tissue heating – and therefore the effect may be more than simply a dose dependent issue.

It is too simplistic to assume that with a particular treatment application there will either be thermal or non thermal effects. It is almost inevitable that both will occur, but it is reasonable to argue that the dominant effect will be influenced by treatment parameters, especially the mode of application i.e. pulsed or continuous. Baker et al (2001) have argued the scientific basis for this issue coherently.

Influence of Ultrasound in Soft Tissue Healing

The effect of US during the repair process varies according to the primary events that are occurring in the tissues. During the inflammatory phase, US has a stimulating effect on the mast cells, platelets, white cells with phagocytic roles and the macrophages (Nussbaum 1997, ter Haar 1999, Fyfe & Chahl 1982, Maxwell 1992). For example, the application of ultrasound induces the degranulation of mast cells, causing the release of arachidonic acid which itself is a precursor for the synthesis of prostaglandins and leukotreine – which act as inflammatory mediators (Mortimer & Dyson 1988, Nussbaum 1997, Leung et al 2004). By increasing the activity of these cells, the overall influence of therapeutic US is certainly pro-inflammatory rather than anti-inflammatory. The benefit of this mode of action is not to 'increase' the inflammatory response as such (though if applied with too greater intensity at

this stage, it is a possible outcome (Ciccone et al 1991), but rather to act as an 'inflammatory opimiser'. The inflammatory response is essential to the effective repair of tissue, and the more efficiently the process can complete, the more effectively the tissue can progress to the next phase (proliferation) as illustrated in Figure 2.
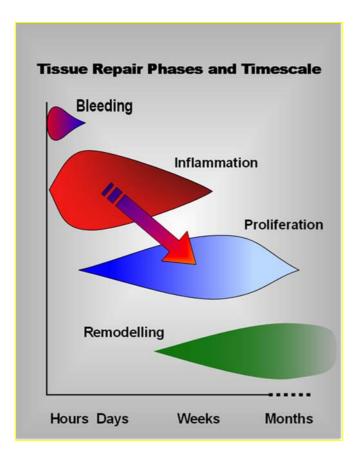

Figure 2 : Enhancement of the inflammatory phase of repair in order to facilitate tissue repair

Studies which have tried to demonstrate the anti inflammatory effect of ultrasound have failed to do so (e.g.Hashish 1986, 1988), and have suggested that US is ineffective. It is effective at promoting the normality of the inflammatory events, and as such has a therapeutic value in promoting the overall repair events (ter Haar 99).

Employed at an appropriate treatment dose, with optimal treatment parameters (intensity, pulsing and time), the benefit of US is to make as efficient as possible to earliest repair phase, and thus have a promotional effect on the whole healing cascade. For tissues in which there is an inflammatory reaction, but in which there is no 'repair' to be achieved, the benefit of ultrasound is to promote the normal resolution of the inflammatory events, and hence resolve the 'problem' This will of course be most effectively achieved in the tissues that preferentially absorb ultrasound – i.e. the dense collagenous tissues.

During the proliferative phase (scar production) US also has a stimulative effect (cellular up regulation), though the primary active targets are now the fibroblasts, endothelial cells and myofibroblasts (Ramirez et al 1997, Mortimer and Dyson 1988, Young & Dyson 1990, Young & Dyson 1990b, Nussbaum 1997, 1998, Dyson & Smalley 1983, Maxwell 1992). These are all cells that are normally active during scar production and US is therefore pro-proliferative in the same way that it is pro-inflammatory – it does not change the normal events, but maximises their efficiency – producing the required scar tissue in an optimal fashion. Harvey et al (1975) demonstrated that low dose pulsed ultrasound increases protein synthesis and several research groups have demonstrated enhanced fibroplasia and collagen synthesis (Ng et al 2004, Ng et al 2003, Tsai et al 2005, Enwemeka et al 1989, 1990, Huys et al 1993, Ramirez et al 1997). Recent and growing evidence suggests that there are further effects of US in this area, with a particular emphasis on the angiogenic effets.

The application of therapeutic ultrasound can influence the remodelling of the scar tissue in that it appears to be capable of enhancing the appropriate orientation of the newly formed collagen fibres and also to the collagen profile change from mainly Type III to a more dominant Type I construction, thus increasing tensile strength and enhancing scar mobility (Nussbaum 1998, Wang 1998). Ultrasound applied to tissues enhances the functional capacity of the scar tissues (Nussbaum 1998, Huys et al 1993). The role of ultrasound in this phase may also have the capacity to influence collagen fibre orientation as demonstrated in an elegant study by Byl et al (1996), though their conclusions were somewhat tentative.

Recent papers have identified the potential role for therapeutic ultrasound in relation to their capacity to influence various cytokines and mediators of the repair process. For example, ultrasound has a capacity to influence the production of TGF-β (Mukai et al 2005) and it is anticipated that this research area will grow significantly in the near future.

The application of ultrasound during the inflammatory, proliferative and repair phases is not of value because it changes the normal sequence of events, but because it has the capacity to stimulate or enhance these normal events and thus increase the efficiency of the repair phases. It would appear that if a tissue is repairing in a compromised or inhibited fashion, the application of therapeutic ultrasound at an appropriate dose will enhance this activity. If the tissue is healing 'normally', the application will, it would appear, speed the process and thus enable the tissue to reach its endpoint faster than would otherwise be the case. The effective application of ultrasound to achieve these aims is dose dependent.

Pulsed Shortwave & Laser Therapy

The effects of Pulsed Shortwave Therapy and Laser Therapy in relation to tissue repair are very similar to those identified for Ultrasound and a summary is included below. The question comes with regards why then are three different modalities needed if they all 'do the same job'? The evidence would support this contention but furthermore, it also identifies the critical difference between the three modalities – that of absorption – i.e. where the effect is achieved. The three different forms of energy are preferentially absorbed in different types of tissue, and thus, the primary benefit is differentially achieved.

Ultrasound is best absorbed (as above) in the dense collagenous tissues. Pulsed Shortwave energy (when delivered with the monode or drum applicator) is preferentially absorbed in the ionic, low impedance tissues (e.g. nerve, muscle, oedematous tissue, haematoma) see Ward (1980) for an excellent discussion with regards RF energy absorption and the laser (light) energy is best absorbed in tissue that is (a) superficial and (b) vascular (Tuner and Hode 2002).

Clearly, it would be wrong to claim an absolute difference between the energy forms, but there is a difference in preferential absorption, and hence, a differential clinical effect. Ultrasound might have some beneficial effect on recently injured muscle, but given a choice, pulsed shortwave or laser (if the muscle is superficial) would be likely to achieve better outcomes.

Laser

The light energy delivered from a therapeutic laser essentially acts as a trigger for physiological reactions in the same way that ultrasound does. Karu did some critical work on this aspect of the therapy several years ago (Karu 1987) and has written on it extensively since then (Karu 1998). Much of the really impressive clinical work with Laser has involved patients who have long term, chronic open wounds though clearly, this is of less importance with regards the context of this paper.

Laser light has a relatively short penetration depth into living tissue, though there is substantial disagreement as to what kind of 'average' distance should be cited. The light energy itself is rapidly absorbed, and a reasonable figure would be that some 95% of the surface energy is absorbed by 10-15mm into the tissues (depending on the light source – infrared laser light will penetrate further than visible red light). It is proposed however, that although the actual absorption is relatively superficial, the cellular and tissue reactions that take place in the superficial tissue initiate chemically mediated cascades, and these are able to influence deeper tissues and those at some distance (Tuner & Hode 2002 for some useful review material).

Recent papers by several authors have illustrated very similar findings to those identified above with ultrasound. For example, Vinick et al (2003) reported on a nicely conducted (lab) study, in which laser irradiation was

shown to stimulate fibroblast proliferation. Interestingly, green light was found to have a stronger effect than red light. The problem with this in the clinical environment is that green light has a very minimal tissue penetration (a millimetre or two) and hence the red light is more clinically appropriate. Brondon et al (2005) demonstrated with a controlled study that laser light increases the metabolic activity and proliferation of a variety of cells in culture – again, in the same way that ultrasound does. One of the more recent publications by Karu (Karu et al 2005) showed that Nitric Oxide (a very trendy inflammatory / healing chemical mediator being investigated by many research groups round the world) is influenced by laser therapy. Nitrous Oxide (NO) is believed to be a signalling agent controlling cell respiration.

Of the most recent papers that might be considered to be more directly relevant to this paper concern the problems of Achilles Tendinitis. Bjordal et al (2006) report the results from a well structured randomised, placebo controlled trial of laser therapy for this problem, working on the basis that laser is thought to act as an inflammatory modulator. A relatively small (n=7) groups of patients with bilateral Achilles tendonitis were treated with an infra red therapy laser. The concentration of prostaglandin E2 (an inflammatory mediator) was significantly reduced following the treatment compared with both the control and placebo conditions, and the pain threshold had increased following intervention.

Fillipin et al (2005) also investigated Achilles Tendinitis (in a rat model) using low level laser therapy (LLLT) in relation to the levels of oxidative stress and fibrosis. It was found that the use of LLLT for 14 or 21 days provided significant improvement over the control condition, reducing histological abnormalities and collagen concentration. The observed reduction in oxidative stress could, it is proposed, result in less fibrosis during the repair phase. The production of reactive oxygen species (from excessive Nitric Oxide production and phagocytic overactivity) is thought to increase cell damage, and the LLLT effect in this study was to ameliorate the effect of the reactive oxygen species, thus assisting in the efficient repair of the tissue.

These studies by Fillipin and Bjordal are supported by a series of studies reported by Demir et al (2004a, b) in which significant benefit was derived from both laser therapy and ultrasound treatments in skin wounds and experimental tendon healing.

Therapeutic laser, when delivered at appropriate doses appears to be capable to enhancing the inflammatory and proliferative cascades in much the same way as US. There is less evidence with regards the effects in the remodelling stage, though further investigation is needed in this area.

Pulsed Shortwave Therapy (PSWT)

Pulsed shortwave therapy is one of the more popular electrotherapy modalities in use in the UK (Pope et al 1995, Al Mandil and Watson 2006).

The effects of the electromagnetic field are primarily achieved in the tissues that preferentially absorb this form of energy, which are the low impedance, ionic tissues e.g. muscle, nerve, areas of oedema, haematoma and effusion. The modality can be employed in either a thermal or a non thermal mode, though it is the latter that will be the focus of this paper. There is no doubt that PSWT is capable of generating thermal effects in the tissues (Bricknell and Watson 1995, Murray and Kitchen 2000, Prentice and Draper 2001), which can give rise to a range of thermal benefits.

Although several of the claimed effects of the modality are not strongly supported by the evidence, there is sufficient quality literature to identify its key mode of action and therapeutic potential. The energy delivery and absorption in the tissues gives rise to micro and macro effects. The micro effects relate to cellular 'up regulation' in the same way as US and laser, and similarity of proposed mechanisms (Ca++ ion flux changes and cell metabolic stimulation appear to be supported mechanisms (Cleary 1996, Rubik et al 1992, Adey 1988).

PSWT is proposed to facilitate (or speed) tissue healing following soft tissue injury by stimulating cellular activity. Fibroblast activation and stimulation of ATP and protein synthesis has been discussed by Cameron et al (1999) and demonstrated by Hill et al (2002) at varying doses. PSWT is proposed to enhance the reabsorption of oedema and haematoma in the tissues (Goats 1989, Golden et al 1981). The promotion of phagocytic activity (Cameron et al 1999) and other inflammatory responses have been demonstrated together with a stimulation of metabolic processes (Vanharanta et al 1982). A variety of papers have identified local vascular changes following the treatment which may be of additional significance in this phase of repair (e.g. Smith et al 2004).

In addition, there is research evidence with regards the stimulation of bone repair following fracture and also for the stimulated regeneration of damaged peripheral nerves, though again, these are beyond the scope of this paper. A series of interesting papers that have evaluated the potential benefit of PSWT combined with active stretching and flexibility gains (e.g. Peres et al 2002, Evans et al 2002) may also be of interest.

The effects of PSWT appear to be dose dependent in the same way as for US and Laser. Dose dependency is a key issue in all electrotherapy, and the work of Hill et al (2002) and Bricknel and Watson (1995) clearly demonstrate this phenomenon on relation to PSWT.

The strong similarity in therapeutic effects of the three modalities discussed here are in many ways not surprising. Each energy mode appears to generate an up regulation of cell activity, based on cell membrane level stimulation, almost certainly related to cell membrane transport changes. That this reaction can be produced by the three different modalities is a reflection of membrane reactivity to energy – whether mechanical (US) light (laser) or electromagnetic (PSWT). The key clinical issue is that these effects are predominantly generated in different tissues depending on energy absorption

profiles. Figure 3 summarises the energy absorption characteristics of the three modalities discussed.

Figure 3 : Energy absorption profiles of different electrotherapy modalities

Future Development and Issues

Growth Factors and Angiogenesis

As identified in the previous article (Watson 2006), there is a growing interest in the relationship between several therapies and their influence on the angiogenic components of repair. It has been shown for example that ultrasound (Reher et al 1999, 2002, Doan et al 1999), Laser (Kipshidze et al 2001, Garavello et al 2004) and electrical stimulation (Inan et al 2005, Zhao et al 2004) have a beneficial influence on this process, and it is anticipated that this research area will continue to develop and become a mainstream element of tissue repair enhancement.

Magnetics

There are many therapeutic devices available that deliver a magnetic (as opposed to an electromagnetic) field, and this is claimed to achieve significant benefit in relation to injured and repairing tissues. Some of the results are rather equivocal at the current time, though there is reasonable evidence already to suggest that this energy will achieve similar if not identical results to the main three therapies discussed in this paper. At the present time, it is not clear which energy delivery systems are the most effective (high power, low

power, pulsed, continuous etc). Much of the research to date has concentrated on wound healing and fractures, though there is some expansion into soft tissue areas e.g. Trock 2000, Shimada et al 2006, Colbert 2002).

Electrical stimulation and microcurrent therapy

The final 'up and coming' area for brief consideration is that of 'microcurrent' type therapy. There are many variations of this modality, often referred to by various and somewhat obscure names, but in principle, the therapeutic approach is based on sound bioelectric research. Current flow in the body under 'normal' and 'injured' conditions is at the microcurrent level, and electrotherapy aside, these endogenous currents appear to have a significant effect in relation to modifying and/or driving the tissue repair process (Watson 1996). The use of an external source of current at these levels is logical and is generating a growing volume of literature e.g. Mercola 1995, Maenpaa et al 2004, McMakin 2004, Lambert et al 2002). A quick search of the literature will reveal tens of similar papers, and a web search will provide even more, though some will lack a degree of credibility in the way it is presented. It is considered to be one of the most interesting areas for growth and development in electrotherapy, especially in relation to tissue repair and recovery following injury.

Summary & Conclusions

In summary, there are currently three mainstream modalities which are evidenced in terms of their capacity to influence tissue repair – Ultrasound, Laser and Pulsed Shortwave Therapies. They appear to have a common mode of action, though their effects are predominantly achieved in different tissues according to differential absorption. Other therapies, including microcurrent type electrical stimulation and magnetic therapy are becoming stronger in their evidence base, and it is anticipated that they will join the list of effective modalities at some point in the future. The responses of the tissues appear to be both modality and dose specific, and therefore electrotherapy, when correctly applied does have the capacity to enhance tissue repair. Applied at 'other than ideal' doses will most likely achieve no significant therapeutic benefit, as in fact would be case for any other therapeutic intervention.

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