

# The structure and physiology of bone and physiotherapeutic modalities to promote fracture healing.

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## *INTRODUCTION*

It has long been an accepted principle in medicine that the healing rate of fractures is pre-set and cannot be influenced by external means. The recent publicity about Wayne Rooney and his fractured 4<sup>th</sup> metatarsal and cuboid has highlighted the fact that, given the optimum circumstances, fractures can be made to heal faster than normal. It may be argued that, rather than causing the fracture to heal faster, proper therapeutic intervention may be responsible for removing the obstructions which may cause fractures to heal slower than they should.

The author has over 30 years experience in treating fresh fractures, especially amongst professional motor-cyclists and racing car drivers and has close contact with the medical officers responsible for the various classes of motor sport. Most physiotherapists, however, are aware that, in other than high-profile cases such as Wayne Rooney, physiotherapy intervention may well not be welcomed by orthopaedic surgeons in managing recent fractures. This article will deal with therapeutic interventions for the treatment of recent fracture for those physiotherapists working with the more modern-thinking orthopaedic surgeons and/or with professional teams when rapid recovery is vital, as well as delayed unions and non-unions - the type of fractures in which the orthopaedic surgeon may welcome physiotherapeutic help, although the physiology of normal as well as abnormal fracture healing will be dealt with.

Non-union fractures can sometimes cause orthopaedic surgeons huge problems and yet there are non-surgical interventions which have been shown in trials to influence fracture healing and can, and perhaps should, be applied by physiotherapists in such cases.

It must be remembered that the longer a limb is non-weight bearing and non-functional, then the greater is the tendency for all bones of that limb, not just the fractured bone, to become osteopaenic due to the lack of weight bearing piezo-electric current. Also the longer the limb is non-functional and it is held in static position by immobilisation, then the longer it will take to re-mobilise and re-strengthen that limb. Therefore, shortening the period of non-weight bearing and immobilisation will make rehabilitation of the patient easier and lessen the time the patient has away from his employment.

Before being able to treat fractures it is essential that clinicians should re-acquaint themselves with the physiology of bone and of bone healing and the ways in which physiotherapists can influence that physiology to the benefit of the patient and the satisfaction of the orthopaedic surgeon.

## *PHYSIOLOGY AND STRUCTURE*

Bone is a rigid yet plastic material. The advantage of a combination of a fibrous substrate and a rigid matrix is exemplified in carbon fibre and fibre glass components. Each element of the material is not, in itself, supportive. Glass fibre sheets can be easily pulled apart and a sheet of polyester or epoxy resin can be easily broken yet, when combined, give a very stable, solid structure. So it is with bone. Combining bone cells, hydroxyapatite, which may also be known as hydroxylapatite, and which crystallizes in the hexagonal crystal system and has the basic formula  $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$  denoting the crystal unit cell comprises two molecules with the formula  $\text{Ca}_5(\text{PO}_4)_3(\text{OH})_7$  -collagen fibres (mostly Collagen Type 1) fibronectin, osteocalcin and osteopontin produces a structure which is rigid yet will respond to compression and traction forces. Compression as in weight bearing and traction as in muscle/tendon pull on their origins and insertions. Bone responds to compression forces by generating an electrical flow along the length of the bone due to compression of the bone producing a piezo-electric current. It is in this way that the skeleton can develop to be able to tolerate large increases in weight. Bones have the ability to thicken in response to increased load and become less thick in response to decreased load, indeed, early astronauts/ cosmonauts living in zero gravity for months on end returned to Earth suffering with severe osteopaenia because of the absence of weight-bearing piezo-electric stimulation over a period of months. This osteopaenia is now prevented in the space station by the use of a shoulder harness fitted to bungee straps fixed to the floor either side of a treadmill. The astronaut puts on the harness and walks, applying the downward compression force of the bungee straps to the spine and legs to create the effects of gravity, reproducing the piezoelectric strain-related potentials in the bone and maintaining bone density. This piezo-electric effect is utilised sometimes when treating delayed unions by allowing the bone ends to transfer weight through the currently unresponsive fracture, generate current through the fracture and stimulate bone production. This may be achieved by allowing weight bearing while in a well-fitted walking cast or functional brace, by removing either the proximal or distal screws in an intra-medullary nail or by otherwise dynamising an intra-medullary nail or external fixator.

The main functions of bone are:-

Mechanical- offering support for muscles, ligaments, tendons etc.

Metabolic- supplying a mineral reservoir for Calcium and Phosphate homeostasis

Protective- physical protection for vital structures via ribs, skull etc.

Haematopoiesis- blood cell formation.

Cortical bone has high density, relatively low surface area. Exhibits a low re-modelling rate and has Haversian systems and is mostly present in the femoral neck and shafts of long bones.

Trabecular bone has low density, relatively high surface area and has a high re-modelling rate and is mostly present in vertebral bodies, calcaneum etc.

Periosteum is very important for normal vascularity and is a very important source of bone-forming cells. It also is well innervated.

Osteoblasts are distinguished by their cuboidal, rounded shape and basophilic cytoplasm and are mono-nucleated. Their function is to form new bone. They exhibit a strong histochemical reaction for alkaline Phosphatase (ALP)—an important histochemical test to assess whether there is osteoblast activity at a fracture site.

They synthesise Type 1 Collagen when mature but a study has found in non-unions that mature osteoblasts express Type 111 Collagen which is a molecule characteristic of an earlier stage of osteoblast differentiation <sup>6</sup>. Osteoblasts are attracted by, and migrate to, areas of bone with a negative net potential and their life span is influenced by oestrogens and other hormones. After fracture healing has taken place, the final osteoblasts turn into lining cells which are involved in the minute to minute release of calcium from the bones while some osteoblasts become osteocytes, remaining in the bone, connected to each other by long cell processes which act as mechanical stress sensors

Osteocytes are mechanoreceptors and effectors present in mature, organised bone.

Osteoclasts are distinguished by being multinucleated and are largely responsible for bone resorption. They test strongly positive for tartarate- resistant acid Phosphatase (TRAP). They develop at the fracture site originally from multi-potential stem cells which then become myeloid precursors. These myeloid precursors develop two ways – some into macrophages and some into mono-nuclear osteoclast precursors which then go on to develop into fully mature multi-nucleated osteoclasts. Following polarisation and resorption apoptosis occurs which is delayed by oestrogen deficiency. Osteoclasts are attracted by, and migrate to, areas of bone with a net positive electrical potential.

Stromal cells produce growth factors for haemopoiesis and help the formation of osteoclasts as well as having the ability to differentiate to osteoblasts.

Within fracture sites there are other important cells to aid fracture repair.

Endothelial cells strip off from the surfaces of blood vessels and help synthesize Collagen Type IV but have a more active role in events such as angiogenesis, wound repair and bone formation.

Osteogenic marrow stem cells which differentiate four different ways:-

- 1) To chondroblasts progenitor cells which further differentiate to chondroblasts.
- 2) To osteoblast progenitor cells which further differentiate to osteoblasts.
- 3) To adipocyte precursors leading to adipocytes
- 4) Other precursors differentiating to fibroblasts, reticular cells and myofibroblasts.

Some factors controlling bone function are cytokines and bone growth factors such as insulin-like growth factors (IGF1 and IGF2), transforming growth factor (TGF $\beta$ ), acidic and basic fibroblast growth factors (aFGF and bFGF), platelet-derived growth factor (PDGF) and bone morphogenetic proteins (BMPs). All these growth factors are at 20X higher concentration in bone than in serum. Most are products of bone cells and are postulated to have effects on their neighbouring cells – paracrine action – or on themselves – autocrine action.

Bone is a unique tissue in vertebrates in that it heals by replication of its own tissue i.e. bone, whereas most other tissues heal by connective tissue formation. Interestingly, the molecular/cellular processes leading to embryonic skeletal development are very similar to the processes of healing in bone. There is a common theme in bone development from primitive mesenchymal cells to well-structured,

organised bone. The constant re-modelling process in adult bone is also modulated through a similar molecular mechanism.

In the embryonic limb bud there is a condensation of primitive mesenchymal cells in the limb bud core. This usually transforms into bone in two different ways:- a) Intra-membranous ossification and b) Intra-cartilagenous ossification.

Intra-membranous ossification occurs by direct ossification of mesenchymal tissues. Primitive mesenchymal cells are transformed into osteo-pregenitor cells, then to pre-osteoblast cells and finally to mature osteoblasts, resulting in the formation of bone. This is the mechanism by which bone is formed in embryonic calvarial bones, mandible and clavicle whereas the bone growth at the epiphyseal growth plate is by intra-cartilagenous ossification. In this process the mesenchymal cells differentiate in a two-step manner to form mature bone. Firstly the mesenchymal cells transform into chondroblasts, form collagen and other bone matrix elements and finally ossify leading to mature bone. In embryos the anatomical site decides the mechanism of the bone formation. Broadly speaking, fracture healing follows the intra-cartilagenous route, although the introduction of bone morphogenetic protein (BMP) can allow ossification via the intra-membranous route.

Bone permits the flow of blood and lymph through the medulla and the Haversian vessels but also via the periosteum. Disruption of this supply of oxygen and nutrition via the circulatory system which is all too frequently severely damaged in many fractures is one principal reason for delayed and non-union. However, this should not come as a surprise to us as physiotherapists, since we are fully aware that most other non-healing conditions, such as varicose ulcers, diabetic ulcers etc are caused by poor vascularity and that the same wound in a patient with normal, healthy and vascular tissue would recover in weeks or even days.

We know that, in injuries such as muscle tears, where bleeding can be extensive, creating a large area of compression due to the pressure of extra-vasated blood which dramatically restricts blood flow to, or very importantly from, the damaged area, our first aim is to reduce that tissue pressure in order to restore blood flow through the injured tissue and effect more rapid healing. Reduction of the obstructions to normal healing is our principal aim and it is this philosophy which we can apply to assisting the healing of non-union fractures.

## *PHYSIOTHERAPY*

“Physiotherapy” is defined in Longman’s Dictionary of the English Language as “The treatment of disease by physical and mechanical means (e.g. massage and regulated exercise)”. The word stems from the Greek words “physis” – growth, nature, “phyein” – to bring forth and “therapeuein” – to attend, treat.

Many physiotherapists would feel that this definition of “massage and regulated exercise” is far too narrow, and that the scope of practice of physiotherapy has expanded enormously, particularly over the past 40 years. Although a large proportion

of physiotherapists are involved in musculo-skeletal problems, there are now SIGs and CIGs representing animal therapy, cranio-sacral therapy, chronic pain management (PPA), accident and emergency, injection therapy, continence, moving and handling, acupuncture, none of which had significant representation 40 years ago.

## *FRACTURES*

Historically, it has not been the usual practice in **any** branch of medicine, to **treat** fractures i.e. to influence the rate of healing. Fractures, rather than being treated, tend to pass through three main stages of management:-

- 1) Recognition, using X-rays, CAT scans, MRI imaging etc in order to establish the site and severity of the fracture.
- 2) Stabilisation, by various means.
  - A) Open reduction and internal fixation (ORIF) with K-wires, screws, plates and screws, pins, intra-medullary nails (IMNs)
  - B) External stabilisation using POP/ Baycast, functional splinting, Ex-Fix (Ilizarov frame etc).
- 3) Rehabilitation. After healing of the bone has been deemed to be at a sufficiently advanced stage, rehabilitation, involving mobilisation, strengthening and return to normal function.

It is at this final stage that most physiotherapists currently do most of their work, although many will be involved during Stage 2 to prevent problems in other parts of the same limb.

## *PROBLEMS WITH FRACTURES*

Although most fractures heal within an accepted norm of passage of time, something like 5-10% of fractures, in spite of correct management, result in delayed or non-union. Classically, the treatment for non-union fractures is surgical intervention which could involve bone grafting, removal of an existing IMN, re-reaming the medulla and re-inserting a larger IMN. Surgeons may also dynamise existing IMN s by removing the proximal or distal fixing screws and may dynamise certain types of ex-fix to allow longitudinal sliding. This may be advocated for certain delayed or non-unions as it is known that weight transfer through a fracture stimulates the bone to heal more readily, probably by way of the piezo- electric effect, but possibly by stimulating the quiescent bone ends to re-enter the inflammatory phase of bone fracture healing. This “re-inflaming” process is the manner by which some of the modalities physiotherapists can employ are thought to operate. This inflammatory phase is essential in the early stages of bone healing and is highly influenced by the production of cyclo-oxygenase 2, (COX 2) which is the precursor of prostaglandin E2 (PGE2). PGE2 is produced by most types of tissue and is rapidly degraded in the body. PGE2 works by stimulating osteoblast proliferation and differentiation, collagen synthesis and osteoclast differentiation and bone resorption with one study by Suponitzky and Weinreb in 1998 showing that, when administered

systemically PGE2 has anabolic properties and produced a 54% increase in tibial cancellous bone area, a 24.2% increase in fracture load plus 19% increase in stiffness after a three week daily administration of 6mg/kg in three week old rats. Reduction of COX 2 and prostaglandin E2, however, has been shown to reduce the rate of bone formation. Studies have shown that the ingestion of NSAID's, which all inhibit COX 2 (older, non-specific NSAID's also inhibit COX 1 at the same rate) can slow fracture healing, especially when taken during the inflammatory phase of bone healing.

### *REASONS FOR NON-UNION*

Certain bones have a greater tendency to develop delayed or non-unions such as scaphoid, neck of talus and the junction of the middle and lower thirds of the tibia with up to 10% of all such tibial fractures resulting in protracted delayed union, with this incidence being even greater in high energy injuries e.g. motor cycle racing and when complicated by open or compound fractures. Scaphoid fractures, when accompanied by peri-lunar dislocation, (the anterior displacement of the lunate with associated anterior displacement of the medial portion of the scaphoid causing wide separation of the two fragments of scaphoid) has a greater tendency to result in non-union. However, scaphoid fractures with associated peri-lunar dislocation are virtually always dealt with surgically since anterior displacement of lunate always compresses the median nerve which is directly anterior to the lunate and this requires median nerve decompression and surgical stabilisation of lunate and scaphoid fracture, usually with K-wires.

It is important to note that these three types of fracture share one main characteristic, a relatively poor blood supply. The proximal and distal thirds of the tibia are fairly well vascularised whereas the junction of the middle and lower thirds is poorly vascularised and both the scaphoid and neck of talus have a vascular supply which is uni-directional with few, if any, vascular anastomoses.

High energy fractures involve extensive periosteal stripping and trauma to the surrounding soft tissue and blood and lymph vessels, frequently resulting in greatly reduced vascularity to the centre and epi-centre of the trauma – the fracture itself. This reduced vascularity results in lowered O2 tension at the fracture site, with the bone cells at the “coalface” effectively working at altitude. Angio-neo-genesis can be encouraged by various modalities at the physiotherapist's disposal, resulting in improved vascularity, higher O2 tension at the fracture site and greater chance of bone healing. The high speed nature of these fractures often result in bone piercing skin and even clothing, sometimes embedding in soil and even fragments being lost on a roadside or race track. Such pollution of the bone ends often results in infection and non-union.

It must be understood that, as well as infection being caused by bone piercing skin and protruding into a bacterially polluted area, there is a percentage of cases in which the infection may be introduced surgically and result again in non-union.



## *TYPES OF NON-UNION*

The Weber-Cech classification of non-unions is the most widely used classification to describe types of non-union, and are classified according to radiographic appearance as follows:-

### *Hypertrophic non-unions*

These are non-unions with extensive formation of callus, with good vascularity and have good potential for healing providing the correct environment is provided. This type of non-union is thought to result from inadequate fracture immobilisation. Good immobilisation will often be successful, but good therapeutic intervention may also be of great benefit.

### *Atrophic non-unions*

These types of non-union are distinguished by an absence of callus and atrophic opposing bone ends which may appear tapered and osteopaenic, but are sometimes sclerotic. Bone vascularity is very poor and the fracture has poor healing potential. This type of non-union is often divided into two sub-types:-

- a) Simple, atrophic non-unions and
- b) Synovial atrophic non-unions.

The simple type is adequately described above and has the potential to respond to physiotherapeutic intervention to encourage angio-neo-genesis. The synovial type, however, forms a fibrous capsule around the relatively mobile non-union. This capsule fills with a viscous fluid, very similar to synovial fluid, creating the appearance of a joint and is referred to as a synovial pseudarthrosis. In certain bones, the existence of a synovial pseudarthrosis may be of interest only since they can be relatively well tolerated and may not result in significant pain or reduction in function. The clavicle is a prime example of such a bone and even mid-shaft fibular fractures may quite happily heal in this way. Clearly, such a pseudarthrosis in the tibia or femur is not functional and not acceptable. This type of non-union is not believed to have the capacity to achieve bony union and, if bony union is deemed to be vital, then surgery to remove the synovial capsule and freshen the bone ends is required. Because of the presence of the dense fibrous capsule and pseudo-synovial fluid, even the best physiotherapeutic modality intervention is unlikely to be able to affect a bone-bone union, leaving surgery as the only potential option.

### *Normotrophic non-unions*

These non-unions share the characteristics of the other two types of non-union. The bone ends have moderate vascularity and have a moderate healing potential. This type is eminently suitable for treatment by several different modalities.

### *Mobility Classification*

Non-unions can be classified according the degree of mobility found on clinical examination:-

- 1) Stiff - less than 5 degrees of mobility
- 2) Partially mobile - between 5 and 20 degrees of mobility
- 3) Flail - greater than 20 degrees of mobility

### *Congenital pseudarthrosis*

This can occur in rare cases, most commonly in the clavicle and tibia. It is thought that neurofibromatosis and fibrous dysplasia may be factors but many are idiopathic.

### *MODALITIES*

Therapeutic modalities have arrived as additions to the physiotherapist's therapeutic armamentarium over the past 40 years such as TENS, laser therapy, interferential therapy, biofeedback, etc., all designed to assist the physiotherapist in treating and rehabilitating soft tissue injuries by assisting in haematoma resorption, reduction of oedema, prevention and/or treatment of fibrosis, re-vascularisation, pain reduction etc – all designed to effect more normal and pain-free range of motion and return to normal function. Physiotherapy is becoming a prescribing profession, so mention is also made of drug therapies that may influence bone healing, though not necessarily advantageously.

As there has been so much recent publicity in the media about the efficacy of hyperbaric oxygen therapy in treating Wayne Rooney's fractured metatarsal and in improving the condition of Lisa Norris who had been administered a potentially fatal radiation overdose for a brain tumour and as many hyperbaric chambers in professional sports clubs are supervised by Chartered Physiotherapists, it is pertinent to include this form of therapy which can also be beneficial in treating fractures.

The modalities to be covered in this paper are:-

- 1) Pulsed magnetic field therapy
- 2) Laser therapy
- 3) Interferential therapy
- 4) Hyperbaric oxygen therapy
- 5) Extra-corporeal shock wave therapy
- 6) Low intensity pulsed ultra-sound

### *PULSED MAGNETIC FIELD THERAPY*

Pulsed magnetic field therapy (PMFT), sometimes referred to as pulsed electro-magnetic field therapy (PEMFT) is defined in the treatment of fractures as the application of time-varying magnetic fields that induce voltage wave-form patterns in bone similar to those resulting from mechanical deformation.<sup>37</sup> The electrical voltage is induced at right angles to the pulsed, or dynamic, magnetic field. The strength of the magnetic field in clinical applications is usually from 30 Gauss (30G) to as much as 1,000G – the Earth's magnetic



field in comparison is in the region of 0.5G – and a frequency range of 1Hz to about 200Hz is typically used. All the studies quoted in this section of the article are regarding pulsed magnetic fields and NOT static magnetic fields. Although there is a wealth of firms peddling static magnetic therapy, the research evidence did not merit its inclusion in this article. Magnetic fields may be measured in tesla. There are 10,000 Gauss units to one tesla.

The FDA in America approved the use of PMFT in the treatment of fractures and non-union fractures in 1979.

Nelson et al [25](#) demonstrated that application of PMFT caused up-regulation of messenger RNA (mRNA) along with protein synthesis of TGF $\beta$  and BMP gene group, all of which have been shown to enhance fracture repair. They concluded that PMFT is indicated in established non-unions, failed arthrodeses and congenital pseudarthrosis. Ryaby et al [29](#) showed that PMFT causes differentiation of osteogenic precursor cells along with up-regulation of TGF $\beta$ , BMPs and IGF. Gossling et al [30](#) in a literature review in 1992 concluded that PMFT was at least as effective as surgery in cases of non-union with an overall success rate of 81% against 82% for surgery, although infected non-unions showed a success rate of 81% against 69%. Mooney [31](#) in 1990, in a study of the efficacy of PMFT in lumbar inter-body fusions showed a success rate of 92% in the PMFT group compared to 64.9% in the placebo group. In the same study, previously failed fusions showed a 67% fusion rate after 90 days of PMFT. A similar study by Marks [32](#) in 2000, also regarding lumbar inter-body fusions, showed a fusion rate of 97.6% in the PMFT group compared to 52.6% in the controls ( $p < 0.001$ )

Bassett et al [35](#) in 1982 researched results in treating ununited fractures and failed arthrodeses with PMFT. In a group of patients with an average of 4.7 years non-union, 3.4 previous surgical failures and a 35% infection rate, bony healing took place in 75% of the patients. In the same study, overall success in healing non-unions was recorded as 81% at the Columbia – Presbyterian Med. Centre, 79% internationally and 76% in other patients in the USA. After failed arthrodeses following failed total knee prosthesis, PMFT produced healing in 85% of the patients and of the 15% unsuccessful, further surgery combined with PMFT was effective in all cases.

In 1994 Hart [36](#) did a study on induced current in bone in relation to PMFT. He demonstrated that the variation in the conductivity of the fracture gap during healing caused the induced current density pattern to change accordingly, whereas the induced electrical field remained relatively unchanged.

The effects observed in bone in studies involving fracture non-unions and failed arthrodeses have included angiogenesis, increased mineralization and increase in endochondral – intra-cartilagenous – ossification. Increase in osteoblastic activity and decrease in osteoclastic activity have been observed, along with the all-important angiogenesis, in studies on spinal fusions and osteonecrosis.

Bassett [38](#) in 1993 demonstrated the effectiveness of PMFT. In a prospective, double-blind trial of fracture non-unions there was a 75%-95% success rate, in a prospective study of failed arthrodeses a success rate of 85%-90%, in a prospective study of spinal fusions a 90%-95% success rate, in a prospective, double-blind trial of congenital pseudarthrosis a 70%-80% success rate and in a prospective study of osteonecrosis of the hip a 80%-100% rate of success.

Magnetic fields will penetrate virtually everything, so a POP or Baycast cast is no obstacle to treatment with this modality. The physiotherapist would need to mark on the cast the approximate area of the fracture, referring to the X-rays for guidance.

## *LASER THERAPY*

“Laser” stands for Light Amplification by Stimulated Emission of Radiation. The main differences between Laser light and high-intensity light is that Lasers emit a coherent beam i.e. all photons are in phase and synchronised, the light is monochromatic i.e. one single, very specific wavelength and the Laser is applied with a specific dosage in mind, usually measured in Joules per square centimetre. Some Lasers are used in contact with, or very close to, skin and usually have an optical lens giving a divergent beam, frequently in the region of 6degrees, while some more powerful Lasers emit a non-divergent beam which can scan along easily set parameters along X and Y axes to cover a larger area. The use of a non-divergent beam means that the inverse square law does not apply although clearly it does in the case of the 6 degree divergent beams.

The usual therapeutic wavelengths are in the far red to near infra- red (FR/NIR) wavelengths, ranging from about 600nm (visible red) to 1000nm (non-visible infra-red). Most therapeutic Lasers typically have outputs ranging from 5mW (0.05W) to 1000mW (1.0W) and treatment times can vary from mere seconds to several minutes. Some more powerful scanning Lasers can deliver 3W continuous output and have the capability to produce a thermal burn if applied inappropriately. Some research studies indicate tissue response may be dose dependent <sup>8</sup> as well as being dependent on the irradiation time and irradiation mode.<sup>9</sup> Dickson et al <sup>9</sup> showed a 300% increase in ALP expression in rat femoral fractures irradiated at 10-15 J/cm<sup>2</sup> using a 820-830nm laser. The main effect is photo-chemical and not thermic.

Photon irradiation by light in the FR/NIR spectral range has been found to modulate various biological processes in cell culture and animal models. The mechanism of photo-bio-modulation by FR/NIR at the cellular level has been ascribed to the activation of mitochondrial respiratory chain components. Growing evidence suggests that cytochrome oxidase is a key photo-acceptor of light in the FR/NIR spectral range.

Cytochrome oxidase is an integral membrane protein having a strong absorbance in the FR/NIR spectral range, detectable in vivo by NIR spectroscopy.

Far red cellular irradiation has been shown to increase electron transfer in cytochrome oxidase, increase levels of mitochondrial respiration and ATP synthesis in isolated mitochondria and also to up-regulate cytochrome oxidase activity in cultured neuronal cells. This photo-stimulation also induces a cascade of signalling events such as activation of immediate early genes, transcription factors, cytochrome oxidase subunit gene expression as well as other enzymes and pathways related to increased oxidative metabolism. Photo-stimulation of mitochondrial electron transfer is known to increase the generation of reactive oxygen species which may function as signalling molecules to provide communication between mitochondria and cytosol and nucleus.

Yaakobi and Oron <sup>10</sup> showed that osteoblast/osteoclast population was altered by a 120% increase in ALP and 40% reduction in TRAP in the rat tibia. Histomorphometric analysis showed volume fraction of new reparative compact bone in the irradiated animals as being 27+/- 9% against 9+/- 7% at 10 days, 88+/-9% against 44+/-9% at 13 days and 94+/- 6% against 58+/-5% at 15 days. The wavelength used in this study was in the far red spectrum of 630-640nm.

Khadra et al <sup>11</sup> investigated the weight percentages of calcium and phosphorus in rabbit tibial bone irradiated by an 810nm GaAlAs laser. These were found to be higher in the irradiated group compared to the control group with P=0.037 for calcium and P=0.034 for phosphorus, suggesting bone matured faster in the irradiated group.

When Guzzardella GA et al [12](#) used a GaAlAs laser to irradiate hydroxyapatite implants in rabbit femora at 300J/cm<sup>2</sup>, 1W,300Hz,10 minutes, they found at 3 weeks there was a higher affinity index in the irradiated group (P=<0.0005) and at 6 weeks (P=0.001).

## *ELECTRICAL STIMULATION including INTERFERENTIAL THERAPY*

### *EFFECTS OF ELECTRICITY ON BONE*

Electrical potentials are generated in a bone when that bone is subjected to mechanical stress [1,2](#). These strain-related potentials are due to mechanical deformation of bone e.g. during weight bearing. Hastings and Mahmud [3](#) in 1988 postulated these piezoelectric currents were produced when bone was subjected to sufficient compression force to cause the collagen fibres to slide past each other.

Resting potentials in bone range from 0.1 mV to 10mV, increasing to 20mV on mild physical activity. In the region of fracture sites potential gradients are elevated to 10mV to 50mV/cm, with current densities of 5 to 15  $\mu$ A/cm<sup>2</sup> [1](#). Areas of compressive strain can develop negative potentials of 10 to 100 mV, with the bone responding with osteogenesis [4](#). This net negative charge is noted at bone-bone interfaces when under compression. A net overall positive charge can develop due to distraction of bone and instead of osteogenesis, bone resorption can occur.

Friedenburg and Brighton [5](#) in 1966 showed the presence of another type of electrical potential observable only in living bone and known as the bioelectrical or steady-state potential. This potential is electro-negative in bone undergoing growth or repair when compared with resting bone.

There are various modalities available in order to apply electrical current to bone, some of which are invasive, requiring surgical intervention for the insertion of electrodes into bone, but some of which can be applied via skin electrodes. Pulsed magnetic field therapy may also be included in this section as it induces a current voltage in bone but is dealt with in a separate section.

Direct current electrical stimulation (DCES) :is applied via a surgically implanted device which uses titanium cathodes attached to the bone near to the fracture site. The net negative charge at the cathodes attracts osteoblasts and repels osteoclasts. The anode is implanted in soft tissue since, if it were attached to the bone, the net positive charge would attract osteoclasts to the anode site, causing an area of localised osteopaenia. A constant current of between 20 $\mu$ A and 40 $\mu$ A is applied 24 hours a day for between 6 and 12 months. Brighton<sup>39</sup> in 1981 showed that constant DCES was more effective in its osteogenic effect than pulsed DCES. The use of DC stimulation was granted approval in 1979 by the FDA for the treatment of established non-union fractures.

There are obvious drawbacks to the use of DCES in that it is an invasive procedure, requiring open surgery to implant the electrodes and again open surgery to remove them at a later date with the associated problems of occupying theatre time, potential of infection and the post-operative discomfort for the patient.

Capacitively coupled electrical stimulation (CCES) : Brighton and Pollack<sup>40</sup> in 1985 first reported on the use of a 60KHz sine wave with a continuous current of between 7-10 mA at a voltage of 5V peak to peak being applied via skin electrodes placed either side of the fracture.

There are relatively few studies to be found in the literature regarding the efficacy of CCES in the treatment of fractures although in a series carried out by Abeed et al 41 he showed a healing rate of 11 out of 16 in patients treated with CCES for established non-unions. Goodwin et al 42 reported that there was a statistical increase in the fusion rates of spinal fusions with CCES. According to Nelson et al 43 treatment is carried out over a period of about 25 weeks.

**Interferential therapy (IF):** Most physiotherapists should be fully acquainted with the theory and practice of IF. IF may be applied using quadri-polar or bi-polar techniques. As in all electrical therapies, the exact site of the lesion is identified – in this case, the fracture – and the electrodes are placed accordingly, bearing in mind the depth and extent of the fracture site. Care must be observed in patients with associated loss of skin sensation due to local nerve damage since patient feedback on the extent of the current sensation is essential in the application of IF.

The fact that capacitive skin resistance at 4KHz is 80 times lower than with a frequency of 50 Hz means that dosage can be significantly increased, so improving the ability of the current to access deeper structures. Laabs 49 demonstrated in 1980 that when IF is applied across a bone, the IF field is present within the fracture site, with the highest intensity being within the medullary cavity.

It has been suggested that the 4 main clinical applications for IF are :-

- Analgesia
- Skeletal muscle stimulation
- Vasodilation
- Oedema reduction

Claims are also made for the role of IF in stimulating healing and repair, which is likely to be due to the above effects and, although the benefits of vasodilation and oedema resorption in the environs of a fracture are self-evident, no definitive studies exist proving that these effects do apply to IF current when applied to bone. It could, however, also be argued that there should be no physiological reason to suppose that IF would not produce these effects in bone.

The importance of increased alkaline phosphatase (AP) in fracture sites has already been stressed to demonstrate increased osteoblastic activity. Nikolova and Davidov 48 demonstrated that IF applied to injured sciatic nerves in rats resulted in a sharp rise in AP in the treated area accompanied by an increase in capillary density. However, the question remains as to whether increased osteoblastic activity causes higher AP levels or whether higher AP levels cause increased osteoblastic activity.

Shim et al 50 demonstrated the effects on bone blood flow when sympathetic tone was released, a known effect of IF. Ganne et al 51, in a small study of patients with mandibular fractures with a pre-disposition to non-union had a non-union rate of 0% in the number treated with IF compared with 2% in the control group.

It may be postulated that the known effects of IF on oedema reduction may be applied directly to bone where bone marrow oedema is known to exist or possibly indirectly by stimulating absorption of the soft-tissue oedema surrounding the fracture site, thereby improving the venous and lymphatic drainage of the bone and allowing improved blood flow, enhanced oxygenation and more rapid healing.

## HYPERBARIC OXYGEN THERAPY

Atmospheric air is a gaseous mix by volume of 78.08% N, 20.94% O<sub>2</sub> and 0.04% other gases, including CO<sub>2</sub>, but for convenience we will state the mix to be 79% N and 21% O<sub>2</sub>.

Dalton's Law states that, in a mixture of gases, each gas will exert its pressure according to its proportion of total volume.

**Partial gas pressure = absolute pressure X proportion of total gas volume.**

Since the total pressure of air at sea level is 760mmHg, therefore the partial pressure of O<sub>2</sub> (pO<sub>2</sub>) =  $760 \times 21/100 = 160\text{mmHg}$ .

Henry's Law states that the concentration of a gas in a fluid is determined by the pressure and solubility co-efficient of the gas.

**Concentration of dissolved gas = pressure X solubility co-efficient**

97% of O<sub>2</sub> in blood is in combination with haemoglobin in red blood cells and only 3% in solution in plasma and Haemoglobin is 97% saturated with O<sub>2</sub> at atmospheric pressure, therefore having only a 3% potential for extra O<sub>2</sub>-carrying capacity. However, at sites of trauma, capillary damage occurs, denying the cells at the centre and epicentre of the trauma access to the O<sub>2</sub> via haemoglobin. Plasma cascade, however, can continue to bathe the site with O<sub>2</sub>-poor saline solution – plasma.

The partial pressure of O<sub>2</sub> in alveoli (pAO<sub>2</sub>) when breathing air at sea level is 104mmHg, whereas breathing pure medical breathing O<sub>2</sub> at twice atmospheric pressure, or two atmospheres absolute (2ATA) raises that pressure to 1433mmHg.

One gram of haemoglobin (Hb) can combine with 1.34 ml.O<sub>2</sub> and, as there is usually 15 grams of Hb per 100ml of blood and that Hb is 97% saturated with O<sub>2</sub> then 100 ml of blood is seen to carry 19.5 ml of O<sub>2</sub>.

The pO<sub>2</sub> in capillaries is reduced to 40mmHg so only 5ml of O<sub>2</sub> per 100ml of blood reaches the tissues. This pO<sub>2</sub> reduces further at the cellular level with only 1-3mmHg at mitochondrial level, and it is the mitochondria that utilise 80% of molecular O<sub>2</sub> with the other 20% taken up by microsomes, nuclei and plasma membranes. O<sub>2</sub> combines with electrons to release free energy which is used to pump H<sup>+</sup> ions against the electrochemical gradient from within mitochondria. As the H<sup>+</sup> ions diffuse back energy is released to change ADP into ATP. A pO<sub>2</sub> of only 1-3mmHg in the tissue is required, since only a small amount of O<sub>2</sub> is necessary for normal intra-cellular chemistry. Under normal circumstances the cell wall/ capillary wall distance is seldom more than 50µm but this distance can increase dramatically when trauma destroys local capillaries, leaving cells at the trauma site severely hypoxic. Under normal circumstances the rate of O<sub>2</sub> utilisation is blood flow limited but if damaged cells are located further away from the nearest capillaries, then the O<sub>2</sub> utilisation becomes diffusion limited. ATP synthesis can therefore no longer occur and mitochondrial function ceases. Healing cannot begin to occur until O<sub>2</sub> supply is restored, either by angiogenesis or by otherwise increasing the pO<sub>2</sub> in the plasma which continues to perfuse the injured area.



## TREATMENT

HBO therapy is usually carried out in a specially constructed chamber, some being designed for one patient at a time – monoplace chamber, or for many at a time – multiplace chamber. Some monoplace chambers use O<sub>2</sub> to pressurise the patient who breathes the intra-chamber atmosphere but many consider these to be somewhat more dangerous because the environment around the patient, while not in itself inflammable, will readily support combustion. Many modern monoplace chambers and all multiplace chambers pressurise the patients with compressed air while they breathe pure medical breathing O<sub>2</sub> through a mask which vents the exhaled air, still rich in O<sub>2</sub>, direct to the outside of the building. Pressure within the chamber is raised to between 1.5ATA and 2.4 ATA and is maintained at that pressure for 60-90 minutes. The pressure is raised and decreased relatively slowly while the patients are constantly monitored for any signs of discomfort such as middle ear pain. The hyperbaric technician is in constant contact with the patients to verify they are comfortable. If pressures are kept at or below 2.4 ATA for 60-90 minutes, complications are rarely encountered such as CNS toxicity which can occur if pressures of 3 ATA and above are applied for 2 hours or more. Pulmonary O<sub>2</sub> toxicity is likewise theoretically possible at higher pressures but not encountered in clinical practice at the pressures and times quoted for therapeutic use.

Increasing the pO<sub>2</sub> in the alveoli from 104mmHg to 1433mmHg via hyperbaric oxygenation at 2ATA will dramatically increase the availability of O<sub>2</sub> in solution in the plasma but, as hyperoxia is known to cause peripheral vaso-constriction to effectively limit O<sub>2</sub> supply to tissues, traumatised tissue benefits from reduced fluid volume flow, hence reduced oedema, while maintaining normal, or above normal, pO<sub>2</sub> in the tissues so that mitochondrial function can be maintained or restored.

Lack of O<sub>2</sub> is thought to be a limiting factor in fracture healing. Multipotential precursors of fibroblastic origin form cartilage, which is relatively avascular, in the presence of low pO<sub>2</sub> but form bone when tissue pO<sub>2</sub> is elevated. <sup>22</sup> Not unsurprisingly, cartilage abounds at fracture sites in cases of non-union. It must be remembered that, at fracture sites, ossification takes the intra-cartilagenous route, with the cartilage/ collagen matrix being invaded by new capillaries during angiogenesis and osteoblasts replacing the cartilage with new bone. This process of osteogenesis requires much higher pO<sub>2</sub> at the fracture site than chondrogenesis.

Ueng et al investigated the effect of intermittent HBO therapy on bone healing of tibial lengthening in rabbits. The HBO treated group had 2 hours of HBO daily at 2.5ATA and each animal's right tibia was lengthened by 5mm. Using pre-operative bone mineral density (BMD) as internal control the BMD of the HBO group was found to be significantly increased when compared to the control group. The percentage BMD at 3 weeks was 69.5% against 51.6%, at 4 weeks 80.1% against 67.7%, at 5 weeks 87.8% against 70.5% and at 6 weeks 96.9% against 79.2% ( two-tailed test - p<0.01 in each case). Torsional strength at 6 weeks was 88.6% in the HBO group and 76% in the control group.

Tibbles and Edelsberg <sup>27</sup> in 1996 demonstrated that HBO therapy stimulated osteoblastic and osteoclastic activity, proliferation of fibroblasts, angio-neogenesis and collagen formation.

Coulson et al <sup>26</sup> in 1966 demonstrated that HBO, when used to treat fractured femurs in rats, resulted in increased bone strength and resistance to fracture when compared to control.



Work recently completed by Goldstein et al<sup>28</sup> at the University of Pennsylvania Medical Centre shows that HBO therapy, by increasing the nitric oxide (NO) levels in perivascular tissue via stimulation of nitric oxide synthase (NOS), an increase in endothelial progenitor cells (EPC) or stem cells, occurs. These stem cells are known to contribute to wound healing and in this study they show that HBO increases bone marrow NO in vivo. An increased release of EPC up to 8 fold was measured. Their data showed that HBO increased EPC through induction of bone marrow NO with resulting enhancement in ischaemic limb perfusion and healing.

### *EXTRA-CORPOREAL SHOCK WAVE THERAPY*

A shock wave may be defined as a transient pressure disturbance which propagates rapidly in three dimensional space. There is a rise from ambient pressure to maximal positive pressure followed by cavitation consequent to the negative phase of the wave propagation. The positive pressure amplitude is followed by a diffraction induced tensile wave lasting a few  $\mu$ s. Energy densities of up to 1.5mJ/mm<sup>2</sup> and pulse energy of up to 100mJ are used. These are determined by temporal and spatial pressure profile distribution. Energy density measures the maximal amount of acoustical energy transmitted per mm<sup>2</sup> per pulse. The total pulse energy is the sum of all the energy densities across the beam profile multiplied by the total area of the beam profile, and describes the total acoustical energy per shock wave.

There are three types of shock wave generators which are electro-hydraulic, electro-magnetic and piezoelectric.

As Gross et al<sup>17</sup> suggested that gradients of mechanical stress would be produced when sound wave energy is applied to cartilage/bone/fibrous tissue interfaces due to energy being absorbed at a rate proportional to density, it is probable that this mechanism of producing stress gradients in the region of the fracture results in increase in vascular activity<sup>16</sup> and bone re-modelling by applying Wolff's Law. Ikeda et al<sup>44</sup> showed in the intact canine femur that immediately after 500 or more impulses there was periosteal detachment and small fractures of the inner surface of the cortex, and after two months there was callus formation beneath the detached periosteum. This production of periosteal reaction and cortical micro-fractures is significant in areas of non-union. In their clinical research *IBID* on non-unions averaging 14 months from previous unsuccessful surgery, a healing rate of 67% was achieved, although the number of patients was small for this to be a definitive result.

In a study involving 755 non-unions with an average time of failure to unite of 15 months, Schaden et al<sup>45</sup> achieved a union rate of 79% with the best results being in the sub-group of 284 where the extracorporeal shock wave therapy (ESWT) was applied less than 6 months after the fracture or last surgical procedure. Biedermann et al<sup>46</sup> came to the conclusion that previous clinical studies reporting the acceleration of union after ESWT seemed to simply misinterpret the natural history of bone union and that, in their opinion, no evidence supports the treatment of pseudarthroses with ESWT. Finally, Ludwig et al<sup>47</sup> did a study of 22 patients with femoral head necrosis Stages I to III, prior to and then one year after ESWT. They found the scores on the visual pain analogue scale had decreased from 8.5 to 1.2 and the Harris Hip score had increased from 43.3 to 92 points, and suggested ESWT may offer an alternative to invasive treatment modalities for femoral head necrosis.

## *LOW INTENSITY PULSED ULTRA-SOUND (LIPUS)*

Ultra-sound (US) is an acoustic pressure-wave form of mechanical energy which can be transmitted through and into body tissue at above audible frequencies. Depending on the intensity, it can be used diagnostically, therapeutically or surgically. Therapeutic US is usually applied in frequencies of 1MHz – 3MHz, at intensities of 0.3W/cm<sup>2</sup> – 3 W/Cm<sup>2</sup> and with pulse options usually being 1:4, 1:2, 1:1. When used in continuous mode, therapeutic US can have a considerable thermic effect.

Surgically, intensity levels of up to 300 W/Cm<sup>2</sup> are used in bursts for lithotripsy and removal of peri-prosthetic cement in cases of prosthesis revision. <sup>13</sup>

Most studies over the past 20 years and most currently available LIPUS equipment use current intensities varying from 20mW/cm<sup>2</sup> to 200mW/cm<sup>2</sup>. This intensity is now widely accepted as being therapeutically beneficial in the acceleration of fresh fracture healing as well as the initiation of healing in non-unions. LIPUS was approved by the Food and Drug Administration (FDA) in the United States in 1994 for the accelerated healing of fresh fractures and approved by the same body in 2000 for the treatment of established non-union fractures. The studies presented to the FDA demonstrated that LIPUS had a positive effect during the three main stages of fracture healing – inflammatory, reparative and remodelling by enhancing angiogenesis, chondrogenesis and osteogenesis.

Wolff <sup>14</sup> demonstrated that there was a relationship between bone architecture and the forces applied to bone, known as Wolff's Law. Huiskes et al <sup>15</sup> showed that bone adapts to applied forces by remodelling to accommodate the magnitude and direction of the applied stress and Wallace et al <sup>16</sup> showed there was stimulation of vascular activity as part of bone's response to mechanical stress.

Gross et al <sup>17</sup> suggested that, as LIPUS energy is absorbed at a rate proportional to tissue density, gradients of mechanical stress would be produced when applied to a healing callus where cartilage/bone/ fibrous tissue interfaces abound.

In spite of the extremely low intensity, LIPUS may also have a mild thermic effect <sup>18</sup> Heckman et al <sup>19</sup> in 1994 demonstrated in a prospective, randomised double-blind trial of LIPUS on 67 closed or Grade 1 open tibial shaft fractures that clinical healing time was 86+- 5.8 days in the LIPUS group compared with 114+-10.4 days in the control group (P=0.01) as well as significant decrease in overall clinical and radiographic healing time of 96+-4.9 days compared with 154+-13.7 days in the control group (P=0.0001).

Pilla et al <sup>20</sup> in 1990 showed in a bilateral fibular osteotomy study in rabbits that the LIPUS treated animals reached intact bone strength at 17 days (67% stronger than placebo. P=<0.001) compared to 28 days for the placebo.

World-wide clinical studies using LIPUS for treatment on non-unions in a self-paired control study demonstrated a healing rate of 88% in non-unions with an average of 23 months since fracture. When compared with surgery, LIPUS treatment in non-unions has the same success rate as surgery.

The study by Heckman et al [19](#) on delayed union tibial fractures showed just a 6% progression to full non-union in the LIPUS treated patients compared to 36% of the controls.

Kristiansen et al [21](#) in a study on fresh distal radial metaphysis fractures showed a 38% reduction in healing time of the LIPUS treated patients compared with the placebo control.

## SUMMARY

A wound is defined as an injury to the body which causes a disruption of the normal continuity of the body structures. Fractures may be defined as the disruption of continuity of bone and yet, while physiotherapists will be expected to treat disruption of continuity of many other body structures in an attempt to create the ideal physiological environment for healing, they draw a line at trying to create an ideal healing environment for bone injuries. Just as varicose ulcers fail to heal due to poor vascularity, so fractures fail to heal for precisely the same reason and yet physiotherapists will treat varicose ulcers very effectively. If the aim of treatment is to remove tissue oedema and thus lower interstitial pressure, the result is improved vascular flow, increased cellular pO<sub>2</sub> and improved rate of healing. If the aim of treatment is angiogenesis (neo-vascularisation) then, as can be seen in the text, there are many options available in the physiotherapist's armamentarium to achieve that aim. If the aim of treatment is to create an optimal physiological environment for healing, then physiotherapists have been doing just that for years when treating muscles, ligaments, tendons, skin etc. and, with the co-operation of surgeons and other medical officers, have the capability to do precisely the same for bone wounds i.e. fractures. Understanding the physiology of bone and how to influence that physiology for the better are essential for a physiotherapist to be able to treat fractures effectively and successfully. It is hoped this article might encourage some physiotherapists to speak to their local orthopaedic surgeons about allowing physiotherapists to start treating fractures.

It must also be noted that most of the studies in this article focus on the effects of fracture treatment with one single modality at a time whereas physiotherapists might use a combination of therapies to potentially achieve an even better result.

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