Therapeutic Uses of Pulsed Magnetic-Field Exposure: A Review

Naomi M. Shupak

1. Introduction

Bioelectromagnetics is the study of the interaction between non-ionizing electromagnetic fields and biological systems. In the extremely low frequency (ELF, $\leq$ 300 Hz, [1, 2, 3]) part of the electromagnetic spectrum, experimental therapies have been emerging for a variety of medical conditions, such as non-union bone fractures, skin ulcers, migraines, and degenerative nerves. Pulsed electromagnetic fields have been used as therapeutic agents over the last 40 years, following convincing evidence that electric currents can accelerate bone formation [4]. Specifically, electromagnetic-field stimulation gained credibility as a therapy following observations that the application of physical stress on bones promoted the formation of very small electric currents that are related to bone formation. A similar mechanism has been observed for cartilage, whereby electrical stimulation of chondrocytes increased the synthesis of the major component of cartilage matrix, known as proteogylcans [5].

A subset of ELF electromagnetic fields, i.e., pulsed electromagnetic fields (PEMF), displays frequencies at the low end of the electromagnetic spectrum [6], from 6 Hz up to 500 Hz. Another characteristic of PEMF waveforms is their rate of change. High rates of change (e.g., Teslas/second) are able to induce significant biological currents in tissues, thereby enabling them to have greater biological effects than waveforms of lower rates of change, if the biological effect is dependent on the magnitude of the induced current [1].

Extremely low frequency fields are non-ionizing and athermal (defined as either inducing no significant heating of the tissue, or thermal heating below the naturally occurring thermal fluctuations in tissue [2]). The waveforms associated with PEMFs can be asymmetric, biphasic, and quasi-rectangular or quasi-triangular in shape [6]. However, most ELF sources of electromagnetic-field stimulation produce a sinusoidal waveform [1]. In 1979, the United States Food and Drug Administration (FDA) approved both quasi-rectangular and quasi-triangular waveforms as safe and efficacious forms of treatment of disorders associated with fractures [6]. Specific types of low-level EMFs have the ability to produce specific biological responses, depending on the parameters (e.g., magnitude, frequency, waveform) of the field [2]. Intermittent use of PEMF stimulation has been shown to produce superior outcome responses to continuous use [7].

There are two methods in which PEMF stimulation can be non-invasively applied to biological systems: capacitive or inductive coupling. Capacitive coupling does not involve any contact with the body. In contrast, direct coupling requires the placement of opposing electrodes in direct contact with the skin surface surrounding the tissue of interest [7]. For example, if PEMF therapy is desired for the long bone of one's right arm, the opposing electrodes would be placed on the skin on either side of the right arm, surrounding the bone of interest.

Inductive coupling does not require the electrodes to be in direct contact with the skin. Rather, the time-changing magnetic field of the PEMF induces an electric field (Faraday's Law of Induction), which, in turn, produces a current in the body's conductive tissue [7, 8, 9, 10].

Pulsed electromagnetic-field stimulation – used as a treatment for conditions such as non-union bone fractures, failed joint fusions, and congenital pseudarthroses – has yielded success rates of 70% to 95% in prospective and double-blind studies. Treatment times range from 20 minutes to 8-10 hours per day, depending on the condition to be treated and the field parameters used [11]. There is no

Naomi M. Shupak, Frank S. Prato, and Alex W. Thomas are with the University of Western Ontario (Medical Biophysics), Lawson Health Research Institute, St. Joseph's Health Care (London), 268 Grosvenor Street, London, Ontario, Canada N6A 4V2;
Naomi M. Shupak: Tel: +1 (519) 646-6000 ext. 64682; Fax: +1 (519) 646-6135; E-mail: nshupak@lri.sjhc.london.on.ca;
Frank S. Prato: +1 (519) 646-6000 ext. 64140; Fax: +1 (519) 646-6135; E-mail: prato@lri.sjhc.london.on.ca; Alex W. Thomas: Tel: +1 (519) 646-6000 ext. 64191; Fax: +1 (519) 646-6135; E-mail: athomas@lri.sjhc.london.on.ca

Editor's Note: This is one of the *Reviews of Radio Science*, invited by Commission K.

Study	Parameters	Effect of MF
Bassett et al. [18] (Beagle dogs)	2 mV/cm, 1.5 msec, 1 Hz, biphasic; 20 mV/cm, 0.15 msec, 65 Hz, biphasic	Accelerated bone repair
Bassett et al. [19] (Beagle dogs)	2 mV/cm, 1.5 msec, 1 Hz, biphasic; 20 mV/cm, 0.15 msec, 65 Hz, biphasic	Accelerated bone repair
Wilson & Jagadeesh [41] (Rats)	Diapulse; 65 μsec bursts, 80-600 pulses/sec	Increased speed of nerve regeneration
Bassett et al. [20]	ElectroBiology Inc.; quasi-rectangular, assymetrical, 300 μs pulse width; 75 Hz 12-16 hrs daily; 3-6 months	Promoted osteogenesis
De Haas et al. [23] (Rabbits)	0.1 Hz, 0.015 T; 1 Hz, 0.015 T; 4 Hz, 0.025 T 6 hrs/day; 5 days/week; 2 weeks	Not effective; healing initiated at 1 Hz but effect not maintained
Heckman et al. [13]	Electro-biology Inc., Fairfield, N.J. Min. 12 hrs/day; min 3-4 months	Healed 64.4% of ununited fractures
Barker et al. [22]	0.3 T/s, 15 Hz 12-16 hrs/day; 24 weeks	Established tibial unions (questionable effect)
Binder et al. [32]	73 $\pm$ 2 Hz; 2.7 mT (peak) 5-9 hrs daily; 4 weeks	Reduced pain, improved active range
Raji [42] (Rats)	Diapulse; 400 pulses/sec 15 min daily; 3.5 days, 1, 2, 3, 4, or 8 weeks	Acclerated rate of recovery of injured nerve; enhanced regeneration of damaged nerves
Kavaliers et al. [89] (Mice)	Rotating magnetic field, 1.5 G – 90.0 G Several exposure periods	Abolished morphine-induced analgesia
Devereaux et al. [33]	Single pulse of 200 μs, 15 Hz 8+ hrs daily; 1-2 days	No effect on lateral humeral epicondylitis
Kavaliers & Ossenkopp [97]	0.2 mT - 3.5 mT, 30min, 10 consecutive days	Reduced tolerance to morphine
Ossenkopp et al. [83] (Mice)	static: 1470 $\pm$ 0.2 G; radiofrequency: 6.25 MHz, 2 bursts (gaussian, square) every 100 msec pulsed: 8 x 10^3 G/sec (z), 10 x 10^3 G/sec (x, y) 22.5 min pre- and post-morphine injection	Attenuated morphine-induced analgesia
Frykman et al. [12]	Bi-osteogen, System Electro-biology Inc., Fairfield, N.J. 8-10 hrs daily; mean 4.3 months	Healed non-union scaphoid fractures
Prato et al. [86] (Mice)	static: 0.15 T; pulsed: 0.4 mT_{pk} - 0.9 mT_{pk} radiofrequency: Gaussian pulse, 2 and 4 ms widths 23.2 min, 62 MHz	Static component had no effect, radiofrequency component reduced, and pulsed component abolished morphine- induced analgesia
Kavaliers & Ossenkopp [88] (Snail)	0.1 mT - 0.8 mT; 0.5 Hz 15 - 30 min	Inhibited analgesia from opioid agonists
Sisken et al. [44] (Rat)	0.3 mT, 20 msec pulse, 2 Hz repetition 1 hour daily	Regeneration of sciatic nerve
Ieran et al. [38]	2.8 mT, 75 Hz, 1.3 msec 3-4 hrs daily; 90 days	Increased success rate of treating venous skin ulcers; reduced recurrence rate
Mooney [36] (Rabbits)	0.18 mT, 1.5 Hz	Increased success rate of interbody lumbar fusion established effectiveness of bone graft stimulation
Omote et al. [62] (Rats) (Cell culture)	4 mT, 200 Hz, pulse width 2.0 msec 1 hr (once) 4 mT, 250 Hz, pulse width 1.5 msec 2 hrs (once)	Increased survival of rats; survival greatest when PEMF and drug given in combination Colony formation suppressed; greater suppression with Combination PEMF & drug
Tabrah et al. [25]	2.85 mT (peak), 380 μsec quasirectangular, followed by 72 Hz, 6 msec quasitriangular wave 10 hrs daily; 12 weeks	Short-term increased bone mineral density
Bassett & Schink-Ascani [16]	Electo-Biology Inc. (Parsippany, NJ); amplitude set to deliver 1.5 mV/cm for normal cortical bone with periosteum 10-12 hrs daily; 3 months - 4 years	Healed congenital pseudarthrosis of the tibia
Bellossi & Desplaces [59] (Mice)	12 Hz, 9 mT 10 min, 3 non-consecutive days/wk from 2-3 wks after tumours appeared until death	Increased length of survival in early stage of cancer development
Mouchawar et al. [66] (Dogs)	Rectangular pulses 0.1 msec in duration at 50 Hz	Stimulated the heart
Sanseverino et al. [28]	50 Hz solenoid, 3 mT - 6 mT 15-40 min daily; 15 sessions	Removed pain, recovered joint mobility, maintained improved conditions of joints
Stiller et al. [9]	PELUT; ΔB = 2.2 mT; 3 part pulse (+, -, +) of 3.5 msec total width 3 hrs daily; 8 weeks (or earlier is healed); 12 wks total if improvement present at 8 wks	Decreased wound depth and pain intensity
Kanje et al. [43] (Rats)	60 μT or 300 μT, 2 pulse/sec 15 min-24 hrs/day; 1-7 days	Pretreatment increased regeneration of sciatic nerve (not all MFs were effective)
Kavaliers & Ossenkopp [84] (Snails)	0.1 mT - 0.8 mT; 0.5 Hz	Reduced opioid-induced analgesia following administration of naloxone
Roland et al. [48]	0.5 Hz - 17 Hz; 0.1 μT - ~0.15 μT 15 min daily; 1 week	Improved tinnitus
Betancur et al. [87] (Mice)	3 mT - 4 mT	Reduced analgesic effect
Fleming et al. [100] (Rats)	5 μT pulse burst; 1 sec on, 4 sec off 20 minutes	Increased analgesia
Grant et al. [65] (Rabbits)	2.8 mT, 75 Hz, single pulse (280V) 350 min	Lessened cortical ischemic oedema, reduced ischemic neuronal damage

Table 1: Summary of Magnetic Field Effects as Therapeutic Agents in Treatment

Hannan et al. [8] (Mice)	5.2 mT, 250 pulses/sec, 120 μsec ramped pulse 1 hr	Decreased tumour size when in combination with chemotherapy drugs
Jorgensen et al. [39]	1-250 MHz; 2-30 pulses/sec 15-30 min; repeated as necessary	Relief from pelvic pain
Del Seppia et al. [93] (Pigeons)	continuous + 70 μT to - 20 μT; sinusoidal	Hyperalgesia (heightened sensitivity) to painful electrical stimulation
Papi et al. [94]	continuous + 70 μT to - 20 μT; sinusoidal	Increased sensitivity to painful electrical stimulation
Konrad et al. [26]	5 mT, 50 Hz 20 min/session; 20 treatments total	Reduced pain and improved hip movements
Darendeliler et al. [17]	15 Hz, positive duration 200 μsec; 1.8 mT 8 hrs daily; 9 days	Accelerated rate of bone repair
Glazer et al. [35] (Rabbit)	peak (negative) 3 ± 1 T/sec; (positive) 9 ± 4 T/sec 26-msec pulse burst; 670 ± 10-msec burst interval 4 hrs daily; 6 weeks	Reduced the rate of pseudarthrosis
Godley [21]	Electro-biology Inc. (Parsippany, NJ) 10 hrs daily; 3 months	Enabled solid union of carpal scapoid
Harrison & Bassett [27]	PEMF coils 10 hrs nightly; 7.5 to 18.5 months	Not effective in treating Perthes' Disease
Liang et al. [63] (Mice) (Tissue culture)	5.25 mT, 250 pulses/sec, 120 μsec ramped pulse 1 hr weekly; 3 weeks 5.25 mT, 250 pulses/sec, 120 μsec ramped pulse 1 hr weekly; 3 weeks	Decreased tumour volume in combination with anti-cancer drug Enhanced potency of anti-cancer drug only when PEMF was prior to drug injection
Richards et al. [47]	5 μT - 10 μT, 4-13 Hz, 1 msec pulsed waves 10-24 hrs daily; 2 months	Improvement in performance tests; increased alpha EEG during a language task
Sartucci et al. [101]	0.5 Hz; 70 μT to -20 μT; 0.1 msec duration	Reduced pain thresholds and pain-related somatosensory evoked potentials
Thomas et al. [95] (Snail)	100 μT_{pk}, 0.4 T/s 15 min	Induced analgesia, and increased opioid- induced analgesia
DiCarlo et al. [68] (Chick embryos)	60 Hz; 4 μT, 6 μT, 8 μT, or 10 μT 20 min	Increased rate of survival (reduced anoxia- induced mortality)
Jankauskienė et al. [46]	1 mT, 80 kHz 30 min; 10 sessions	Improved soft tissue, reduced inflammation; did not affect visual signs or eye movements
Mann et al. [53]	900 MHz, pulsed with 217 Hz, 577 μsec width 8 hrs (1 night)	Cortisol slightly elevated; no change in growth/ luteinizing hormones, or melatonin
Thomas et al. [98] (Snail)	100 Tpk, 0.4 T/s 15 - 30 min daily; 6 - 9 days	Development of tolerance, and cross- tolerance to repeated MF exposures; effect reduced with novel environmental cues
Albertini et al. [74] (Rats)	Triangular waveform; 75 Hz; 30 mT	Reduced necrotic region of myocardial infarct
DiCarlo et al. [67] (Chick embryos)	60 Hz; 4 μT, 6 μT, 8 μT, or 10 μT 20 min	Increased rate of survival; induced stress response that protected embryo myocardium from anoxia-related mortality
Karasek et al. [57]	2.9 mT, 40 Hz, square impulse shape 20 min daily, 5 days/week; 3 weeks 0.025 mT - 0.08 mT, 200 Hz, complex saw-like impulse shape, bipolar 8 min twice daily, 5 days/week; 3 weeks	Significantly lowered rise in nocturnal melatonin Did not influence melatonin levels
Carmody et al. [73] (Cells)	60 Hz, 8 μT 20 minutes - several hours	Protection from ischemia-reperfusion injuries
Del Seppia et al. [85] (Mice)	hypogeomagnetic field: 4 μT Oscillating magnetic field: 20 μT - 70 μT 90 min in home cage; 30 min restrained	Suppressed stress-induced analgesia
de Seze et al. [61] (Mice)	100 mT, 0.8 Hz square-wave 8 hours daily	Decreased tumour growth;increased survival
Karasek et al. [58]	25 μT - 80 μT, 200 Hz, saw-like impulse shape 8 min twice daily, 5 days/week, 3 week	No effect on melatonin concentrations
Marks [34]	Spinal-Stim (Orthofix Inc., Richardson, TX) 4+ hrs daily, 4-6 months	Enhanced bone bridging in lumbar spinal fusion
Matsumoto et al. [24] (Rabbits)	0.2 mT/ 0.3 mT/ 0.8 mT; 100 Hz; width 25 μsec 4 or 8 hrs daily; 1, 2, or 4 weeks	Promoted bone formation
Jacobson et al. [30]	0.034 μT - 0.274 μT; 0.976 Hz - 7.7 Hz 6 min, 8 sessions; 2 weeks	Reduced knee pain due to osteoarthritis
Pipitone & Scott [14]	50 μT; 3 Hz, 7.8 Hz, or 20 Hz 10 min, 3 times daily; 6 weeks	Improvement from baseline in pain, stiffness, and physical disability
Prato et al. [79] (Mice)	200 μT_{pk}, 0.4 T/s	Increased movement under low intensity light; decreased movement under high intensity light
Thomas, Drost, & Prato [77]	200 μT_{pk}, 0.4 T/s	Improved standing balance
Thomas, White, et al. [78]	200 μT_{pk}, 0.4 T/s	Improved standing balance in fibromyalgics and controls to greater degree than in arthritics during eyes open; all groups had worse standing balance during eyes closed
Williams et al. [60] (Mice)	0, 10 mT, 15 mT, or 20 mT; 120 pulses/s 10 min daily	Reduced tumour growth and vascularization
Robison et al. [64] (Human cell lines)	0.15 ± 0.02 mT_{pk} sinusoidal, 120 W, 60 Hz 4, 12, or 24 hours	Decreased susceptibility to heat-induced apoptosis, leading to proliferation of cancer
Warman et al. [54]	200 μT - 300 μT; 50 Hz 2 hours; 1 night	Changed melatonin onset variability, but not average melatonin onset time

Note: Subjects were humans unless otherwise indicated.

Table 1: Summary of Magnetic Field Effects as Therapeutic Agents in Treatment (continued)

discomfort or known risk associated with this stimulation, it is non-invasive, and the cost of medical treatment is substantially reduced relative to the costs of surgery [2, 6, 7, 11]. The presence of implanted metals does not appear to affect the therapeutic ability of the PEMF exposure [10]. Furthermore, PEMF therapy is simple to use [2]: no surgical procedure is required, the PEMF stimulation can be performed in an office setting, there are no known complications, no anesthetic is required, and the length of treatment is comparable to bone-grafting procedures. However, these advantages of PEMF stimulation are qualified by the cooperation of the patient [12]. Specifically, the patient must sometimes use the PEMF stimulation device for upwards of 10 hours daily, must immobilize the fracture ends, and must ensure no weight-bearing [13].

Of particular concern when considering the use of PEMF stimulation as a clinically therapeutic agent are the health risks associated with exposure to such stimulation. While evidence for carcinogenic effects of magnetic fields (magnetic fields) is small, and there is no evidence supporting the direct damage of DNA by electromagnetic fields, there is some support that magnetic-field stimulation could act as a co-carcinogen in combination with a known genotoxic and/or non-genotoxic carcinogen. There is greater support for the possibility of teratogenic and reproductive effects of ELF magnetic fields [1]. Despite the ongoing debate over the safety of PEMF exposure, it is generally believed and accepted that brief exposure to the fields is safe. Nevertheless, there are still warnings for those with known cancers, those who are pregnant, and those with permanent pacemakers to avoid exposure sessions [7].

This review will examine the therapeutic benefits of PEMF stimulation as used in clinical and experimental settings. Procedures that involve electrode placement in tissue, i.e., capacitive coupling methods, will not be included in this review. Summaries of the discussed findings are provided in Table 1 (studies listed by publication date) and Table 2 (studies listed by disease/ condition category).

2. Musculoskeletal Disorders

To date, the only FDA approvals for the use of PEMF stimulation for clinical treatment are for therapeutically resistant problems of the musculoskeletal system, such as delayed-union bone fractures, failed joint fusions, and congenital pseudarthroses [6, 11, 14]. Several cellular mechanisms, including increases in growth factors, have been implicated as the possible causes of success from PEMF stimulation. For example, fracture non-unions, failed joint fusions, and congenital pseudarthroses are thought to be healed via increases in mineralization [6], angiogenesis, collagen production, and endochondral ossification that result from PEMF stimulation. Congenital pseudarthroses also show decreased osteoclasis following PEMF therapy [11].

2.1 Bone Repair

Bone repair requires the cooperation of bone-specific cell-types: osteoblasts and osteoclasts. Osteoblasts are involved in the formation of bone, while the main function of osteoclasts is in bone resorption. Generally, these two cell types are in normal balance, and the amount of bone is kept constant. When a fracture occurs, osteoblasts and osteoclasts work together to quicken the healing process. However, sometimes healing is not at an optimum, and non-unions result. These types of fractures require an additional stimulus, such as pulsed electromagnetic-stimulation, to assist in the healing process [15].

Pulsed electromagnetic-field stimulation has been shown to have an effect on bone repair via a number of different mechanisms. Firstly, PEMF has been shown to stimulate calcification of the fibrocartilage in the space between the bony segments. Second, the increased blood supply that arises due to PEMF's effects on ionic calcium channels have been implicated as a source of improved bone healing. Thirdly, PEMF has been suggested as having an inhibitory effect on the resorptive phase on wound repair, leading to the early formation of osteoids and calluses [16, 17]. A fourth mechanism by which PEMF is thought to have an effect on bone repair is through its influence on increasing the rate of bone formation by osteoblasts [15].

The degree to which PEMF stimulation is effective is dependent on several factors, including anatomic location, associated surgery, patient age, disability time, date of treatment initiation, adherence to treatment protocol, and infections. In general, non-unions in young adults are more easily stimulated to heal than those in older adults, and stimulation has been found to be more effective if initiated within two years of onset of the original fracture [13].

Non-union fractures are those fractures in which healing does not occur within six months of injury. These fractures represent 3% of all long-bone fractures, and result in a tremendous amount of discomfort and pain. The use of PEMF stimulation as a treatment for non-unions has been very successful, with success rates reaching 80% [7, 12]. The amount of time required prior to having this treatment prescribed is slowly being reduced from its original requirement of nine months following injury. Furthermore, the successful results obtained from this treatment have prompted discussions of the use of these fields for treatment of ordinary fractures. It is anticipated that PEMF stimulation on ordinary fractures would reduce the amount of time that a cast must be worn [7].

The first study to report successful application of PEMF stimulation was conducted by Bassett et al. Using 43 beagle dogs with surgically produced bilateral fibular osteotomies, these researchers were able to demonstrate a non-invasive acceleration of the repair process in the dogs

Disease	Author	Ref.	Effect of MF
Bone			
Osteotomy	Bassett et al.	[18]	Accelerated fibula bone repair
	Bassett et al.	[19]	Accelerated fibula bone repair
	De Haas et al.	[23]	Quickened initiation of long bone healing; did not sig. reduce time for solid union
	Darendeliler et al.	[17]	Increased new bone growth
Non-union bone fracture	Bassett et al.	[20]	Osteogenesis
	Heckman et al.	[13]	Enhanced bone healing
	Barker et al.	[22]	Established tibial unions; not sig. different from controls
	Frykman et al.	[12]	Healed non-union scaphoid fractures
	Godley	[21]	Enabled solid union of carpal scaphoid
Congenital Pseudarthrosis	Bassett et al.	[16]	Healed tibial congenital pseudarthrosis
Bone formation	Matsumoto et al.	[24]	Increased bone contact and bone area with the implant
Osteoporosis	Tabrah et al.	[25]	Initial increase in bone density followed by steady decline
Hip Arthroplasty	Konrad et al.	[26]	Improvement in pain ratings and hip movements
Perthes Disease	Harrison et al.	[27]	No significant difference from controls
Joint			
Joint Disorders	Sanseverino et al.	[28]	Decreased pain ratings and improved mobility of joint
Rheumatoid Arthritis	Ganguly et al.	[29]	Enhanced improvements in pain, swelling, tenderness, and joint function among seronegative relative to seropositive patients
Osteoarthritis	Pipitone et al.	[14]	Improvements in pain, stiffness, and physical disability relative to baseline
	Jacobson et al.	[30]	Greater reduction in pain
Rotator Cuff Tendinitis	Binder et al.	[32]	Decrease in pain ratings, increase in active range
Lateral Epicondylitis	Devereaux et al.	[33]	No significant benefit
Spinal Fusions			
Spinal fusions	Marks	[34]	Enhanced successful bony bridging
Pseudarthrosis	Glazer et al.	[35]	Enhanced solid union, increased stiffness, increased maximum load before fusion failure
Interbody lumbar fusions	Mooney	[36]	Improved success rate of solid fusion
Ulcers			
Venous leg ulcers	Ieran et al.	[38]	Healed ulcers for prolonged period; prevented recurrence
	Stiller et al.	[9]	Decreased wound surface area, wound depth; increased healthy granulation tissue
	Flemming et al.	[37]	Insufficient evidence from reviewed studies to warrant use of PEMF stimulation
Pelvic Pain			
Pelvic Pain	Jorgensen et al.	[39]	Quickened return to normal activities, prevented need for surgery
Nerves			
Median-ulnar nerve	Wilson et al.	[41]	Stimulated and quickened nerve regeneration
Peroneal nerve	Raji	[42]	Quickened toe-spreading reflex, enabled nerve regeneration
Sciatic nerve	Sisken et al.	[44]	Regeneration of nerve
	Kanje et al.	[43]	Enhanced regeneration of nerve
Endocrine ophthalmopathy	Jankauskienė et al.	[46]	Reduced soft tissue involvement and proptosis, improved corneal and optic nerve function
Neurological Disorders			
Multiple Sclerosis	Richards et al.	[47]	Improvement in performance scales;increased alpha EEG during language tasks
Tinnitus	Roland et al.	[48]	Improvements in symptoms; reductions in sensation levels
Neuroendocrine System			
Hormone production	Mann et al.	[53]	Altered cortisol secretion pattern
Melatonin levels	Karasek et al.	[57]	Reduced melatonin profile depending on pulse parameters
	Karasek et al.	[58]	No influence on melatonin concentrations
	Warman et al.	[54]	Changed melatonin onset variability, but not average melatonin onset time
Cancer			
Mammary carcinoma	Bellossi et al.	[59]	Increased length of survival
	Williams et al.	[60]	Reduced tumour growth/ vascularization
KMT-17 / KDH-8 tumours	Omote et al.	[62]	Increased survival rates, decreased colony formation, especially in combination with drug therapy
A431/ HT-29 cell lines	Hannan et al.	[8]	Reduced mean tumour volume, esp. in combination with anti-cancer drugs
Subline KB-ChR-8-5-11	Liang et al.	[63]	Reduced tumour size and enhanced survival
HL-60, HL-60R, and Raji cell lines	Robison et al.	[64]	Decreased susceptibility to heat-induced apoptosis, enabling proliferation of cancerous cell lines
Benzo(a)pyrene- induced tumours	de Seze et al.	[61]	Decreased rates of tumour growth; increased survival
Cerebral Ischemia (Stroke)			
Focal ischemia	Grant et al.	[65]	Reduced extent of cortical oedema, and areas of neocortex and neostriatum
Coronary Protection			
Cardiac Stimulation	Mouchawar et al.	[66]	12 kJ required to achieve closed-chest ectopic beats
Myocardial Protection	DiCarlo et al.	[68]	Incresed survival rates following cardiac anoxia damage
	Albertini et al.	[74]	Reduced necrotic region of myocardial infarct
	DiCarlo et al.	[67]	Increased survival rates following cardiac anoxia damage
	Carmody et al.	[73]	Protection from ischemic-reperfusion injury
Psychophysiological Regulation			
Human Standing Balance	Prato et al.	[79]	Increased movement under low Intensity light; decreased movement under high intensity light
	Thomas, Drost, ...	[77]	Improved standing balance
	Thomas, White,...	[78]	Improved standing balance in fibromyalgics and controls to greater degree than in arthritics during eyes open;all groups had worse standing balance during eyes closed

Table 2: Efficacy of Magnetic Field Therapy, by Disease Category

Pain	Kavaliers et al.	[89]	Abolished morphine-induced analgesia
	Kavaliers & …	[97]	Reduced tolerance to morphine
	Ossenkopp et al.	[83]	Attenuated morphine-induced analgesia in mice
	Prato et al.	[86]	Static component had no effect, radiofrequency component reduced, and pulsed component of MF abolished morphine-induced analgesia
	Kavaliers & …	[88]	Inhibited analgesia from opioid agonists
	Kavaliers & …	[84]	Reduced opioid-induced analgesia following administration of naloxone
	Betancur et al.	[87]	Reduced analgesic effect
	Fleming et al.	[100]	Increased analgesia
	Del Seppia et al.	[93]	Hyperalgesia (heightened sensitivity) to painful electrical stimulation
	Papi et al.	[94]	Increased sensitivity to painful electrical stimulation
	Sartucci et al.	[101]	Reduced pain thresholds and pain-related somatosensory evoked potentials
	Thomas et al.	[95]	Induced analgesia, and increased opioid-induced analgesia
	Thomas et al.	[98]	Development of tolerance and cross-tolerance to repeated MF exposures; effect reduced with presentation of novel environmental cues
	Del Seppia et al.	[85]	Suppressed stress-induced analgesia

Table 2: Efficacy of Magnetic Field Therapy, by Disease Category (Continued)

following 28 days of exposure to low-frequency, low-intensity PEMFs (2 mV/cm, 1.5 ms, 1 Hz, biphasic; or 20 mV/cm, 0.15 ms, 65 Hz, biphasic). The 65 Hz PEMF was more effective in improving healing (i.e., producing new bone tissue) than was the lower-frequency field [18, 19].

2.1.1 Non-Unions

Bassett, Pilla, and Pawluk [20] reported the first account of a therapeutic benefit of ELF PEMFs in humans. These researchers reported that PEMF stimulation (300 ìs pulse width; 75 Hz) on surgically resistant non-unions led to osteogenesis as a result of the therapy. Twenty-five of the 29 patients in the study displayed radiographic evidence of bone formation following one month of stimulation. Furthermore, these researchers were able to prevent several individuals who were recommended for amputations from these painful and debilitating procedures.

Following the success of Bassett et al. [20], further research was conducted investigating PEMF stimulation on fracture healing. Heckman et al. [13], for example, reported a 64.4% success rate in 149 patients who used PEMF stimulation to treat non-unions. For patients who maintained intensive use of the stimulation for three months, effectiveness was seen in 85% of patients. Frykman et al. also reported success of PEMF stimulation. These researchers reported an 80% success rate among 44 patients with non-unions of the scaphoid (a small bone in the wrist joint) treated with PEMF stimulation, and advocated PEMF stimulation as an alternative method for treating non-union scaphoid fractures when long-arm cast treatment proves ineffective [12]. This finding was replicated in 1997 in a case study of a 12-year-old boy with a non-united carpal scaphoid fracture who was successfully treated with PEMF stimulation, such that union of the fracture was established following treatment [21]. The use of PEMF stimulation appears to be effective, and a reasonable choice of treatment, among individuals suffering from non-unions [13].

A more recent reporting by Traina et al. [10] of the successful application of PEMF exposure for the treatment of non-unions claimed a 74% healing rate, with age of patient, site of fracture, type of non-union, and presence of infection as significant factors influencing the results. The presence of infection of the bone tissue or surrounding soft tissue was previously reported to not have an effect on the treatment outcome [10].

The early success of PEMF treatment of non-unions was not replicated in every study. For example, PEMF stimulation (0.3 T/s burst waveform, 15 Hz) was not shown to be effective in the treatment of un-united tibia fractures at 12 months post-injury. Specifically, Barker et al. [22] found that five of the nine patients in the active treatment group, relative to five of the seven patients in the placebo group, displayed united fractures at the end of the 24-week experiment. These data suggest the need for further research; yet, this study included only 16 patients, and so there was very little statistical power to detect a significant difference. Also, the induced electric fields were much lower in this study than in the original work by Bassett [20].

2.1.2 Congenital Pseudoarthrosis

Pulsed electromagnetic-field stimulation has also been shown to have clinical efficacy for the treatment of congenital Pseudoarthrosis [16]. This treatment modality aims at bone consolidation, as well as prevention of re-fracture and misalignment of the bones involved [10]. Specifically, PEMF (8 T/s, 20 pulses repeated at 15 Hz) stimulation, along with immobilization of the fractured area, was found to have an 80% or greater success rate for Type I and Type II lesions (gaps less than 5 mm wide) for which no operations had yet been performed. Type III lesions (lesions which are atrophic, spindled, and had gaps in excess of 5 mm wide) were not as responsive to PEMF stimulation, displaying a 7% success rate in response to treatment that included only PEMF, and an overall 19% success rate for treatments that also included operations. The lesion types were defined according to the lesion's appearance on X-ray photographs [16]. The success of treatment of congenital pseudoarthrosis with PEMF stimulation was outstanding since in the past, amputation was the most frequent outcome for this disorder [6].

2.1.3 Osteotomies

Pulsed electromagnetic field stimulation has been shown to have an additional use in bone repair – one that has yet to be approved by the FDA. Treatment of osteotomies (misaligned bones) in guinea pigs with PEMF therapy (15 Hz, 200 ìs unipolar pulse, 1.8 mT, 3 T/s) has resulted in increased new bone growth in the gap caused by the osteotomy relative to placebo group animals, where loose connective tissue filled the osteotomy sites. This study provides implications to humans about the possibilities of using PEMFs to quicken craniofacial healing [17]. However, disapproval of PEMF stimulation was provided by De Haas et al. [23], who found that recently osteotomized long bones of rabbits given PEMF stimulation experienced a quicker initiation of the healing process, but did not have a significantly reduced time for solid union relative to control rabbits.

The pulse parameters of a magnetic field as well as its duration of use are important characteristics that have been shown to influence the effectiveness of PEMF stimulation. Matsumoto et al. [24] investigated the bone formation surrounding dental implants inserted into the femur of rabbits, and found that bone contact with the implant was greater among PEMF-treated (100 Hz, rise times of 8 T/s, 12 T/s, and 32 T/s for 0.2 mT, 0.3 mT, and 0.8 mT peak, respectively) animals relative to controls. Among treated rabbits, 0.2 mT and 0.3 mT fields had significantly greater bone contact and bone area than the 0.8 mT-treated femurs. No significant difference was observed for bone contact or bone area for those femurs treated four hours/day as opposed to eight hours/day. Furthermore, it was found that two weeks of exposure had a significantly greater effect than one week; yet, the measured outcomes were not significantly lower at two weeks than they were following four weeks of exposure. This study indicated the need to select the proper magnetic-field intensity, duration, and length of treatment to maximize outcome [24].

2.2 Other Orthopedic Disorders

2.2.1 Osteoporosis

Osteoporosis, the most common skeletal disorder, is associated with decreased bone mass. Consequences of this condition include the inability of the skeleton to resist stresses of everyday life, resulting in numerous fractures. The beneficial application of PEMF stimulation in healing non-union bone fractures suggested the possibility that such treatments might be beneficial to patients with osteoporosis. Twenty post-menopausal women participated in an investigation of the effectiveness of PEMF therapy in increasing bone density. During twelve weeks of daily 72 Hz pulsating magnetic field exposure (380 ìs quasirectangular wave, followed by 6 ms quasitriangular wave), bone densities of exposed bone regions increased; however, during the 36 weeks following treatment, bone densities decreased significantly. These rebound results suggest the immediate effectiveness of PEMF therapy, and indicate the need for continued treatment to ensure prolonged increased bone density [25]. A decrease in initial improvement is not exclusive to PEMF treatment; any treatment (including drug therapy) given to improve symptoms associated with osteoporosis is expected to show declines following its removal.

2.2.2 Hip Arthroplasty

Hip arthroplasties are required when individuals are suffering from hip problems. A common side effect of such surgeries, however, is the loosening of the prosthesis that occurs in 15% - 25% of patients within 10 years of the surgery. The successful application of PEMF therapy in orthopedic disorders prompted Konrad et al. [26] to consider its use in a non-blinded, uncontrolled study investigating the treatment of twenty-four patients suffering from aseptic loosening of the hip prostheses. Patients were assessed for levels of pain and hip movements prior to and following exposure to magnetic fields (50 Hz, 5 mT). No patients were randomized to a sham condition. Significant improvements in pain ratings and all hip movements (except for flexion and extension) were noted following exposure sessions in patients suffering from loose hip replacement, but not for those patients suffering from severe pain due to gross loosening of the hip prostheses [26]. This suggests that PEMF therapy may only be beneficial in reducing mild-to-moderate pain associated with hip prostheses, but not severe pain levels.

2.2.3 Perthes Disease

While there have been good results found from the treatment of orthopedic disorders with PEMF, not all diseases or conditions have benefited from such treatment. For example, Perthes' disease, a condition in which young children suffer from a temporary loss of blood supply to the femoral head (the ball part of the hip joint) has not been shown to benefit from PEMF stimulation [27]. Twenty-two boys, randomized to either orthosis plus PEMF treatment or sham treatment, displayed no significant differences in treatment durations (an average of 12.5 months for those receiving PEMF versus an average of 12.0 months for those receiving sham). The treatment time was defined as the amount of time required for the upper femoral epiphysis (the top part of the femoral head) to be resistant to the deforming effects caused by weight-bearing. Based on this controlled study, there does not appear to be a significant effect of PEMF stimulation on the successful treatment of Perthes' disease.

However, there are inconsistencies in the literature with respect to the success of PEMF stimulation in treating diseases associated with the femoral head. For example, research investigating the ways in which PEMF stimulation

enables repair of the dead bone associated with lack of blood supply to the femoral head has found that PEMF exposure enables repair of the dead bone by promoting ingrowth of new blood vessels, while maintaining a balance between the rate of dead bone removal and the formation of new bone [6]. Vallbona and Richards [4], commenting on studies using EMF stimulation to treat femoral-head necrosis, reported that this form of treatment resulted in successful progression for lesions located in the hips, according to both clinical (80% successes) and magnetic resonance (MR) imaging (76.6% successes) evaluations. The combined clinical and MR imaging success rate was reported as 63.3% for the lesions.

2.3 Summary of Orthopedic Literature

Pulsed electromagnetic field exposure has been applied to a variety of orthopedic pathologies, mostly with positive, successful indications. For example, Traina et al. [10] reported that PEMF therapy was a successful modality of treatment of congenital pseudoarthrosis, pseudoarthrosis, delayed union, fracture at risk, recent fracture, bone grafts, vertebral arthrosis, and avascular necrosis. Limb lengthening, however, was not successfully achieved through the use of PEMF stimulation. The reader is directed to the review prepared by Traina et al. [10] on bone healing through pulsed electromagnetic-field exposure and other means of biophysics enhancement for a more comprehensive analysis of bone healing.

3. Rheumatological Disorders

3.1 Joint Diseases

Pulsed electromagnetic-field therapy has been shown to be effective in treating joint diseases; yet, the degree of its success depends on the specific joint disease in question. Specifically, joint diseases involving only one joint, as well as single traumata (suffering from acute lesions), show significant improvement following PEMF stimulation. In contrast, disorders involving multiple joints (e.g., polyarthrosis, rheumatoid arthritis) are much more resistant to the effects of PEMF stimulation, and show less improvement following treatment sessions. In a large 11-year experimental study, 3014 patients suffering from a joint disease were treated with extremely low frequency, low-intensity sinusoidal magnetic fields (0.6 T/s - 1.2 T/s). Patients were given one 15 - 40-minute session daily for 10 - 15 days to assess the effects of the pulsed magnetic field exposure on healing of the joints and associated pain levels. These patients – except females who were pregnant or menstruating, and individuals who carried a pacemaker – were exposed to the magnetic fields. Control patients (in addition to the 3014 patients) were included and provided with sham treatment. Of the 3014 subjects who received PEMF exposure, 78.8% showed good results (i.e., pain disappearance, 40% - 50% increase in degrees of freedom of the sick joint, maintenance of benefit for at least three months, decrease in thermal irradiation of the affected joint after magnetic-field exposure). The best results were obtained with patients who participated in therapeutic exercises following magnetic-field therapy, and maintained control of body weight and bone mineralization. Control patients reported a complete absence of any benefit when (unknowingly) exposed to sham treatment; upon subsequent exposure to the active PEMF unit, these controls obtained the same results as the patients who were exposed to the active unit [28].

3.1.1 Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic condition in which an individual suffers from inflammation of the joints, resulting in feelings of pain, stiffness, and swelling. There is no known cause of this disorder, but it has been implicated as being autoimmune in nature. In testing individuals for the presence of rheumatoid arthritis, screening can be conducted for an antibody known as the rheumatoid factor (RF). The rheumatoid factor is present in the blood of 80% of adults suffering from rheumatoid arthritis [29]; however, its presence or absence does not necessarily indicate that one has rheumatoid arthritis. Individuals who possess the rheumatoid factor are classified as serological-positive, while those lacking the antibody are categorized as serological-negative.

Gunguly et al. [29] conducted a study investigating the effectiveness of PEMF stimulation in reducing pain, tenderness, swelling, joint functional disability, and joint spasm with deformity in 35 patients suffering from rheumatoid polyarthritis (multiple joint disorders). Patients in this study were assessed according to serological grouping. Results indicated that those individuals lacking the rheumatoid factor (i.e., patients who were serological-negative) showed earlier responses to the PEMF (rectangular pulse) for pain and swelling, and a much earlier improvement for pain, tenderness, and joint functional disability relative to serological-positive individuals. The same trend appeared for joint spasm with deformity; however, the overall treatment effect for this symptom was low for both groups. These findings provide empirical support for clinicians to treat individuals with and without the rheumatoid factor differently, as PEMF was not shown to be as effective a therapy for those possessing the antibody [29].

3.1.2 Osteoarthritis

Osteoarthritis is the most common rheumatic disorder, affecting older people in industrial countries [5]. It is characterized by degeneration of articular cartilage (cartilage at a joint), and the presence of hypertrophic (enlargement of organ due to increase in size of constituent cells) tissues [30]. Those suffering from the disorder experience pain, swelling, tenderness, and stiffness in the weight-bearing

joints of the lower extremities [5]. Approximately 80% of the population over 75 years of age displays radiological signs of osteoarthritis, with 40% - 80% of these individuals also having clinical symptoms of the disease [14, 30].

Treatment for osteoarthritis has begun to shift away from drug therapies – which have, in large part, been found to be ineffective and toxic – and towards more unconventional modes of healing [5]. This shift has resulted despite the firm position of the American College of Rheumatology that there is currently inadequate scientific documentation to warrant the use of PEMF therapy for treatment of osteoarthritis of the hips and knees [14]. Nevertheless, PEMF stimulation has been gaining increasing support as a treatment for osteoarthritis. It has been suggested that magnetic fields are beneficial in the treatment of osteoarthritis because they suppress inflammatory responses at the level of the cell membrane [31].

An attempt to demonstrate the clinical importance of magnetic-pulse treatment for knee osteoarthritis was conducted by Pipitone and Scott [14]. These authors found no significant improvement of magnetic-field-treated patients (unipolar pulse, 7.8 Hz in morning, 3 Hz in evening; < 50 T/s) relative to placebo-treated patients at the end of the study. However, the authors did find that magnetic-field-treated patients reported significant improvements in a questionnaire assessing pain, stiffness, and physical disability at the end of the study relative to their baseline scores on these measures. In contrast, no significant changes were observed for placebo-treated patients in these measures between baseline and the end of the study. This work suggests that PEMF stimulation should be included as a part of the treatment protocol for individuals suffering from osteoarthritis; however, further experimentation using different magnetic devices, treatment populations, and experimental protocol should be considered.

3.1.3 Rotator-Cuff Tendinitis

Rotator-cuff tendinitis, inflammation of one or more of the muscles that holds the ball of the shoulder joint tightly against the socket, is a common cause of shoulder pain among adults. Conventional treatments, such as corticosteroid injections, are not always effective; therefore, alternative therapies have been evaluated. A randomized double-blind experiment designed to assess the effect of PEMF stimulation [73 $\pm$2 Hz; 2.7 mT_{pk}, 7.9 T/s] on individuals suffering from rotator-cuff tendonitis was conducted. The design of this experiment consisted of three phases. During the first phase, one group of patients received PEMF treatment, while the other group received sham treatment. The second phase involved the administration of PEMF exposure for *both* groups of patients. In the third phase, no PEMF stimulation was given to either group. This design allowed for obvious group differences to be detected upon the introduction of the second phase, and also enabled all subjects to receive the PEMF treatment following four weeks (the beginning of second phase), as opposed to only offering such therapy to the treatment group. Upon presentation of PEMF stimulation to the control group at the beginning of the second phase, a remarkable decrease in pain ratings and an increase in active range were noted. These scores were in the direction of those of the treatment group, with no significant group differences present following the four-week mark of the study. These findings demonstrate the ability of PEMF stimulation to reduce pain and increase activity among individuals suffering from rotator-cuff tendinitis, and implicate such therapy for individuals who suffer from the disorder, and are unresponsive to, or noncompliant with the administration of, corticosteroid injections. Overall, Binder et al. found that more than 70% of all patients in this study improved following PEMF therapy [32].

3.1.4 Lateral Humeral Epicondylitis

The success of PEMF therapy in treating rotator-cuff tendinitis prompted rheumatologists to consider the use of such therapy for other chronic tendon lesions, such as lateral humeral epicondylitis (better known as “tennis elbow”). A randomized, double-blind assessment of the effectiveness of PEMF therapy in treating this condition (a minimum of eight weeks of treatment) in 30 patients failed to find a significant beneficial effect of PEMF stimulation (single pulse, 200 ìs duration, 15 Hz) to warrant its use over placebo conditions. This conclusion may be related to the 53% spontaneous healing found among patients in the placebo group, or to the use of different pulses in treating lateral humeral epicondylitis relative to other rheumatological disorders [33].

4. Spinal Fusions

Spinal fusions occur when an individual is suffering from a painful vertebral segment, and wishes for the motion at the vertebral region to be reduced to help alleviate the pain. This type of surgery is invasive, and is used only after more conservative methods of treatment have been explored (e.g., bed rest, drug therapy, exercise, massage) [34]. Once spinal fusions are deemed medically necessary, the surgical team wants to ensure that recovery will be as quick as possible, and that minimal pain will be endured. One method in which to achieve these goals is through the use of PEMF stimulation. Marks [34] found that spinal fusions for discogenic low back pain were successful (i.e., incorporation of the graft, no radiolucency between graft and vertebral bone, no motion at level of fusion) in 97.6% of the surgeries of patients in the PEMF stimulation group, as opposed to the low 52.6% success rate among patients in the unstimulated group, indicating that PEMF stimulation allows for bony bridging in lumbar spinal fusions. Furthermore, successful spinal fusions correlated with good or excellent clinical outcomes [34].

A complication of spinal fusions arises when an individual also suffers from Pseudoarthrosis, the failure of a union to develop in fusion. The use of PEMF therapy to

reduce Pseudoarthrosis has been shown to be effective in a rabbit fusion model [35]. Twenty adult white rabbits were randomly assigned to either a PEMF or a sham exposure for four hours daily for six weeks. Characteristics of the electromagnetic field included asymmetric rise and fall times (3 ± 1 T/s and 9 ± 4 T/s) using a 26-ms pulse burst, a 670 ± 10-ms burst interval, and a pulse rise and fall time of 400 ns. The animals were euthanised at six weeks, at which time radiologic and histologic samples were taken. Radiographic analysis indicated that six of the 10 animals in the placebo group, and eight of the 10 animals in the PEMF group, had solid fusions. In the rabbits that demonstrated solid fusion, there was a significant increase in stiffness of the fusion mass, a significant increase in area under the load-displacement curve (representing energy absorbed by each motion segment), as well as a significant increase in the maximum load before fusion failure among the PEMF-exposed animals relative to the placebo controls [35]. The implication of these findings to human studies is of importance, as this study provided preliminary support for the idea that exposure to PEMFs can reduce Pseudoarthrosis, thereby reducing pain among human patients with lower back pain.

4.1 Interbody Lumbar Fusions

Interbody lumbar fusions are performed to help release stress from a damaged disk that has caused a pinched nerve root. The rates of lumbar fusion are unpredictable; however, following evidence that PEMFs have the ability to aid in bone formation, it has been shown that the presence of these fields has a significant effect on spinal fusions. Using a double-blind prospective approach, Mooney [36] assessed the success of spinal fusions in 195 patients who were undergoing initial attempts at interbody spinal fusions. Success rates were defined as radiographic evidence of solid fusion. For those patients who complied with the methodology of using the brace for at least eight hours each day, there was a success rate of 92.2% in the active treatment group (PEMF, 0.18 mT, 1.5 Hz). This rate was significantly higher than the 67.9% success rate found among patients in the placebo group. The patients' age, sex, fusion level, number of grafts, graft type, or internal fixation did not affect these success rates. Smoking made very little difference, yet showed a decreased trend in success rates for both active and placebo group patients [36]. It should be noted that there is controversy as to whether interbody lumbar fusions are an orthopedic indication.

5. Soft-Tissue Regeneration

5.1 Venous Leg Ulcers

Leg ulceration is a chronic, recurring condition, affecting more women than men, and increasing in prevalence with increasing age. Venous leg ulcers are caused by a blockage in the veins of the legs. Compression can heal most of these ulcers; however, it is not an effective form of treatment for all such sores [37]. Pulsed electromagnetic-field stimulation has been investigated as a therapy for wound healing following results that PEMFs can promote healing by potentially increasing collagen synthesis, angiogenesis, and bacteriostasis [9, 37].

The use of PEMF stimulation to reduce the size and eliminate pain associated with venous leg ulcers was investigated in a double-blind study of patients suffering from skin lesions present for at least three months [38]. Using a 2.8-mT magnetic field with a 75-Hz frequency and pulse width of 1.3 ms over a treatment protocol of 90 days, these researchers found a significantly higher success rate (66% versus 32%) among patients exposed to the active PEMF device relative to those exposed to identical dummy devices. Furthermore, the effect of the field exposure was prolonged, evident at follow-up of at least one year, and protected the patient from ulcer recurrence. These findings suggest that PEMF stimulation is a useful complement to the treatment protocol for venous leg ulcers [38].

A prospective, multi-center, double-blind, randomized study was conducted to assess the efficacy of a portable PEMF stimulation device, PELUT (pulsed electromagnetic limb ulcer therapy). The PELUT device (bi-directional $2.2\,mT_{pk}$, three-part pulse of 3.5 ms total width, induces a low-level, non-thermal electrical field of 0.06 mV/cm in the skin above the wound dressing) was modeled after devices that have been successful in treating non-union fractures. Subjects suffering from recalcitrant venous stasis ulcers were randomized into either treatment or placebo group conditions, and were assessed at baseline, four weeks, eight weeks, and 12 weeks from the start of the experiment. All subjects were also given standard wound dressings as part of the treatment protocol. At week eight, relative to placebo group subjects, those individuals treated with the PELUT exhibited a 47.7% (significant) decrease in wound surface area, a significant decrease in wound depth, and a 15% increase in healthy granulation tissue. Those patients who had shown improvement at the eight-week mark, and chose to remain in the treatment program for an additional four weeks, exhibited further improvement, showing a 66% decrease in wound surface area at that time. The investigators' global assessments of the ulcers revealed a 50% improvement among those in the treatment group relative to a 0% improvement rate among the ulcers in the placebo group. None of the ulcers on subjects in the treatment group worsened following treatment; however, 54% of the ulcers in the placebo group worsened over the course of the eight weeks [9].

A review conducted by Flemming and Cullum [37] to investigate the effectiveness of PEMF in treating venous leg ulcers reported that, to date, there is insufficient evidence to warrant the clinical use of PEMF stimulation for the treatment of such ulcers. However, given the results reported in Stiller et al. [9], there is a need to perform further investigations into the true ability of PEMF stimulation in treating these ulcers.

6. Pelvic Pain

Another useful clinical application of PEMF radio-frequency (RF) stimulation is for the treatment of pain arising from pelvic disorders such as dysmenorrhoea, endometriosis, ruptured ovarian cyst, and acute lower urinary tract infection. In a study involving a total of 20 episodes of pain arising from pelvic disorders, pain was reduced following PEMF stimulation in 90% of the cases (i.e., 18 episodes). Pulsed electromagnetic stimulation involved brief 15-minute – 30-minute exposures to short pulses (1.0 MHz - 250 MHz; 2 - 30 pulses/s). The pain relief was evident following PEMF stimulation, and permitted a quicker return to normal life activities and prevented surgery. Patients suffering from the remaining two episodes of pain did not report pain relief following treatment. Recurrence of the pain condition occurred in one, or possibly two, of the treated episodes, and there were no adverse side effects reported either during or following treatment [39].

7. Nerves

Investigations into possible therapies and treatments for damaged nerves are essential, as these injuries can have detrimental and devastating effects in humans. However, human research is not always the best first approach for introducing and subsequently assessing nerve damage. Rather, animal models provide an excellent avenue for establishing an injury to a nerve to enable an understanding into what methods are successful in the repair of the injury. Animal studies investigating repair of damaged peripheral nerves have focused on the use of PEMF exposure sessions to aid in the regeneration of the nerve [40].

Wilson and Jagadeesh [41] conducted an experiment designed to assess regeneration of the median-ulnar nerve in the upper forelimb of 132 rats using PEMF (Diapulse Corporation of America; 65-ms pulse bursts) and sham treatments. Nerve-conduction studies indicated a return to nerve conduction of degenerated nerves following Diapulse treatment, but not following sham treatment. Histology slides revealed regenerating nerve fibers 30 days post-surgery in PEMF-treated rats; slides taken 60 days post-surgery in control rats showed evidence of regeneration, but not to the level found in the treated rats at 30 days post-surgery. Taken together, these results indicated that PEMF treatment is effective in stimulating and quickening the regeneration of the median-ulnar nerve in rats [41].

Further research into treating injured nerves with PEMF treatment investigated a nerve that is fairly important to humans: the peroneal nerve. Located in the leg and used for walking, when damaged, the peroneal nerve prevents individuals from lifting their foot and moving their toes. Raji [42] conducted an animal study investigating the degeneration and regeneration of this nerve using PEMFs. These researchers inflicted injury to the left peroneal nerve of male Lewis rats to assess the effects of both PEMF (Diapulse; 400 pulses/s) and sham treatments on the recovery of the rat's injured leg. Regeneration of functionally complete motor nerves was assessed via a test of reflex spreading of the toes upon being lowered suddenly to the ground. Results from the test suggest the beneficial usage of Diapulse, as the toe-spreading reflex was significantly quicker to appear in treated as opposed to untreated animals. Furthermore, microscope slides revealed accelerated progressive improvement in the appearance of transverse sections of the nerve, as well as increases in the number of nerve fibers, among magnetic-field-treated animals relative to rats in the sham group. These results suggest that PEMF therapy is beneficial in aiding the regeneration of the peroneal nerve in male rats [42].

Continued research on nerve repair and PEMF treatment has enabled investigations into other nerves of interest. In particular, the largest nerve in the body, the sciatic nerve, has followed the success of previous research, and has shown enhanced regeneration following exposure to PEMFs relative to animals (e.g., male and female rats) given sham treatment [43]. Sisken et al. [44] have seen regeneration in the sciatic nerve after a crush lesion following one hour of exposure (0.3 mT, 20 ms pulse, 2-Hz repetition) daily; the regeneration did not improve significantly with longer exposure periods. Furthermore, rats pre-treated with 0.38 T/s PEMFs (20 ms pulse, 2 Hz) were shown to have enhanced regeneration of the sciatic nerve after a crush lesion, while those exposed to 60 ìT fields did not experience this effect. This indicates that the regeneration process might be receptive to specific fields [43]. Overall, these results suggest that PEMF treatment can be used to successfully repair the sciatic nerve.

The animal studies conducted on nerve repair and PEMF treatment, considering nerves from both the arms and the legs, all converged on the finding that PEMF therapy was effective in nerve regeneration relative to results obtained from animals given sham treatment. The regeneration rate following PEMF exposure was enhanced to the same degree as obtained by other treatment methods, including conditioning lesions, hormones, and growth factors [45].

7.1 Endocrine Ophthalmopathy

Endocrine ophthalmopathy is considered an organ-specific autoimmune disorder, caused by an abnormality in immune-response mechanisms. Possible treatments for this disorder include corticosteroids and nonsteroidal anti-inflammatory drugs to reduce the inflammation of the eye (an identifying characteristic of this condition). When these drugs are ineffective, alternative forms of treatment are required. The success of PEMF stimulation in improving metabolic processes in tissues and organs led to the study of the effectiveness of PEMF therapy in treating endocrine ophthalmopathy [46]. Following exposure to magnetic fields of 1 mT with pulses emitted at a frequency of

8.0×10^4 Hz, patients diagnosed with endocrine ophthalmopathy enjoyed reductions in soft-tissue involvement and proptosis (displacement of the eyeball). Limitations in ocular movements were reduced, while corneal and optic-nerve function improved following magnetic-field exposure; these measures did not, however, reach statistical significance. The study showed that PEMF therapy is only useful for those suffering from endocrine ophthalmopathy who show signs of soft-tissue involvement; nonetheless, given the gravity of this disorder, the evidence for the usefulness of and necessity for a non-invasive treatment method is great [46]. Further work is required to determine the significance of PEMF exposure on treating diseases such as endocrine opthalmopathy; a Pubmed search yielded this paper as the only one investigating such effects.

8. Neurological Disorders

8.1 Multiple Sclerosis

The findings that PEMF stimulation was successful in improving nerve conduction and regeneration indicates a possibility that its use might be effective in treating disorders of the central nervous system, such as multiple sclerosis (MS), for example. Multiple sclerosis is a neuro-degenerative disorder in which the myelin sheath surrounding neurons is damaged, and nerve conduction is slowed. In a randomized, double-blind study, Richards et al. [47] found significant improvement in performance scales (assessing bladder control, cognitive function, fatigue level, hand function, mobility, sensation, spasticity, and vision) among magnetic-field-exposed patients (PEMF: 5 - 10 μT, 4 Hz - 13 Hz, 10 - 24 hours daily, two months) relative to non-exposed patients. All subscales of the performance test, except for those of hand function and sensation, as well as the combined performance (all eight tests) were significantly improved among the PEMF-exposed individuals. Electroencephalograph recordings indicated significant improvements among the PEMF-treated individuals between pre- and post-exposure for six of the 19 electrodes, as well as increased alpha EEG during a language task among MS patients exposed to the magnetic fields relative to MS patients who were not exposed to the magnetic fields. No significant differences between pre- and post-treatment scores were found for the test of clinical ratings. These findings suggested that PEMF therapy is a beneficial short-term treatment for individuals suffering from MS [47].

8.2 Auditory Disorders: Tinnitus

Tinnitus, more commonly known as "ringing in the ears," is a disorder of the auditory system in which a bodily condition, such as disturbances of the auditory nerve, causes the affected individual to hear sensations of noises (e.g., ringing) that are only audible to that individual. The high prevalence of this condition warrants alternative methods, such as PEMF stimulation, to be considered as possible treatments [48].

A double-blind randomized trial assessing the effectiveness of PEMF stimulation as a treatment for tinnitus found significant improvements in symptoms and significant reductions in sensation levels among the group of patients treated with the active PEMF device (0.5 Hz - 17 Hz; 0.1 - ~0.15 iT). Overall, significantly more PEMF-group patients (45%) than placebo-group patients (9%) reported subjective improvement throughout the trial [48]. The study thus provided another useful and efficacious application of PEMF stimulation, and submitted evidence that PEMF therapy should be considered among other therapies for use among individuals suffering from tinnitus.

8.3 Psychiatric Disorders: Affective Disease

Transcranial magnetic stimulation (TMS), a safe and non-invasive method of exciting neurons through strong, brief, and focused [49] magnetic-field pulses, is currently the only ethically approved technique of modulating neuronal activity in the human brain. This method of stimulation works via the principle of induction: a capacitor is discharged to enable a strong current to pass through a coil placed over the scalp [50]. The strength of the induced current is a function of the rate of change of the magnetic field, which is affected by the current in the coil. The coils used today have a magnetic field peak intensity of 1.5 T to 2 T at the face of the coil, and neurons can be activated as far as 1.5 cm to 2.0 cm from the surface of the coil in the cortex [51]. The magnetic-field intensity used in TMS is many orders of magnitude larger than that present in ELF magnetic-field exposure, i.e., of the order of 10,000 T/s, as compared to maxima around 10 T/s.

Single-pulse TMS has been distinguished from repetitive TMS (rTMS) in that the latter is a modification of the former in which the magnetic field is repeated over a small time interval, allowing the stimulation of nerves during their refractory period. The multiple pulses that exist in rTMS are discharged through one coil using multiple stimulators, and are classified as fast rTMS if stimulation is greater than or equal to 1 Hz, and slow rTMS if stimulation is less than 1 Hz [49]. The use of rTMS has been considered for the treatment of psychiatric disorders such as depression, as it shares many of the behavioral and biochemical actions as other antidepressive treatments, such as electroconvulsive shock (ECT). Specifically, both treatments use transcranial brain stimulation; however, rTMS produces a localized effect, while ECT's effect is more generalized. Despite promising results with rTMS, its use has not yet produced evidence of beneficial results matching the effectiveness of the more-conventional treatment options [52].

9. Neuroendocrine System

The neuroendocrine system, a combination of hormone secretion and central nervous system activity, can be studied to investigate the biological effects of PEMFs [53]. To assess this link, the effects of an RF PEMF (modulated electromagnetic field) on hormone production were assessed in a healthy male population. Using a 900 MHz PEMF (217 Hz) set to provide a near-homogeneous field distribution, Mann et al. [53] determined nocturnal hormone profiles (growth hormone, luteinizing hormone, cortisol, melatonin) during both sham and RF PEMF exposure. The only significant difference in hormone secretions noted between the placebo and exposure trials was the significant interaction between field exposure and time, suggesting a different cortisol secretion pattern between the two sessions. No difference was reported between total cortisol production between the sham and exposure sessions, indicating a temporal difference in secretion of the hormone while under the influence of the RF PEMF [53]. Another study, designed to determine the effects of magnetic-field exposure on the human melatonin profile, used two-hour pulses of high-level circularly polarized 50 Hz magnetic fields (200 - 300μT) delivered at different circadian times [54]. Blood samples taken every 30 minutes to 60 minutes over a 17-hour overnight period provided multiple plasma melatonin measurements. Results from the study revealed that while no significant changes were present in average melatonin onset time following magnetic-field exposure, melatonin onset was significantly more variable following magnetic-field as opposed to sham exposure. The authors of the study discussed the possibility, on the basis of preliminary data, that the circadian time of the magnetic field might have an influence on the magnitude and direction of the observed response. This possibility might be the mediating link to explain why magnetic-field exposure has not been shown to consistently affect human melatonin profiles [54].

Further investigations of the effects of PEMFs on melatonin levels were conducted. Melatonin, a hormone derived from the pineal gland in the brain and controlled by the light-dark environment [55], is associated with pathological conditions – including cancer – when its levels are altered [56]. Levels of this hormone are generally high at night and low during the day [55]. Melatonin is believed to be important in synchronizing circadian rhythms [56], helping to induce sleep, reducing insomnia, eliminating jet lag, and has been speculated to be a contributor to anti-inflammatory and analgesic responses, as well as to soft-tissue repair [57]. As such, determining ways in which to modify melatonin levels is important to helping with these ailments that melatonin is thought to "cure." The presence of melatonin helps to retard the growth of tumors; however, exposure to ELF PEMFs has an inhibitory effect on the production of melatonin from the pineal glands at night, resulting in increased growth of tumor cells [56].

The ability of melatonin to reduce tumor growth may be a function of its role as hydroxyl ($\bullet$ OH) and peroxyl (ROO $\bullet$) radical scavengers. Free radicals can be toxic and can damage DNA, leading to cancer. Melatonin's antioxidant properties, present through its indole functional group, enable the protection of DNA from oxidative damage (through less free radical attack on the DNA), resulting in reduced incidence of cancer [56]. Since it has been shown that magnetic-field exposure can suppress melatonin secretion, and it has also been shown that melatonin, as a hormone, acts to stop cancer growth, it may be possible to design specific magnetic fields to stimulate melatonin secretion as a treatment for cancer patients [31].

Karasek et al. [57] utilized two PEMFs (2.9 mT, 40 Hz, square impulse shape, bipolar; 0.025 - 0.08 mT, 200 Hz, saw-like impulse shape, bipolar) to assess whether exposure to either had an effect on melatonin levels in men suffering from low back pain. Results from that experiment revealed a significantly reduced melatonin profile following exposure to the 2.9 mT pulse, but no significant difference relative to baseline when exposed to the 0.025 - 0.08 mT pulses. These findings suggested that melatonin levels can be altered by specific PEMF parameters [57], and implied that further research should be conducted to further elucidate the exact "best" parameters for altering melatonin levels in humans.

Further research conducted by Karasek et al. [58], investigating whether the effect of melatonin concentrations in patients with low back pain could be influenced by magnetic-field exposures of different characteristics (e.g., different magnitudes), revealed negative results: chronic exposure to magnetic fields varying in magnitude between 25 and 80μT and having a frequency of 200 Hz did not influence human serum melatonin concentrations. However, those magnetic-field amplitudes were lower than those used by Karasek et al. [57].

10. Cancer

Cancer research is essential, since this disease affects a large proportion of the population, and is one of the major causes of death in North America. Given the promising results of PEMF stimulation in treating other disorders and human conditions, Bellossi and Desplaces [59] conducted an experiment investigating the effects of PEMF exposure on survival rates in C3H/Bi female mice with mammary carcinoma. Using a 9-mT PEMF, set at either 12 Hz or 460 Hz, these researchers found increased length of survival during the early stages of the disease when the mice were exposed to the 12-Hz magnetic field, and increased length of survival during the late stages of the disease when exposed to the 460-Hz field [59]. Williams et al. [60] conducted further work assessing the effects of therapeutic EMF on mammary carcinoma vascularization and growth in C3H/HeJ mice. These researchers found that daily 10-min sessions of 10-, 15-, or 20-mT pulsating magnetic field (120 pulses/s) significantly reduced tumor growth and the extent of vascularization relative to mice not exposed to the

magnetic field. The ability of magnetic-field exposure to prolong survival was replicated in later work conducted by de Seze et al., using tumor-induced male and female mice. These researchers found that eight hours of daily exposure to the 100-mT, 0.8-Hz square-wave magnetic field resulted in significantly decreased rates of tumor growth and increased survival [61]. These three studies indicated that survival and tumor growth can be positively influenced by magnetic-field exposure.

In addition to using PEMF stimulation as a treatment for cancer growth, it is also possible to use this therapy as an adjunct to drug therapy. A combination treatment of pulsing magnetic fields (PMF) and an anti-tumor drug, mitomycin C (MMC), was shown to be successful in treating two experimentally-induced tumors [62]. Either the KMT-17 or the KDH-8 tumor cells were implanted subcutaneously into the right thigh of a male rat. Seven days following implantation, an intravenous injection of MMC was given to the rat; one hour later, PEMFs (2 T/s, 200 Hz) were applied over the thigh region. Rats were placed into one of four experimental groups: no treatment, MMC-only, pulsed-magnetic-field-only, or a combination of MMC and pulsed magnetic field. Survival rates of the KMT-17 implanted rats at 90 days were 0% for the untreated group, 34% in the MMC-only group; 47% in the pulsed-magnetic-field-only group, and 77% in the combination group. None of the rats implanted with the KDH-8 tumor survived to day 90; however, percentages of increased life span relative to untreated rats were 3.4% for the MMC-only group, 7.6% for the pulsed-magnetic-field-only group, and 17.6% for the combination group. Analysis of the cultured cells treated in each of the three treatment groups revealed a significant decrease in colony formation in the combination group relative to either the MMC-only or pulsed-magnetic-field-only (2.7 T/s, 250 Hz) groups. These results indicated the ability of pulsed magnetic field treatment to enhance treatment above that provided solely by MMC injections, and offer hope for possible alternative treatments for cancer [62].

The combination treatment of pulsed magnetic stimulation and anti-tumor drugs has been used in further research following the promising, successful results obtained by Omote et al. [62]. Using an average field strength of 0.525 mT_{rms}, three different chemotherapeutic drugs (cisplatin, carboplatin, and doxorubicin), and either A431 or HT-29 human cell lines implanted into nude or NIH-III female mice, the results consistently showed that mean tumor volume was reduced by the combination treatment (i.e., drug + pulsed magnetic field group). Specifically, the volumes of the tumors in combined-treatment mice were 52%, 34%, and 35% of those found in the cisplatin, carboplatin, and doxorubicin drug-only treatment groups, respectively. This consistent finding demonstrates the generality of pulsed magnetic field augmentation of anti-tumor drug effects [8].

Liang et al. [63] conducted more complex investigations of the combined effect of pulsed magnetic field and drug therapy. These researchers investigated the effects of the combined treatment (i.e., Daunorubicin + pulsed magnetic field) approach on a multi-drug-resistant (MDR) human carcinoma subline KB-Ch^R-8-5-11. For the in vivo part of the study, female mice were inoculated with the KB- Ch^R-8-5-11 cells, and subsequently treated with one hour of pulsed magnetic field treatment (44 T/s, 250 pulses/s) and intravenous injection of Daunorubicin. The only significant differences in tumor volume were between the pulsed-magnetic-field-only and pulsed magnetic field + drug groups at both 39 and 42 days [63]. Thus, it appeared that the combination effect was significantly better at reducing tumor size relative to either treatment alone. The in vitro study revealed that the efficacy of Daunorubicin was enhanced when pulsed magnetic field (44 T/s, 250 pulses/s) was given before the drug was injected, but not when the pulsed magnetic field was given post-injection [63]. These findings provide additional support for the common trend among cancer research that a combination treatment of pulsed magnetic field and drug works best at reducing tumor volume and enhancing survival.

Despite these encouraging results regarding the beneficial effect of PEMF exposure on cancer reduction, the effect of such exposure sessions has not always been found to be positive. Robison et al. [64] have shown that electromagnetic field exposure (54 mT/s, 60 Hz) for 4, 12, or 24 hours resulted in decreased susceptibility to heat-induced apoptosis for three human cancer cell lines, indicating that the cancerous cell lines were able to proliferate. Furthermore, these exposure sessions also resulted in time-dependent decreased DNA repair rates among two of the three cell lines, allowing for propagation of the damaged DNA. Thus, there are conflicting results with respect to the effect of electromagnetic field exposure on cancer, possibly related to the significantly different characteristics of the PEMF exposures (for example, the study by Robison et al. [64] had a much lower T/s than the positive studies).

11. Cerebral Ischemia (Stroke)

The clinical implications of determining a model to protect against cerebral ischemia are important, since strokes have devastating and sometimes life-threatening effects on many individuals in society. Given this importance, Grant et al. [65] designed an experiment to assess the effects of low-frequency PEMF exposure on cerebral injury in a rabbit model of focal ischemia. Twelve male white rabbits underwent occlusion of the left internal carotid, proximal left anterior cerebral, and proximal left middle cerebral arteries for two hours, followed by four hours of reperfusion. Six of these rabbits subsequently underwent treatment, which included PEMF exposure (2.8 mT, 75 Hz) beginning 10 minutes following the onset of ischemia until the end of reperfusion. At the end of the six hours, the 12 rabbits were sacrificed, and magnetic-resonance-imaging (MRI) studies, as well as histological examinations, took place. The MRI studies revealed high-intensity lesions in the anterior and

ventral cortical regions in the middle cerebral artery. PEMF exposure appeared to significantly reduce the extent of cortical oedema at the anterior level by 65% relative to controls. Histology slides revealed ischemic neuronal damage (IND) in the lateral neocortex and neostriatum within the middle cerebral artery ipsilateral to the occlusions. Subsequent to PEMF exposure, the areas of neocortex at the anterior level and the ischemic neuronal damage in the neostriatum were significantly reduced by 69% and 43%, respectively, relative to controls. These results suggest that exposure to PEMFs following focal cerebral ischemia can protect against the development of neuronal damage in the neocortex and neostriatum [65].

The success of combination treatment of pulsed magnetic fields and drugs for cancer treatment might be of benefit to researchers investigating possible therapies for cerebral ischemia. Specifically, given the effectiveness of the combined treatment in cancer, treatment for strokes may also be enhanced by the combined effect of drugs that are effective in treating acute focal ischemia [e.g., N-methyl-D-aspartate (NMDA) antagonists] and PEMF exposure [65]. The success of this approach can possibly be due to the enhanced ability of drugs in the presence of magnetic-field exposure to get across the blood-brain barrier.

12. Coronary Protection

12.1 Cardiac Stimulation

Stimulation of the heart is a necessary medical intervention to prevent coronary failure. Magnetic stimulators are capable of stimulating nerves; however, if the stimulation is too great, cardiac arrhythmias, or alterations in the rhythm of the heartbeat, can occur. Magnetic stimulation of the heart is preferred over stimulation with electrodes in direct contact with the skin since it is a less painful method of achieving the same result. To assess a method in which magnetic-field stimulation can be achieved without causing harm, Mouchawar et al. [66] investigated the threshold for cardiac stimulation by magnetic fields in 11 dogs. The PEMF was delivered via two coplanar coils placed on the surface above which the heart was located in the dogs. To induce a reversible and temporary cardiac arrest in the dogs, the researchers used rectangular pulsed magnetic fields (0.1 ms; 50 Hz) to stimulate the dogs' right vagus nerve. Once arrest was established (after approximately 3 s), electroencephalogram (ECG) and blood-pressure recordings were taken. If the PEMF coils produced an ectopic beat after the dog was in induced cardiac arrest, the voltage was reduced in decrements of 10% until the PEMF no longer evoked ventricular contractions. If, however, no ectopic beat was produced, the voltage was increased by 10% increments until such a beat was produced. The threshold was then defined as the voltage at which 10% less did not stimulate the heart. Results from the study indicated that an average energy of 12 kJ was required to achieve closed-chest ectopic beats via a PEMF. These findings acknowledge the importance of determining safe levels of magnetic fields, and suggest that it is possible to determine safety parameters for PEMF, such as those produced by MRI scanners [66].

12.2 Myocardial Protection

In addition to determining safe levels of PEMF stimulation for the heart, the determination of protective benefits of PEMF treatment for the myocardium would be of great importance to clinicians seeking ways in which to inhibit/ attenuate damage to the heart muscle following reduced oxygen to the area. DiCarlo et al. [67] showed that chick embryos (fertilized White Leghorn eggs) exposed to low-frequency (4-, 6-, 8-, and 10-μT; 60 Hz) PEMFs prior to exposure to an anoxia chamber had significantly increased survival rates (68.7%) relative to the survival rates of control embryos (39.6%) following cardiac anoxia damage. Anoxia was achieved by maintaining oxygen levels below 1% during the experiment. The embryos were subsequently re-exposed to ambient oxygen levels (21%) at the time at which 15% - 45% of control embryo hearts were still beating. Survival was objectively determined as the presence of a heart beat [68]. Further investigations revealed that the protection was due to the PEMF itself, and not due to thermal heating. This research provides encouraging results for human clinical studies, suggesting that preconditioning a human with exposure to PEMF stimulation prior to surgery and transplantation might minimize myocardial damage [67].

Human research, investigating methods in which the myocardium can be protected, is essential to enable potential longevity of human lives. Ischemia (interruption of blood flow) - reperfusion (reintroduction of blood flow) injuries to organs, such as the heart, have potential detrimental effects such as lack of oxygen that can kill ischemic cells, and subsequent reperfusion can introduce harmful oxygen radicals into the organ. Preconditioning a tissue with a non-lethal ischemia-reperfusion (I/R) can help protect the tissue from later, more fatal I/R events. Preconditioning a vital organ by inducing mild heat shock to the tissue or by exposing the tissue to electromagnetic fields helps to protect the organ from subsequent heat shocks [67, 69]. Heat-shock proteins produce heat-shock preconditioning; these proteins act to protect the cell from excess heat, free oxygen radicals, and I/R, and are important for a cell's survival [70, 71]. Heat-shock proteins produced in the presence of PEMFs [72] provide an alternative to other induction methods that are harmful and use non-localized stimuli, such as hyperthermia, or are controversial, such as gene transfection. The production of heat-shock proteins in specific cells is likely dependent on the magnetic-field susceptibility of those cells. For example, cardiomyocytes appear to be consistently stimulated during 60 Hz, 8 ìT magnetic-field exposure [67, 73, 74]. The magnetic-field exposure time required to provide protection from I/R injuries is also cell-

dependent, and ranges from 20 minutes to several hours [73].

Heat-shock proteins are produced within the body, and provide the potential of protecting myocardial tissue from permanent damage due to I/R. However, a problem with the suggested use of PEMF exposure to induce production of heat-shock proteins is that clinically, patients are unlikely to present themselves prior to ischemia. Nonetheless, since most of the damage to the myocardial cells occurs during reperfusion, there is likely still to be a benefit of heat-shock protein production. Specifically, reperfusion therapy and transplantation cause injury that could be ameliorated with heat-shock proteins. It is still unknown whether cardioprotection is conferred by heat-shock proteins, or whether magnetic-field stimulation might be activating opiate agonists that then protect the cell from further damage [75]. Therefore, there is still much more work that must be done to determine the ultimate protector of cardiac cells, to ensure that the best possible, and most appropriate, treatment options are implemented to prevent further cardiac tissue damage.

13. Psychophysiological Regulation

13.1 Human Standing Balance

Pulsed electromagnetic-field stimulation has been shown to produce detectable physiological and behavioral effects in both animals and humans. The investigation of potential magnetic-field effects on human standing balance (postural sway) is important, since disturbances in this behavioral trait can indicate the presence of underlying diseases [76]. "Normal standing balance," defined as "the ability of a human to stand in a fixed position for a period of time [77]," is an automatic behavior in humans. When performed with "eyes open," little perturbations are noted in standing balance; however, this robust behavior is greatly affected when an individual is in the "eyes closed" state. Thomas et al. [77, 78] have extensively investigated this topic. Using a three-dimensional force plate to measure center-of-pressure movements, these researchers have included an objective measure of a behavioral response. Each subject in their studies was given four two-minute exposure conditions (eyes open/eyes closed, sham/magnetic field). Results from these studies suggested that specific ELF PEMF (200 μT_{pk} , 0.4 T/s; generated at head level) exposure has beneficial effects on standing balance, such that standing balance was improved significantly in both the "eyes-open" and "eyes-closed" conditions during magnetic-field exposure sessions relative to sham exposure sessions. The effect of PEMF exposure on standing balance appeared to be mediated by light intensity during the eyes-closed trials, as movement was significantly increased under low-intensity (0.12 W/m^2), and was decreased under high-intensity (0.51 W/m^2) light [79]. These results held for both genders and for all ages (range: 18 - 34 years), despite past findings that postural sway is sensitive to factors such as age and gender [76].

The influence of magnetic-field exposure on standing balance was affected by a subject's physical condition. Specifically, fibromyalgia patients (FM) and normal controls had similar standing balance during eyes open and sham exposure that was better than the standing balance recorded for rheumatoid-arthritis patients (RA). When eyes were closed, the postural sway of all three groups of subjects deteriorated, but to a greater degree in the two patient groups relative to the controls. Magnetic-field exposure was shown to improve the eyes-closed-to-eyes-open ratio in all three groups of subjects [78]. These results suggest that PEMF exposure has the ability to affect behavioral traits in both healthy controls and chronic pain patients.

14. Pain

Most of the therapeutic uses of magnetic-field exposure include a component of pain reduction; however, there are controversial reports in the literature regarding the effects of magnetic-field exposure on specific investigations of pain. Acute pain, or nociception, can be used as an outcome measure to determine sensitivity to stimuli. Nociception is a measure of an animal's or human's sensitivity to an adverse environmental stimulus. An understanding of how an organism responds to such stimuli enables researchers to determine its capacity to perform adaptive behaviors [80].

There is evidence to suggest that endogenous as well as exogenous opioid systems are affected by exposure to magnetic fields [80, 81, 82, 83, 84, 85]. Early investigations of the use of magnetic-field exposure on subsequent pain sensations revealed increases in pain following exposure sessions. Following knowledge that magnetic-resonance exposure can suppress analgesia in mice that have received morphine injections [83], Prato et al. [86] conducted a study to determine which of the various components of the magnetic field (static, time-varying, radio frequency) were responsible for the inhibitory effects of the exposure. The static component from the resistive magnet was 0.15 T; the time-varying component had peak magnetic fields of 0.4 mT and 0.9 mT, which corresponded to rise times of 2 ms and 3 ms, respectively; and the radio-frequency component at 6.25 MHz was a Gaussian-modulated pulse with widths of either 2 ms or 4 ms. Male mice were exposed to 23.2 min of one of the field components both before and after an injection of morphine sulphate (10 mg/kg), and analgesia was defined as the amount of time during which mice were on a hot surface (50 °C) before they displayed an aversive behavior (paw-lick, jump, etc). Results from the study indicated that exposure to the time-varying (pulsed) component of the magnetic field completely abolished, the radio-frequency component significantly reduced, and the static-field component had no effect on morphine-induced

analgesia. These findings may have relevance to humans who have ingested drugs such as morphine, and are subsequently exposed to these components of the magnetic field during magnetic-resonance imaging [86].

Exposures to hypogeomagnetic and oscillating magnetic fields have also been shown to have inhibitory effects in male mice. Specifically, Del Seppia et al. [85] found that mice removed from the normal geomagnetic field and placed in mu-metal boxes showed suppressed stress-induced analgesia; these mice displayed significantly lower latencies than mice exposed to a normal geomagnetic field. Hypogeomagnetic-field exposed mice displayed an effect similar to that observed in mice after exposure to an oscillating magnetic field. These results suggest that in addition to time-varying PEMFs, the presence of hypogeomagnetic fields also has the ability to reduce stress-induced analgesia.

Further work investigating the inhibitory effect of magnetic-field exposure on analgesia in mice focused on the possible modulatory effect of light [87]. Mice, displaying stress-induced analgesia, were found to have significantly lower analgesic levels following stable magnetic-field exposure (3 - 4 mT) under white light, but unaltered analgesic levels following either red light or total darkness. These results replicated previous findings found using lower magnetic-field intensities [86], and suggest that magnetic-field exposure might exert its effect only under certain light-intensity conditions.

Other early work found similar results in the land snail, Cepaea nemoralis. Specifically, Kavaliers and Ossenkopp [88] determined that 15 - 30 min exposures to weak rotating magnetic fields (0.1 - 0.8 mT; 0.5 Hz) inhibited analgesia from opioid agonists. (Absence of analgesia was previously reported in mice following exposure to a similar magnetic field [89]). The latency of nociceptive responses (the elevation of the snail's anterior portion of its extended foot) was shown to increase following the administration of opioid agonists (morphine and U-50, 488H, respectively); however, the concurrent application of an opioid agonist and magnetic-field exposure resulted in significantly reduced nociceptive responses, indicating significant inhibitory effects of magnetic-field exposure on opioid-mediated analgesia. The reduction in opioid-induced analgesia apparent with the magnetic-field exposure sessions was similar to that observed following opioid-antagonist (naloxone) injections [88]. Exposing the snails to 0.1 mT_{rms} , 60 Hz magnetic fields yielded similar results, with reduced opioid-induced analgesia present following magnetic-field exposure sessions. This finding was upheld for a variety of magnetic-field exposure periods (0.5 - 120 hours), and the inhibitory effect was significantly greatest during the dark period of the snail's light-dark cycle [80]. Snails that received daily administrations of naloxone, an opioid antagonist, experienced increased opioid-induced analgesia in a manner similar to that apparent following the magnetic-field exposures [84]. A possible mediating variable that could explain the magnetic field's inhibitory effect on opioid-agonist analgesia is altered calcium channel activity. Calcium-channel antagonists, such as diltiazem, verapamil, and nifedipine, significantly reduced, but did not completely block the inhibitory effects of the magnetic fields on morphine-induced analgesia, while calcium-channel agonists, such as BAY K8644, further inhibited the effects of morphine-induced analgesia that were present with magnetic-field exposure [88]. Administration of either the calcium-channel antagonists or the calcium-channel agonists had no significant effect on the reductions in opioid-induced analgesia achieved by injections of naloxone. It is possible that magnetic-field exposure alters calcium-channel functioning, resulting in differential distribution of calcium ions. This finding was supported by research conducted by Fanelli et al. [90], who showed that exposure to static magnetic fields prevented apoptosis via the flux of calcium into U937 and CEM cells. McCreary et al. [91] provided further support for the change in calcium-ion concentrations following magnetic-field exposure; these authors reported significant changes in cytosolic calcium concentrations following exposure to alternating-current (AC), direct-current (DC), or a combination of AC/DC magnetic fields after cell cycle, pH of suspension medium, and response to monoclonal antibody were controlled. These findings support the possibility that redistribution of calcium ions may have an effect on the functioning of opiates such as morphine [92].

The inhibitory effect of exposure to magnetic fields on analgesic responses was a consistent finding among many researchers. Studies conducted on pigeons [93] found that exposure to weak, oscillating magnetic fields (sinusoidal; continuous induced magnetic flux between +70 and – 20 μT) resulted in hyperalgesia, or heightened sensitivity, to a painful electrical stimulation. The pigeons, when exposed to these specific magnetic-field parameters, displayed significantly decreased thresholds to the electrical stimuli following magnetic-field exposure. In comparison, control pigeons not exposed to the magnetic fields displayed significantly increased thresholds to the stimuli over time, attributable to the formation of stress-induced analgesia. Using the same magnetic-field parameters as in the study on pigeons, Papi et al. [94] reported that humans experienced increased sensitivity, observed via decreased thresholds, following magnetic-field exposure relative to the sham condition. Specifically, assessment of dental sensory threshold (DST), dental-pain threshold (DPT), cutaneous sensory threshold (CST), cutaneous pain threshold (CPT), and cutaneous tolerance value (CTV), revealed no significant change in value for any of these measurements between pre- and post-sham conditions. However, when the same measurements were assessed in the same subjects before and after magnetic-field exposure, significant decreases were observed in the DST, CPT, and CTV measurements post-exposure. These two studies investigating the use of sinusoidal magnetic field exposures on pain sensitivity in pigeons and humans extend past research in showing that in addition to pain sensitivity in animals, such sensitivity in

humans is also negatively affected by magnetic-field exposure.

In contrast to these aforementioned studies, further research has discovered that exposure to magnetic fields does, in fact, have positive pain-relieving, anti-nociceptive, effects. For example, Thomas et al. [95] found that 15-min exposures to an ELFMF (100 μT_{pk}, 0.4 T/s) in land snails induced analgesia, and increased opioid-induced analgesia, rather than producing inhibitory effects. Subsequent injection of an opioid antagonist, naloxone, resulted in a reduced, but not completely abolished, analgesia effect. These results demonstrate the anti-nociceptive action of a specific PEMF via an endogenous opioid mechanism. Specifically, the ability of naloxone to reduce, but not abolish, the analgesia effect suggests the presence of at least partial δ-opioid receptor mediation [96]. Furthermore, the ability of the specific PEMF – but not of the random or burstx PEMFs also tested in the study – to induce analgesia suggests that the opioid analgesia did not arise from a non-specific magnetic-field stress response, but rather seemed to be related to the specific ELF magnetic field pulse form [95].

Further investigation of the effects of the specific PEMF exposure on inducing and augmenting opioid-induced analgesia involved the development of tolerance. Tolerance is defined as reduced drug effectiveness that presents itself following repeated drug exposure. Kavaliers and Ossenkopp showed that tolerance to opioid agonists (e.g., morphine) was reduced if animals are exposed to rotating magnetic fields prior to morphine injections, for animals that had not developed complete tolerance, and that environmental cues provided by magnetic stimuli were important determinants of development of tolerance [97]. Tolerance is apparent in land snails following five to seven days of repeated administration of morphine, and can also extend to other, similar opioids, via an effect known as cross-tolerance [98]. Thomas et al. [98] studied the effects of tolerance to the δ-opioid receptor agonist DPDPE, (D-Pen^2, D-Pen^5) enkephalin in land snails, and found that the magnitude and duration of the magnetic-field-induced analgesia was reduced following repeated (six days - nine days) daily (15 or 30-min) exposures: an effect indicative of the development of tolerance. The same effect of tolerance was present if snails received the nociceptive testing (assessed via the hot-plate test of latency) each day, or only on the first and last days. The effect was nearly completely removed when the land snails were presented with novel environmental cues. Furthermore, snails that received repeated daily exposures of the specific PEMF (100 μT_{pk}) displayed reduced sensitivity to the δ-opioid receptor agonist DPDPE. This reduced sensitivity provides evidence for the development of cross-tolerance of DPDPE to the opioid component of the PEMF [98]. Overall, these results provided insight into the development of tolerance and how magnetic-field exposure sessions can have (negative) effects similar to those of repeated drug administrations. This has great relevance for human clinical trials, as drug tolerance is known to be a problem among humans.

A discrepancy with respect to the effect of ELF magnetic-field exposure on land snails exists, as such exposure sessions have been shown to both increase [95, 96, 98] and decrease [88, 84, 92] analgesia. A possible mediating variable that explains the inconsistency in the literature is the presence of light, as opposed to dark, field conditions [99]. Prato et al. showed that the increases and decreases in opioid analgesia associated with magnetic-field exposure were consistent with the predictions of Lednev's parametric-resonance model (PRM) for the calcium ion [99]. Refer to Section 16.1 for a further explanation of potential mechanisms of action.

The results of increased analgesia following magnetic-field exposure extend beyond the work done on land snails. Briefly, it has also been shown that exposure to a pulsed magnetic field (5 μT burst firing pattern; 1 s on, 4 s off; 20 min) resulted in increased analgesia in female rats, as evaluated via flinch thresholds to electric shock. The analgesia seen was a 50% increase in flinch threshold, and was greater than that seen following the administration of a dose (4 mg/kg) of morphine [100].

In addition to animal research, human research has begun to reveal positive effects of magnetic-field exposure. Sartucci et al. [101] examined the effect of weak, oscillating magnetic-field exposure (constant-current rectangular pulses; 0.5 Hz; 0.1 ms duration; 70 to –20 μT) on human pain perception and pain-related somatosensory evoked potentials (SEPs). Pain thresholds were reduced, and pain-related SEPs were significantly reduced, following magnetic-field exposure; pain thresholds were significantly increased following sham sessions. These results provide the first evidence that human SEPs are influenced by magnetic-field exposure. Ongoing work in our lab is investigating other possible effects of pulsed magnetic-field exposure on human pain perception and analgesia.

15. Discussion and Concluding Remarks

This paper has discussed the effectiveness of magnetic-field stimulation as a treatment for a variety of health-related conditions. To date, of the articles included in this review, magnetic-field stimulation was shown to be effective for treatment of bone disorders (osteotomies, non-union bone fractures, congenital Pseudoarthrosis, bone formation, hip arthroplasty), joint disorders (including rheumatoid arthritis and osteoarthritis), rotator-cuff tendonitis, spinal fusions (including Pseudoarthrosis and interbody lumbar fusions), pelvic pain, neurological disorders (e.g., multiple sclerosis, tinnitus), nerve (median-ulnar, peroneal, sciatic) regeneration, endocrine ophthalmopathy, cancer, focal ischemia, cardiac and myocardial protection, and human standing balance. Stimulation was ineffective for treatment of Perthes Disease and lateral humeral epicondylitis. Magnetic-field stimulation is as yet inconclusive as an effective treatment for conditions such as osteoporosis,

venous leg ulcers, imbalance of the neuroendocrine system (including hormone production and melatonin levels), and pain.

The preceding summary of results discussed in this paper indicates the great success of magnetic-field stimulation in treating a variety of conditions and disorders. Given the study outcomes, the next logical step in understanding what other medical conditions might benefit from this treatment requires a detailed analysis of the mechanisms of action that underlie this form of treatment. The following section will discuss possible mechanisms by which magnetic-field therapy is suggested to work.

15.1 Possible Mechanisms of Action

As can be appreciated from this review, there is a very significant body of literature that supports the idea that therapeutic effects can be achieved from ELF magnetic-field exposure. However, except for application to orthopedics (i.e. non-unions), these therapies have not been accepted as conventional medical practice. One of the reasons is that positive results are often not confirmed when a replication attempt is made, and different magnetic-field exposure conditions are often used. As there are infinite combinations of ELF magnetic-field parameters to choose from, the optimization of treatment regimens is very difficult given the lack of a predictive theoretical framework. This is made more difficult by the nature of the measured endpoints: changing one exposure parameter would require at least two exposure groups along with a sham control where patients must be treated for months (at hours per day), making such experiments strategically and financially almost impossible. Hence, it is not surprising that mechanism discovery has been difficult. However, progress has been made and new tools associated with molecular biology and medical imaging could dramatically accelerate the discovery of mechanism.

What do we mean by mechanism? In this field we are faced with a real challenge, because the mechanism to be discovered includes two discrete steps: a) the initial biophysical mechanism by which the ELF magnetic field is detected and converted to a biological signal; and b) the cascade of events by which the initial biological signal results in the behavioral/physiological event.

For the determination of the initial biophysical detection mechanism, it is generally accepted that the responding system can be treated as a black box. The parameters of the ELF magnetic field can be stepwise changed and the response measured. As there are infinite numbers of possible field combinations, it is helpful to start with some a priori concepts so that exposure conditions can be first set to discriminate between fundamentally different mechanisms, and then further experiments can select between similar mechanisms. For ELF magnetic fields with the parameters used in therapy that have been reviewed here, there are two fundamentally different biophysical transduction mechanisms: induced current and magnetic dipole. The induced current assumes that the time-changing magnetic field induces a current in the conductive tissue (Faraday's Law of Induction). In comparison, the applied magnetic fields could interact directly with the magnetic fields in the tissue associated with an endogenous magnet (e.g., magnetite) or with the magnetic moment produced by a nucleus, atom, or molecule [102]. Engstrom [103] and Engstrom and Fitzsimmons [104] have demonstrated that a limited number of experiments (i.e., five) would be needed. Perhaps the best example of this kind of approach has been undertaken by Prato et al. (see Table 3; [99, 105, 106, 107, 108, 109, 110, 111]). This work suggests that the magnetic fields were detected by a magnetic molecular dipole. However, in the work on snails, using a much different pulse, Thomas et al. [95, 96, 98] presented evidence suggesting that it is an induced-current mechanism. Hence, modification of opioid-like behaviors in land snails using two different magnetic fields (both in the ELF) may involve two very different mechanisms! Note that this work on land snails has been possible in large part because hundreds of animals could be studied in a few hours. A similar approach to study, for example, bone healing in humans would be all but impossible. A different approach is needed if significant mechanism discovery is to be achieved in the majority of therapeutic applications, and especially if validation is to be done in humans.

Fortunately, two significant developments over the last decade have made it possible to dissect the mechanisms, both at the detection/transduction stage and to follow the events to the final behavioral/physiological outcome. These are the combined advances in molecular biology and non-invasive imaging, resulting in the field of molecular imaging.

For example, in 1981 the first commercial bone-density units were being used to evaluate treatments for osteoporosis, but relatively large groups had to be followed for years because of the uncertainty in the measurements. Twenty years later, the success of treatment in a single woman can be determined in six to 12 months. Not only do such advances allow the evaluation of mechanism, but they also allow the fine-tuning of therapy for the individual patient. In the future, ELF magnetic-field therapy will be image-guided. For example, in the treatment of patients with unipolar depression with transcranial magnetic stimulation, positron-emission tomography studies of brain blood flow and metabolism can predict the effectiveness of different magnetic-field parameters, the targeting of different brain structures, and the effectiveness of therapy in the individual patient [112]. These imaging methods are powerful. For example, Huber et al. [113] demonstrated that subtle differences in brain microwave irradiation resulted in significant differences in EEG and regional cerebral blood flow as measured with PET. In the future, advances in molecular imaging, such as the identification of number and activity of opioid receptors [114, 115], will allow

Experiment	Mechanism				Reference
	Induced Current	Free Radical	Magnetite	Parametric Resonance	
Variation of B_{AC} at 60 Hz	x	-	-	✓	Prato et al. 1995 [108]
Variation of frequency for B_{AC} and B_{DC}	x	x	-	✓	Prato et al. 1995 [108]
Variation of angle between B_{AC} and B_{DC}	x	-	x	✓	Prato et al. 1996a [109]
Variation B_{AC} and B_{DC} at 30 Hz	x	x	x	✓	Prato et al. 2000 [102]
Variation of angle between B_{AC} and B_{DC} in light and dark	-	-	x	-	Prato et al. 1996b [110]
Investigation of light/dark effects at 30, 60, 120 Hz	x	x	-	✓	Prato et al. 1997 [111]
Investigation of light/dark effects during day/night	-	-	-	✓	Prato et al. 1998 [112]
Role of nitric oxide synthase and related light/dark effects	-	-	-	✓	Kavaliers et al. 1998 [113], and Kavaliers & Prato 1999 [114]

✓ mechanism supported
x mechanism not supported
- mechanisms neither supported nor unsupported

Table 3: Summary of Evidence Supporting the Parametric Resonance Model as the Detection Mechanism Associated with ELF Magnetic Field Modulation of Opioid-Induced Analgesia

individual tailoring of pulsed ELF PEMFs in the treatment of pain.

Non-invasive anatomical, functional and molecular imaging will provide the platform by which elucidation of mechanisms will be possible and optimization of the treatment for the individual will be routine; these advances will result in a very significant acceptance of magnetic-field therapy for a wide variety of conditions.

15.2 Conclusion

There are many questions that require answers prior to the general acceptance of magnetic-field therapy as a primary treatment, rather than its use mainly as an adjunct therapy. For example, controlled, randomized, and double-blind studies must be used to assess optimal magnetic-field conditions and average duration of effect [4] in producing the best possible treatment. Furthermore, the cost-effectiveness of this form of therapy with respect to more traditional treatment protocols (e.g., non-steroidal anti-inflammatory drugs, analgesics, and massage) must be evaluated prior to use.

Difficulties in bioelectromagnetic research include the inability to reproduce and replicate work conducted in other laboratories. Furthermore, the lack of concrete mechanisms of action has impeded research regarding therapeutics [2]. Through continued research, and more solidified mechanisms of action, it is hoped that the therapeutic value currently associated with some ELF magnetic fields will become a mainstream intervention.

16. References

1. J. Juutilainen and S. Lang, "Genotoxic, Carcinogenic and Teratogenic Effects of Electromagnetic Fields: Introduction and Overview," *Mutation Research*, **387**, 1997, pp. 165-171.

2. B. Rubik, "Bioelectromagnetics & the Future of Medicine," *Administrative Radiology Journal*, **16**, 8, 1997, pp. 38-46.

3. C. Polk and E. Postow (eds.), *CRC Handbook of Biological Effects of Electromagnetic Fields*, Boca Raton, FL, CRC Press, 1986.

4. C. Vallbona and T. Richards, "Evolution of Magnetic Therapy from Alternative to Traditional Medicine," *Physical Medicine and Rehabilitation Clinics of North America*, **10**, 3, 1999, pp. 729-754.

5. J. Hulme, V. Robinson, R. DeBie, G. Wells, M. Judd, and P. Tugwell, "Electromagnetic Fields for the Treatment of Osteoarthritis," *(Cochrane Review), Cochrane Library*, **3**, Oxford, Update Software, 2002.

6. C. A. Bassett, "Fundamental and Practical Aspects of Therapeutic Uses of Pulsed Electromagnetic Fields (PEMFs)," *Critical Reviews in Biomedical Engineering*, **17**, 5, 1989, pp. 451-529.

7. D. H. Trock, "Electromagnetic Fields and Magnets: Investigational Treatment for Musculoskeletal Disorders," *Rheumatic Disease Clinics of North America*, **26**, 1, 2000, pp. 51-62.

8. C. J. Hannan Jr., Y. Liang, J. D. Allison, C. G. Pantazis, and J. R. Searle, "Chemotherapy of Human Carcinoma Xenografts during Pulsed Magnetic Field Exposure," *Anticancer Research*, **14**, 1994, pp. 1521-1524.

9. M. J. Stiller, G. H. Pak, J. L. Shupack, S. Thaler, C. Kenny, and L. Jondreau, "A Portable Pulsed Electromagnetic Field (PEMF) Device to Enhance Healing of Recalcitrant Venous Ulcers: A Double-blind, Placebo-controlled Clinical Trial," *British Journal of Dermatology*, **127**, 1992, pp. 147-154.

10. G. C. Traina, L. Romanini, F. Benazzo, R. Cadossi, V. Canè, A. Chiabrera, M. Marcer, N. Marchetti, and F. S. Snatori, "Use of Electric and Magnetic Stimulation in Orthopaedics and Traumatology: Consensus Conference," *Italian Journal of Orthopaedics and Traumatology*, **24**, 1, 1998, pp. 1-31.

11. C. A. L. Bassett, "Beneficial Effects of Electromagnetic Fields," *Journal of Cellular Biochemistry*, **51**, 1993, pp. 387-393.

12. G. K. Frykman, J. Taleisnik, G. Peters, R. Kaufman, B. Helal, V. E. Wood, and R. S. Unsell, "Treatment of Nonunited Scaphoid Fractures by Pulsed Electromagnetic Field and Cast," *The Journal of Hand Surgery*, **11A**, 1986, pp. 334-349.

13. J. D. Heckman, A. J. Ingram, R. D. Loyd, J. V. Luck Jr., and P. W. Mayer, "Nonunion Treatment with Pulsed Electromagnetic Fields," *Clinical Orthopaedics and Related Research*, **161**, 1981, pp. 58-66.

14. N. Pipitone and D. L. Scott, "Magnetic Pulse Treatment for Knee Osteoarthritis: A Randomised, Double-blind, Placebo-controlled Study," *Current Medical Research and Opinions*, **17**, 3, 2001, pp. 190-196.

15. R. A. Luben, "Effects of Low-energy Electromagnetic Fields (pulsed and DC) on Membrane Signal Transduction Processes in Biological Systems," *Health Physics*, **61**, 1, 1991, pp. 15-28.

16. C. A. L. Bassett and M. Schink-Ascani, "Long-term Pulsed Electromagnetic Field (PEMF) Results in Congenital Pseudarthrosis," *Calcified Tissue International*, **49**, 1991, pp. 216-220.

17. M. A. Darendeliler, A. Darendeliler, and P. M. Sinclair, "Effects of Static Magnetic and Pulsed Electromagnetic Fields on Bone Healing," *International Journal of Adult Orthodontic and Orthognathic Surgery*, **12**, 1, 1997, pp. 43-53.

18. C. A. L. Bassett, R. J. Pawluk, and A. A. Pilla, "Acceleration of Fracture Repair by Electromagnetic Fields: A Surgically Non-invasive Method," *Annals of the New York Academy of Sciences*, **238**, 1974, pp. 242-262.

19. C. A. L. Bassett, R. J. Pawluk, and A. A. Pilla, "Augmentation of Bone Repair by Inductively Coupled Electromagnetic Fields," *Science*, **184**, 136, 1974, pp. 575-577.

20. C. A. L. Bassett, A. A. Pilla, and R. J. Pawluk, "A Non-operative Salvage of Surgically-Resistant Pseudarthroses and Non-unions by Pulsing Electromagnetic Fields," *Clinical Orthopaedics and Related Research*, **124**, 1977, pp. 128-143.

21. D. R. Godley, "Nonunited Carpal Scaphoid Fracture in a Child: Treatment with Pulsed Electromagnetic Field Stimulation," *Orthopedics*, **20**, 8, 1997, pp. 718-719.

22. A. T. Barker, R. A. Dixon, W. J. Sharrard, and M. L. Sutcliffe, "Pulsed Magnetic Field Therapy for Tibial Non-union: Interim Results of a Double-blind Study," *Lancet*, **1**, 8384, 1984, pp. 994-996.

23. G. De Haas, M. A. Lazarovici, and D. M. Morrison, "The Effect of Low Frequency Magnetic Fields on the Healing of the Osteotomized Rabbit Radius," *Clinical Orthopaedics and Related Research*, **145**, 1979, pp. 245-251.

24. H. Matsumoto, M. Ochi, Y. Abiko, Y. Hirose, T. Kaku, K. Sakaguchi, "Pulsed Electromagnetic Fields Promote Bone Formation around Dental Implants Inserted into the Femur of Rabbits," *Clinical Oral Implants Research*, **11**, 2000, pp. 354-360.

25. F. Tabrah, M. Hoffmeier, F. Gilbert Jr., S. Batkin, and C. A. L. Bassett, "Bone Density Changes in Osteoporosis-prone Women Exposed to Pulsed Electromagnetic Fields (PEMFs)," *Journal of Bone and Mineral Research*, **5**, 5, 1990, pp. 437-442.

26. K. Konrad, K. Sevcic, K. Fõldes, E. Piroska, and E. Molnár, "Therapy with Pulsed Electromagnetic Fields in Aseptic Loosening of Total Hip Prostheses: A Prospective Study," *Clinical Rheumatology*, **15**, 4, 1996, pp. 325-328.

27. M. H. M. Harrison and C. A. L. Bassett (deceased), "The Results of a Double-blind Trial of Pulsed Electromagnetic Frequency in the Treatment of Perthes' Disease," *Journal of Pediatric Orthopaedics*, **17**, 1997, pp. 264-265.

28. E. R. Sanseverino, A. Vannini, and P. Castellacci, "Therapeutic Effects of Pulsed Magnetic Fields on Joint Diseases," *Panminerva Medica*, **34**, 4, 1992, pp. 187-196.

29. K. S. Gunguly, A. K. Sarkar, A. K. Datta, and A. Rakshit, "A Study of the Effects of Pulsed Electromagnetic Field Therapy with Respect to Serological Grouping in Rheumatoid Arthritis," *Journal of the Indian Medical Association*, **96**, 9, 1998, pp. 272-275.

30. J. I. Jacobson, R. Gorman, W. S. Yamanashi, B. B. Saxena, and L. Clayton, "Low-amplitude, Extremely Low Frequency Magnetic Fields for the Treatment of Osteoarthritic Knees: A Double-blind Clinical Study," *Alternative Therapies*, **7**, 5, 2001, pp. 54-69.

31. B. Rubik, R. O. Becker, R. G. Flower, C. F. Hazlewood, A. R. Liboff, and J. Walleczek, "Bioelectromagnetics: Applications in medicine," in B. M. Berman, D. B. Larson, et al., *Alternative Medicine, Expanding Medical Horizons*, NIH Publication No. 94-066, Washington, DC, US Government Printing Office, 1994.

32. A. Binder, G. Parr, B. Hazleman, and S. Fitton-Jackson, "Pulsed Electromagnetic Field Therapy of Persistent Rotator Cuff Tendinitis: A Double-blind Controlled Assessment," *The Lancet*, **1**, 8379, 1984, pp. 695-698.

33. M. D. Devereaux, B. L. Hazleman, and P. P. Thomas, "Chronic Lateral Humeral Epicondylitis - A Double-blind Controlled Assessment of Pulsed Electromagnetic Field Therapy," *Clinical and Experimental Rheumatology*, **3**, 1985, pp. 333-336.

34. R. A. Marks, "Spine Fusion for Discogenic Low Back Pain: Outcomes in Patients Treated with or without Pulsed Electromagnetic Field Stimulation," *Advances in Therapy*, **17**, 2, 2000, pp. 57-67.

35. P. A. Glazer, M. R. Heilmann, J. C. Lotz, and D. S. Bradford, "Use of Electromagnetic Fields in a Spinal Fusion: A Rabbit Model," *Spine*, **22**, 1997, pp. 2351-2356.

36. V. Mooney, "A Randomized Double-blind Prospective Study of the Efficacy of Pulsed Electromagnetic Fields for Interbody Lumbar Fusions," *Spine*, **15**, 7, 1990, pp. 708-712.

37.K. Flemming and N. Cullum, "Electromagnetic Therapy for Treating Venous Leg Ulcers" *(Cochrane Review),. Cochrane Library*, **3**, Oxford, Update Software, 2002.

38.M. Ieran, S. Zaffuto, M. Bagnacani, M. Annovi, A. Moratti, and R. Cadossi, "Effect of Low Frequency Pulsing Electromagnetic Fields on Skin Ulcers of Venous Origin in Humans: A Double-blind Study," *Journal of Orthopaedic Research*, **8**, 2, 1990, pp. 276-282

39.W. A. Jorgensen, B. M. Frome, and C. Wallach, "Electrochemical Therapy of Pelvic Pain: Effects of Pulsed Electromagnetic Fields (PEMF) on Tissue Trauma," *The European Journal of Surgery*, **574** (Supplement), 1994, pp. 83-86.

40.B. F. Sisken, J. M. Jacob, and J. L. Walker, "Acute Treatment With Pulsed Electromagnetic Fields and Its Effect on Fast Axonal Transport in Normal and Regenerating Nerve," *Journal of Neuroscience Research*, **42**, 1995, pp. 692-699.

41.D. H. Wilson and P. Jagadeesh, "Experimental Regeneration in Peripheral Nerves and the Spinal Cord in Laboratory Animals Exposed to a Pulsed Electromagnetic Field," *Paraplegia*, **14**, 1976, pp. 12-20.

42.A. M. Raji, "An Experimental Study of the Effects of Pulsed Electromagnetic Field (Diapulse) on Nerve Repair," *The Journal of Hand Surgery*, **9-B**, 2, 1984, pp. 105-112.

43.M. Kanje, A. Rusovan, B. Sisken, and G. Lundborg, "Pretreatment of Rats with Pulsed Electromagnetic Fields Enhances Regeneration of the Sciatic Nerve," *Bioelectromagnetics*, **14**, 1993, pp. 353-359.

44.B. F. Sisken, M. Kanje, G. Lundborg, E. Herbst, and W. Kurtz, "Stimulation of Rat Sciatic Nerve Regeneration with Pulsed Electromagnetic Fields," *Brain Research*, **485**, 1989, pp. 309-316.

45.B. F. Sisken, J. Walker, and M. Orgel, "Prospects on Clinical Applications of Electric Stimulation for Nerve Regeneration," *Journal of Cellular Biochemistry*, **52**, 1993, pp. 404-409.

46.J. Jankauskienë, A. Paunksnis, A. Bluþienë, and J. Saulgozis, "The Effect of Pulsed Electromagnetic Field on Patients with Endocrine Ophthalmopathy," *European Journal of Ophthalmology*, **8**, 4, 1998, pp. 253-257.

47.T. L. Richards, M. S. Lappin, J. Acosta-Urquidi, G. H. Kraft, A. C. Heide, F. W. Lawrie, T. E. Merrill, G. B. Melton, and C. A. Cunningham, "Double-blind Study of Pulsing Magnetic Field Effects on Multiple Sclerosis," *The Journal of Alternative and Complementary Medicine*, **3**, 1, 1997, pp. 21-29.

48.N. J. Roland, J. B. Hughes, M. B. Daley, J. A. Cook, A. S. Jones, and M. S. McCormick, "Electromagnetic Stimulation as a Treatment of Tinnitus: A Pilot Study," *Clinical Otolaryngology and Applied Sciences*, **18**, 1993, pp. 278-281.

49.M. S. George, F. R. Sallee, Z. Zahas, N. C. Oliver, and E. M. Wassermann, "Transcranial Magnetic Stimulation (TMS) as a Research Tool in Tourette Syndrome and Related Disorders," *Advances in Neurology*, **85**, 2001, pp. 225-235.

50.R. J. Ilmoniemi and J. Karhu, "Transcranial Magnetic Stimulation – Towards Navigated Targeting," *Business Briefing: Global Healthcare*, **3**, 2002, pp. 1-4.

51.M. S. George, E. M. Wassermann, and R. M. Post, "Transcranial Magnetic Stimulation: A Neuropsychiatric Tool for the 21st Century," *Journal of Neuropsychiatry*, **8**, 4, 1996, pp. 373-382.

52.E. M. Wassermann and S. H. Lisanby, "Therapeutic Application of Repetitive Transcranial Magnetic Stimulation: A Review," *Clinical Neurophysiology*, **112**, 2001, pp. 1367-1377.

53.K. Mann, P. Wagner, G. Brunn, F. Hassan, C. Hiemke, and J. Rõschke, "Effects of Pulsed High-frequency Electromagnetic Fields on the Neuroendocrine System," *Neuroendocrinology*, **67**, 1998, pp. 139-144.

54.G. R. Warman, H. Tripp, J. English, and J. Arendt, "Effects of 50 Hz EMF on the Human Melatonin Profile," in 24th Annual Bioelectromagnetics Meeting Abstract Book, 2002, (available from The Bioelectromagnetics Society, 2412 Cobblestone Way, Frederick, MD 21702 USA), p. 251.

55.R. J. Reiter, "A Review of Neuroendocrine and Neurochemical Changes Associated with Static and Extremely Low Frequency Electromagnetic Field Exposure," *Integrative Physiological and Behavioral Science*, **28**, 1, 1993, pp. 57-75.

56.R. J. Reiter, "Reported Biological Consequences Related to the Suppression of Melatonin by Electric and Magnetic Field Exposure," *Integrative Physiological and Behavioral Science*, **30**, 4, 1995, pp. 314-330.

57.M. Karasek, M. Woldanska-Okonska, J. Czernicki, K. Zylinska, and J. Swietoslawski, "Influence of Low-frequency Magnetic Field of Different Characteristics on Serum Melatonin Concentrations in Humans," *Advances in Experimental Medicine and Biology*, **460**, 1999, pp. 459-462.

58.M. Karasek, J. Czernicki, M. Woldanska-Okonska, K. Zylinska, and J. Swietoslawski, "Chronic Exposure to 25 - 80 µT, 200 Hz Magnetic Field Does Not Influence Serum Melatonin Concentrations in Patients with Low Back Pain," *Journal of Pineal Research*, **29**, 2000, pp. 81-85.

59.A. Bellossi and A. Desplaces, "Effect of a 9 mT Pulsed Magnetic Field on C3H/Bi Female Mice with Mammary Carcinoma: A Comparison between the 12 Hz and the 460 Hz Frequencies," *In Vivo*, **5**, 1991, pp. 39-40.

60.C. D. Williams, M. S. Markov, W. E. Hardman, and I. L. Cameron, "Therapeutic Electromagnetic Field Effects on Angiogenesis and Tumor Growth," *Anticancer Research*, **21**, 6A, 2001, pp. 3887-3891.

61.R. de Seze, S. Tuffet, J-M. Moreau, and B. Veyret, "Effects of 100 mT Time Varying Magnetic Fields on the Growth of Tumors in Mice," *Bioelectromagnetics*, **21**, 2000, pp. 107-111.

62.Y. Omote, M. Hosokawa, M. Komatsumoto, T. Namieno, S. Nakajima, Y. Kubo, and H. Kobayashi, "Treatment of Experimental Tumors with a Combination of a Pulsing Magnetic Field and an Antitumor Drug," *Japanese Journal of Cancer Research*, **81**, 1990, pp. 956-961.

63.Y. Liang, C. J. Hannan, B. K. Chang, and P. V. Schoenlein, "Enhanced Potency of Daunorubicin against Multidrug Resistant Subline KB-ChR-8-5-11 by a Pulsed Magnetic Field," *Anticancer Research*, **17**, 1997, pp. 2083-2088.

64.J. G. Robison, A. R. Pendleton, K. O. Monson, B. K. Murray, and K. L. O'Neill, "Decreased DNA Repair Rates and Protection from Heat Induced Apoptosis Mediated by Electromagnetic Field Exposure," *Bioelectromagnetics*, **23**, 2002, pp. 106-112.

65.G. Grant, R. Cadossi, and G. Steinberg, "Protection against Focal Cerebral Ischemia following Exposure to a Pulsed Electromagnetic Field," *Bioelectromagnetics*, **15**, 1994, pp. 205-216.

66.G. A. Mouchawar, J. D. Bourland, J. A. Nyenhuis, L. A. Geddes, K. S. Foster, J. T. Jones, and G. P. Graber, "Closed-chest Cardiac Stimulation with a Pulsed Magnetic Field," *Medical & Biological Engineering & Computing*, **30**, 1992, pp. 162-168.

67.A. L. DiCarlo, J. M. Farrell, and T. A. Litovitz, "Myocardial Protection Conferred by Electromagnetic Fields," *Circulation*, **99**, 6, 1999, pp. 813-816.

68.A. L. DiCarlo, J. M. Farrell, and T. A. Litovitz, "A Simple Experiment to Study Electromagnetic Field Effects: Protection Induced by Short-term Exposures to 60 Hz Magnetic Fields," *Bioelectromagnetics*, **19**, 1998, pp. 498-500.

69.J. M. Shallom, A. L. DiCarlo, D. Ko, L. M. Penafiel, A. Nakai, and T.A. Litovitz, "Microwave Exposure Induces HSP70 and Confers Protection Against Hypoxia in Chick Embryos," *Journal of Cellular Biochemistry*, **86**, 2002, pp. 490-496.

70.L. H. E. H. Snoeckx, R. N. Cornelussen, F. A. Van Nieuwenhoven, R. S. Reneman, and G. J. Van der Vusse, "Heat Shock Proteins and Cardiovascular Pathophysiology," *Physiological Reviews*, **81**, 2001, pp. 1461-1497.

71.M. Vayssier and B. S. Polla, "Heat Shock Proteins Chaperoning Life and Death," *Cell Stress & Chaperones*, **3**, 4, 1998, pp. 221-227.

72.H. Lin, M. Blank, and R. Goodman, "A Magnetic Field-Responsive Domain in the Human HSP70 Promoter," *Journal of Cellular Biochemistry*, **75**, 1999, pp. 170-176.

73.S. Carmody, X. L. Wu, H. Lin, M. Blank, H. Skopicki, and R. Goodman, "Cytoprotection by Electromagnetic Field-Induced HSP70: A Model for Clinical Application," *Journal of Cellular Biochemistry*, **79**, 2000, pp. 453-459.

74.A. Albertini, P. Zucchini, G. Noera, R. Cadossi, C. P. Napoleone, and A. Pierangeli, "Protective Effect of Low Frequency Low Energy Pulsing Electromagnetic Fields on Acute Experimental Myocardial Infarcts in Rats," *Bioelectromagnetics*, **20**, 1999, pp. 372-377.

75.H. H. Patel, A. Hsu, and G. J. Gross, "Attenuation of Heat Shock-Induced Cardioprotection by Treatment with the Opiate Receptor Antagonist Naloxone," *American Journal of Physiology: Heart and Circulatory Physiology*, **282**, 2002, pp. H2011-H2017.

76.H. Kollegger, C. Baumgartner, C. Wõber, W. Oder, and L. Deecke, "Spontaneous Body Sway as a Function of Sex, Age, and Vision: Posturographic Study in 30 Healthy Adults," *European Neurology*, **32**, 1992, pp. 253-259.

77.A. W. Thomas, D. J. Drost, and F. S. Prato, "Human Subjects Exposed to a Specific Pulsed (200 μT) Magnetic Field: Effects on Normal Standing Balance," *Neuroscience Letters*, **297**, 2001, pp. 121-124.

78.A. W. Thomas, K. P. White, D. J. Drost, C. M. Cook, F. S. Prato, "A Comparison of Rheumatoid Arthritis and Fibromyalgia Patients and Healthy Controls Exposed to a Pulsed (200 μT) Magnetic Field: Effects on Normal Standing Balance," *Neuroscience Letters*, **309**, 2001, pp. 17-20.

79.F. S. Prato, A. W. Thomas, and C. M. Cook, "Human Standing Balance is Affected by Exposure to Pulsed ELF Magnetic Fields: Light Intensity-dependent Effects," *NeuroReport*, **12**, 7, 2001, pp. 1-5.

80.M. Kavaliers and K.-P. Ossenkopp, "Opioid Systems and Magnetic Field Effects in the Land Snail, Cepaea nemoralis," *Biological Bulletin*, **180**, 1991, pp. 301-309.

81.E. Choleris, C. Del Seppia, A. W. Thomas, P. Luschi, S. Ghione, G.R. Moran, and F. S. Prato, "Shielding, but not Zeroing of the Ambient Magnetic Field Reduces Stress-induced Analgesia in Mice," *Proceedings of the Royal Society of London, Series B: Biological Sciences*, **269**, 2002, pp. 193-201.

82.J. H. Jeong, K. B. Choi, B. C. Yi, C. H. Chun, K. -Y. Sung, J. -Y. Sung, Y. -M. Gimm, I. H. Huh, and U. D. Sohn, "Effects of Extremely Low Frequency Magnetic Fields on Pain Thresholds in Mice: Roles of Melatonin and Opioids," *Journal of Autonomic Pharmacology*, **20**, 2000, pp. 259-264.

83.K. -P. Ossenkopp, M. Kavaliers, F. S. Prato, G.C. Teskey, E. Sestini, and M. Hirst, "Exposure to Nuclear Magnetic Resonance Imaging Procedure Attenuates Morphine-induced Analgesia in Mice," *Life Sciences*, **37**, 16, 1985, pp. 1507-1514.

84.M. Kavaliers and K.-P. Ossenkopp, "Repeated Naloxone Treatments and Exposures to Weak 60-Hz Magnetic Fields have 'Analgesic' Effects in Snails," *Brain Research*, **620**, 1993, pp. 159-162.

85.C. Del Seppia, P. Luschi, S. Ghione, E. Crosio, E. Choleris, F. Papi, "Exposure to a Hypogeomagnetic Field or to Oscillating Magnetic Fields Similarly Reduce Stress-induced Analgesia in C57 Male Mice," *Life Sciences*, **66**, 14, 2000, pp. 1299-1306.

86.F. S. Prato, K.-P. Ossenkopp, M. Kavaliers, E. Sestini, and G. C. Teskey, "Attenuation of Morphine-induced Analgesia in Mice by Exposure to Magnetic Resonance Imaging: Separate Effects of the Static, Radiofrequency and Time-Varying Magnetic Fields," *Magnetic Resonance Imaging*, **5**, 1987, pp. 9-14.

87.C. Betancur, G. Dell'Omo, and E. Alleva, "Magnetic Field Effects on Stress-induced Analgesia in Mice: Modulation By Light," *Neuroscience Letters*, **182**, 1994, pp. 147-150.

88.M. Kavaliers and K.-P. Ossenkopp, "Magnetic Fields Inhibit Opioid-mediated 'Analgesic' Behaviours of the Terrestrial Snail, Cepaea nemoralis," *Journal of Comparative Physiology A*, **162**, 1988, pp. 551-558.

89.M. Kavaliers, K. –P. Ossenkopp, and M. Hirst, "Magnetic Fields Abolish the Enhanced Nocturnal Analgesic Response to Morphine in Mice," *Physiology & Behavior*, **32**, 2, 1984, pp. 261-264.

90.C. Fanelli, S. Coppola, R. Barone, C. Colussi, G. Gualandi, P. Volpe, and L. Ghibelli, "Magnetic Fields Increase Cell Survival by Inhibiting Apoptosis Via Modulation of Ca2+ Influx," *FASEB*, **13**, 1999, pp. 95-102.

91.C. R. McCreary, A. W. Thomas, and F. S. Prato, "Factors Confounding Cytosolic Calcium Measurements in Jurkat E6.1 Cells During Exposure to ELF Magnetic Fields," *Bioelectromagnetics*, **23**, 2002, pp. 315-328.

92.M. Kavaliers and K.-P. Ossenkopp, "Calcium Channel Involvement in Magnetic Field Inhibition of Morphine-induced Analgesia," *Naunyn-Schmiedeberg's Archives of Pharmacology*, **336**, 1987, pp. 308-315.

93.C. Del Seppia, S. Ghione, P. Luschi, and F. Papi, "Exposure to Oscillating Magnetic Fields Influences Sensitivity to Electri-

cal Stimuli. I. Experiments on Pigeons," *Bioelectromagnetics*, **16**, 1995, pp. 290-294.

94.F. Papi, S. Ghione, C. Rosa, C. Del Seppia, and P. Luschi, "Exposure to Oscillating Magnetic Fields Influences Sensitivity to Electrical Stimuli. II. Experiments on Humans ," *Bioelectromagnetics*, **16**, 1995, pp. 295-300.

95.. W. Thomas, M. Kavaliers, F. S. Prato, and K.-P. Ossenkopp, "Antinociceptive Effects of a Pulsed Magnetic Field in the Land Snail, Cepaea nemoralis," *Neuroscience Letters*, **222**, 1997a, pp. 107-110.

96.A. W. Thomas, M. Kavaliers, F. S. Prato, and K.-P. Ossenkopp, "Pulsed Magnetic Field Induced "Analgesia" in the Land Snail, Cepaea nemoralis, and the Effects of μ, d, and k Opioid Receptor Agonists/Antagonists," *Peptides*, **18**, 1997, pp. 703-709.

97.M. Kavaliers and K. -P. Ossenkopp, "Tolerance to Morphine-induced Analgesia in Mice: Magnetic Fields Function as Environmental Specific Cues and Reduce Tolerance Development," *Life Sciences*, **37**, 1985, pp. 1125-1135.

98.A. W. Thomas, M. Kavaliers, F. S. Prato, and K.-P. Ossenkopp, "Analgesic Effects of a Specific Pulsed Magnetic Field in the Land Snail, Cepaea nemoralis: Consequences of Repeated Exposures, Relations to Tolerance and Cross-Tolerance with DPDPE," *Peptides*, **19**, 2, 1998, pp. 333-342.

99.F. S. Prato, M. Kavaliers, and A. W. Thomas, "Extremely Low Frequency Magnetic Fields Can Either Increase or Decrease Analgaesia in the Land Snail Depending on Field and Light Conditions," *Bioelectromagnetics*, **21**, 2000, pp. 287-301.

100.J. L. Fleming, M. A. Persinger, and S. A. Koren, "Magnetic Pulses Elevate Nociceptive Thresholds: Comparisons with Opiate Receptor Compounds in Normal and Seizure-Induced Brain-Damaged Rats," *Electro- and Magnetobiology*, **13**, 1, 1994, pp. 67-75.

101.F. Sartucci, L. Bonfiglio, C. Del Seppia, P. Luschi, S. Ghione, L. Murri, and F. Papi, "Changes in Pain Perception and Pain-Related Somatosensory Evoked Potentials in Humans Produced by Exposure to Oscillating Magnetic Fields," *Brain Research*, **769**, 1997, pp. 362-366.

102.C. Polk, "Dosimetry of Extremely-Low-Frequency Magnetic Fields," *Bioelectromagnetics Supplement*, **1**, 1992, pp. 209-235.

103.S. Engstrom, "What is the Time Scale of Magnetic Field Interaction in Biological Systems?" *Bioelectromagnetics*, **18**, 1997, pp. 244-249.

104.S. Engstrom and R. Fitzsimmons, "Five Hypotheses to Examine the Nature of Magnetic Field Transduction in Biological Systems," *Bioelectromagnetics*, **29**, 1999, pp. 423-430.

105.F. S. Prato, J. J. L. Carson, K. -P. Ossenkopp, and M. Kavaliers, "Possible Mechanisms by which Extremely Low Frequency Magnetic Fields Affect Opioid Function," *FASEB*, **9**, 1995, pp. 807-814.

106.F. S. Prato, M. Kavaliers, and J. J. L. Carson, "Behavioural Evidence that Magnetic Field Effects in the Land Snail, Cepaea nemoralis, might not depend on Magnetite or Induced Electric Currents," *Bioelectromagnetics*, **17**, 1996, pp. 123-130.

107.F. S. Prato, M. Kavaliers, and J. J. L. Carson, "Behavioural Responses to Magnetic Fields by Land Snails are Dependent on Both Magnetic Field Direction and Light," *Proceedings of the Royal Society of London, Series B: Biological Sciences*, **263**, 1996, pp. 1437-1442.

108.F. S. Prato, M. Kavaliers, A. P. Cullen, and A. W. Thomas, "Light-dependent and independent Behavioural Effects of Extremely Low Frequency Magnetic Fields in a Land Snail are Consistent with a Parametric Resonance Mechanism," *Bioelectromagnetics*, **118**, 1997, pp. 284-291.

109.F. S. Prato, M. Kavaliers, A. W. Thomas, and K. -P. Ossenkopp, "Modulatory Actions of Light on the Behavioural Responses to Magnetic Fields by Land Snails Probably Occur at the Magnetic Field Detection Stage," *Proceedings of the Royal Society of London, Series B: Biological Sciences*, **265**, 1998, pp. 367-373.

110.M. Kavaliers, E. Choleris, F. S. Prato, and K. -P. Ossenkopp, "Evidence for the Involvement of Nitric Oxide and Nitric Oxide Synthase in the Modulation of the Opioid-induced Antinociception and the Inhibitory Effects of Exposure to 60-Hz Magnetic Fields in the Land Snail," *Brain Research*, **809**, 1998, pp. 50-57.

111.M. Kavaliers and F. S. Prato, "Light-dependent Effects of Magnetic Fields on Nitric Oxide Activation in the Land Snail," *NeuroReport*, **19**, 1999, pp. 1863-1867.

112.T. A. Kimbrell, R. T. Dunn, M. S. George, A. L. Danielson, M. W. Willis, J. D. Repella, B. E. Benson, P. Herscovitch, R. M. Post, and E. M. Wassermann, "Left Prefrontal-Repetitive Transcranial Magnetic Stimulation (rTMS) and Regional Cerebral Glucose Metabolism in Normal Volunteers," *Psychiatry Research*, **115**, 2002, pp. 101-113.

113.R. Huber, V. Treyer, A. A. Borbely, J. Schuderer, J. M. Gottselig, H. -P. Landolt, E. Werth, T. Berthold, N. Kuster, A. Buck, and P. Achermann, "Electromagnetic Fields Such as Those from Mobile Phones, Alter Regional Cerebral Blood Flow and Sleep and Waking EEG," *Journal of Sleep Research*, **11**, 2002, pp. 289-295.

114.P. Petrovic, E. Kalso, K. P. Petersson, and M. Ingvar, "Placebo and Opioid Analgesia Imaging A Shared Neuronal Network," *Science*, **295**, 2002, pp. 1737-1740.

115.J. K. Zubieta, Y. R. Smith, J. A. Bueller, Y. Xu, M. R. Kilbourn, D. M. Jewett, C. R. Meyer, R. A. Koeppe, and C. S. Stohler, "Regional Mu Opioid Receptor Regulation of Sensory and Affective Dimensions of Pain," *Science*, **293**, 2001, pp. 311-315.