Magnetic and electromagnetic field therapy

Marko S. Markov[a,*] and Agata P. Colbert[b]
[a]*EMF Therapeutics, Chattanooga, TN 37405, USA*
[b]*Tufts University, School of Medicine, Boston, MA, USA*

There is increasing interest in the application of magnetic/electromagnetic fields for therapeutic purposes. Magnetotherapy provides non-invasive, safe and easy to apply methods to directly treat the site of injury, the source of pain and inflammation as well as other types of dysfunction. This review summarizes several decades of experience worldwide in studying biological and clinical effects initiated by various magnetic and electromagnetic fields. The physiological basis for tissue repair as well as physical principles of dosimetry and application of magnetic fields are discussed. An analysis of magnetic/electromagnetic stimulation is followed by a discussion of the advantage of magnetic field stimulation compared with electric current stimulation. Finally, the proposed mechanisms of action are discussed.

Keywords: Magnetic field, electromagnetic field, electric current, therapy

1. Introduction

There is increasing interest in the therapeutic use of magnetic fields, stimulated in large part by recent advances in alternative and complementary medicine [1].

Magnetic fields (MF) and electromagnetic fields (EMF), including both natural electric and magnetic fields, such as geomagnetic field, and man-made electromagnetic fields, such as power lines, utilities, computers, diagnostic and therapeutic units are now recognized as real physical entities existing in the environment (Fig. 1).

It is possible that the widespread use of therapeutic EMF in the first decade of the new millennium may mark a revolutionary new approach to the treatment of various injuries and diseases. Western medicine is mainly based on the achievements of biochemistry which have been further utilized and expanded by the pharmaceutical industry. Oral medications, which are by their nature systemic, influence not only the tar-

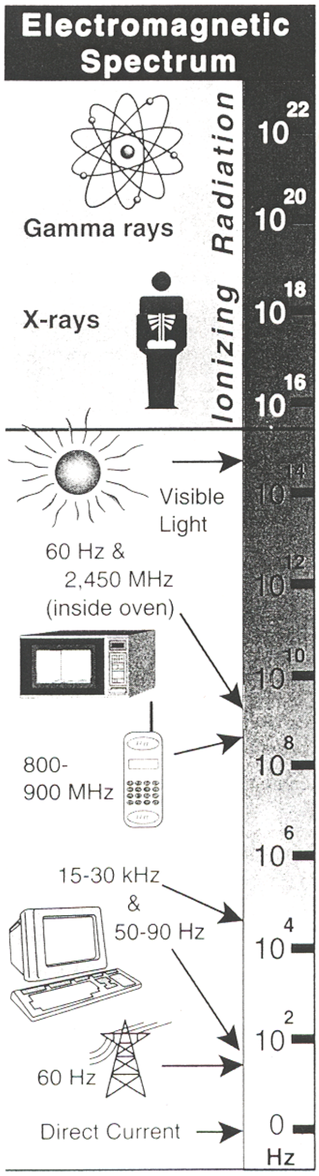

Fig. 1. EMF spectrum.

*Address for correspondence: Marko Markov, Ph.D., EMF Therapeutics, Four Squares Business Center, 1200 Mountain Creek Road, Suite 160, Chattanooga, TN 37405, USA. Tel.: +1 423 876 1883; Fax: +1 423 876 1851; E-mail msmarkov@emftherapy.com.

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Table 1
The origins of magnetobiology and magnetotherapy

1600 –	Gilbert – Book "The magnet and the big Magnet – Earth" – London
1752 –	Shaeffer – Book "Elektrishe Medizin" – Regensburg, Germany
1786 –	Galvani – Frog experiment for "animal electricity" – Bologna, Italy
1793 –	Volta – Further developed Galvani's ideas
1812 –	Birch – first application of electric stimulation for bone healing
1848 –	Du Bois-Reymond – Movement of electrical particles along nerve fiber
1864 –	Maxwell – Created the foundations of modern electromagnetic field theory
1891 –	Tesla (in USA) and d'Arsonval (France) – Suggested the use of high frequency electric current in medicine
1897 –	French Academy of Sciences – Reported large use of high frequency currents
1907 –	Nagelschmidt – At medical conference in Dresden demonstrated deep tissue heating by high frequency currents
1908 –	Nagelschmidt – Introduced DIATHERMY as a method for uniform heating of deep tissues
1913 –	Jex-Blake – Power-frequency electric force can cause destructive efffect on living system
1928 –	Esau used a vacuum-tube amplifier to generate 100 MHz EMF with several hundred watts of output power
1938 –	Hollman – Microwaves with wavelength of 25 cm could be focused to produce heating of deep tissues without excessive heating of skin
1946 –	Ratheon Co. provided Mayo Clinic with microwave generators for clinical use

get tissue, but also the entire organism and are usually associated with a variety of adverse effects. Physical medicine in general, and magnetobiology in particular, can provide non-invasive, safe and easy to apply methods to directly treat the site of injury or the source of pain, inflammation and dysfunction.

The original approach of ancient physicians was used intuitively in China, Japan and Europe by applying natural magnetic materials for the treatment of various diseases [2]. Numerous publications over the past 25 years suggest that exogenous magnetic and electromagnetic fields may have profound effects on a large number of biological processes, most of which are important for therapy [3–10].

Epidemiological studies on the potential hazards of electromagnetic fields (EMF) with respect to the initiation of cancer [11–13] have generated much controversy and attracted attention of the newsmedia and the general public. During the period 1991–1996 the United States Congress dedicated 60 million dollars for research into possible harmful effects of EMF. Neither federal nor state funding was, however, available in the USA for studying the beneficial effects of magnetic and electromagnetic fields for the treatment of various injuries and diseases.

During the last three decades a rigorous scientific approach toward the clinical application of electromagnetic fields (EMF) has evolved worldwide. Several International Journals and International Scientific Societies are involved in this research resulting in a plethora of published papers on the effects of MF and EMF (See Table 2).

Both static and time varying magnetic fields have been successfully applied primarily to treat therapeu-

Table 2
Professional and scientific societies involved in studying biological and clinical effects of EMF

Abbreviation	Full name
BEMS	Bioelectromagnetics Society
EBEA	European Bioelectromagnetic Association
BES	Bioelectrochemical Society
SPRBM	Society for Physical Regulation in Biology and Medicine
IEEE	Engineering in Medicine and Biology

Table 3
Frequently used terms

- *Field* Any physical quantity that takes different values at different points in space
- *Electric field* A field describing the electrical force on a net electrical charge in space
- *Magnetic field* A field describing the force experienced by magnetic body or moving in space electrical charge
- *Geomagnetic field* The Earth's natural magnetic field
- *Ambient electromagnetic field* The natural and man-made electromagnetic fields surrounding any given body
- *Direct current* A continuous unidirectional flow of charged particles due to applied voltage
- *Permanent magnetic field* A magnetic field created by permanent magnets or by passing a direct current through a coil
- *Low frequency sine wave electromagnetic field* A field created by sinusoidal current/voltage (50 Hz in USA and Canada, 50 Hz in Europe and Asia)
- *Pulsed electromagnetic fields* Low frequency electromagnetic fields with specific wave shapes
- *Pulsed radiofrequency field* Electromagnetic field in the radiofrequency part of the spectrum (in USA and Canada 13.56 MHz, 27.12 MHz and 40.68 MHz are specified for medical use)

Table 4
Comparison of electric current versus MF/EMF stimulation

Electric current	MF/EMF
Electrodes required	No electrodes required
Skin contact	Non-contact application
Full barrier limitation	Some barrier limitations
Disruptive	Non-disruptive
Possibility of infection	No possibility of infection
Tissue pathway dependent	Tissue pathway independent

tically resistant problems in the musculoskeletal system [3,5–10,14–28]. In addition, a number of diagnostic devices also exploit EMF. The most popular among them are MRI units. Relatively unknown among the medical community are magnetocardiograms or magnetoencephalograms whose sensitivity provide information an order of magnitude higher than electrocardiograms and encephalograms.

2. Categories of EMF therapeutic modalities

Electromagnetic therapeutic modalities can be categorized into six groups: (I) permanent magnetic fields, (II) low frequency sine waves, (III) pulsed electromagnetic fields (PEMF), (IV) pulsed radiofrequency fields (PRF), (V) transcranial magnetic stimulation, (VI) millimeter waves:

(I) *Permanent magnetic fields* can be created by various permanent magnets as well as by passing direct current (DC) through a coil.

(II) *Low frequency sine wave electromagnetic* fields mostly utilize 60 Hz (in USA and Canada) and 50 Hz (in Europe and Asia) frequency used in distribution lines.

(III) *Pulsed electromagnetic fields* (*PEMF*) are usually low frequency fields with very specific shape and amplitude. The large variety of commercially available PEMF devices makes it difficult to compare their physical and engineering characteristics, presenting a major obstacle when attempting to analyze the putative biological and clinical effects obtained when different devices are used.

(IV) *Pulsed radiofrequency fields* (*PRF*) utilize the selected frequencies in the radiofrequency range: 13.56 MHz, 27.12 MHz and 40.68 MHz.

(V) *Transcranial magnetic stimulation* is a method of treatment of selected area of the brain with short, but intensive magnetic pulses.

(VI) *Millimeter waves* have a very high frequency of 30–100 GHz. In the last 10 years this modality has been used for treatment of a number of diseases, especially in the countries of the former Soviet Union [29–31].

EMF provide a practical, exogenous method for inducing cell and tissue modifications which correct selected pathological states [3,5,6,17]. Despite a relatively long history of interest by scientists and clinicians, very little is known about the mechanisms of action and this limitation has restricted the application of magnetic and electromagnetic fields in clinical practice in the United States. In contrast, after the World War II in Japan, and later in Romania and the former Soviet Union, magnetotherapy developed very quickly. During the period 1960–1985 most European countries had produced magnetotherapeutic systems [3,5,20,32, 33]. The first clinical application of electromagnetic field stimulation in the USA is dated 1974 [15]. The first book on magnetotherapy, written by N. Todorov, was published in Bulgaria in 1982 [3].

3. Barriers to research and the therapeutic use of magnetic fields

Despite years of experience elsewhere, documented successful use of magnetic field stimulation, and more than 2000 papers on the beneficial effects of magnetic and electromagnetic stimulation [3,5–10,14–17,19–28, 37–47] magnetotherapy remains circumscribed in the US. It should be noted that most of those papers present results of open studies, and only a few have been done as double blind, controlled studies. Essential elements of the rapidly growing and expanding world database on reproducible biological and clinical effects of numerous magnetic fields are largely unknown or inaccurately interpreted by the physical, medical, regulatory and public sector of society. Reasons for this may be:

– Clinics have little or no exposure to the principles of thermodynamics, electrodynamics, biomechanics, electricity and magnetism during their training
– Regulatory activity is unnecessarily restrictive
– Public concern about the safety of magnetic and electromagnetic fields is engendered by misinformation via the news media
– Government funding for therapeutic EMF research is minimal

The very important question: "Whether and to what extent magnetic fields may represent a hazard for users?" needs to be answered. The scientific reports and newsmedia publications are based on epidemiological studies that assumed continuous exposure to weak, low frequency electromagnetic fields [11–13]. Epidemiological studies deal with a very complex living and working environment and often lack adequate information with regard to changes in all physical and chemical pollutants during the time of analysis [48–50]. However, to date, the epidemiological data are inconsistent and no human cancer has been associated with exposure to electromagnetic fields [51]. It appears that long-term follow up which may provide adequate information on the possible hazards of the therapeutic application of magnetic fields will be extremely difficult to obtain, due to the complexity of the problem and the high cost of such follow up [33]. Based on available evidence worldwide it is, however, highly unlikely that the therapeutic application of magnetic fields would create a dangerous situation for the patient. One should consider the fact that to be effective any applied magnetic field must be orders of magnitude stronger than ambient magnetic fields. Several important documents of the World Health Organization and various national protection agencies stated that there is no convincing evidence that low frequency EMF are a human health hazard. In addition WHO documents state that "the available evidence indicate the absence of any adverse effects on human health due to exposure to magnetic fields up to 2 T [52,53].

4. What should be done to assure reproducibility of reported bioeffects?

In order to achieve good reproducibility of observed bioeffects, each study should pay special attention to the following: detailed dosimetry of the study, use of a well-established biological and clinical protocol, and a complete report of the experimental conditions of each study [54]. Failure to reproduce the reported effects of a biological or clinical study is, in many cases, due to a failure to explain the exact conditions and/or neglect of some details which appear to be obvious. Model systems and magnetic field parameters vary largely and, in most cases, their selection is not based on rigorous analysis but on the engineering and physics of a given exposure system and on the intuition of the investigator. This situation is, however, improving and better conditions for reproduction of therapeutic effects are being created as researchers acknowledge that magnetic field parameters must be matched with the bioprocesses being studied. Threshold or "window" requirements must be coupled with proper exposure conditions and a receptive functional target state for a beneficial effect to occur [55–57].

Stimulation with electric and magnetic fields has been proven to provide salutary and reproducible healing effects when other methods have failed [3,5–7]. However, there is often confusion among medical practitioners with respect to application of these modalities due to the variety of methods of stimulation, parameters of the applied fields, and lack of a defined biophysical mechanism capable of explaining the observed bioeffects. Animal and human studies demonstrate that the physical parameters and patterns of application can affect both the type of effect and the efficiency in producing a given response. Evidence of bioresponse specificity has been collected in a number of tissue culture, animal, and clinical settings. More details are available elsewhere [4,16,17] which indicate that the amplitude, frequency, and exposure pattern windows apparently determine whether a bioeffect will occur and, if it does occur, what its nature will be. Therefore a systematic study of EMF action on any particular biological system [54] has to consider the following parameters:

– type of field
– intensity or induction
– gradient (dB/dt)
– vector (dB/dx)
– frequency
– pulse shape
– component (electric or magnetic)
– localization
– time of exposure
– depth of penetration.

5. Differences between electric current and MF/EMF stimulation

Significant differences exist between electric current and EMF/MF modalities. Electric current stimulation requires skin contact electrodes which may be placed either on both sides of the injury or wound or with one electrode placed over the affected area, the other over normal adjacent tissue. Electrode size, spacing and polarity are the most critical factors in delivering of an adequate stimulating current. Closely spaced, small electrodes generally make the effective area of stimulation rather superficial due to the lower impedance of the current path through proximal tissue; large, further apart electrodes allow for deeper penetration, especially in case of wound healing. The conduction of electrical current through biological tissues occurs as a result of movement of charges along specific pathways. This charge transfer might result in electrothermal, electrochemical, and/or electrophysical effects depending on the type of electrical current and can occur at the membrane, cellular or tissue level. Best studied are the effects of electrical stimulation on chemical reactions which in turn may enhance cellular metabolism [14, 18]. The direct responses usually result in a multitude of indirect cellular reactions, which may subsequently alter further steps in biochemical and physiological pathways. The actual current density at any particular point within the tissue will depend on tissue composition and geometry and will change as these parameters vary during healing. A further complication of using electrodes is the generation of potentially toxic electrolysis products, particularly if the electrode is placed inside an open wound.

Another important feature of magnetic/electromagnetic stimulation, especially in the relatively low frequency range, is that electric and magnetic field components behave differently. Once an electric field reaches a material surface, it is transferred into electric current along the surface. Conversely, most materials are transparent to the magnetic field component which penetrates deep into the body. The depth of penetration depends on the technique of generating the magnetic field. A common problem when assessing the effects initiated by different devices is that each manufacturer uses its own systems and methods of characterizing the product. Many research and clinical trials have been performed without complete dosimetry of the magnetic field at the site of injury and adequate documentation of the exposure conditions. As a consequence, when reviewing publications it is difficult to compare or generalize results obtained at different research or clinical sites. Explanations of experimental protocols even if perfect from a biological or clinical point of view are often incomplete in their characterization of the EMF at the target site.

6. Literature review of the clinical application of MF and EMF

Today there is an abundance of experimental and clinical data which suggest that various exogenous MF at surprisingly low levels can have a profound effect on a variety of biological systems and processes, most of which are of critical importance for diagnostics and therapy [3,4,6,16–19,58].

The most common effective clinical applications of magnetic fields are related to bone unification and the reduction of pain and edema in soft tissues. For musculoskeletal injuries and post-surgical, posttraumatic and chronic wounds, magnetic fields are recognized as a modality that contributes to reduction of edema [3,5,6,16,17,19,21–24]. Noninvasive EMF are now a common part of some orthopedists' practices for the care of fresh and delayed fractures. Recalcitrant fracture repair (delayed and non-union of bone) has had the longest history of EMF clinical application in the USA [6,16,25,26].

During the past 25 years more than a million patients have been treated worldwide, in almost all areas of fracture management. This large number of patients exhibited a success rate of approximately 80%, with virtually no reported complications after nearly three decades of use [6,17,19]. While the success rate for EMF therapies is comparable to that produced surgically for delayed and non-union fractures, the cost of this non-invasive therapy is significantly less. Even greater cost reductions are apparent when appropriate permanent magnets are applied directly to the site of injury. To continue this analysis the following information may be useful: Each year approximately 2 million long-bone fractures occur in the United States. Of these, 5% fail to heal normally within 3–6 months, and some never heal, perhaps ending in amputation. Considering that 80% of these fractures will be healed more quickly by electromagnetic stimulation, this is of enormous benefit for the patient, his/her family, the health care system and society.

7. Therapeutic magnetic field

A number of clinical studies, in vivo animal experiments and in vitro cellular and membrane research suggest that magnetic and electromagnetic field stimulation may accelerate the healing processes [3,6–8,17,27]. MF and EMF are also capable of influencing nerve repair and regeneration [5,8,59]. It is now clear that endogenous electromagnetic and magnetic interactions are associated with many basic physiological processes ranging from ion binding and molecular conformation in the cell membrane to macroscopic alterations in tissues. The investigation of the mechanisms of action of MF on biological systems which are in a state different than their normal physiological one represent the next frontier in electromagnetic biology and medicine. Currently, a number of experiments have demonstrated that both weak electromagnetic and magnetic fields are capable of eliciting in vivo and in vitro effects from different biological systems, inducing changes at the organism, tissue, cellular, membrane and subcellular levels [4,6,28,54,59–61].

Efforts must be made by researchers from basic science to establish dosimetry data and methodology of this type of stimulation. Saying that a patient was "magnetically stimulated" is essentially as nonspecific as saying a patient was "given a drug". Magnetic field stimulation requires as precise dosage and modality information as any other therapy. This "dosage" is even more complicated since it must take into account a number of physical parameters which characterize any magnetic field generating system. An exact diagnosis of the injury or pathology is also very important for later generalization of magnetotherapy. For example, to stimulate the blood-coagulation system, a physician needs one combination of parameters of the applied field, while stimulation of the anticoagulation system requires another field configuration [3,4]. Space does not permit more than a superficial presentation of evidence here to support the statement that "different MF produce different effects in different biotargets under differing conditions of exposure".

8. Physiological basis for the use of magnetic stimulation in tissue repair

A careful analysis of successful healing in different tissues can highlight the cellular and tissue components that may be plausible targets for MF action. Basic science studies suggest that nearly all participants in the healing process (such as fibrinogen, leukocytes, fibrin, platelets, cytokines, growth factors, fibroblasts, collagen, elastin, keratinocytes, osteoblasts, and free radicals) [3,5–8,14,23,37,38,59,62–67] exhibit alterations in their performance when exposed to the action of MF. Magnetic fields may also affect vasoconstriction and vasodilation, phagocytosis, cell proliferation, formation of the cellular network, epithelization, and scar formation [5,6,17,20,58].

An analysis of a number of injuries in human and animal models has shown that when an injury disturbs the integrity of the tissue, there will be a net flow of ionic current through the low resistance pathway of the injured cells [17,62]. The ionic currents between normal and injured tissue play an important role in the repair processes that are essential for restoration of the normal functional state of the tissue. Healing occurs via a series of integrated stages, each of which has particular objectives essential to repair processes. Therefore, it is important to evaluate the contribution of the basic cellular activities occurring at any one of the distinct stages of tissue repair and the potential influence of the MF on any of these steps. This extremely complex phenomenon involves a number of well-orchestrated processes such as vascular responses, cellular and chemotactic activity and release of chemical mediators within the injured tissues. The list may also include regeneration of parenchymal cells, migration and proliferation of both parenchymal and connective tissue cells, synthesis of extracellular matrix proteins, remodeling of connective tissue, collagenization, and acquisition of tissue strength. Basic science and clinical data indicate that the interactions of MF with any structure in the human organism could initiate biophysical and biochemical changes which in turn modify the physiological pathways that contribute to the healing process. Since the applied magnetic fields have energy below the threshold level, it is more likely that MF trigger some important biophysical/biochemical cascade, and affect signal/transduction pathways.

The low level magnet initiates a chain of biological events for healing

8.1. *Magnetic and electromagnetic stimulation*

Several decades of clinical application of various magnetic fields clearly demonstrate the potential benefit from using selected magnetic fields for treatment of specific pathologies. The success of magnetotherapy strongly depends upon proper diagnostics and selection of suitable physical parameters of applied fields. It should be noted that we do not have adequate information to link diagnosis to suggested therapeutic parameters of the selected MF. Also, practically there are no reports available for replication of clinical studies. Each and any new report is completed with at least a slight variation of the previous parameters of treatment.

8.1.1. *Bone and cartilage repair*

A survey of the existing literature indicates that a wide variety of electric and magnetic modalities have been developed to heal fracture non-unions and wounds [6,14,15,19,23]. In the US the first EMF-generating device was approved as a medical device for treatment of non-union. For the last 30 years a set of non-invasive EMF signals have been approved for spinal fusion and treatment of delayed fractures and non-unions [6,68–71]. It should be noted that most of the European countries have their own therapeutic devices [5,58,72].

8.1.2. *Treatment of soft tissues*

The non-invasive EMF most often employed in the USA for soft tissue applications is short wave pulsed radio frequency (PRF), based on the continuous 27.12 MHz sinusoidal diathermy signals which have been employed for decades for deep tissue heating. The pulsed version of this signal was originally reported to elicit a nonthermal biological effect by Ginsberg [34]. Since this pioneering work, PRF magnetic fields have been applied for the reduction of post-traumatic and post-operative pain and edema in soft tissues, wound healing, burn treatment, ankle sprains, hand injuries, and nerve regeneration [17,35,36,68]. An excellent review paper on scientific bases of clinical application of electromagnetic fields for soft tissue repair was published by Canady and Lee [73].

8.1.3. Wound healing

Besides faster healing of stimulated wounds, these modalities have been shown to significantly increase local blood flow in the stimulated area. There is a body of data from in vitro studies that suggests significant alterations in cell division or differentiation occur as a response to MF treatment [6,37,58]. Magnetic and electric stimulation have been associated with increased collagen deposition, enhanced ion transport, amino acid uptake, fibroblast migration, ATP and protein synthesis, including an increased rate of synthesis of protein and DNA after stimulation of human fibroblasts in tissue culture. Another area of research interest is the effect of EMF and MF on cell proliferation. Most cells normally differentiate for specific morphology and functions. In pathological conditions cell proliferation is usually suppressed (in chronic wounds) or enhanced (in the case of neoplastic growth). Researchers suggest a favorable alteration of the proliferative and migratory capacity of epithelial and connective tissue cells involved in tissue regeneration and repair [17,63,64]. As most of the modalities in use in medicine, the evaluation of the potential beneficial or harmful effects is based on experiments with animals. However, despite the physiological similarities of animal skin and human skin, there are also differences which could alter the effectiveness of the stimulation. Therefore, the elementary extrapolation of data obtained in animal experiments to humans, and especially, their interpretation in terms of epidemiology, may result in an incorrect estimation of the reasons, mechanisms and long-term effects of electromagnetic radiation on humans.

We know that EMFs decrease ATP production in the mitochondria, which is why we say we counteract the effects!

8.1.4. Pressure ulcers

One of the most important applications of electromagnetic stimulation, functional electrical stimulation (FES), has been routinely used for over three decades to treat paretic and paralyzed patients. It has been reported that in addition to the neurological benefit of functional stimulation, these patients developed significantly fewer pressure ulcers compared with patients who did not receive FES [65,74,75]. In addition, existing chronic ulcers healed at a faster rate. Improved blood perfusion in the electrically stimulated tissue has been an assumed mechanism for the stimulatory effects on the regenerative processes [76]. These clinical observations, along with the findings that blood flow and metabolic activity increase after long-term muscle stimulation [66] motivated a multicenter study of the effects of pulsed currents on wound healing [76]. A pulsed radiofrequency magnetic field was used [391] for treatment of pressure sores in patients aged between 60 and 101 years resulting in significant reduction (up to 47%) in the mean sore area after 2 weeks of treatment.

8.1.5. Peripheral vascular disease

Several methods of peripheral vascular system therapy using static magnetic fields have been developed during the last two decades [5,25,45]. The clinical outcome of this therapy should include analysis of hemodynamics, microcirculation, transcapillary phenomena, as well as morphological and cytochemical characteristics of blood components, such as lymphocytes, erythrocytes, leukocytes, trombocytes. It has been shown that low intensity static MF stimulates microcirculation, and initiates compensatory/adaptational reactions in elderly patients with arteriosclerosis [38].

Therapeutic efficacy depends on the status of the patient (age, general health, and gender) as well as on the stage of pathology/disease. It has also been found that there is a distinct relationship between specific diseases and MF parameters which initiate optimal response for these particular pathologies. Using non-contact methods for analysis of the histochemical permeability of capillaries and partial oxygen pressure, Zukov and Lazarevich [38] developed a method for dosage of the therapy.

8.1.6. Nerve regeneration

Even not yet approved by regulatory agencies, magnetic fields appear to be very promising modality in nerve regeneration [59]. The reported animal studies involved both ends of the electromagnetic spectrum – very low (72 Hz) frequency and radiofrequency (27.12 MHz) electromagnetic fields applied in a pulsed mode [59].

8.2. Permanent magnets for pain control

Several double blind clinical studies on the effects of magnetic field stimulation have been published recently [40–44]. These recent studies reported on pain management for patients with different etiologies and sites of pain. They demonstrate the potential of a static magnetic field to provide significant pain relief in different disorders. In a double blind study it was shown that a static magnetic field of 300–500 G significantly decreases the pain score in postpolio pain syndrome patients when compared with a placebo group [40]. Another double blind study performed by Colbert et al. [43] demonstrated that sleeping on mattresses in which ceramic permanent magnets with a surface field strength of about 1000 G are embedded provided significant benefits to pain, fatigue and sleep in patients suffering from fibromyalgia. The status of the patients in the real treatment group which received 200–500 G magnetic field was improved by more than 30%. In a pilot study Weinthraub [41] reported a significant improvement in 75% of patients with diabetic neuropathy who used permanent magnetic field stimulation on the soles of their feet. It appears that the proper choice of magnetic field strength, application site, duration and frequency of application are of critical importance for the success of the therapy.

9. Mechanisms of action

One of the main reasons that MF/EMF are still not widely accepted as treatment modalities could be the absence of agreement about a common mechanism of action for EMF bioeffects. MF are capable of inducing selective changes in the microenvironment around and within the cell, as well as in the cell membrane. Therefore, MF might be a suitable and practical method for inducing modifications in cellular activity which in turn may correct selected pathological states. Assuming that the exogenous signal can be detected at the cell or tissue level, the biophysical mechanism(s) of interaction of weak electric and magnetic fields with biological tissues as well as the biological transductive mechanism(s) remain to be elucidated. Some specific reactions and processes in different biological systems suggest that most of the observed bioeffects strongly depend on the parameters of the applied electromagnetic fields. At present, the following areas are subjects of extensive evaluation:

– search for cellular or subcellular targets of magnetic and electromagnetic fields
– examine *in vivo* and *in vitro* biophysical mechanisms of EMF action on living systems
– study the adaptation of living system to applied EMF
– evaluation of “window” effects
– creation of standards for EMF in occupational conditions and everyday life
– documented long-term after effects of electromagnetic exposure.

The study of biophysical mechanisms is essential, beginning with identification of the nature of the initial physicochemical interaction of EMF with biological systems, and the expression of these physicochemical changes as a biological response. Starting from cell size and shape, going through the composition and architecture of the cellular membrane, one can also take into account the different sensitivity of cells based on the above described characteristics. The cell cycle is equally important for cell response: is the cell differentiating, resting or synthesizing new building components. When cells are organized in a tissue, the expected response should include cell-cell communications (mainly via gap-junctions). To properly conduct and analyze *in vivo* experiments the complexity of the animal/human organism and the existence of compensatory mechanisms which work on the organism level must be considered. The mechanisms based on classical physics can not take into account the problems related to thermal movement of any single atom or molecule. A number of nonequilibrium models have been proposed to explain field induced structural and functional perturbation that occur at different structural levels under the EMF influence.

Most of the suggested biological mechanisms of action of MF/EMF, even if they are correct, are not very likely to take place at the therapeutic/clinical level. For example, an excellent recent review paper of Valbona and Richards [45] suggested for consideration the following mechanisms:

– Solid state theory of cell function [77,78]
– Biological closed electrical circuits [62]
– Association-induction hypothesis [79–81]
– Ion cyclotron resonance [82]
– Ion parametric resonance [83,84]

Each of the above mentioned mechanisms was a subject of a number of theoretical studies, however it appears that they are reasonably applicable only at the level of ion movement. For complex biological systems, such as different tissues and organs in the human organism more likely the effect should be searched in a different direction. From a clinical point of view it is also difficult to believe that each of these mechanisms might be useful in explaining the beneficial effects of magnetotherapy, especially the significant and rapid pain relief observed in several different studies such as postpolio patients [40], diabetic neuropathy [41], post-surgical wounds [42], and fibromyalgia [43]. Therefore, further discussion will be concentrated on some other possibilities.

10. Role of signal transduction pathways in EMF and MF effects

The cell membrane is most often considered the main target for EMF signals. It has been suggested that even small changes in transmembrane voltage could trigger a significant modulation of cell function. There is a rapidly growing body of information that implicates the cell membrane as a primary site of EMF interactions [58,85–87].

An examination of the signal transduction pathways appears to be very important in studying reactions of living systems to any EMF [86]. The best demonstration of signal transduction pathways is the role of the cellular membrane to react to applied external signals, such as ion/ligand binding to appropriate receptors, and further transfer information and/or conformational changes or electron transport to the cell interior. Most of the signal transduction pathways offer enzymatic amplification of EMF stimuli into a measurable cellular response at the level of the second messenger. Beginning with the electrochemical information transfer hypothesis [88], most results point to an EMF effect on the rate of ion or ligand binding to the enzyme and/or receptor site acting as a modulator of the ensuing biochemical cascades relevant to cell function, often involving Ca/calmodulin dependent processes, cAMP and growth factors [67,89]. The local tissue effect is supported by the marked increase of ATP and protein synthesis observed in animal tissues or cell culture experiments. It has been demonstrated that EMF can affect cell proliferation in both directions: acceleration of cell growth and division when the rate is too low, and inhibition when cell proliferation becomes abnormally high. In pathological conditions cell proliferation is usually suppressed (as in chronic wounds) or enhanced (as in neoplastic growth). The electrochemical information transfer hypothesis [88] postulates that the cell membrane could be the site of interaction of low level EMF by altering the rate of binding of, for example, calcium ion to enzyme and/or receptor sites. Any change in the electrochemical microenvironment of the cell can cause modifications in the structure of its electrified surface regions by changing the concentration of a specifically bound ion or dipole, which may be accompanied by alterations in the conformation of molecular entities (such as lipids, proteins and enzymes) in the membrane structure. The role of ions as transducers of information in the regulation of cell structure and function is widely accepted. Therefore, the regulatory interactions at a cell's surface are considered to have both voltage and kinetic functional relationships with the specific biochemical events to which these processes may be coupled. Examples of ionic control mechanisms can include: growth factor activation of Na-K ATPase in fibroblasts [90]; nerve growth factor effects regulated by Na-K ATPase [91]; and Ca2+ regulation, via calmodulin, of the cell cycle [60,89,92]. Calcium signaling became a widely popular theory in the search of second messengers involved in the signal-transduction pathways [86,87,93–95].

A Larmor precession/dynamic model has been recently proposed to explain the possibility of weak, ambient range magnetic fields to affect ion/ligand binding in the presence of thermal noise [92]. Conventional thinking, especially in physical chemistry, suggests that to be potentially effective, any applied physical or chemical signal should introduce into the system sufficient energy to overcome the thermal movement of ions or molecules. Looking only from this point of view one can easily conclude that no magnetic field from the range of amplitudes used in biological and clinical research fulfil this requirement. The model proposed by Pilla et al. [92] analyzes the possibility of magnetic fields to initiate biological effects even in the presence of thermal noise. The model treated ion binding to any potential binding site at the membrane or biopolymers. Further alteration in the signal-transduction cascade may be of crucial importance for healing processes.

The interactions of ions at the electrically charged interfaces of a cell is an example of a potential or voltage dependent process [86–88,92]. This is of great importance in understanding the nature of electromagnetic stimulation since any electric current or EMF interacts with an electrically charged surface or macromolecule. Note that in injured tissue most cell membranes are destroyed or at least modified. A series of studies of EMF influence on various biological systems [54–56] demonstrated the appearance of "windows" effects.

The "windows" represent combinations of amplitude and frequency within which the optimal response is observed, outside this range the response is significantly smaller. In other words, this demonstrates the principle "more does not necessarily mean better".

Two major factors in healing of chronic injuries are tissue ischemia and restoration of normal communication between cells and their environment. Healing requires an optimization of the supply of nutrients and oxygen to allow surrounding tissues to grow and restore physical and chemical barrier functions. An important part of intracellular communication is performed by peptide signaling molecules – growth factors. They also enable communication between cells involved in the healing process and between cells and their environment, thus restoring local homeostatic equilibrium. It has been suggested [62] that at least five components of any vascularized part of the body might participate in EMF initiated bioeffects: (i) blood vessel walls, (ii) intravascular plasma conduction, (iii) insulating tissue matrix, (iv) conducting interstitial fluid, and (v) electrical junctions for redox reactions (transcapillary junctions). This approach emphasizes the necessity first to restore the blood vesel system in the injured area which will further contribute to restoration of the next component in this chain mainly by assuring an optimal supply of ions, oxygen and nutrients [37,63,93].

The results from the treatment of edema indeed suggested that EMF affect sympathetic outflow, inducing vasoconstriction which restricts movement of blood constituents from vascular to extravascular compartments of the injury site [97].

All available modalities which utilize electric current, electromagnetic fields and even static magnetic fields suffer from the requirement that the patient should be available for certain periods of time daily at treatment facilities. The search for portable and easy to apply sources of magnetic fields leads the science and technology to permanent magnets. Increasing use of permanent magnets provides evidence that static magnetic field may be a plausible modality for treatment of various injuries [40–43]. One of the main advantages is that permanent magnets are easy to use due to their size and weight. They do not require contact with the site of injury, therefore application through a cast or bandage is very easy. In addition, they may be recommended for home use at convenient times at patient discretion. Magnets with different shape, size and configuration can be placed over the injured area after surgical intervention. Both bone unification and wound healing exhibited significant acceleration following application of permanent magnets [3,38,42]. When applied postoperatively to patients who have undergone cosmetic surgery magnetic field therapy was remarkably effective in the treatment of postsurgical symptoms as well as in alleviation of pain [42]. The significant reduction of postoperative pain in this study resulted in a decreased need for analgesic medication. The most plausible mechanism to be considered is the increased blood flow to the site of surgery, which delivers more oxygen and nutrients, thereby speeding the overall healing process.

11. Summary

In summary, there is an abundance of experimental and clinical data which demonstrates that exogenous electromagnetic fields of surprisingly low amplitudes can have a profound effect on a wide variety of biological systems. The data on in vitro systems suggests that the biological activity of the cell (e.g., division or differentiation) can be modulated by magnetic fields. Perhaps the greatest challenge for what we may term electromagnetic biology and medicine is to establish the proper dosimetry for modulation of the desired biochemical cascade. This may have a far-reaching impact on the cost of health care worldwide.

The correct choice of effective electromagnetic stimulation to accelerate healing requires measurement and computation of a variety of parameters, such as amplitude, field frequency and shape, duration of exposure, and site of application. Not only the precise characteristics of the applied or driving field/current, but also the exact diagnosis and all other clinical data should be considered. Further research in the area of magnetic and electric stimulation should clarify and optimize the choice of the appropriate magnetic field, electric current or EMF signals that are optimal for modulation of defined cellular or subcellular structures and processes which are involved in healing. Also, the cellular and tissue responses to applied signals need to be verified. A precise evaluation of electromagnetic field initiated bioeffects becomes increasingly important since the number of electromagnetic technologies and devices used in clinical practice, continues to grow.

As with any biotechnology, magnetotherapy requires rigorous interdisciplinary research efforts and coordinated educational programs. This research should include not only interdisciplinary teams of scientists, but more importantly, an integration of knowledge from such distinct areas as physics, engineering, biology and medicine. A very important role is relegated to the large group of medical practitioners, especially physical and occupational therapists, who routinely use the variety of physical modalities.

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