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Magnetic Field Therapy: A Review

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There is increasing interest in using permanent magnets for therapeutic purposes encouraged by basic science publications and clinical reports. Magnetotherapy provides a non invasive, safe, and easy method to directly treat the site of injury, the source of pain and inflammation, and other types of disease. The physiological bases for the use of magnetic fields for tissue repair as well as physical principles of dosimetry and application of various magnetic fields are subjects of this review. Analysis of the magnetic and electromagnetic stimulation is followed by a discussion of the advantage of magnetic field stimulation compared with electric current and electric field stimulation.

Keywords Magnets; Magnetic fields; Therapy.

Introduction

Increasing interest in the application of magnetic fields (MF) in conventional and alternative/complimentary medicine has attracted scientists and clinicians to the potential benefit of using MF for therapeutic purposes. Magnetic and electromagnetic fields are real physical entities existing in the environment and this has created both public interest and fear regarding the potential harmful effects of these physical factors.

Early interest, both scientific and public, focused on the potential hazard of electromagnetic fields (EMF) especially the initiation of cancer (Deno and Carpenter, 1994; Wartenberg and Savitz, 1993; Werheimer et al., 1995). From 1991–1996, the U. S. Congress appropriated 60 million dollars to this research. In the last decade, that research has been principally concerned with the hazards of cellular phone communications. Both power line and cell phone issues have attracted the attention of the news media, industry, and policy makers and, as a result, there has been significant funding for research in these areas.

Unfortunately, practically no government money has been made available for the study of beneficial effects of magnetic and electromagnetic fields for treatment of injury and disease. The advancement of magnetotherapy is a result of funding

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provided by manufacturers and distributors of magnetotherapeutic devices. This has led to the claim that reports funded by manufacturers are biased because of funding pressure. Therefore, if no independent funding is made available for research there will be no studies, and if private funding is provided there is the concern that the results reported from those studies will be labeled as biased. Historically, some research in science and medicine has been biased, though society relies on, and should rely mainly on, the scientific honesty and integrity of the researchers, rather than on business interests.

Despite insufficient funding, the next decade will mark a revolutionary new approach toward treatment of various pathologies by using modalities such as magnetic and/or electromagnetic fields.

Humans have known for centuries that there are natural stones that attract metals. A legend suggests that a Greek shepherd in the hills near the village of Magnesia (which exists today in Turkey under the same name) found stones that attracted his sandals, and soon these stones were used to treat certain maladies.

Ancient physicians in China, Japan, and Europe applied natural magnetic materials for the treatment of disease. One of the earliest scientific accounts is in the book *De Magnete*, written in 1600 by William Gilbert, the personal physician of the English Queen (Gilbert, 1600). This brilliant scientist used "load stones" to treat variety of health problems of the Queen of England and ordinary citizens.

Over the past several decades, physicians and scientists, mainly in Europe and Asia, have used a rigorous scientific approach to clinical application of MF/EMF. Both static and time varying MF have been successfully applied to treat therapeutically resistant problems in the musculoskeletal system. MF have been proven to be clinically safe, and it is well accepted that MF provide a practical, non invasive method for inducing cell and tissue modifications which can correct selected pathological states. Numerous publications suggest that exogenous magnetic and electromagnetic fields can have profound effects on a large number of biological processes, most of which are of critical importance for diagnostics and therapy (Adey, 2004; Bassett, 1989, 1994; Lawrence et al., 1998; Markov, 1987; Markov and Todorov, 1984; Markov and Pilla, 1995; Pilla, 1993; Pilla and Markov, 1994; Rosch and Markov, 2004; Shupak, 2003; Sisken and Walker, 1995; Todorov, 1982).

After World War II, magnetotherapy developed quickly in Japan and later in Romania and the former Soviet Union. In Japan, magnetotherapeutic devices are registered under the Drug Regulation Act of 1961 as # 81, and by 1976 such devices were in common use in Japan, mainly through the efforts of Kyochi Nakawa. Magnetotherapy has a long history in Europe. During the period 1960–1985, most European countries had produced magnetotherapeutic systems. The first clinical application of electromagnetic stimulation in the USA appears to be 1977 (Bassett, 1977). The first book on magnetotherapy, written by Todorov, was published in Bulgaria in 1982 and reviewed the use of magnets for treatment of more than 2,700 patients with 33 different pathologies (Todorov, 1982).

There is now experimental and clinical data which suggests that exogenous MF at surprisingly low levels can have a profound effect on a large variety of biological systems (Bassett, 1989, 1994; Bental, 1990; Detlavs, 1987; Detlavs et al., 1994; Markov, 1994; Pilla, 1993; Rosch and Markov, 2004; Shupak, 2003; Todorov, 1982).

The most effective clinical applications of these fields over the past 25 years relate to bone unification, pain reduction, and soft tissue edema. More than a million patients have been treated worldwide in practically all areas of fracture management including: non unions, pseudo-arthroses, osteonecrosis, and chronic refractory tendinitis. The treatment success rate for these patients approaches 80%, with virtually no reported complications after nearly three decades of use (Bassett, 1989; Markov, 1994; Pilla, 1993). While the success rate for EMF therapies are comparable to surgical for delayed and non union fractures, the cost of non invasive therapy is significantly less. Cost substantially decreases when appropriate permanent magnets are applied directly to the site of injury.

For many musculoskeletal injuries and post-surgical, post-traumatic and chronic wounds, MF are recognized as a modality that contributes to reduction of edema. Edema reduction can be a major therapeutic factor in the acceleration of pain and stress relief which in turn contribute toward the healing processes.

A number of clinical studies, *in vivo* animal experiments, and *in vitro* cellular and membrane research suggest that magnetic stimulation can accelerate the healing processes (Adey, 2004; Bassett, 1989, 1994; Cleary, 1994; Jerabek, 1994; Markov, 2006; Morris and Skalak, 2005; Ohkubo and Xu, 1997; Okano and Ohkubo, 2001, 2003a,b, 2005a; Rosch and Markov, 2004; Takeshige and Sato, 1996). MF may also enhance such fundamental properties as nerve repair and regeneration, and immune and endocrine function. Endogenous magnetic fields are associated with many basic physiological processes ranging from ion binding and molecular conformation in the cell membrane to the macroscopic mechanical properties of tissues.

The investigations of the mechanisms of the effects of MF on biological systems, which are in a state different from their normal physiological one, represent the next frontier in electromagnetic biology and medicine. Currently, the biological effects of weak magnetic fields on living systems are being intensively studied, and a number of experiments have demonstrated that these weak fields are capable of eliciting *in vivo* and *in vitro* effects from different biological systems (Bassett, 1994; Jerabek, 1994; Rosch and Markov, 2004; Shupak, 2003). It has also been shown that MF and EMF may induce changes in living systems on the organism, tissue, cellular, membrane, and subcellular levels.

Therapeutic Magnetic Fields

What should magnetotherapy (MT) be, and how should it be developed? Magnetotherapy is a part of bioelectromagnetic technology, and therefore requires rigorous interdisciplinary research efforts and coordinated, educational outreach programs. The medical community should be aware that MT cannot be developed successfully without the joint efforts of physicists, engineers, biologists, and physicians. An important role will be played by medical practitioners, including physical and occupational therapists, who routinely use physical modalities, and basic scientists need to create dosimetry and methodology for MT. Saying that a patient was "magnetically stimulated" is about as non specific as saying a patient was given a drug; magnetic field stimulation requires as precise dosage as any other therapy. However, "dosage" is more complicated because it requires understanding a number of physical parameters which characterize the magnetic field generating system. It is important to establish the proper target for magnetotherapy. For example, it has been shown that to stimulate coagulation, one combination of parameters of applied field are required, whereas stimulation of anticoagulation requires an other field configuration (Markov and Todorov, 1984; Todorov, 1982).

Space does not permit more than a superficial presentation of the relevant evidence here to support the statement that "different MF produce different effects in different biotargets under differing conditions of exposure."

An evaluation of the efficacy of these modalities should be based on recognition of the clinical problem, identification of the physiological responses, and a critical review of the reported basic science and clinical data (which includes patient characteristics). Any magnetic stimulation starts with identification of the MF parameters needed for the desired target tissue. The ability of MF to modulate biological processes is determined first by the physiological state of the injured tissue, which establishes whether or not a physiologically relevant response can be achieved and, secondly, by achieving effective dosimetry of the applied MF at the target site. The therapeutic effect depends upon the spatial distribution of MF in the injured site.

In general, EMF therapeutic modalities can be categorized in five groups:

- permanent magnetic fields
- low-frequency sine waves
- pulsed electromagnetic fields (PEMF)
- pulsed radiofrequency fields (PRF)
- transcranial magnetic/electric stimulation.

Permanent magnetic fields can be created by various permanent magnets as well as by passing direct current (DC) through a coil. *Low-frequency sine wave electromagnetic fields* mostly utilize a 60 Hz (in USA and Canada) and a 50 Hz (in Europe and Asia) frequency used in power lines. *Pulsed electromagnetic fields (PEMF)* are usually low frequency fields with very specific wave shapes and amplitude. The variety of commercially available PEMF devices makes it difficult to compare the physical and engineering characteristics of devices, and it is the main obstacle in the analysis of the biological and clinical effects of those devices. *Pulsed radiofrequency fields (PRF)* utilize the frequency of 27.12 MHz in two modifications: in continuous mode it usually produce deep heat, while pulsed (non thermal) mode is used for soft tissue stimulation. More recently, *millimeter waves* (having very high frequency of 30–100 GHz) have been used in the treatment of a number of diseases, especially in the countries of the former Soviet Union (Devjatkov and Betskii, 1994; Pakhomov et al., 1998; Rojavin and Ziskin, 1998). *Transcranial magnetic stimulation* represents stimulation of selected portion of the brain by applying very short magnetic pulses of up to 8 Tesla.

Magnetic stimulation provides beneficial and reproducible healing effects even when other methods have failed. However, there is a lack of uniformity among medical practitioners with respect to stimulation, the parameters of the applied fields, and lack of defined biophysical mechanism capable of explaining the observed bioeffects. Therefore a systematic study of MF action on biological systems has to consider the following important parameters:

- type of field
- intensity of induction
- gradient (dB/dt)
- vector (dB/dx)
- frequency
- pulse shape
- component (electric or magnetic)

- localization
- time of exposure
- depth of penetration.

In the case of permanent magnets and static magnetic fields, parameters like time gradient (dB/dt), frequency, and pulse shape components are not applicable because there is no time dependence.

An important feature of magnetic/electromagnetic stimulation is that for most electromagnetic fields (especially in the relatively low-frequency range), electric and magnetic field components behave differently. Once an electric field reaches a surface, it develops an electric current along the surface. In contrast, most materials are transparent to the magnetic field component, which can penetrate deeply, and the depth of penetration depends on the technology used to generate the magnetic field, and on the composition and geometrical shape of the applied magnets.

A common problem when comparing the effects of magnetic devices is that each manufacturer uses their own system of characterizing the product and in most cases the stated magnetic field strength is often different than direct measurement. My own experience with distributors of permanent magnets suggests that the description of the field strength of magnets in the promotional and technical materials is overstated when indicating the magnet strength. Unfortunately, in MT, more does not necessarily mean better.

The industry that manufactures permanent magnets has 22 levels in its standard manufacturing procedure, each one related to a different level of magnetization of the metal pieces. Magnetization occurs by exposing the metal pieces to an electric current/field that orients the elementary magnetic particles/components in the same direction. The process relies on the basic physics of magnetization, and the strength of the magnet reflects volume magnetization, not the surface field strength of the magnet. Therefore, when a manufacturer claims that the “gauss rating” is 3950 Gauss, it means only that this is a magnet corresponding to class five in the 22-stage scale. Due to the lack of knowledge concerning the manufacturing process and to marketing competition, a consumer purchasing a 3950 Gauss rated magnet might get one which has less than 1000 Gauss surface field strength that decreases to 500 Gauss at 2 mm from the surface of the magnet.

Limited Medical Acceptance of the Use of Magnetic Fields

Magnetotherapy has limited acceptance in the Western medicine despite years of experience elsewhere, documented successful use of, and considerable literature describing the beneficial effects of magnetic and electromagnetic stimulation. Some of the essential elements of the rapidly growing and expanding database on reproducible biological and clinical effects of selected magnetic fields are not well known or interpreted too narrowly by physics, medicine, and the regulatory and public sectors of society. As a result:

- Medical practitioners are unprepared to utilize this technology.
- Regulatory activity is unnecessarily restrictive to the detriment of patient care and cost containment.
- Public concern about the safety of magnetic and electromagnetic fields is sensationalized in news media.

In order to reproduce observed effects, all terms in the equation must be correct: complete dosimetry of the study, a well-established biological and clinical protocol, and a complete report of the experimental conditions of each study. Any failure to reproduce the reported effects of biological or clinical study is, in many cases, due to the failure to explain the exact conditions and/or omitting some of the relevant details. Models and magnetic field parameters vary greatly and, in most cases, they are selected not as a result of rigorous analysis, but by the engineering and physics abilities of a given exposure system and by the intuition of the investigator.

Medical students approach anatomy, physiology, and disease through chemistry and biochemistry with little attention to physics and biophysics. In general, their analysis of biological responses and clinical outcomes rarely would include physics and biophysics. Despite knowledge of biochemistry and pharmacology, to move forward with MT, physicians at all levels would benefit from a stronger foundation in the principles of thermodynamics and electrodynamics, biomechanics, electricity, and magnetism.

Another obstacle facing MT is the question of mechanism of action. The fact that a single exact answer to this question is not yet available (and probably years and/or decades away) should not prevent people from having confidence in the application of this modality. Although the mechanism(s) of action of MF are not completely understood, in many cases, the mechanism of action of many pharmaceuticals is not completely understood.

There is probably not one unique mechanism of action of MT. Magnetic fields differ in their physical parameters, so it is unlikely that a complex system like the human body will respond in one way. For example, static magnetic fields may generate a different biological response than that occurring in the same system when a high frequency magnetic field is applied.

Another important question is to what extent magnetic fields represent a hazard for the users. It is very unlikely that the therapeutic application of magnetic fields is a hazard to the patient. The therapeutic procedures are conducted by skilled professionals who are trained to recognize and respond to a problem. If one is to argue that the use of MT has potential hazard, the risk is more to operators of devices, since they are potentially exposed to magnetic fields during treatment and non treatment time. Although many people have benefited from the use of magnetic field stimulation, there are patients who (as with any therapy) have not responded to treatment, and some who have experienced adverse effects.

Physiological Basis for the Use of Magnetic Stimulation in Tissue Repair

Analyzing the successful treatment of diseases and healing of injuries could elucidate the cellular and tissue components that may be plausible targets for MF action. Since an important clinical principle of health management is to provide a natural physiological environment for optimum healing, the proper choice of the MF parameters may significantly enhance the healing process. It is possible, then, that exogenous MF could recreate normal physiological conditions, and return the tissue or body to a disease/injury free status.

Basic scientific studies suggest that nearly all participants in the healing process (such as fibrinogen, leukocytes, fibrin, platelets, cytokines, growth factors, fibroblasts, collagen, elastin, keratinocytes, osteoblasts, free radicals) exhibit alterations in their performance when exposed to the action of MF (Bourguignon and Bourguignon, 1989; Detlavs, 1987; Katz et al., 2005; Leszczynski et al., 2003; Markov, 1995, 2004a,b; Polk, 1994; Rosch and Markov, 2004; Shupak, 2003). MF may also affect vasoconstriction and vasodilation, phagocytosis, cell proliferation, formation of cellular network, epithelization, and scar formation (Bassett, 1989, 1994; Markov and Pilla, 1995; Markov and Colbert, 2000; Rosch and Markov, 2004).

It has been shown that MF stimulation can trigger most of the processes involved in bone and soft tissue healing. Several animal models have been developed to investigate, in well-controlled clinical and experimental conditions, the effects of MF stimulation on healing of fractures, wounds and pressure ulcers in animals (Alvarez et al., 1983; Pilla, 1993). This approach allows results to be collected more quickly, including in a double-blind study.

Both animal and clinical data demonstrate that physical parameters and patterns of the application can affect the type of effect, and the efficiency in producing a response. Evidence of bioresponse specificity has been collected in a number of tissue culture, animal, and clinical settings. Studies indicate that amplitude, frequency, and exposure pattern windows apparently determine whether a bioeffect will occur and, if it does occur, what its nature will be (Bassett, 1978, 1989; Markov and Todorov, 1984; Markov and Pilla, 1995; Pilla and Markov, 1994).

Biochemical and physiological processes are based on the flow of electrical charges (ions, electrons) or charge redistribution in case of conformational changes. Therefore, when an injury disturbs tissue integrity, a net flow of ionic current through the low resistance pathway of the injured cells occurs. 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. Due to its ability to penetrate deeply, exogenous MF can effectively influence normal and injury currents, thus contributing to the healing process. Basic science and clinical data indicate that the interactions of MF with any structure in the human could initiate biophysical and biochemical changes, which in turn modify the physiological pathways and could contribute to the healing process. Since the energy applied is below the thermal threshold level, it is more likely that MF triggers some important biophysical/biochemical cascade, and affects signal/transduction pathways.

Healing occurs via a series of integrated stages, each of which is essential to the repair processes. Therefore it is important to evaluate the contribution of basic cellular activities occurring at a stage in tissue repair. 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.

Magnetic and Electromagnetic Stimulation

Several decades of clinical application of various magnetic fields have clearly demonstrated the potential benefit of the use of selected magnetic fields for treatment. The success of MT depends on the proper diagnosis and selection of physical parameters of applied fields. Soft tissue and bone/cartilage systems have been successfully treated with the most notable being treatments for problems related to muscular-skeleton system (Bassett, 1994; Detlavs, 1987; Jerabek, 1994; Markov, 1987; Todorov, 1982). However, there are also reports applying magnetotherapeutic systems to treat vascular, immune, and endocrine systems (Jerabek, 1994; Rosch and Markov, 2004; Todorov, 1982).

A literature survey indicates that many electric and magnetic modalities have been developed to heal non union fractures and wounds (Bassett, 1989; Markov, 1995; Markov and Pilla, 1995; Pilla, 1993; Vodovnik and Karba, 1992). The non invasive EMF most often employed in the U.S. for soft tissue applications is short-wave pulsed radio frequency (PRF), based on the continuous 27.12 MHz sinusoidal diathermy signals and used for decades for deep tissue heating. The pulsed version of this signal was originally reported to elicit a non thermal biological effect by Ginsberg (1934). PRF magnetic fields have reduced post-traumatic and post-operative pain and edema in soft tissues, and applied to wound healing, burn treatment, ankle sprains, hand injuries, and nerve regeneration (Barclay et al., 1983; Markov, 1995; Markov and Pilla, 1995; Wilson, 1974). Pulsed radiofrequency magnetic field treated pressure sores in patients 60–101 years old resulting in significant reduction (up to 47%) in the mean sore area after 2 weeks of treatment; the mean duration of pressure sores (before treatment) was 13.5 weeks (Seaborne et al., 1996).

In addition to accelerated wound healing, MF modalities have been shown to significantly increase local blood flow in the stimulated area improving the status of the ischemic tissue. There are *in vitro* studies suggesting significant alterations in cell division or differentiation which are important for wound healing (Bassett, 1989; Dunn et al., 1988; Markov, 1994). Magnetic and electric stimulation has been associated with increased collagen deposition, enhanced ion transport, amino acid uptake, fibroblast migration, ATP, and protein synthesis, including a significant increase in the rate of protein and DNA synthesis after stimulation of human fibroblasts in tissue culture (Dini and Abbro, 2005; Luben, 1994; Okano et al., 2005b; Rosch and Markov, 2004; Sisken and Walker, 1995). One area of interest is the effect of EMF and MF on cell proliferation. Most cells normally differentiate to a specific morphology and function. In pathological conditions, cell proliferation is usually suppressed (in conditions of chronic wounds) or enhanced (in the case of neoplastic growth). Magnetic field stimulation of the skin fibroblast resulting in significant increase in collagen secretion and protein concentration has been reported, and these results suggest a favorable alteration in the proliferative and migratory capacity of epithelial and connective tissue cells involved in tissue regeneration and repair (Bourguignon and Bourguignon, 1989; Rodeman et al., 1989).

Over the past two decades, several methods for therapy of the peripheral vascular system using SMF have been developed (Jerabek, 1994; Zukov and Lazarovich, 1989). The clinical outcome of this therapy includes analysis of hemodynamics, microcirculation, transcapillary phenomena, morphological, and cytochemical characteristics of blood components, including lymphocytes, erythrocytes, leukocytes, and thrombocytes. Low-intensity SMF stimulates the microcirculation, and initiates compensatory/adaptational changes in elderly patients with arteriosclerosis. The therapeutic efficiency was dependent on the status of the patient (age, general health, gender) as well as on the disease stage. There is also a distinct relationship between specific diseases and the MF parameters which initiate optimal response. Using non contact methods for analysis of the histochemical permeability of capillaries, as well as partial oxygen pressure, developed a method for dosage of the therapy (Zukov and Lazarovich, 1989). Improved blood perfusion in the magnetically stimulated tissue has been an assumed mechanism for the stimulatory effects on the regenerative processes (Illis, 1982). These clinical observations, along with the findings that blood flow and metabolic activity increase after long-term muscle stimulation, motivated a series of studies of the effects of magnetic fields on different health problems.

Double-blind studies have demonstrated the potential of a static magnetic field to provide significant pain relief (Colbert et al., 1999; Takeshige and Sato, 1996; Valbona et al., 1997). Valbona's study showed that an SMF of 300–500 G decreases the pain score in postpolio patients as 76% vs. 19% in placebo group, and Colbert's study used mattresses that utilize ceramic permanent magnets with surface strength of about 1,000 G (Colbert et al., 1999), Valbona et al., 1997). The estimated field strength on the body surface in Colbert's study was in the range 300–500 G, depending on the body mass of the patient. This magnetic field helps patients suffering from fibromyalgia, and improves the status of the patients in the real treatment group with more than 30%. Weintraub's pilot study reported significant improvement in 75% of patients with diabetic neuropathy who used permanent magnetic field stimulation (Weintraub, 1998). These three studies dealt with pain management for patients having quite different symptoms, and the proper choice for application of the magnet, in particular on trigger points for post-polio patients, is important for therapeutic success.

Advantages of MF Stimulation Compared with Current Stimultion

Electric current stimulation has a long history of application as a therapeutic modality in Western medicine. However, there are significant differences between electric current and MF modalities. Electric current stimulation requires skin contact electrodes placed either on both sides of the wound/injury or with one electrode on top of the wound, and the other over normal adjacent tissue. Electrode size, spacing, and polarity are the most critical factors for delivering 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. 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, or electrophysical effects depending on the type of the electrical current, and can occur at membrane, cellular, or tissue level immediately after applying the voltage. The direct responses usually result in many indirect cellular reactions, which may subsequently alter biochemical and physiological pathways.

MF represents a significantly more effective approach to the healing process—it is an easier to apply, less expensive comfortable therapy. MF modalities do not exhibit the complications of contact electrodes because the fields are inductively coupled, i.e., contact is not necessary to achieve the desired dose at tissue level. Thus, MF can be applied in the presence of a cast or wound dressing. The risk of infection is significantly reduced, and dressings may remain as long as the therapy requires. An advantage of this modality is to know the value of the magnetic field in any section of the tissue. The magnetic flux density remains unchanged while tissue dielectrics change as a function of healing, resulting in consistent dosimetry throughout the healing process.

MF can stimulate migratory, proliferative, and biosynthetic responses in cells and tissues that have an important role in soft tissue repair. Because cells involved in these repair processes are very heterogeneous, depending on the stage of injury and magnetic field parameters, results may vary. Therefore, more research into all these effects and processes in experimental and clinical conditions is of considerable importance, particularly as the number of electromagnetic technologies and devices used in clinical practice grows. Cooperation between researchers from different areas of expertise would significantly improve magnetotherapy.

The choice of a therapeutic device is based on its biological and clinical effectiveness. The field amplitude, spatial distribution, and duration of exposure must be adequate to meet the requirement of therapy. MF treatment requires placement of the patient and applicator in close proximity, therefore a permanent magnet may be fixed to the site of pathology during therapy. Modalities which utilize electric current or electromagnetic fields may require the patient to be available at specified time periods at treatment facilities. The use of the equipment and the treatment protocol requires simple and easy manipulation with stimulation devices by clinicians and, in some countries, by patients.

By contrast, static magnetic fields generated by permanent magnets are usually small, portable, safe, and easy to operate. In addition, permanent magnets resolve safety problems: there are no problems with electrical contacts or with the amplitude of applied field. The World Health Organization recommends fields up to 20,000 G for therapy (WHO, 1987).

However, the advantages of using magnets with minimal clinical supervision can be a disadvantage for executing double-blind studies, since a patient can discover whether they are using as active or placebo device, and this is a criticism of these studies. However, this article is discussing the therapeutic use of MF, not double blind studies.

An up-to-date reference discussing research in magnetic/electromagnetic therapy is Bioelectromagnetic Medicine, co-edited by Rosch and Markov (2004).

Therapy that Utilizes Static Magnetic Fields

There has been significant interest in the U.S. recently to alleviate pain of different origins using permanent magnets. For most of the market in the U.S. there are two types of magnets: “hard” materials including ceramic or metal such as neodymium-iron-boron or samarium-cobalt, and “flexible” materials in magnetic sheets referred to as plastilloy. The use of static magnetic fields for therapeutic purposes represents only part of magnetotherapy, and it should be emphasized that a magnet cannot heal by itself. Beneficial therapeutic effects are due to the magnetic fields applied to the target tissues using permanent magnets as the delivery system.

Basic science and clinical data support the use of permanent MF in the treatment of acute and chronic injuries, especially where conventional methods fail. Theoretically, the beneficial effects could occur by direct interaction between MF and biomolecules and structures, or indirectly involving signal-transduction pathways. MF are also important in the diagnosis and treatment of the central and peripheral nervous system and in reducing pain and discomfort, with a faster return to an improved lifestyle and to work.

Characterizing the potential of a magnetic field to alter existing biochemical and biophysical processes requires knowing the characteristics of the magnetic field, and the appropriate sequence is physics-biology-therapy, incorporating all three. Distributors of magnets may pay less attention to proper characterization of their products, and more to claims of efficacy. Once a serious scientific approach is taken, acceptance of anecdotal studies decreases. For example, most permanent magnets are marketed with unrealistically high magnetic field strength. Only a few companies use the term "gauss rating" to characterize their products. But this term could also be misleading, since "gauss rating" may be used to characterize the magnet itself, but not the magnetic field outside the magnet. As discussed previously, the magnetic field strength at close proximity to the surface of magnet is likely to be 4–10 times smaller than the manufacturer's "gauss rating" of the magnet.

Another problem is the difference between "unipolar" and "bipolar" magnets. "Bipolar" are magnets with a repeatable north/south polarity created on the same side of the material. These magnets are usually thin and flexible, made by specific materials called "plastic alloy" that use patterns such as concentric circles, checkerboard, and others. The term "unipolar" indicates that there is only one magnetic pole at a given surface and it is used as an alternative to the "bipolar" where plastic alloy designs have both polarities on the same side of the magnet. It is impossible to have magnets with only one pole, and more appropriate is to use the term "unidirectional application" to describe the use of these magnets, since most of the products available include a number of magnets in a pad. These types of magnets may be neodymium, ceramic, or plastic alloy.

A basic physical principle states that the magnetic field strength strongly depends on the number of elementary magnets in a unit volume, which during the magnetization process orient unidirectionally and metal-based magnets have the potential to deliver stronger magnetic fields. With "unipolar" magnets, the poles are on different sides of the material which allows deeper penetration of the magnetic field. Magnetic fields are described with field lines that connect both poles. For that reason, having both poles on the same side is characterized by a shorter arc of connection between the poles. When the poles are on either side of the magnet, the arc is longer and goes farther in the 3-D space around the magnet. Physics also suggests that the continuum of magnetic field lines will have a significantly smaller arc when both poles are on the same side of the magnet. In general, there is 4–8 times difference in the depth of penetration of "unipolar" vs. "bipolar" magnets in favor of the "unipolar" magnets.

A biologically and clinically relevant characteristic of the magnetic field is the field strength at the target site. The 3-D dosimetry of the magnetic field is extremely important to analyze and further predict the biological effects at the given target. A number of studies of *in vitro* biological response to applied magnetic field suggest the existence of biological "windows". The "windows" represent combinations of amplitude and exposure duration within which the optimal response is observed, and once outside this range, the response is found to be significantly smaller. This demonstrates the principle that "more does not necessarily mean better". For static magnetic fields, several "windows" have been detected at 5–20 G, 150–200 G, and 450–500 G (Markov, 2004; Markov et al., 1975; Zukov and Lazarovich, 1989).

It should be emphasized that expected therapeutic results depends on the magnetic field strength at the target tissue. Therefore, "gauss rating" and even the field strength at the surface of the magnet are insufficient and irrelevant to predict expected therapeutic effects. The relevant physical parameter is the magnetic field at the target site. Therefore, bipolar magnets are capable of creating biologically significant magnetic fields at a relatively short distance from the surface of the magnet (usually with the range of 1–1.5 cm). By contrast, the magnetic field created by "unipolar" magnets penetrates to a greater depth. In a very well-designed study, the data suggested that not only the field strength, but also the gradient of the field might be of importance for achieving the desired biological and clinical effects (Hirai et al., 2005; McLean et al., 1995). This was further reconfirmed by using myosin phosphorylation approach in estimating potential effects of magnetic fields (Engstrom et al., 2002).

Mechanisms of Action

MF/EMF are not widely used treatments, possible due to the absence of a well-established mechanism for EMF bioeffects. MF may enhance blood circulation, but few publications support that statement (Kobluk et al., 1994; Zukov and Lazarovich, 1989). It appears that the vascular and lymphatic systems can be activated by MF and some of the beneficial effects, especially reducing of edema, can be attributed to the MF action.

Magnetic and electromagnetic fields of different types (static and time-varying, continuous and pulsed) with a broad intensity range (1 μT–15 T) have been reported to interact with immune cells (Markov et al., 2006). However, most of the publications lack the basic information to explain the choice of a particular signal. In vivo, MF and EMF have been shown to significantly reduce pain levels in patients suffering from a number of diseases (Alvarez et al., 1983; Bassett, 1992, 1994; Bental, 1990; Brown et al., 2000, 2002; Colbert et al., 1999; Darendeliler et al., 1997; Detlavs, 1987; Eccles, 2005; Holcomb et al., 2000; Jerabek, 1994; Karba et al., 1995; Lawrence et al., 1998; Markov and Pilla, 1995; McLean et al., 1995; Markov et al., 2006; Rogachefsky et al., 2004; Rojavin and Ziskin, 1998; Shupak, 2003; Sisken and Walker, 1995; Todorov, 1982; Tofani et al., 2002, Vodovnik et al., 1986; Xu et al., 1998, 2000; Zukov and Lazarovich, 1989). This led to the hypothesis that the beneficial effects of EMFs could be achieved by regulating inflammatory immune processes. Studying B and T lymphocytes from healthy and sick subjects exposed to MF/EMF is a plausible way to improve our understanding of how MF functions as medical therapy (Markov et al., 2006). Numerous immunological studies reporting MF effects in the refereed literature establish the fact that even low-intensity MF can interact with immune cells and tissues (for review, see Markov, 2006). The challenge to successfully implement MF therapy is to develop new models of the interactions between MF fields and biological material.

MF are, in principle, capable of inducing selective changes in the microenvironment around and within the cell, as well as in the cell membrane. Therefore, MF might provide a method for modifying cellular activity that in turn may correct selected pathologies. Assuming that the exogenous signal can be detected at the cell or tissue level, the biophysical mechanism(s) of interaction of weak magnetic fields with biological tissues as well as the biological transductive mechanism(s) remain to be elucidated. At present, the following areas appear to be of scientific and medical interest:

- search for possible targets for magnetic fields
- examining biophysical mechanisms of MF action on living systems

- evaluation of “window” effects
- adaptation of living system to applied MF
- long-lasting effects.

Permanent magnets are being used as therapeutic modalities often to alleviate pain, and some authors suggest that magnets relax tense muscles or improve sleep. Some of the proposed mechanisms include acceleration of capillary blood flow, relaxation of muscles and connective tissues, and analgesic effects. The possibility of enhancing the removal of lactic acids and other metabolic byproducts has also been considered (Markov, 2004a,b).

The investigation of the biophysical mechanisms of action is important because it examines the nature of the initial physicochemical interaction of MF 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, and when cells are organized in a tissue, cell-cell communications (mainly via gap-junctions) should be considered. The proper conduct and analysis of *in vivo* experiments requires an awareness of the complexity of the animal/human organism and existence of compensatory mechanisms. The cell membrane is often considered the main target for MF signals, and it has been suggested that even a small change in transmembrane voltage could trigger a significant modulation of cell function (Adey, 1993; Markov, 1994, 2004a,b; Sisken and Walker, 1995; Traikov et al., 1994). Examination of signal transducing pathways also appears to be important in studying reactions of living systems to any MF (Luben, 1994). Most of the signal transduction pathways offer enzymatic amplification of MF stimulus into measurable cellular response at the level of the second messenger. Beginning with the electrochemical information transfer hypothesis, most results point to an MF effect on the rate of ion or ligand binding to enzyme and/or receptor site acting as a modulator of the ensuing biochemical cascades often involving calcium/calmodulin dependent processes, cAMP, and growth factors (Liboff et al., 2003; Markov and Pilla, 1995; Markov, 2004a,b; Pilla, 1974). A local tissue effect is supported by increased ATP and protein synthesis observed in animal tissues and cell culture. MF 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 conditions of dealing with chronic wounds) or enhanced (as in the case of neoplastic growth) (Markov, 2004; Rosch and Markov, 2004; Shupak, 2003).

The cell membrane may be a site of interaction of low-level MF by altering the rate of binding of 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 has widespread acceptance. 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.

The interactions of ions at the electrically charged interfaces of a cell are an example of a potential or voltage dependent process, important in understanding the nature of magnetic and/or electromagnetic stimulation since any EMF interacts with an electrically charged surface or macromolecule. In injured tissue, cell membranes are destroyed or at least modified. Magnetic fields change the structure of the double electrical layer around the cellular membrane (Blank, 1988), as well as to initiate redistribution of the surface electrical charges over the membrane (Markov, 1990).

There has been recent interest in explaining MF initiated bioeffects by studying the existence of specific domains for MF in several heat-shock proteins. (Blank, 1997, 2004a,b; Leszczynski et al., 2003).

Several authors have considered the role of iron-containing molecules such as transferrins, with their specific receptor on the cell surface, and heme-containing proteins that couple receptors to enzymes at cellular membranes (Adey, 1993; Phillips, 1986). Some biological organisms and structures contain magnetite which could be a detector of magnetic fields, although it may play a more important role in magnetic diagnostics than in magnetotherapy (Kirschvink et al., 1992).

Two problems related to 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 which allows surrounding tissues to grow and restore physical and chemical functions. An important part of intracellular communication in healing is performed by peptide signaling molecules—growth factors, which enable communication between cells involved in the healing process and between cells and their environment, thus restoring local homeostatic equilibrium. It has been suggested (Nordenstrom, 1983) 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). The results from treatment of edema indeed suggested that EMF affects sympathetic outflow, inducing vasoconstriction which restricts the movement of blood constituents from vascular to extravascular compartments of the injury site (Reed, 1988).

Modalities which utilize electric current, electromagnetic fields, and even certain static magnetic fields suffer from the requirement that the patient should be available for certain periods of time at treatment facilities, and the use of portable and easy to apply permanent magnets has reduced this requirement. Increasing use of permanent magnets provides evidence that static magnetic field may be a plausible modality for medical therapy, and an advantage is that permanent magnets are small and light-weight. They do not require immediate contact with the site of injury, therefore can be applied through a cast or bandage, and may be recommended for home use during that part of the day which is most convenient for the patient.

In clinical studies, bone unification and wound were accelerated when magnets were applied therapeutically (Bassett, 1994; Markov, 1995; Rosch and Markov, 2004; Yan, 1998). When applied to patients who underwent cosmetic surgery, magnetic field therapy was found to be helpful in the treatment of postsurgical symptoms and alleviation of pain, and the reduction in postoperative pain resulted in a decrease in the need for analgesic medication (Man et al., 1999; Markov, 1987). The action of permanent magnetic field includes a reduction of edema, an anti-inflammatory effect, and an analgesic effect. A possible mechanism for this is the increased blood flow to the site of surgery, which is pooling oxygen and nutrients, speeding the overall healing process.

Eccles' review of published randomized, double-blinded, placebo-controlled studies investigating the effectiveness of permanent magnets on pain relief found that 73% of well-controlled studies demonstrated that a statistically significant analgesic effect, achieved across a broad range of pain types: neuropathic, inflammatory, musculoskeletal, fibromyalgic, rheumatic, post surgical (Eccles, 2005).

Summary

Experimental and clinical data demonstrate that exogenous low-level magnetic fields can have profound effects on biological systems. The data on *in vitro* systems suggests that the biological activity of the cell (e.g., division or differentiation) can be modulated. Perhaps the greatest challenge for what we may term electromagnetic biology is to evaluate the dosimetry that will modulate biochemical cascades. This will have a profound impact upon the cost of health care worldwide.

The correct evaluation of the efficacy of magnetic stimulation for the acceleration of healing requires measurements and computations of a variety of parameters, such as amplitude, field gradients, duration of exposure, and others. Not only should the precise characteristics of the applied MF be taken into account, but also the exact diagnosis and all relevant clinical data. Further research into magnetic stimulation needs to identify which magnetic fields are detectable by cells or subcellular structures, and what are the cellular and tissue responses to the applied signals. These evaluations are important since there are a growing number of magnetic and electromagnetic technologies and devices being used in clinical practice. Cooperation between experts from physical sciences, engineering, biological sciences, and clinical medicine would significantly improve EMF-based therapy.

The application of magnetic fields for soft tissue, bone, and nerve healing and regeneration represent a frontier in electromagnetic biology and medicine. Laboratory and clinical data documented over the past 20 years suggests that selected MF could be used to treat a number of diseases other than skeleton pathologies which includes:

- chronic ulcers of venous and diabetic origin
- pressure ulcers
- burns
- neuropathy
- nerve and spinal cord injuries
- diabetes
- bronchial asthma
- ischemic skin flaps
- immune disorders
- intracerebral disorders
- myocardial pathology.

It appears logical to conclude this review with the following quote: "In the decade to come, it is safe to predict, bioelectromagnetics will assume a therapeutic importance equal to, or greater than, that of pharmacology and surgery today. With proper interdisciplinary effort, significant inroads can be made in controlling the ravages of cancer, some forms of heart disease, arthritis, hormonal disorders and neurological scourges such as Alzheimer's disease, spinal cord injury and Multiple Sclerosis. This prediction is not pie in-the-sky. Pilot studies and biological mechanisms already defined in primordial terms, form a rational basis for such a statement" (Bassett, 1992).

Work done in the years since the death of this prominent physician involved in the clinical application of electromagnetic field therapy have confirmed these predictions.

Appendix 1

Some recent publications in the English literature:

One quick review of the publications over the last seven years may reveal that moderate intensity static magnetic fields have enormous proven potential to alleviate or heal various ailments, such as pain (Brown et al., 2002; Holcomb et al., 2000; Hinman, 2002; Harlow et al., 2004; Panagos et al., 2004; Weintraub et al., 2003; Wolsko et al., 2004), bone repair and formation (Xu et al., 2001; Yamamoto et al., 2003), inflammation and wound healing (Man et al., 1999; Rogachefsky et al., 2004; Segal et al., 2001; Taniguchi et al., 2004), evocation of epileptiform activity (Dobson et al., 2000; Fuller et al., 1995), anticonvulsant effects (McLean et al., 2003), enhanced chemotherapy (Gray et al., 2000), central nervous system function (Veliks et al., 2004), and channel currents (Coots et al., 2004; Rosen, 1996, 2003a,b). In addition, action potential generation (Wieraszko, 2000; Ye et al., 2004), ATPase activity (Danielyan et al., 1999), cell shape and plasma membrane alterations (Chionna et al., 2003, 2005; Dini and Abbro, 2005; Pagliara et al., 2005), cell growth and gene expression (Potenza et al., 2004), accelerated osteoblast differentiation (Yuge et al., 2003), myosin phosphorylation (Engström et al., 2002; Liboff et al., 2003), increased release of cytokines (Salerno et al., 1999), enhanced cellular metabolic rate (Motta et al., 2001; da Motta et al., 2004), enhanced bioelectrocatalytic reactions (Katz et al., 2004, 2005), increased ion transport rate (Ohata et al., 2004), decreased expression of microtubule-associated protein-2 (MBP-2) (Hirai and Yoneda, 2004; Hirai et al., 2005), decreased expression of neuronal nuclei (Hirai and Yoneda, 2004), increased expression of glialfibrillary acidic protein (GFAP) (Hirai and Yoneda, 2004), increased bone sialoprotein (BSP) (Shimizu et al., 2004), apoptosis modulation (Buemi et al., 2001; Chionna et al., 2005; Dini and Abbro, 2005; Flipo et al., 1998; Fanelli et al., 1999; Tofani et al., 2001, 2002; Teodori et al., 2002a,b), reduced endothelin-1release (Pacini et al., 1999), decreased thymidine incorporation (Pacini et al., 1999, 2003), decreased chemotaxis of neutrophils (Sipka et al., 2004) and inhibition of angiogenesis (Ruggiero et al., 2004) have been reported.

Two recent books of interest are:

1. *Bioelectromagnetics: Current Concepts*. (2006). Ayrapetyan, S., Markov, M. Eds. Consists of 28 papers presented at the NATO Advanced Research Workshop that took place in Yerevan (Armenia). in Published by: Springer (ISBN#1-4020-4276-0).

2. *Bioelectromagnetic Medicine*. (2004). Rosch, P., Markov, M. Eds. Marcel Dekker.

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