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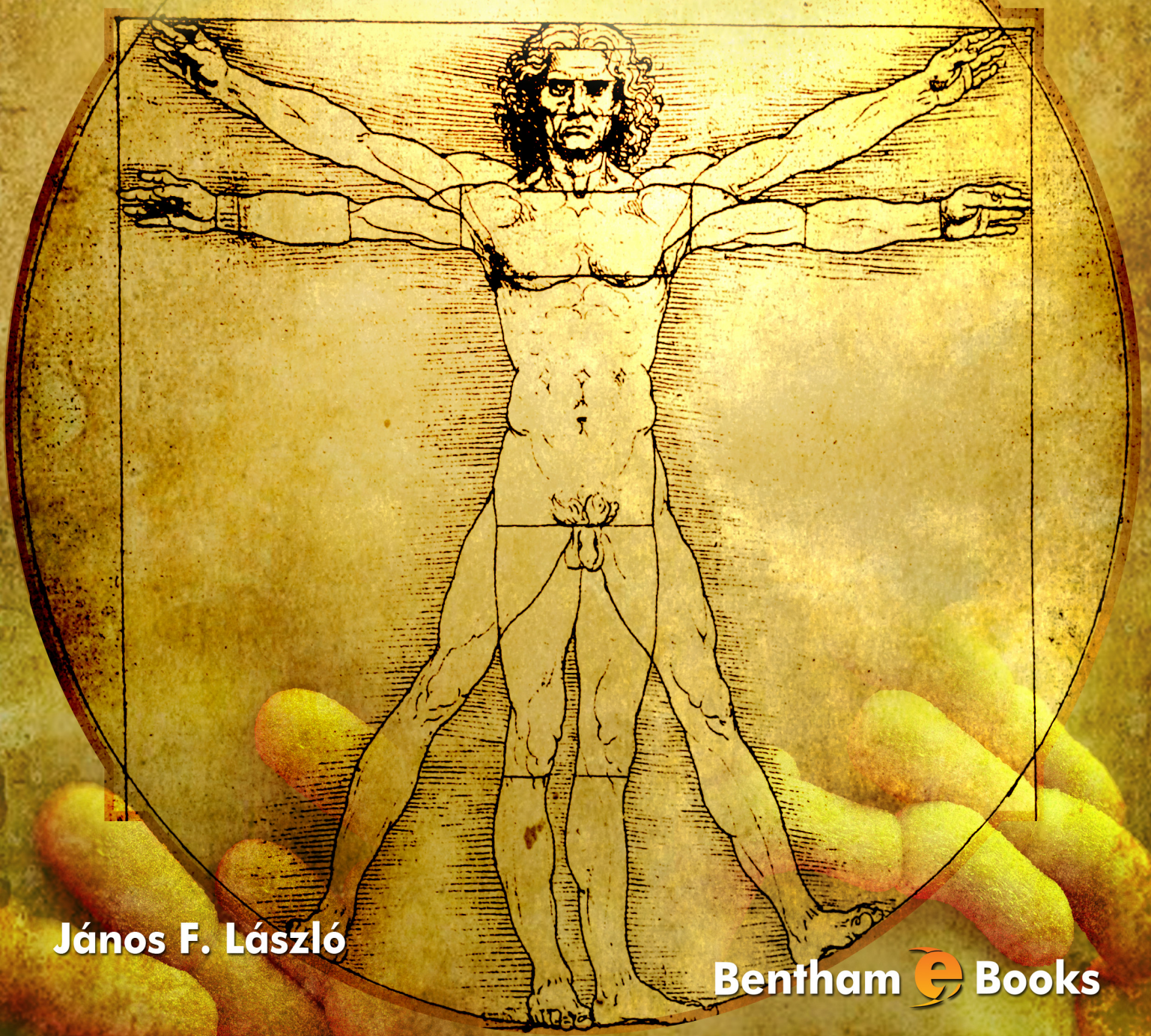
FROM MICROBE TO MAN

BIOLOGICAL RESPONSES IN MICROBES, ANIMALS, AND HUMANS UPON EXPOSURE TO ARTIFICIAL STATIC MAGNETIC FIELDS



János F. László

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From Microbe to Man

Biological Responses in Microbes, Animals, and Humans upon Exposure to Artificial Static Magnetic Fields

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Foreword

Dear highly distinguished reader,

Writing a foreword to a unique, fascinating, and excellent book is a great honor. The honor is combined with the feeling of pleasure and satisfaction as the whole creative process, the original concept, the brilliant ideas, as well as the experimental work I have known from the very beginning. The execution of original ideas needs enthusiasm, insistence, hard work, and first of all belief in that the concept is correct.

Dr. János F. László had original ideas, optimism, enthusiasm, and belief. He was a highly qualified physicist who approached the question of biological effects of static magnetic fields from the physicist's point of view. He aimed at obtaining legitimate evidence on the biological effects of static magnetic field under both *in vitro* and *in vivo* circumstances. In addition, he and his coworkers, collaborators, colleagues were not satisfied with providing merely a description of the effect of static magnetic field, but tried to clarify the mechanism of action, the time-dependency of the effect, and the "dose-dependency" of the SMF-induced action. Why is this important? Static magnetic field (SMF) therapy is used by large numbers of people for self-care all over the world; however, the SMF dosage, treatment regimens, and mechanism of action have not yet been established. Therefore, it is of utmost importance to elucidate, first under experimental conditions, the mechanism of action, the optimal duration to SMF exposure, and the effective dosage. The research initiated, carried out, and permanently stimulated by János László focused on these unanswered questions.

As the book quite adequately reflects, the analysis and examination of the biological actions of SMF were based on a well-designed systemic study. Experiments were carried out first in microorganisms (bacteria) than in mollusks, followed by mammals (mice and rats), and finally in humans. Thus, the book synthetizes the biological effects obtained from both animal and human subjects – and what is exceptional is that the outcome and conclusion were based on the author's own results – as opposed to the data in the literature. The final goal of all the studies was to establish the potency, efficacy, and safety of SMF which are the basis of its human application. Consequently, the results summarized in the present book have not only importance for basic science but also for clinical practice.

To my greatest sorrow, the preface cannot be finished by wishing the author further successful research and encouraging him to write the next volume about his newest findings. János László, shortly after finishing his excellent book, passed away leaving behind him many unanswered questions and unresolved problems. The present volume, however, will convince everyone that his oeuvre is complete, and this book which is based on wide

collaboration of different fields of science will certainly constitute a determinant reference book for a long time in the field of magnetic field research.

February 24, 2015. **Prof. Dr. Klara Gyires MD, Phd, DSc**

Preface

I am fully aware of the risk I undertook when, accepting the challenge; I decided to write this book. The challenge appeared in a crystal clear form of a kind request from Bentham Science. This very distinguished publishing company expressed their feeling that my experience with static magnetic fields (SMF) may be of interest to a broader audience. I hope they were right…

I spent almost 2 decades in the research field of controlled thermonuclear fusion, while being employed at the Technical University of Budapest, Hungary. Stellarators use very complex external SMF to keep the plasma focused inside the vacuum vessel. When facing the problem of SMF-exposure on living organisms, I felt predestined to contribute to this unique and challenging exploration.

What do I mean when I say I undertook some risk? The effect of SMF-exposure on living tissues is namely like sport. Few have adequate knowledge about it, while many have opinion or prejudice. It is also not widely acknowledged that in the past 60 years, parallel with the discovery and development of nuclear magnetic resonance spectroscopy (NMRS) and its entry to medical diagnosis (as magnetic resonance imaging or MRI), serious research has been done resulting in 7 Nobel Prize winners. This made it all the more important to clarify whether the result of the diagnosis of MRI would have a correlation with the SMF-exposure itself. Let us immediately clear some points:

- An SMF exists that has a clinically significant analgesic and anti-inflammatory effect,
- This response relies in the biology of the subject itself mobilizing its own defense systems in overcoming pathological conditions.

Taking risks happens when strong motivation is at hand. I happen to have several. I wrote this book, because (i) I wanted to overview what we have done in the past 7 years in a concise form, (ii) I want to encourage fellow scientists to join us and share our efforts and victories, (iii) I am looking for sponsors who would provide sources for research but leave research independent.

I am often asked by laypeople as well as professionals whether this or that jewelry, band, mattress, pillow, or disk including permanent magnets, available in the market would really "act" as pain-killer or anti-inflammatory device. Well, my best answer to that query is "I don't know. They may." My experience tells me that there are some arrangements, structures of permanent magnets that exert measurable (patho)physiological effects when living tissues are exposed to it. Such arrangements are discussed in this book, which makes up for the

evidence-based part of it. The scientifically non-evaluated and/or non-reproducible experiments with other arrangements “may still act”. They certainly “act” at the psychosomatic level. The placebo effect induced by magnetic fields can rise up to 60%. Is this good or bad news? Placebo effect itself has a good reputation and an evidence-based foundation in medicine, and serves as one of the most effective therapeutical strategies in otherwise unmanageable diseases. It is inexpensive, it acts immediately, and it can have a long lasting beneficial effect. However, placebo also has side effects. Unfortunately, there's no such thing as a free lunch.

A well-founded hope is slowly evolving that we might create a method for analgesia and anti-inflammation that is at least as effective as conservative options but may have fewer side effects and interactions.

Is it really a surprise for the respected Reader that static magnetic fields (SMF) can affect a living object? An ever increasing annual number of publications reporting about evidence-based medical research prove that living objects respond to external magnetic fields in a wide range of frequencies. These results are briefly reviewed in the preliminaries of the chapters. However, I feel encouraged to concentrate on our own studies which provide the first pieces of evidence in some fundamental aspects of research that exposure to an external, artificial SMF can induce or assist certain (patho)physiological effects.

This book basically covers all phases of studies regarding the effect of SMF-exposure on living matters starting from *in vitro* assays, through *in vivo* experimental tests, ending with human trials. In the beginning, though, I must be a little more technical in order to introduce the fundamental steps of medical device development to the Reader. Most of the developmental steps follow the rule: The stronger, the longer lasting, and the more prompt the beneficial response to SMF-exposure compared to sham-exposure, the further we got with the optimization of the SMF-producing generator.

In all honesty, I must admit that not all experiments provided evidence for the beneficial effect of SMF-exposure on the specific biological response tested. Even if a positive response was found, we were not always convinced that it was the exclusive action of SMF-exposure. Therefore, we had to differentiate between several options to the best of our knowledge.

1. Is there really no effect that can be measured?
2. Would there be an effect if we chose a more appropriate model?
3. Can we still miss observability of an effect in a perfect model by superficial execution?

These are concerns probably every researcher must deal with. However, we have never encountered a situation in which the exposure in the applied magnetic induction range and the

applied short periods of time would have caused negative (that is harmful) main or side effects.

Although the viability of a number of healthy microorganisms was tested *in vitro*, human lymphocytes and macrophages resulted in more interesting insight when SMF-exposure followed gamma-irradiation or lipopolysaccharide-activation. The Reader will soon realize that we spent most of our time with *in vivo* experimental research. The reason for this is that these tests have provided the most positive results; consequently, they were more applicable for device development. Within *in vivo* animal tests, we selected pain models in invertebrates and also in mammals, further divided into acute and chronic pain models, inflammation tests is mammals, as well as an allergy test. The human trials presented here must be considered incidental; nevertheless, they still open up new vistas of future research and development.

I am personally proud to have succeeded in getting a little beyond the level of phenomenology by revealing some of the possible background mechanisms in action. It seems obvious today that a living object that has self-motion in an external SMF is subject to an induced time-dependent magnetic flux and, consequently, to internal electric potential differences; however, the point whether these changes can be scientifically measured in the biological response is still open for discussion. A model is presented to physically correctly simulate and thus assess the generated magnetic potentials in rodents that move in an inhomogeneous SMF within geometric restraints.

When designing a model to test SMF-exposure, the first consideration, contrary to therapy, is (i) to expect a positive result. This condition was unfortunately very effective in limiting the number of models. (ii) Science in general must advance Based on experimental results; such results have either not yet existed or if existed, were ambiguous. (iii) The result should have a clinical relevance. Other factors that have also played a restricting role were (iv) time- and budget-restrictions. (v) Also, a laboratory should be picked for the measurement that has a traditional practice in the field of the model. This choice provided further advantages: The experience in the lab furnished us with immediately comparable results to those achieved with other (mostly chemical) agents in the same model. (vi) We started with *in vitro* and *in vivo* measurements where the role of placebo (and other psychosomatic) effects could be minimized. (vii) We always aimed at (but were not always successful in) repeating the experiment in another laboratory in order to check reproducibility. Another important point in the choice of experiment was the (viii) level of hospitality of the host institute for a new and important research field. I have astonishingly positive experiences with this latter factor.

Research in the field of SMF-induced or -assisted biological responses is a rather new, but very important and promising field with high expectations from both the research society as well as the average man. On one side of the topic is the knowledge we can gain from natural

sciences: The method of nuclear core and electron resonance, the spectroscopy methods of molecular, even atomic resolution, and the quantum mechanics describing their operation. On the other side there is the knowledge we obtain from life sciences, where explanation is given on the level of receptors and enzymes. The imaginary tunnel of scientific cognition is bored from both sides. Although we are unfortunately far from joining the 2 bores, the present book hopefully serves as a step from the direction of receptors toward magnetic spins.

The manuscript of this book is based on materials published in 2 book chapters:

Series in Mathematics and Life Sciences 1 (Antoniouk AV, Melnik RVN Eds.), De Gruyter, Berlin, Germany, 2013, *pp*. 247-275.

Recent Developments in Brain Research 1 (Pandalai SG Ed.), Research Signpost, Kerala, India, 2012, *pp*. 1-43.

and in the following papers (in anti-chronologic order and alphabetic order of journal name within):

Authors	**Article title**	**External reference**	**Year**	**Reference page number in this book**	**Publisher**
Kiss B, Gyires K, Kellermayer M, László JF	Lateral gradients significantly enhance static magnetic field-induced inhibition of pain responses in mice—a double blind experimental study	Bioelectromagnetics 34:385-396	2013	79, 97	Wiley
Mészáros Sz, Tabák AG, Horváth Cs, Szathmári M, László JF	Influence of local exposure to static magnetic field on pain perception and bone turnover of osteoporotic patients with vertebral deformity—a randomized controlled trial	International Journal of Radiation Biology 89:877-885		241	Informa Healthcare
Vergallo C, Dini L, Szamosvölgyi Zs, Tenuzzo BA, Carata E, Panzarini E, László JF	*In vitro* analysis of the anti-inflammatory effect of inhomogeneous static magnetic field-exposure on human macrophages and lymphocytes	PLOS ONE 8:e72374		183	PLOS

Authors	Article title	External reference	Year	Reference page number in this book	Publisher
László JF, Hernádi L	Whole body static magnetic field exposure increases thermal nociceptive threshold in the snail, Helix pomatia	Acta Biologica Hungarica 63:441-452	2012	51	Akadémiai
László JF, Farkas P, Reiczigel J, Vágó P	Effect of local exposure to inhomogeneous static magnetic field on stomatological pain sensation a double-blind, randomized, placebo-controlled study	International Journal of Radiation Biology 88:430-438		215	Informa Healthcare
László JF, Pórszász R	Exposure to static magnetic field delays induced preterm birth occurrence in mice	American Journal of Obstetrics and Gynecology 205(4):362.e26-e31	2011	145	Elsevier
László JF, Szilvási J, Fényi A, Szalai A, Gyires K, Pórszász R	Daily exposure to inhomogeneous static magnetic field significantly reduces blood glucose level in diabetic mice	International Journal of Radiation Biology 87:36-45		133	Informa Healthcare
Kovács-Bálint Zs, Csathó Á, László JF, Juhász P, Hernádi I	Exposure to an inhomogeneous static magnetic field increases thermal pain threshold in healthy human volunteers	Bioelectromagnetics 32:131-139		197	Wiley
László JF, Kutasi J	Static magnetic field exposure fails to affect the viability of different bacteria strains	Bioelectromagnetics 31:220-225	2010	41	
Kubinyi Gy, Zeitler Zs, Thuróczy Gy, Juhász P, Bakos J, Sinay H, László J	Effects of homogeneous and inhomogeneous static magnetic fields combined with gamma radiation on DNA and DNA repair	Bioelectromagnetics 31:488-494		175	
László J, Pivec N	Effect of inhomogeneous static magnetic field on dental pain in humans	Clinical Journal of Pain 26:49-55		205	Wolters Kluwer
Gyires K, Zádori ZS Rácz B László J	Analysis of inhomogeneous static magnetic field-induced antinociceptive activity in mice	Progress in Electromagnetics Research Symposium Online 6:307-313		79, 97	PIERS Online

Authors	Article title	External reference	Year	Reference page number in this book	Publisher
Antal M, László J	Exposure to inhomogeneous static magnetic field ceases mechanical allodynia in neuropathic pain in mice	Bioelectromagnetics 30:438-445	2009	125	Wiley
László J, Tímár J, Gyarmati Zs, Fürst Zs, Gyires K	Pain-inhibiting inhomogeneous static magnetic field fails to influence locomotor activity and anxiety behavior in mice: No interference between magnetic field- and morphine-treatment	Brain Research Bulletin 79:316-321		63, 79	Elsevier
Gyires K László JF	3 T homogeneous static magnetic field of a clinical MR significantly inhibits pain in mice	Life Sciences 84:12-17		91	
Gyires K, Zádori ZS, Rácz B, László J	Pharmacological analysis of inhomogeneous static magnetic field-induced antinociceptive action in the mouse	Bioelectromagnetics 29:456-462	2008	117	Wiley
László J, Reiczigel J, Székely L, Gasparics A, Bogár I, Bors L, Rácz B, Gyires K	Optimization of static magnetic field parameters improves analgesic effect in mice	Bioelectromagnetics 28:615-627	2007	79	
Sándor K, Helyes Zs, Gyires K, Szolcsányi J, László J	Static magnetic field-induced anti-nociceptive effect and the involvement of capsaicin-sensitive sensory nerves in this mechanism	Life Sciences 81:97-102		71	Elsevier

The Reader must be warned though that this book does not aim to summarize the complete craftsmanship accumulated about the medical applications of SMF-exposure, neither can it reveal all the gaps in knowledge. It certainly tries to untangle some areas that seem to be important from the clinical viewpoint. This book is not intended to be a review even if it contains a large enough amount of references to start a research in this field for a newcomer. It basically accounts for the author's own experience in life sciences during the past 7 years. Having a background in electric engineering and a history of almost 2 decades of university physics lecturing, the biology-related topics collected in this book come from the fresh aspect

of a particular and positively skeptic "outsider". By definition, a person is positively skeptic if he does not believe his own eyes, but is ready to learn, "to strive, to seek, to find, and not to yield" (from Alfred Lord Tennyson, English poet, 1809-1892). I personally take responsibility that every single statement I formulated in this book reflects evidence provided by our own experimental data, measured in the best possible way. Although double blinding could not always be carried out, we always strived after reproducibility.

In good faith,

János F. László,*
Budapest, Hungary, 2014
Email: anna.laszlo@connect.polyu.hk

*Dr. János F. László passed away after writing the manuscript. The book has been published post humously. It is the manifestation of the author's deep dedication to science and it represents the helping hand that researchers can grab to further their research in this field.

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I would never have been able to focus on the research enclosed in the present book without my family: My late parents, György and Éva László, my daughters, Anna and Júlia, and first of all my wife, Éva who has been a constant encouragement. Anna was an indispensable language corrector to this book.**

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Dedication

To my daughters, Anna and Júlia,
the greatest motivators

CHAPTER 1

Introduction

A special tribute is due here to those Hungarian researchers who substantiated the area of biophysics dealing with how different living tissues respond to SMF-exposure. Júlia Lengyel, a Hungarian physicist, was probably the first scientist, to have "scientifically conducted investigations" on SMF-exposure-related issues specifically on cancer more than 80 years ago [1] as referred to in the 2nd chapter: "Rejection of transplanted tumors in mice" by J. Barnóthy in the book Biological Effects of Magnetic Fields first published in 1964 [2]. The Barnóthy family, Jenő (who died 20 years ago) and Madeleine (born Magda Forró 110 years ago) primarily deserve the Reader's attention since they worked and published extensively in the area.

The present book does not need to prove that natural SMF like that of the Earth otherwise known as geomagnetic field influences living objects in multiple modalities. This fact has been evidenced and can be regarded as notorious. In the course of the 100 million years of phylogenesis, living organisms have gotten used to the geomagnetic field which has a vertical component of 43.6814 μT, a North-South component of 21.1571 μT, and an East-West component of 1.5483 μT at the place and in the time of my writing this text, 150 m above sea level [3]. Some animals developed special receptors that assist them in navigation. Magnetotactic bacteria [4], migratory fish, and bird species [5] have such animal "GPS". A receptor sensitivity level of 2 orders of magnitude below geomagnetic field induction of the Lorenzini ampoules help cartilaginous fish (rays and sharks) detect the hidden prey [6]. It has recently been revealed that even a type of mammal (a bat species) uses the geomagnetic field for navigation [7].

Human habitat on Earth creates a very complex system. Concentrating on merely natural magnetic phenomena, we can create a triangle with the vertices magnetism, climate, and biosphere, see Fig. (**1.1**). It has not yet been decided whether the geomagnetic field has a direct measurable effect on mammals, but little doubt occurs as to whether its changes in time cause measurable responses [8, 9].

Alterations in the geomagnetic fields, on the other hand undoubtedly lead to climate changes. Needless to say that this indirect effect of the magnetic field determines the health of a human, *i.e*. his homeostasis [10].

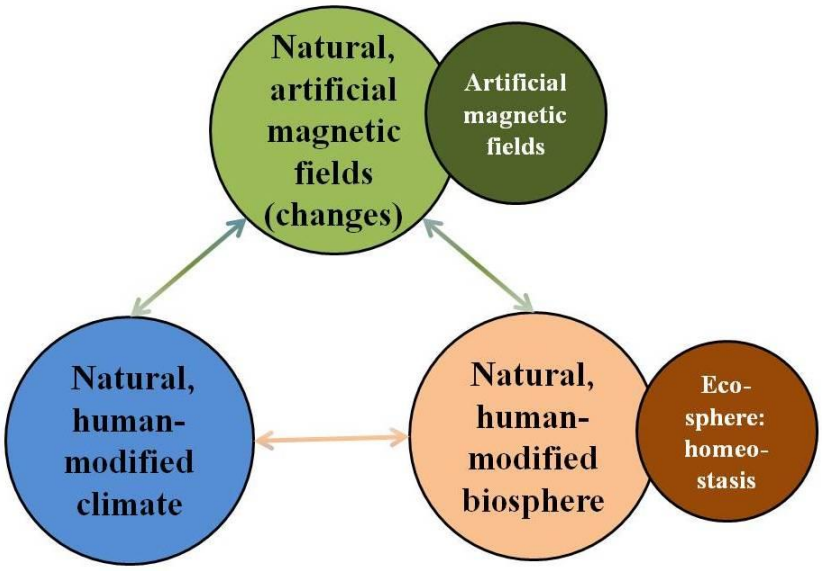

Fig. (1.1). Model of human habitat concerning magnetism, the essence of which is that the effects are introduced through time-dependence.

All 3 above mentioned components are interrelated directly as well as indirectly. The present book will allow me to focus only on a small but singular part of this complex system: The relationship between artificial SMF and human homeostasis within the global ecological biosphere.

We can suppose that the effect of artificial SMF-exposure on humans is also widely known. Nuclear magnetic resonance spectroscopy (NMR) was invented in 1945. Later, in the seventies it was completed with scanning and computer image processing, and was called magnetic resonance imaging (MRI). MRI has since become an important tool as a non-invasive method in modern medical diagnostics primarily useful for soft tissues. The importance of NMR (and MRI) has been punctuated 7 times so far, when 9 excellent scientists were rewarded with the Nobel Prize: Otto Stern in 1943, Isidor I. Rabi in 1944, Felix Bloch and Edward Purcell in 1952, Richard Ernst in 1966, Nicolaas Bloembergen in 1981,

Kurt Wüthrich in 2002, Paul C. Lauterbur and Sir Peter Mansfield in 2003. Raymond V. Damadian was the first in 1971 who initiated the "MRI industry" with his publication in Science as well as with the first whole-body diagnosis [11]. Magnetic fields were in the focus of research of Hendrik A. Lorentz and Pieter Zeeman, who won a Nobel Prize in 1902, Willis E. Lamb and Polykarp Kusch were awarded in 1955, while Robert B. Laughlin, Horst L. Störmer, and Daniel C. Tsui received one in 1998.

One current concern of MRI designers is how to improve visual resolution. One method is relatively straightforward; the SMF component of the MRI, B_0 should be increased. One of the first commercial MRI devices had a B_0 of 50 mT; companies today offer a wide range of machines in the 3-14 T range. Such high fields can be sustained exclusively by superconductive magnets, the cooling of which requires significant technical background, maintenance, and huge overhead costs.

Since the European Union (EU) banned the trade restrictions regarding the sale of medical devices with permanent magnets in 2002, the market was swarmed with "magic" and "enchanting" devices for practically all purposes: The same apparatus would increase low blood pressure (BP), while decreasing high BP at the same time. The question obviously arose: Do these devices have any influence on the human organism beyond psychosomatics?

SMF-exposure (MRI included) has progressed step by step to become a broadly examined physical agent; the database of NCBI (National Center for Bio-technology Information, in short PubMed) produces the following time development (Table **1.1**) if searched for "static magnetic":

Table 1.1. Number of publications in PubMed database, which contain "static magnetic" in the decades after 1960.

	before 1960	**sixties**	**seventies**	**eighties**	**nineties**
number of publications	1	10	31	258	1136

Similar data for this century until February 14, 2014 (Table **1.2**):

CHAPTER 2

Physical Properties of Static Magnetic Fields

Keywords: Hall-effect, Magnetic induction, Magnet therapy, Physical properties, Vector.

An SMF is conventionally described by the 3 dimensional magnetic induction ($\vec{B}$) or magnetic field strength ($\vec{H}$) vector. Since most applications in this book use SMF perpendicular to the surfaces of the living matter (except the 3 T clinical MRI), we choose to use magnetic induction whose component perpendicular to the interface between materials with different susceptibilities remains unchanged. I shall sometime abbreviate magnetic induction vector to induction bearing in mind that magnetic induction is a quantity, not a phenomenon. SMF is a special type of magnetic field in which induction does not change in time. In other words, it is time-independent, its time derivative is zero, or the field is simply static. However, even an SMF can and, as a matter of fact, always does change is space. We refer to SMF as inhomogeneous if at least one of its components has a non-zero induction derivative (gradient) in space. In the hypothetical situation when a magnetic field does change neither in time, nor in space, we call it homogeneous SMF. This is a mathematical model, an abstraction, since there are no infinite sources of magnetic fields, not to mention that along the edges the SMF will necessarily be inhomogeneous. The sources of SMF are electric currents or atomic particles (molecules) that have a net magnetic spin. We shall speak about the sources a little more in a little more detail in Chapter 3 (**Sources of Static Magnetic Fields**). Earth itself is a complex natural source of SMF due to the huge amount of minerals that are either magnetically anisotropic or in motion. Anisotropy is a term for being directionally dependent. Artificial magnetic fields generated by man are usually produced by electric currents. If the current is direct (DC) the resultant field is SMF; otherwise it becomes an electromagnetic field in the broader sense (AC, non-zero frequency). Nowadays, due to the development of materials science, permanent magnets that generate SMF easily 5-6 orders of

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magnitude beyond that of Earth and 2-4 orders of magnitude beyond that of natural magnetic ores can be manufactured. In some of the experiments reported in this book, we used magnetized cubes of size 10×10×10 mm that have a remanent magnetic induction (induction remaining even if the source magnetic field strength gets back to zero) of 1.47 T!

We stick to SI units in this book; accordingly, magnetic induction (or magnetic flux density or intensity in the English literature) has a unit named after Nikola Tesla (1856-1943), Serbian inventor. T (=Vs/m^2=Wb/m^2=N/A/m). magnetic flux is measured in Wb (=J/A=Tm^2) named after Wilhelm Eduard Weber (1804-1891), German physicist (the surface density of 1 Wb magnetic flux is 1 T, this is where the English nomenclature for magnetic induction originates from). magnetic field strength is in A/m (named after André-Marie Ampère, French physicist, 1775-1836). A particle carrying a charge of 1 C (after Charles Augustin de Coulomb, French physicist, 1736-1806) and passing through a magnetic field of 1 T at a speed of 1 m/s perpendicular to SMF experiences a force with magnitude 1 N (after Sir Isaac Newton, English physicist, 1642-1727). The unit V was named after Alessandro Giuseppe Antonio Anastasio Volta (Italian physicist, 1745-1827).

The grade of a permanent magnet relies on the maximum energy product of the materials the magnet is made of ($B\times H$), frequently provided by the manufacturers in English units. A grade N50 magnet, for example, is made of a material with a maximum magnetic load of 50 MGOe (megaGauss Oersted named after Carl Friedrich Gauss, German mathematician, 1777-1855 and Hans Christian Ørsted, Danish physicist, 1777-1851), *i.e.* about 4×10^5 TA/m.

MEASUREMENTS

In principle, the $\vec{B}(\vec{r})$ vector-vector function must be known (measured or calculated) at all $\vec{r}$ positions within the finite volume of the exposure chamber to fully describe the SMF. We actually measured all 3 components of the specific magnetic induction vector in our studies. Usually 2 of them were ignorable for their absolute values were orders of magnitude below the so-called dominant component as well as they decayed in the magnetic background. Such negligible

components were regarded as fringe field components.

TOOLS, SAMPLING

Magnetometers are used to determine the direction or magnitude of an SMF. Basically a magnetometer can be either "fluxgate" or based on the Hall-effect (named after Edwin Herbert Hall, American physicist, 1855-1938). Either way, one vector component can be measured at a time. The fluxgate magnetometer is a sensitive device; the mechanism is based on the different magnetic saturation of ferromagnetic materials. The probe consists of 2 parallel ferromagnetic cores, close to each other. A coil is wound around the cores, and thus the secondary AC current generated in the coil is detected. The signal of the coil is proportional to the induction of the external SMF, depending on the orientation of the SMF and the cores relative to each other. Fluxgate magnetometers have a measurement range between 1 nT to 10 mT. A special application of such magnetometers is using the corresponding component of the geomagnetic field as a basically constant bias allowing for the detection of SMF below that of Earth.

A probe based on the Hall-effect consists of a thin square pad or foil made of gallium- or indium arsenide semiconductor furnished with 4 electric terminals. DC is lead through the pad or foil between 2 opposing main terminals, and the potential difference between the other 2 cross terminals gets measured. The so-called Hall-potential is proportional to the magnetic flux through the pad or foil, to the cosine of the angle formed by the magnetic induction, to the main direction of the pad or foil (polarization dependence!), and to the DC current between the main terminals. Hall-probes can measure between 100 μT up to 100 T, in principle.

I wish to mention the superconducting quantum interference device (SQUID) here that is capable of measuring very small magnetic inductions (down to 5×10^{-18} T) based on superconducting loops containing Josephson junctions (after Brian David Josephson, Welsh physicist, 1940).

We used Hall-probes exclusively. In order to scan SMF along lines in a generator, the generator was set up on its side on a stable, solid surface, and its position was marked for repeated measurements. The active part of the Hall-probe (Model 420

CHAPTER 3

Sources of Static Magnetic Fields, Generators

Keywords: Generator description, Magnet arrangement, Magnet origin.

Several SMF types have been tested and are reported in this book. As mentioned in **Measurements**, from the viewpoint of a life sciences experiment an SMF must be considered a 6 dimensional vector space, given that every point of the SMF should be described by 3 components of the magnetic induction and 3 components of its gradient. It has been proven (and the Reader will see this shortly) that both induction and its gradient play an important role in the evocation of biological response independently of each other in certain ranges. If the sources of the SMF are permanent magnets, these 6 components depend on different parameters: Individual magnets (shape, size, and magnetization), and arrangement of the magnets (number, position, and polarity). The first step for us was to investigate 17 different arrangements and watch, which one induced the highest average response rate in a specific *in vivo* acute pain test, the writhing test in mice (see **Visceral action: The writhing test**). The optimal arrangement or its variations have then been used for a number of different measurements. We also developed more sophisticated SMF generator models in the hope that these will be more effective than the previously chosen ones regarded as optimal in selected tests. Such a special generator was used, for example, in section **On healthy volunteers**. The highest magnetic induction we used was the 3 T SMF provided in the bore of a clinical MRI in everyday use at Szentágothai János Knowledge Centre of Semmelweis University.

MAGNET MATERIALS

Since Hungary has never been famous of its magnet production, most individual magnets had to be imported. The question then raises, which country, which company would provide the highest quality for the most reasonable price. A company should be preferred, where production and trade is in one hand, so

quality control is not autotelic. At the same time, reliability should be present not only in the quality of the product, but in shipping and payment as well. What exactly did we expect from a magnet? Table **3.1** and Table **3.2** gives the answer with respect to the materials we finally used.

Table 3.1. Manufacturing, magnetic, mechanical, and material features of the material individual magnets were made of.

NdFeB	Barium ferrite
History	
Neodymium-iron-boron ($Nd_2Fe_{14}B$) tetragonal crystalline structured magnets were developed in 1982 by General Motors and Sumitomo Special Metals. This is the newest and strongest (per mass) type of permanent magnets. The alloy they are made of, together with samarium-cobalt, belong to rare earth metals group of materials. Their production technology is very similar.	A ferrite is a chemical compound of ceramic materials mostly consisting of iron oxide (Fe_2O_3). They were invented in 1930 at Tokyo Institute of Technology. Due to the low price and inexhaustible source of ingredients, their price is the lowest. On the other hand, because of their beneficial magnetic features, they present a good price/value ratio. Especially one type of hard ferrites is barium ferrite with the composition of $BaFe_{12}O_{19}$ ($BaO{\cdot}6Fe_2O_3$).
Manufacturing	
First raw material containing the necessary composition of ingredients are melted in a furnace, cast into a mold, and cooled to form ingots. Ingots are pulverized and milled to fine dust. This material undergoes a process of liquid-phase sintering which the powder is magnetically aligned into dense blocks. The blocks are then heat-treated, cut to shape, surface treated, and finally magnetized. Preventing corrosion, a galvanic coating with nickel or zinc is used. Better magnetic features and much lower price are the advantage of such magnets over samarium-cobalt ones.	Ferrites are produced by heating a mixture of finely-powdered precursors of 80% iron oxide and 20% barium carbonate ($BaCO_3$) pressed into a mold. The resulting mixture undergoes sintering (ferritization). Afterwards, the cooled product is milled to single crystals with particles small enough to consist of a single magnetic domain each. The powder is then dry- or wet-pressed into a shape, dried, and re-sintered. The shaping may be performed in an external magnetic field in order to achieve the preferred orientation of the particles (anisotropy). The volume of the material decreases by about 17% during the production, size tolerance is acceptable only after grinding.

(Table 3. 1) contd.....

NdFeB	Barium ferrite
Magnetic features	
The coercitive field strength of magnets made of neodymium-iron-boron is higher than for samarium-cobalt. Remanent induction is identical to that of AlNiCo magnets. Their maximal B×H product is 50% over that of samarium-cobalt. Disadvantages are the ability for corrosion and the limited range of allowed external temperature (T_{max}=80-180° C depending on material quality).	Isotropic magnets can be magnetized to any preferred direction and their features are basically independent of direction. Anisotropic magnets are produced in a strong external magnetic field during pressing, have therefore, a so-called easy direction of magnetization, in which direction the magnetic features are much better than in the other directions. Containing large crystal anisotropies, ceramic magnets have high coercitive field strength making them resistant toward external demagnetizing fields and provide them long-time stability. Due to the small remanent induction, higher pole surfaces must be designed. The maximum external temperature is 250° C.
Mechanical features	
Neodymium-iron-boron are very rigid and brittle, grounding needs diamond tools. Because of their rigidity and strong magnetic field they easily break or get damaged when clashed to other magnets. In case of bigger volumes this represents a high risk of accident. They corrode under standard circumstances; this is why they need galvanic coating.	Ceramic magnets are also hard and brittle, diamond tools are needed to grind them. They are excellently resistant to corrosion, acids, salts, oils, and gases.
Material features	
Made by powder metallurgy, chemical composition: $Nd_2Fe_{14}B$. High resistance against demagnetization. Magnetic field-characterizing values are high remanent induction (B_r), coercitivity of B (bH_c), intrinsic coercitivity (iH_c), and energy product (BH_{max}). Excellent ratio of price/power. The temperature coefficient of intrinsic field strength is high. Thermal stability is limited. Rigid and fragile. Susceptive to corrode, galvanic coating is needed. Not suitable for high operating temperatures.	Made by powder metallurgy, chemical composition: $BaO_6Fe_2O_3$. High resistance against demagnetization. Intrinsic coercitivity (iH_c) is high. Has high electric resistance. Excellent ratio of price/power. The temperature coefficient of intrinsic field strength is high. Thermal stability is good. Rigid and fragile. Resistant to corrosion. Not suitable for high operating temperatures.

CHAPTER 4

In Vitro Experiments on Microorganisms

Keywords: *Bacillus circulans*, *E. coli*, *Micrococcus luteus*, *Pseudomonas fluorescens*, *Saccharomyces cerevisiae*, *Salmonella enteritidis*, *Serratia marcescens*, *Staphylococcus aureus*.

STATIC MAGNETIC FIELD-EXPOSURE FAILS TO AFFECT THE VIABILITY OF DIFFERENT BACTERIA STRAINS

Preliminaries

As mentioned in the **Introduction**, the proliferation of magnetic resonance imaging (MR) and the ever increasing need to achieve better graphical resolution of the image brought about the necessity of the examinations of bacteria under strong SMF again. This does not happen exclusively because of the possible adverse side effects microorganisms can cause during imaging, *e.g.* direct effect on bacterial growth [47] and/or changes in the antibiotic resistance in case of bacterial diseases [48], but also their possible long lasting effects, *e.g.* altering the DNA repair processes [49].

Several authors used bacterial strains and plant cells to study the effects of SMF-exposure. Stasiuk already in 1974 [50] exposed *Mycobacterium tuberculosis* to 180 mT SMF and found that though exposure of up to 1 h did not change the bacterial growth, but longer exposure (2 h and more) resulted in significant inhibition in their growth. No changes were observed on the sensitivity to antibiotics or growth in tissues in infected animals. Khar'kova *et al.* [51] studied the effect of long exposures of *Staphylococcus* in a 5 mT SMF. Permanent changes in the color of colonies (after 16 days), changes in their morphology and in the fermentation of proteins and hydrocarbons were observed by 18 months. After 8 months, the sensitivity to antibiotics increased significantly. The mortality increased in mice upon their infection with SMF-exposed *Staphylococcus*. More recently, Grosman *et al.* [52] studied the effect of 0.5-4 T SMF-exposure on

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Escherichia coli (*E. coli*) and *Staphylococcus aureus* with 30-120 min exposure times. They found no effect on growth. Benson *et al.* [53] observed enhancement of the effect of the antibiotic gentamicin to *Pseudomonas aeruginosa* exposed to 0.5-2 mT for 20 min. They could not claim with all certainty that the decreased growth might have been influenced by the different light conditions. Stansell *et al.* [48] exposed *E. coli* to 8-60 mT for 19.5 h and studied the effect of the antibiotic piperacillin. SMF-exposure increased the resistance to the antibiotic. Kohno *et al.* [54] examined *Streptococcus mutans*, *Staphylococcus aureus*, and *E. coli* determining growth rate, maximum numbers of bacteria, and (3H)-thymidine incorporation in the exposure of ferrite block magnets of inductions 30, 60, 80, and 100 mT. Although no effect of SMF-exposure on (3H)-thymidine incorporation and on the growth of *E. coli* cultures could be identified, the magnetic induction was found to inhibit both the growth rate and the maximum number of *Streptococcus mutans* and *Staphylococcus aureus* when cultured under anaerobic conditions. There was no effect under aerobic conditions. Binhi *et al.* [55] used *E. coli* cells for exploring effects by studying anomalous viscosity time dependencies. They found that within the range of 0 to 110 μT the spectrum showed several extremes. They explained the effect by the rotation of magnetically active complexes, such as Ca^{2+}, Mg^{2+}, and Zn^{2+}. Zhang *et al.* [56] concluded that the growth of *E. coli* was inhibited due to the presence of SMF. They modified field intensity and applied the Series Piezoelectric Quartz Crystal (SPQC) sensing technique. By relating 3 kinetic growth parameters, *i.e.* the asymptote, the maximum specific growth rate, and the lag time to the SMF-exposure, they established a response model for the frequency shift. Piatti *et al.* [57] found that the exposure of *Serratia marcescens* to 8±2 mT SMF inhibited the growth of the bacteria. For *Hordeum vulgare*, they observed a decreased viability, whereas for *Rubus fruticosus*, SMF remained ineffective. Potenza *et al.* [47] devoted a series of experiments to *E. coli* under the influence of 300 mT SMF. Their focus was on biomass growth of different strains of bacteria in 3 different media when exposed to SMF for up to 50 h. They could not identify a difference in growth between *E. coli* in the standard medium and the unexposed control. Triampo *et al.* [58] investigated cell division of *Leptospira interrogans serovar canicola* under the influence of long exposure to a 140±5 mT SMF. Their data showed a somewhat lower density of the bacterium under SMF treatment than the

control; however, no statistical analysis was provided. The subject of the study of Gao *et al.* [59] was *Shewanella oneidensis*. This strain was exposed to 14.1 T SMF for 12 h and the post-exposure growth was observed for another 18 h. They found no difference between treated and control cells in terms of optical density, colony forming unit, or post-exposure growth of cells. Morrow *et al.* [60] used *Streptococcus pyogenes* to reveal potential differences in growth rate between 0.3-0.5 T SMF-exposure for 8 h and control. They correlated a significant decrease in growth rate to 0.3 T as well as a significant increase to 0.5 T exposure provided the growth was under anaerobe conditions. The contradictory data of the literature regarding the potential of SMF-exposure to promote or inhibit cell growth are summarized in Table **4.1**.

Table 4.1. Summary of literature regarding the potential of SMF-exposure to promote or inhibit cell growth in different bacterium strains.

reference	subject	SMF	exposure time	findings
Grosman *et al.* [52]	*E. coli, Staphylococcus aureus*	0.5-4 T	30-120 min	no effect on growth
Kohno *et al.* [54]	*Streptococcus mutans*, *Staphylococcus aureus*, *E. coli*	30, 60, 80, 100 mT	?	
Piatti *et al.* [57]	*Serratia marcescens*	8±2 mT	24 h ?	growth inhibition
	Hordeum vulgare			
	Rubus fruticosus			no effect on growth
Potenza *et al.* [47]	*E. coli*	300 mT	50 h	
Triampo *et al.* [58]	*Leptospira interrogans*	140±5 mT	1, 2, 3, 4, 5, 6 d	growth inhibition, but no statistics
Gao *et al.* [59]	*Shewanella oneidensis*	14.1 T	12 h	no effect on growth
Morrow *et al.* [60]	*Streptococcus pyogenes*	300 mT	8-15 h	growth inhibition
		500 mT		growth promotion

Goals

We decided to start at an early phase of phylogenesis. We considered the question whether we can establish the boundary of biological development under which an observable reaction to external SMF-exposure can be expected at all? Experiments on the viability of bacteria *in vitro* seemed to be an adequate method

CHAPTER 5

In Vivo Animal Experiments

Keywords: Behavioral test, Capsaicin-sensitive, *Cepaea nemoralis*, Circadian cycle, Epsom salt challenge, *Helix pomatia*, Hot plate test, Mechanical hyperalgesia model, Mice, Morphine, Neuropathic, Opioid-receptor, Preterm birth, Resiniferatoxin, Serotonergic system, Writhing test.

MODELS AND ASSAYS

Table **5.1** summarizes the animal models, the assays, and the corresponding (pre)-treatments (if any) we shall focus in this chapter.

Table 5.1. Animal models, tests, and corresponding (pre)-treatments (if any) discussed in this chapter.

Animal	Invertebrates	Vertebrates				
	Land snail	Mouse				
	Helix pomatia	BALB/c	CD1	C57BL/6	CFLP	CSJLF1
Test						
Hot plate	naloxone serotonin tryptamine					
Elevated plus maze					morphine	
Locomotor activity					morphine	
Rotarod		×				
Seltzer		×				
Timed-pregnancy				lipopoly-saccharide		
Von Frey		carrageenan formalin resiniferatoxin	strepto-zotocin			
Writhing					β-funaltrexamine morphine naloxone naltrindole norbinaltorphimine	

The professional expectations in *in vivo* experimental models are:

i. The model should reflect a pathological condition including symptoms similar to that occurring in humans,
ii. the model should be specific, sensitive, valid, reliable, and reproducible [63].

Supposing that all these requirements are met, data derived from observation of *in vivo* experiments are of utmost importance with regard to the therapeutic method under investigation since the psychosomatic/placebo effects can be excluded under experimental conditions.

Preclinical pain models can be separated into 3 functional divisions based on their potential mechanisms. Nociception can be induced acutely by thermal, mechanical, or chemical stimulus (*e.g.* hot plate test, or tail flick test), it can be based on tissue injury (*e.g.* writhing, formalin, inflamed joint, or paw test), or can originate in nerve injury [64].

In the experiment, detailed in this section, we used an animal cage made of Plexiglas with air holes on all sides, except on the bottom. The size of the cage was 140×140×46 mm. The 2 opposite side walls of the cage were transparent, the other 2 and the top were covered with opaque, air permeable material. Similar environmental conditions could be actualized for both SMF- and sham-exposed animals. The support under the cage was always plane and stable.

No efforts were ever made to magnetically shield the experimental setup from the geomagnetic field. Creatures throughout the hundred millions of years of phylogenesis on Earth have adapted to this field. Therefore, shielding might have introduced unwanted effects (*c.f.*, [27]).

ETHICAL ISSUES

All experimental procedures described in Chapter 5 were carried out according to the European Communities Council Directives (86/609/ECC) complying with the

i. Hungarian Act for the Protection of Animals in Research (law 1998/XXVIII, par. 32),
ii. edict 243/1988 of the Hungarian Parliament on Animal Protection and

Consideration Decree of Scientific Procedures of Animal Experiments,
iii. recommendations of the International Association for the Study of Pain [65], and the
iv. Helsinki Declaration.

Each study was approved by one of the following committees.

a. Animal Care and Protection Committee at the University of Debrecen (No.: IV/1813-1/2002 or No.: 7/2011/DE MAB),
b. Animal Care Committee of Semmelweis University, Budapest (No.: 1810/003/2004),
c. Ethics Committee on Animal Research of the University of Pécs according to the Ethical Codex of Animal Experiments (No.: BA02/2000-16-2006), and
d. Hungarian Ethical Committee for Animal Research at Debrecen University (No.: 26/2007).

MATERIALS

Chemicals were purchased from (in alphabetical order) Invitrogen (Carlsbad, CA, USA), Merck (Whitehouse Station, NJ, USA), Molecular Probes (Eugene, OR, USA), Pharmacy of the University of Pécs, Sigma-Aldrich (St. Louis, MO, USA), and Tocris Bioscience (Bristol, UK). Beyond those inbred, animals were provided by Charles River (Budapest or Isaszeg, Hungary) and Toxicoop (Budapest, Hungary). Kits and devices came from (in alphabetical order) Abcam (Cambridge, UK), Bio-Tek Instruments (Winooski, VT, USA), Experimetria (Budapest, Hungary), Lab Vision (Fremont, CA, USA), Nikon (Tokyo, Japan), Osram (Munich, Germany), Photometrics (Tucson, AZ, USA), Supertech (Pécs, Hungary), Techno Plastic Products (Trasadingen, Switzerland), and Ugo Basile, Comerio, Italy).

EXPERIMENTS ON INVERTEBRATES *IN VIVO*

Pharmacological Analysis of Response Latency in the Hot Plate Test Following Whole-Body Static Magnetic Field-Exposure in the Snail *Helix Pomatia*

CHAPTER 6

Human Investigations

Keywords: γ-ray irradiation, Cytokines, Dental, DNA repair, Human cell, Human subjects, Lymphocytes, Macrophages, Osteoporotic, Stomatological, TPT, VAS pain rating.

Table **6.1** summarizes the subjects with the disease (if any) and methods of testing we shall focus in the present chapter.

Table 6.1. Subjects with disease (if any) and methods of testing.

	Healthy volunteers	Patients with erosive gastritis	Patients with vertebral deformity	Patients with alveolitis	Patients with oral aphta	Patients with temporo-mandibular disorder	Patients with caries	Patients in preparation of prosthetics
Laboratory			×					
Numerical rating scale							×	×
Thermal pain threshold	×							
Tolerance threshold measurement							×	×
Visual analogue scale		×	×	×	×	×		

The WHO [12] in a Research Agenda encouraged the following in terms of human studies: “Cognitive and behavioral effects of static magnetic fields with the rationale: The cognitive and behavioral effects due to exposure to static magnetic fields should be investigated further. However, the available data do not suggest particular risks to specific aspects of cognition nor do they suggest which

parameters should be tested in the laboratory. In the absence of a clear direction, a possible approach would be to investigate the effects of exposure on the performance of a battery of cognitive tasks that encompass standard tests of attention, reaction time and memory, if only to act as an initial screen pending more focused work. The initial work could be done with volunteers as part of experimental studies."

Taking up the challenge and following Galen's indication, who advocated the application of magnetic therapy for curing scars that are caused by infectious materials [339], interesting human experiments have been carried out during the past 2 decades concentrating on the applicability of SMF-exposure and low frequency (<1 Hz) electromagnetic field irradiation in medicine as a non-contact, non-invasive, and cheap physiotherapeutic method. An increasing amount of evidence indicates that SMF or low frequency electromagnetic fields can induce *AE* in humans, mostly with regard to chronic pain. The beneficial effect of SMF in curtailing the inflammatory period was also observed [340]. Among the participants of published trials were patients with pain in the abdomen and genitals (see Holcomb *et al.* [263]), with musculoskeletal disorders due to prolonged sitting (see Capodaglio and Vicenzi [341]), with fibromyalgia (see Alfano *et al.* [264]), with foot disorders (see Suomi *et al.* [342] and Simoncini *et al.* [343]), with chronic pelvic pain (see Brown *et al.* [266]), with chronic knee pain (see Hinman *et al.* [233]), with osteoarthritis [344], spine disorders [345], with myofascial pain syndrome (see Smania *et al.* [346]), or even diabetic neuropathic pain [267]. In these studies, the beneficial effect of SMF-exposure in the form of either *AE* or the shortening of the inflammatory period was observed and reported. Engström *et al.* [347] conducted an experiment on how exposure to strongly inhomogeneous SMF influenced myosin phosphorylation and found that the magnitude of magnetic induction alone could not be responsible for the effect. Gmitrov and Ohkubo [9] suggested the use of local SMF-exposure to moderate sympathetic activation and baroreceptor dysfunction. Salvatore *et al.* [348] showed how SMF could be fruitfully combined with chemotherapy in patients with advanced malignancy. Others found no effect of SMF on nociceptive transmission and pain symptoms in humans [272, 349]. Yet other studies dealt with the effects caused by SMF-exposure in humans, such as Mayrovitz *et al.*

[350] who found no change in the resting skin blood flow in humans under the influence of 85 mT SMF measured by laser-Doppler.

Precise evaluation of the efficacy of several differently applied magnetic therapies has led to conflicting conclusions in meta-analysis; SMF therapy showed no benefits compared to placebo controls [42]. These contradictory results are mainly due to human factors that are inevitable. Many clinical studies are limited either because of subject awareness of the control group (lack of magnetic properties of sham devices is easily detectable); because of an incorrect or incomplete characterization of the applied SMF [351],or because there is high variability in the biological response to pain [352]. Colbert *et al.* [29] fortunately enumerated a 10point list of conditions for the standardized description of SMF-exposure in a trial. In the long-run this list will foster inter comparability of measured results.

MATERIALS

Chemicals were purchased from (in alphabetical order) Abbott (Chicago, IL, US A), ALK-Abello (Hørsholm, Denmark), Beckman Coulter (Brea, CA, USA), Cambrex BioScience (Verviers, Belgium), Roche Diagnostics (Mannheim, Germany), DiaSorin (Stillwater, OK, USA), GIBCO (Carlsbad, CA, USA), ICN Biomedicals (Irvine, CA, USA), Merck (Whitehouse Station, NJ, USA), Reanal (Budapest, Hungary), Sanofi (Paris, France), Sigma-Aldrich (St. Louis, MO, US A). Kits and devices were provided by (in alphabetical order) Denjoy Dental (Changsha, Hunan, China), Iwaki (Tokyo, Japan),Kinetic Imaging (Bromborough, UK), Lincoln Diagnostics (Decatur, IL, USA), GE Healthcare (Little Chalfont, Bucks, UK), Metripond Plus (Hódmezővásárhely, Hungary), Nikon (Kawasaki, Kanagawa, Japan), OMRON Electronics (Budapest, Hungary), Pharmacia Biotech (Stockholm, Sweden), Roche Diagnostics (Basel, Switzerland), Siemens (Munich, Germany), and Spektrum-3D (Debrecen, Hungary).

IN VITRO EXPERIMENTS

DNA Damage

Static magnetic field-exposure fails to affect repair of DNA damage damage

CHAPTER 7

Summary

The Author as a positive skeptic has certainly learned an awful lot in the course of the experiments and trials described in this book. Beyond personal gain though, let us guide the Reader through the most important findings. *In vitro* experiments are summarized in Table **7.1**.

Table 7.1. *In vitro* experiments described in this book with reference chapter or point within this book, subject, outcome measure, exposure conditions, other treatment if applies, and the observations.

reference link in this book	subject of measurement	observed quantity, model	SMF-exposure conditions	other treatment (if any)
***In Vitro* Experiments on Microorganisms**	microorganisms: *Bacillus circulans, Escherichia coli, Micrococcus luteus, Pseudomonas fluorescens, Saccharomyces cerevisiae, Salmonella enterica serovar Enteritidis, Serratia marcescens, Staphylococcus aureus*	endpoint viability, standard incubation	3 different iSMF (all in generator 11) for 10, 30, 50 min, or 24 h	
Result: No significant difference between SMF-exposed and sham cell numbers was found at the 95% confidence level for any strain, for any exposure time or layer with the exception of *P. fluorescens* 30 min, layer 2 (p<0.001), *B. circulans* 30 min, layer 3 (p<0.05) and layer 4 (p<0.05), and *E. coli* 50 min, layer 1 (p<0.05).				
DNA damage	human leukocytes	DNA analysis, single-cell gel electrophoresis	3 different iSMF (all in generator 11) or hSMF (generator 15) for 0.5, 1, 2, 4, 6, 18, 20, or 24 h	^{60}Co-γ irradiation

(Table 7.1) contd.....

reference link in this book	subject of measurement	observed quantity, model	SMF-exposure conditions	other treatment (if any)
Result: Statistically significant differences were found at 1 h (iSMF), and 4 or 18 h (hSMF) if samples were exposed to only SMF, compared to control. When the SMF-exposure followed the ^{60}Co-γ irradiation, statistically significant differences were found at 1 h (iSMF) and 4 h (hSMF). If exposure to SMF preceded γ irradiation, no statistically significant difference was found compared to γ irradiated group.				
Anti-inflammatory effect	human macrophages and lymphocytes	endpoint analysis of IL-6, IL-8, TNF-α, and IL-10, enzyme-linked immunosorbent assay	iSMF (generator 11) for 6, 18, or 24 h	lipopoly-saccharide
Result: Exposure caused visible morphological changes on macrophages as well as on lymphocytes, and also seemed to be toxic to lymphocytes (37-42%, $0.308<p<0.444$), but not to macrophages (<1.43%, $p>0.987$). Analysis of concentrations showed a significantly reduced production of pro-inflammatory cytokines IL-6, IL-8, and TNF-α from macrophages compared to negative control (57-88%, $p=0.031$) and IL-6 compared to positive control (45-56%, $p=0.035$). The production of anti-inflammatory cytokine IL-10 from macrophages and from lymphocytes was enhanced compared to negative control, significantly from lymphocytes ((-184%)-(-28.75%), $p=0.042$). The secretion of IL-6 from lymphocytes was significantly decreased compared to positive control ((-115%)-(-27%), $p=0.039$).				

Conclusions from the *in vitro* studies: Microorganisms have not been activated by any means of external agent; they have remained in their normal habitat. Under such circumstances, they were not affected by the SMF-exposure in the dose range applied. Neither was the repair of DNA-damaged human leukocytes influenced by the exposure. However, when macrophages and lymphocytes were activated with LPS, SMF-exposure exerted an anti-inflammatory action in the release of different cytokines. This latter study has an extremely important lesson for us. SMF-exposure itself without any kind of induced electric phenomenon has the capability of significantly affect cytokine secretion.

Similarly to Table **7.1**, Table **7.2** contains similar results for the *in vivo* animal experiments.

Table 7.2. *In vivo* animal experiments described in this book with reference chapter or point within this book, subject, outcome measure, exposure conditions, other treatment if applies, and the observations.

reference link in this book	subject of measurement	observed quantity, model	SMF exposure conditions	other treatment (if any)
Experiments on invertebrates *in vivo*	land snail, *Helix pomatia*	response latency to thermal stimulus, hot plate test	hSMF (generator 15), or iSMF (generator 11) for 20, 30, or 40 min	naloxone and/or serotonin, or tryptamine
Result: Both hSMF and iSMF-exposure increased the thermo-nociceptive threshold: 40%, 29%, or 42% after hSMF-exposure for 20, 30, or 40 min by $p<0.001$ for all, and 33% or 46% after iSMF-exposure for 20 or 40 min by $p<0.05$ or $p<0.001$, resp. The response latency depended on the day-night cycle; response latency was higher by 51% ($p<0.001$) during the night. This trend also held for SMF-exposure (29%, $p<0.001$). Serotonin alone increased response latency (56%, $p<0.001$), whereas serotonin antagonist tryptamine decreased it (-98%, $p<0.001$). Using naloxone, response latency decreased (-52.5%, $p<0.001$); however, both SMF-exposure and serotonin in combination with naloxone rose it back to above the control level (117% or 150%, resp. by $p<0.001$ either).				
Locomotor activity and anxiety behavior in healthy mice	CFLP mouse	number of entries, EPM test; time of walking, running, rearing, and immobility in locomotor activity test	iSMF (generator 11) for 30 min	acetic acid
Result: Exposure failed to affect anxiety behavior and hyperlocomotion-inducing effect of morphine.				
Peripheral action	BALB/c mouse	MWT, resiniferatoxin-, formalin-, carrageenan-test, resiniferatoxin desensitization, von Frey and rotarod test	iSMF (generator 11) for 5, 20, 30 min	resiniferatoxin, formalin, carrageenan
Result: SMF-exposure reduced the number of formalin-evoked paw lickings and liftings in both phase I and phase II (30-60%, $p<0.05$). It diminished mechanical hyperalgesia evoked by *i.pl.* injection of carrageenan (26%, $p<0.05$) as well as the TRPV1 capsaicin receptor agonist resiniferatoxin (27%, $p<0.05$). Selective inactivation of capsaicin-sensitive sensory fibers by high dose resiniferatoxin pretreatment decreased nocifensive behaviors in phase II of the formalin test to a similar extent. Significant inhibitory effects of SMF on formalin-induced nociception and carrageenan-evoked hyperalgesia were absent in resiniferatoxin-pretreated mice. No significant difference was found in the rotarod performance.				
Optimization of SMF parameters	CFLP mouse	number of writhings, writhing test	hSMF or iSMF (generators 1-16) for 5, 20, 30, or 40 min	acetic acid, Epsom salt

CHAPTER 8

Plans

I must admit at this point that although the book is close to its end, there is much more research ahead of us than behind us. As already mentioned, we have learned a lot and through this process of cognition doors opened, where no openings had been assumed. Here are some doors I plan to close behind me in the future. This Chapter may be the most relevant for those, who are thinking of initiating research in this field.

SHORT-TERM ISSUES

At this time, when the Reader is holding this book, 3 journal articles have been published all of which I kindly refer the Reader to kind attention with the abstracts of the papers. An *in vivo* animal model, experimental autoimmune encephalomyelitis (EAE), a model for human multiple sclerosis (MS) was used in rodents [458]. Static magnetic field (SMF)-exposure was shown to be beneficial in specific cases of inflammatory nature, where it could suppress symptoms. The null-hypothesis was that animals with induced EAE exposed to SMF would show different seriousness of symptoms, than those in the sham-exposed control group. Three replicated series of repetitive, 30 min/day whole-body exposure to SMF with 477 mT magnetic induction and 48 T/m lateral induction gradient were conducted on female CSJLF1 mice with a mild, mouse spinal cord homogenate emulsion-induced EAE. Conventional scores of animal response to EAE were compared between sham- and SMF-exposed groups. Following a pilot test, we used 18 animals/group. The primary outcome measure was the daily group average of standard EAE scores. Results show that SMF-exposure has a strong, reproducible, and significantly beneficial effect up to 51.82% (p<0.001) over sham-exposure on symptoms of EAE throughout the 25 days of the experiment. This study aimed at laying the experimental research foundation for a later therapy option for SMF-exposure in the clinical management of MS.

Another experimental series published includes an *in vivo* mouse allergy model

and a skin prick human test under SMF-exposure [459]. Previous observations suggest that static magnetic field (SMF)-exposure acts on living organisms partly through reactive oxygen species (ROS) reactions. In this study, our goal was to determine the impact of SMF-exposure on ragweed pollen extract (RWPE)-induced allergic inflammation closely associated with oxidative stress. Inhomogeneous SMF was generated with an apparatus validated previously providing a peak-to-peak magnetic induction of the dominant SMF component 389 mT by 39 T/m lateral gradient in the *in vivo* and *in vitro* experiments, and 192 mT by 19 T/m in the human study at the 3 mm target distance. Effects of SMF-exposure were studied in a murine model of allergic inflammation and also in human provoked skin allergy. We found that even a single 30min exposure of mice to SMF immediately following intranasal RWPE challenge significantly lowered the increase in the total antioxidant capacity of the airways and decreased allergic inflammation. Repeated (3 consecutive days) or prolonged (60 min) exposure to SMF after RWPE challenge decreased the severity of allergic responses more efficiently than a single 30 min treatment. SMF-exposure did not alter ROS production by RWPE under cell-free conditions, while diminished RWPE-induced increase in the ROS levels in A549 epithelial cells. Results of the human skin prick tests indicated that SMF-exposure had no significant direct effect on provoked mast cell degranulation. The beneficial effects of SMF are likely due to the mobilization of cellular ROS-eliminating mechanisms rather than direct modulation of ROS production by pollen NAD(P)H oxidases.

The third paper was devoted to the effect of static magnetic field (SMF)-exposure on erosive gastritis [460]. The randomized, self- and placebo-controlled, double-blind, pilot study included 16 patients of the 2nd Department of Internal Medicine, Semmelweis University diagnosed with erosive gastritis. The instrumental analysis followed a qualitative (pre-intervention) assessment of the symptoms by the individual patients, which included lower heartburn (in the ventricle), upper heartburn (in the oesophagus), epigastric pain, regurgitation, bloating, and dry cough. Medical diagnosis included a double-line upper panendoscopy followed by 30 min local inhomogeneous SMF-exposure intervention at the lower sternal region over the stomach with peak-to-peak magnetic induction of 3 mT and 30 mT/m gradient at the target site. A qualitative (post-intervention) assessment of

the same symptoms served as the closing of the examination. Sham- or SMF-exposure was used in a double blind manner. The authors succeeded in justifying the clinically and statistically significant beneficial effect of SMF- over sham-exposure on the symptoms of erosive gastritis the average effect of inhibition being 56% by p=0.001, n=42+96. This pilot study was meant to encourage gastroenterologists to test local, inhomogeneous SMF-exposure on erosive gastritis patients in order for this intervention to become an evidence-based alternative or complementary method in the clinical use, especially in cases when conventional therapy options are contraindicated.

Voltage-gated sodium channels play an important role in the transport of frequency-coded information in generating the action potential. CNS develops primarily Nav1.1, Nav1.2, Nav1.3, and Nav1.6 subtypes; the expression of Nav1.2 neuron is specific. Nav1.2 is essential in the pathogenesis of not only neurodegenerative diseases like epilepsy, but also of inflammatory illnesses implying high fever. Evidence shows that exposure to an external SMF can alter the permeability of ion channels [70], thus may modify Nav1.2 expression [70, 461]. The biophysical characterization of conformation changes in the course of the opening-closing of a channel by an experimental series concerned with human embryonic kidney (HEK) 293 cells may then be informative.

Diffusion and segregation processes as well as solidification are seriously dependent on the magnetic induction and geometry of an external SMF [462 - 465]. We have good reason to hypothesize that SMF-exposure may equally contribute to such changes in living matter. Confocal laser scanning microscopy could provide a solution in looking for induced cell death in slices of rat *cornu ammonis* 3 (CA3) hippocampal regions either untreated, treated with kainic acid, and/or exposed to SMF. Even the diffused depth profile of propidium iodide (PI) dye can be monitored this way.

Strong assumptions hint at exposure to SMF interacting with the orientation or the result of the differentiation of developing cells [360, 466 - 469]. The effect of SMF-exposure on the rate of sympathetic preganglionic axonal outgrowth could be investigated on a grid where neurons can grow only along parallel channels while they are treated with BDNF and/or SMF.

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SUBJECT INDEX

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