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INTERACTION MECHANISMS, BIOLOGICAL EFFECTS AND BIOMEDICAL APPLICATIONS OF STATIC AND EXTREMELY-LOW-FREQUENCY MAGNETIC FIELDS

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Introduction

Interest in the mechanisms of interaction and the biological effects of static and time-varying magnetic fields has increased significantly since the early 1970's as a result of the growing number of applications of these fields in research, industry and medicine [1,2]. A major stimulus for research on the bioeffects of static magnetic fields has been the effort to develop new technologies for energy production and storage that utilize intense magnetic fields (e.g., thermonuclear fusion reactors and superconducting magnet energy storage devices). In addition, the rapid emergence of magnetic resonance imaging as a new clinical diagnostic procedure has, in recent years, provided a strong rationale for defining the possible biological effects of magnetic fields with high intensities.

The numerous sources of time-varying magnetic fields with frequencies in the extremely-low-frequency (ELF) range* has also led to an increased emphasis on defining the interactions of these fields with biosystems. Of particular interest has been the potential biological effects of fields with 50 and 60 Hz frequencies, which are used throughout the world for electric power transmission and distribution. However, fields with other frequencies in the ELF range are also of interest because of their use in communication systems and in certain medical procedures. For example, pulsed fields with frequencies in the ELF range are used medically for the facilitation of bone fracture reunion. In addition, time-varying magnetic fields with frequencies in the ELF range result from the rapidly switched gradient fields that are used for signal localization in magnetic resonance imaging.

In this chapter the principal interaction mechanisms of static and time-varying magnetic fields will be described, and a summary will be given of the current state of knowledge on the biological effects of these fields based on laboratory studies. Detailed reviews of these subjects have been

* ELF denotes frequencies below 300 Hz.

published during the past year [3-9]. The final section of this chapter will be devoted to several useful applications of magnetic fields in medicine and biological research.

Static Magnetic Fields

Interaction mechanisms. Three classes of physical interactions of static magnetic fields with biosystems are well established on the basis of experimental data: (1) electrodynamic interactions with ionic conduction currents; (2) magnetomechanical effects, including the orientation of magnetically anisotropic structures in uniform fields and the translation of paramagnetic and ferromagnetic materials in magnetic field gradients; (3) effects on electronic spin states of the reaction intermediates in certain types of charge transfer processes. Each of these physical interaction mechanisms, along with relevant experimental data, will be described in this section.

(1) Electrodynamic interactions. Ionic currents interact with static magnetic fields as a result of the Lorentz forces exerted on moving charge carriers. Under steady state conditions this electrodynamic interaction gives rise to an induced electric field $\vec{E}_i = - \vec{v} \times \vec{B}$, where $\vec{v}$ is the velocity of current flow and $\vec{B}$ is the magnetic flux density. This phenomenon is the physical basis of the Hall effect in solid state materials, and it also occurs in several biological processes that involve the flow of electrolytes in an aqueous medium. Examples of such processes are the ionic current flows that occur in the circulatory system, in nerve impulse propagation and in visual phototransduction processes.

A well-studied example of electrodynamic interactions that leads to measurable biological effects is the induction of electrical potentials as a result of blood flow in the presence of a static magnetic field. It is a direct consequence of the Lorentz force exerted on moving ionic currents that blood flowing through a cylindrical vessel of diameter, d, will develop an electrical potential, ψ, given by the equation [3]:

$$\psi = |\vec{E}_i| \, d = |\vec{v}| \, |\vec{B}| \, d \sin \theta \qquad (1)$$

where Θ is the angle between $\vec{B}$ and the axial velocity vector, $\vec{v}$.

The induced blood flow potentials within the central circulatory systems of several species of mammals exposed to large static magnetic fields have been characterized from electrocardiogram (ECG) records obtained with surface electrodes [10-16]. As demonstrated by the data shown in Fig. 1 for a Macaca monkey exposed to static fields up to 1.5 T [1 Tesla (T) = 10^4 Gauss], the primary change in the ECG is an augmentation of the signal amplitude at the locus of the T-wave. Based on its temporal sequence in the ECG record, this change in T-wave amplitude has been attributed to the electrical potential that is induced within the aortic vessel during pulsatile blood flow in the presence of a magnetic field [11-16]. The opening and closing of the aortic heart valve have been shown to be correlated with the timing of the appearance and disappearance of the magnetically-induced potential at the locus of the T-wave [17]. In small animal species such as rats, the aortic blood flow potential can be detected in the ECG when the magnetic flux density exceeds 0.3 T [15]. For larger animal species such as dogs, monkeys and baboons, the threshold field level that induces a measurable potential is approximately 0.1 T [13,16,17]. For all of these animal species, the change in T-wave signal amplitude observed during magnetic field exposure has been shown to be completely reversible upon removal of the field. In addition, the linear dependence of the aortic blood flow potential on magnetic field strength and its variation as a function of animal orientation within the field [see Eq.(1)] have been experimentally confirmed [13, 15-17].

The linear dependence of a magnetically-induced blood flow potential on vessel diameter, as shown in Eq.(1), leads to the prediction that these potentials should have greater magnitudes in humans than in the smaller animal species that have been studied in the laboratory. This prediction is supported by a calculation based on Eq. (1) that the maximum magnitudes of the induced

aortic blood flow potentials in a rat and a man placed within a 2 T field should be 0.5 and 13.4 mV, respectively. An increase in the magnitude of magnetically-induced blood flow potentials as a function of animal size has also been demonstrated directly by experimental data obtained for rats, baboons, monkeys and dogs [4,13-17].

The electrodynamic interaction between a static magnetic field and a flowing conductor such as blood also produces a net volume force within the fluid that is equal to $\vec{J} \times \vec{B}$, where $\vec{J}$ is the ionic conduction current. The hydrodynamic consequence of this electrical force is a reduction in the axial blood flow velocity. From magnetohydrodynamic theory the fractional reduction in blood flow rate can be predicted to a good approximation by the equation [17]:

$$\frac{v(B=0) - v(B)}{v(B=0)} = \frac{R^2 B^2 \sigma}{4\eta} \qquad (2)$$

where R is the vessel radius and σ and η are, respectively, the electrical conductivity and kinematic viscosity of blood. From Eq. (2) the estimated reduction in aortic blood flow rate for a man in static fields of 1 T and 5 T is about 1% and 7%, respectively. In accord with theoretical predictions, less than a 1% reduction in aortic blood flow rate was observed in direct laboratory measurements on 9 adult rats exposed to a 1.5 T field [17]. Also, as demonstrated by the intraarterial blood pressure measurements shown in Fig. 1, no hemodynamic alterations were observed during the exposure of 3 Macaca monkeys to a 1.5 T field [16].

Another important physiological process that is potentially sensitive to electrodynamic interactions with static magnetic fields is the conduction of nerve impulses. Simple theoretical calculations, however, demonstrate that the interaction of a magnetic field with the ionic currents in an axonal membrane is extremely weak [18,19]. For example, it has been estimated that

a static magnetic field in excess of 24 T would be required to produce a Lorentz force on nerve ionic currents equal to one-tenth the force they experience from the electric field of the nerve membrane [18]. The absence of a measurable interaction of a 2 T static field with the ionic currents of an isolated sciatic nerve has been demonstrated experimentally. In various studies with isolated neurons, fields of 1.2-2.0 T applied in either a parallel or perpendicular configuration relative to the nerve axis have been found to have no influence on the amplitude or conduction velocity of evoked action potentials [20-22]. Static magnetic fields were also found to have no effect on other bioelectric properties of sciatic nerves, including the threshold for nerve excitation and the duration of the absolute and relative refractory periods that follow the passage of an action potential [22].

(2) Magnetomechanical interactions. Macromolecules with a high degree of magnetic anisotropy will rotate in a static magnetic field and reach an equilibrium orientation that represents a minimum energy state. In general, these macromolecules have a rodlike shape and magneto-orientation occurs as a result of anisotropy of the magnetic susceptibility tensor along the different axes of molecular symmetry. The total interaction energy, U, within the field is obtained by integrating the tensorial product of the magnetic flux density, $\vec{B}$, and the magnetic moment per unit volume, $\vec{M}$, over the molecular volume, V. The resulting expression for U is:

$$U = - VB^2[\chi_z + (\chi_z - \chi_r)\cos^2\theta]/2\mu_o \qquad (3)$$

where χ_z and χ_r are the axial and radial components of the magnetic susceptibility, Θ is the angle between the direction of the field and the z axis, μ_o is the magnetic permeability of free space (μ_o = 1 in CGS units and $4\pi \times 10^{-7}$ N/A^2 in MKS units). Because the rodlike molecules will rotate in the field to achieve a minimum energy, then the equilibrium orientation will be at $\Theta = 0$ or π if $\chi_z > \chi_r > 0$ (paramagnetic molecules) or $\chi_r < \chi_z < 0$ (diamagnetic

molecules). The equilibrium orientation will be at $\Theta = \pi/2$ if $\chi_r > \chi_z > 0$ (paramagnetic) or $\chi_z < \chi_r < 0$ (diamagnetic).

For individual macromolecules of biological importance, the magnetic interaction energy given by Eq. (3) is small compared to the thermal energy, kT, where k is Boltzmann's constant and T is the absolute temperature. As a result, the extent of orientation of individual molecules in strong magnetic fields is very small. For example, optical birefringence measurements on calf thymus DNA in solution have demonstrated that a field of 13 T is required to produce orientation of 1% of the molecules [23]. In contrast, there are several examples of macromolecular assemblies that can be completely oriented by fields on the order of 1 T. These assemblies behave as structurally coupled units in which the summed magnetic anisotropy is large, thus giving rise to a large magnetic interaction energy. Examples of molecular aggregates that exhibit magneto-orientation include retinal rod outer segments [24-29], muscle fibers [30], photosynthetic systems (chloroplast grana, photosynthetic bacteria and Chlorella cells)[31-35], purple membranes of Halobacteria [36], and filamentous virus particles [37]. Although the magneto-orientation of biologically important structures such as retinal rods can be demonstrated by optical techniques when these units are suspended in an aqueous medium [28], the implications of this effect for visual functions in vivo is unclear. As discussed in a later section of this chapter, there is no experimental evidence that the visual apparatus of mammals is influenced by static fields up to 1.5 T [17]. It is likely that a magnetic orientational torque has little influence on the strong structural matrix in which retinal rods are imbedded within the intact retina.

One example of an intact cell that can be oriented magnetically is the deoxygenated sickled erythrocyte. It has been shown that these cells, in which the deoxygenated hemoglobin is paramagnetic, will align in a 0.35 T static field with the long axis of the sickled cell oriented perpendicular to the

magnetic flux lines [38]. This equilibrium orientation results from the stacking of the planar haem moieties parallel to the long axis of the sickled erythrocyte, with the net magnetic moment oriented perpendicular to the long axis.

Another type of magnetomechanical interaction is the translation of paramagnetic and ferromagnetic substances in static magnetic field spatial gradients. Denoting the magnetic susceptibility as χ and the volume as V, the force, F(z), experienced in a linear magnetic field gradient, dB/dz, is equal to the product of the net magnetic moment and the gradient:

$$F(z) = \frac{\chi V B}{\mu_0} (dB/dz) \tag{4}$$

The forces exerted on paramagnetic and ferromagnetic substances by strong static magnetic field gradients provide the physical basis for a number of useful biological separation processes. Several examples of magnetic separation techniques are described in a later section of this chapter.

(3) Magnetic field effects on electronic spin states. There are several classes of organic chemical reactions that can be influenced by static magnetic fields in the range of 10-100 mT as a result of effects on the electronic spin states of the reaction intermediates [7,39,40]. One well-studied example of such reactions that involves an important biological process is the photo-induced charge transfer reaction in bacterial photosynthesis [41-46]. This reaction involves a radical pair intermediate state through which electron transfer occurs to the ultimate acceptor molecule, a ubiquinone-iron complex. Under natural conditions the electron transfer occurs within 200 picosec following flash excitation of the bacteriochlorophyll. However, chemical reduction of the acceptor molecules extends the lifetime of the intermediate state to about 10 nsec. With an extended lifetime, the singlet state of the radical pair intermediate evolves into a triplet state via the hyperfine mechanism. However, in the presence of an external magnetic field greater

than approximately 10 mT, the triplet channels are blocked and the resulting yield of triplet product is expected to decrease by two thirds. This predicted blocking of triplet channels by a weak magnetic field has been confirmed experimentally using laser pulse excitation and optical absorption measurements [44].

It should be emphasized that the magnetic field effects on charge transfer reactions studied to date occur only when the photosynthetic system is placed in an abnormal state by chemical reduction of the electron acceptor molecules. The possibility cannot be excluded, however, that similar magnetic field effects may occur in other radical-mediated biological processes under natural conditions. For example, Schulten et al. [47] have proposed that an anisotropic Zeeman interaction with a radical-mediated reaction system could provide a basis for geomagnetic direction finding. Several types of enzymatic reactions also involve radical intermediate states that may exhibit sensitivity to static magnetic fields [4].

Biological effects of static magnetic fields. As discussed in a later section of this chapter, several species of marine animals and various lower life forms possess an inherent sensitivity to static magnetic fields with intensities as low as that of the geomagnetic field. In higher organisms, however, laboratory studies of static magnetic field interactions have produced numerous contradictory findings, and the only *in vivo* effect that is well established at the present time is the induction of electrical potentials in the central circulatory system. There are also numerous instances in which contradictory results have been reported in the literature. For example, the report [48] of cell transformation resulting from exposure to a 0.5 T field at 4 K was shown to be an artifact resulting from unconventional culture techniques [49]. A second example is the finding that thermoregulation in rodents is influenced by strong magnetic field gradients [50], which could not

be replicated in a second laboratory [51].

During the past decade a significant number of studies have been conducted in which the bioeffects of static magnetic fields were examined under well-controlled laboratory conditions, including the use of precise dosimetry, large numbers of experimental subjects, quantitative biochemical and physiological end points, and careful attention to environmental conditions other than the magnetic field that could influence the experimental outcome. Based on experiments conducted with field levels of 1 T or greater, the following important biological processes appear not to be influenced by static magnetic fields at high intensities:

- cell growth and morphology [49,52-54];
- DNA structure and gene expression [55-59];
- reproduction and development (pre- and post-natal) [60-62];
- bioelectric properties of isolated neurons [20-22];
- animal behavior [63];
- visual response to photic stimulation [17];
- cardiovascular dynamics (acute exposures) [15,16];
- hematological indices [64,65];
- immune responsiveness [66];
- physiological regulation and circadian rhythms [4,67].

It should also be noted that in several of the reports cited above, no bioeffects were observed as a result of exposing cellular, tissue and animal systems to static fields with flux densities less than 1 T. In general, there is no convincing evidence to support the existence of narrow ranges of static magnetic field intensities ("windows") below 1 T in which biological responses might occur that would not be detected at higher field strengths.

Although there is an increasing database which suggests that mammals experience no adverse effects from exposure to fields with flux densities up to the highest levels to which man is generally exposed, additional research

is needed in several key areas. These include: (1) studies of cardiovascular performance in mammals exposed chronically to magnetic field levels that induce electrical potentials on the order of 1 mV or larger within the central circulatory system; (2) electroencephalographic measurements of evoked and non-evoked electrical activity in the central nervous system, which has previously been reported to exhibit both excitatory and inhibitory responses to static magnetic fields [68-69]. (3) cellular, tissue and animal studies are needed to assess the effects of static magnetic fields at intensities greater than 2 T; information of this nature would advance our understanding of magnetic field interaction mechanisms, and would also provide baseline data for assessing the potential bioeffects resulting from the exposure of living systems to ultrahigh fields such as those proposed for use in NMR units designed for _in vivo_ spectroscopy.

A need also exists for additional laboratory investigations on the response of biosystems to static magnetic fields under conditions of stress that may impose a high degree of sensitivity. One example is provided by recent studies on the transport properties of liposome phospholipid membranes exposed to static magnetic fields. These investigations revealed a unique magnetic field sensitivity that is linked to temperature [70]. Significant changes in the permeability of liposomal bilayer membranes to a low-molecular-weight solute, cytosine arabinoside (MW = 243 D), were observed when the liposomes were exposed to static magnetic fields exceeding 10 mT at temperatures in the thermal phase transition region of 40.0-40.7 ^{o}C. At temperatures below 40.0 ^{o}C or above 40.7 ^{o}C, no effect on liposome membrane transport was observed in fields as high as 7.5 T. The physical interaction mechanism underlying the magnetic field sensitivity of liposome membranes in the phase transition region has not been elucidated. It has been hypothesized that the clustering of membrane lipids, which occurs at prephase transition temperatures,

may predispose phospholipid domains to diamagnetic orientation in a static magnetic field [70]. This effect, in turn, could significantly influence membrane transport properties.

The implications of these findings for eukaryotic cell membranes are presently unclear. However, the possibility should be examined that natural cell membranes may be sensitive to static magnetic fields of moderate intensity in temperature ranges that correspond to structural phase transitions.

Time-Varying Magnetic Fields with ELF Frequencies

Interaction mechanisms. The primary physical interaction of time-varying magnetic fields with living systems is the induction of electric fields and currents in tissue. In accord with Faraday's law of induction, the relationship between the induced electric field intensity, $\vec{E}$, and the time rate of change of the magnetic flux density is given by the equation:

$$\oint \vec{E} \cdot d\vec{\ell} = - d/dt \iint \vec{B} \cdot d\vec{S} \tag{5}$$

In Eq. (5) the line integral is around a closed curve and $d\vec{\ell}$ is a differential element of length along the curve; $\vec{B}$ is the magnetic flux density and $d\vec{S}$ is a differential surface area element directed normal to the surface enclosed by the curve over which the line integral is taken. For the specific case of a circular loop with radius R intersected by a spatially uniform, time-varying magnetic field orthogonal to the loop, Eq. (5) gives for the magnitude of the average electric field tangent to the loop surface:

$$E = (R/2) \frac{dB}{dt} \tag{6}$$

If the magnetic field is sinusoidal with an amplitude, B_0, and a frequency, ν, then $B = B_0 \sin(2\pi\nu t)$ and from Eq. (5):

$$E = \pi\nu R B_0 \sin(2\pi\nu t) \tag{7}$$

From Ohm's law, the current density, $\vec{J}$, induced in tissue with an average conductivity, σ, is given by:

$$\vec{J} = \sigma \vec{E} \tag{8}$$

Various physical characteristics of time-varying magnetic fields are of importance in assessing their biological effects, including the fundamental field frequency, the maximum and average flux density, the presence

of harmonic frequencies, and the waveform and polarity of the signal. Several types of waveforms have been used in biological research with ELF magnetic fields, including sinusoidal, square-wave, and pulsed waveforms. Two characteristics that are of key importance in analyzing the effects of square-wave and pulsed fields are the rise and decay times of the magnetic field waveform. These parameters determine the maximum time rate of change of the magnetic field and hence the maximum instantaneous electric field and resulting conduction current density induced in tissue.

Although the primary physical interaction of ELF magnetic fields with living systems is the induction of electric currents in tissue, a number of secondary events may occur that involve biochemical and structural alterations at the cellular and subcellular levels. It has been proposed, for example, that the pericellular currents induced by an ELF field could produce alterations in components of the membrane surface [71]. The various mechanisms through which ELF fields could influence membrane properties have recently been reviewed [6,72]. These mechanisms include nonlinear interactions (e.g., solitons) producing long-range cooperative phenomena at the surfaces of living cells, magnetic resonance interactions with biologically important ions, electrochemical effects on ions and larger macromolecular structures, and distortion of counterion motion at cell surfaces. At the present time, there is no convincing experimental evidence to indicate that any of these proposed interactions occurs in living tissues. However, this aspect of the interaction of ELF magnetic fields with living systems deserves careful attention in future research.

Magnetophosphenes. A well-established effect of time-varying magnetic fields on humans is the induction of a flickering illumination within the visual field known as magnetophosphenes [73-82]. This phenomenon occurs as an immediate response to stimulation by either pulsed or sinusoidal

magnetic fields with frequencies less than 100 Hz, and the effect is completely reversible with no apparent influence on visual acuity. The maximum visual sensitivity to sinusoidal magnetic fields has been found at a frequency of 20 Hz in human subjects with normal vision [80]. At this frequency the threshold magnetic field intensity found by Lövsund et al. [80] to elicit phosphenes is approximately 10 mT, as shown in Fig. 2. The corresponding time rate of change of the field is 1.26 T/sec. In recent studies Silny [83] has observed thresholds for magnetophosphene perception in human volunteers as low as 5 mT with 18-Hz sinusoidal fields. In studies with pulsed fields having a rise time of 2 msec and a repetition rate of 15 Hz, the threshold values of dB/dt for eliciting phosphenes ranged from 1.3 to 1.9 T/sec in five adult subjects [82]. There was a trend in the data which suggested that the threshold was lower among younger subjects. In related studies it was also observed that the stimulus duration is an important parameter, since pulses of 0.9 msec duration with dB/dt = 12 T/sec did not evoke phosphenes.

Several types of experimental evidence indicate that the magnetic field interaction leading to magnetophosphenes occurs in the retina: (1) magnetophosphenes are produced by time-varying magnetic fields applied in the region of the eye, and not by fields directed toward the visual cortex in the occipital region of the brain [77]; (2) pressure on the eyeball abolishes sensitivity to magnetophosphenes [77]; (3) the threshold magnetic field intensity required to elicit magnetophosphenes in human subjects with defects in color vision was found to have a different dependence on the field frequency than that observed for subjects with normal color vision [80]; (4) in a patient in whom both eyes had been removed as the result of severe glaucoma, phosphenes could not be induced by time-varying magnetic fields, thereby precluding the possibility that magnetophosphenes can be initiated

directly in the visual pathways of the brain [80].

Although experimental evidence has clearly implicated the retina as the site of magnetic field action leading to phosphenes, it is not as yet resolved whether the photoreceptors or the neuronal elements of the retina are the sensitive substrates that respond to the field. In a series of experiments on in vitro frog retinal preparations, extracellular electrical recordings were made from the ganglion cell layer of the retina immediately following termination of exposure to a 20-Hz, 60-mT field [84,85]. It was found that the average latency time for response of the ganglion cells to a photic stimulus increased by 5 msec ($p < 0.05$) in the presence of the magnetic field. In addition, the ganglion cells that exhibited electrical activity during photic stimulation ("on" cells) ceased their activity during magnetic field stimulation (i.e., they became "off" cells). The converse behavior of ganglion cells was also observed. These observations indicate that stimulation of the retina by light and by a time-varying magnetic field elicits responses in similar post-synaptic neural pathways.

Several other phenomena related to the sensitivity of the visuosensory system to time-varying magnetic fields have also been studied by Silny [83]. In experiments with human subjects it was found that distinct flickering could be elicited in the visual field by sinusoidal magnetic fields in the frequency range 5-60 Hz. The threshold field intensity varied with the field frequency and background light level, but was as low as 5 mT under optimal conditions. Alterations in visually evoked potentials (VEP) were also reported to occur in sinusoidal ELF magnetic fields at intensity levels that are 5-10 times greater than those which produce magnetophosphenes [83]. The change in VEP is characterized by a reversal of polarity and a decreased amplitude of the three major evoked potentials. These effects were observed within 3 min following onset of the magnetic field exposure, and the VEP returned to normal only after a recovery period of approximately

30-70 min following termination of the exposure. The relationship of these changes in the VEP to the mechanism of magnetophosphene induction is not clear from the evidence that is presently available.

Other biological effects of ELF magnetic fields. Time-varying magnetic fields that induce current densities above 1 A/m^2 in tissue lead to neural excitation and are capable of producing irreversible biological effects such as cardiac fibrillation. Several investigators [86-93] have achieved direct neural stimulation using pulsed or sinusoidal magnetic fields that induced tissue current densities in the range of 1-10 A/m^2. In one study involving electromyographic recordings from the human arm [92], it was found that a pulsed field with dB/dt greater than 10^4 T/sec was required to stimulate the median nerve trunk. The duration of the magnetic stimulus has also been found to be an important parameter in the excitation of nerve and nerve-muscle specimens. Using a 20-kHz sinusoidal field applied in bursts of 0.5 to 50 msec duration, Öberg [89] found that a progressive increase in the magnetic flux density was required to stimulate the frog gastrocnemius neuromuscular preparation when the burst duration was reduced to less than 2-5 msec. A similar rise in threshold stimulus strength has been observed for frog neuromuscular stimulation using pulsed magnetic fields with pulse durations less than approximately 1 msec [90,93].

ELF magnetic fields that induce peak current densities greater than approximately 1-10 mA/m^2 have been reported to produce various alterations in the biochemistry and physiology of cells and organized tissues. One example is the effect of the bidirectional pulsed fields used to facilitate bone fracture reunion in humans, as described in a later section of this chapter. A large number of laboratory investigations have also led to reports of a broad spectrum of alterations in cellular, tissue and animal systems in which current densities exceeding 1-10 mA/m^2 were induced by

ELF magnetic fields [6,8,9]. Briefly summarized, these effects include:

- altered cell growth rate;
- decreased rate of cellular respiration;
- altered metabolism of carbohydrates, proteins and nucleic acids;
- effects on gene expression and genetic regulation of cell functions;
- teratological and developmental effects;
- morphological and other nonspecific tissue changes in adult animals, frequently reversible with time following exposure;
- endocrine alterations;
- altered hormonal responses of cells and tissues, including effects on cell surface receptors;
- altered immune response to antigens and lectins.

In assessing these reported effects of ELF magnetic fields, it is important to recognize that very few of the observations have been independently replicated in a second laboratory. In some instances where attempts at replication were carried out, the results were contradictory. For example, Maffeo et al. [94] were unable to replicate the finding by Delgado et al. [95] that pulsed magnetic fields with low intensities produce teratological effects in developing chick embryos.

Time-varying magnetic fields that induce tissue current densities less than approximately 1-10 mA/m^2 have been found to produce few, if any, biological effects [6,8,9]. This general observation is not surprising, insofar as the endogenous current densities present in organs such as the brain and heart lie in the range of 1-10 mA/m^2 [96].

Organisms Possessing Unique Magnetic Field Sensitivity

Several types of organisms have been demonstrated to possess sensitivity to extremely weak magnetic fields, comparable in intensity to the geomagnetic field ($\sim$ 50 μT). In several instances, there is direct experimental evidence indicating that this magnetic sensitivity is linked to direction-finding ability. The two basic mechanisms of magnetoreception are magnetic induction of signals in specialized sensory receptors, and magnetic field interactions with localized deposits of single-domain magnetite crystals. These two mechanisms of geomagnetic field detection are discussed in the following paragraphs.

Elasmobranch fish. A well-established example of electrodynamic interactions with weak magnetic fields is the electromagnetic guidance system of elasmobranch fish, a class of marine animals that includes sharks, skates and rays [97-99]. The heads of these fish contain long jelly-filled canals with a high electrical conductivity, known as the ampullae of Lorenzini. As an elasmobranch swims through the lines of flux of the geomagnetic field, small voltage gradients are induced in its ampullary canals. These induced electric fields can be detected at levels as low as 0.5 μV/m by the sensory epithelia that line the terminal ampullary region [100]. The polarity of the induced field in an ampullary canal depends upon the relative orientation of the geomagnetic field and the compass direction along which the fish is swimming. As a consequence, the $-\vec{v} \times \vec{B}$ fields induced in the ampullae of Lorenzini provide a sensitive directional cue for the elasmobranch fishes.

Magnetotactic bacteria. An example of a cellular structure in which significant magnetic orientational effects occur in response to the geomagnetic field is the magnetotactic bacterium originally discovered by Blakemore [101]. Approximately 2% of the dry mass of these aquatic organisms is iron, which has been shown by Mössbauer spectroscopy to be predominantly

in the form of magnetite: Fe_3O_4 [102]. The magnetite crystals are arranged as chains of approximately 20-30 single domain crystals, as shown in Fig. 3. The orientation of the net magnetic moment is such that magnetotactic bacteria in the northern hemisphere migrate towards the north pole of the geomagnetic field, whereas strains of these bacteria that grow in the southern hemisphere move towards the south magnetic pole [103]. Magnetotactic bacteria that have been found at the geomagnetic equator are nearly equal mixtures of south-seeking and north-seeking organisms [104]. The polarity of the microbial magnets can be reversed by applying a strong pulsed magnetic field that reverses the direction of the net magnetic moment [105]. As a result, the swimming direction of the bacteria within the geomagnetic field is reversed (see Fig. 3).

Because of the polarities of their magnetic moments, the magnetotactic bacteria in both the northern and southern hemispheres migrate downwards in response to the vertical component of the geomagnetic field. It has been proposed that this downward directed motion, which carries the bacteria into the bottom sediments of their aquatic environment, may be essential for the survival of these microaerophilic organisms [101,103]. Recent studies indicate that fossil bacterial magnetite may be responsible for the natural remanent magnetization in deep-sea sediments [106].

Birds, bees, mollusks, and other animal species. It has been found that weak magnetic fields exert an influence on the migratory patterns of birds [107-110], the waggle dance of bees [111], and the kinetic movements of mollusks [112]. A possible mechanism underlying the magnetic sensitivity of these organisms is related to the discovery of small deposits of magnetite in the cranium and neck muscles of pigeons [113,114], the abdominal region of bees [115], and the tooth denticles of mollusks [116,117]. It has been argued on theoretical grounds that weak magnetic interactions with the

small magnetite deposits identified in avians and in bees could provide somatosensory inputs that convey directional information (118,119].

Magnetite has also been reported to be localized in various anatomical sites in dolphins [120], tuna [121], butterflies [122], turtles [123], salmon [124], mice [125] and humans [126]. The possible role of magnetite in the geomagnetic direction-finding mechanism apparently possessed by some of these species has not as yet been established, nor is it clear that a sensitivity to the geomagnetic field direction exists for all of the mammalian species (e.g., humans) in which magnetite deposits have been reported to occur [127,128].

Magnetic Field Applications in Research and Medicine

In recent years there has been a rapid increase in the number of applications of magnetic fields in medicine and biological research. Several examples of technological developments in this area are described in the following paragraphs.

Nuclear magnetic resonance imaging and in vivo spectroscopy. A major advance in clinical radiology during the past decade has been the demonstration that nuclear magnetic resonance (NMR) can be used to obtain high-resolution images of biological tissues [129-131]. In this technique, nuclear magnetic moments are aligned by the application of a static magnetic field, B_0, and undergo a precessional motion about the field direction with a characteristic frequency $\upsilon = \gamma B_0/2\pi$. The constant γ is the gyromagnetic ratio, defined as the nuclear magnetic moment divided by the spin angular momentum. When a radiofrequency field is applied transverse to the direction of B_0, it can undergo a resonant interaction with the aligned magnetic moments that cause them to adopt the antiparallel state. As the nuclear moments return to their equilibrium state, they radiate a quantum of energy that is proportional to the resonant frequency. The overall strength of the radiated signal picked up in a receiver coil reflects the total tissue concentration of magnetic nuclei with the characteristic resonant frequency υ.

In addition, the time variation in the decay of the NMR signal provides a rich variety of information about the local environment of magnetic nuclei such as protons. These time parameters include the spin-lattice relaxation time T_1, which conveys information on the regional temperature and viscosity, and the spin-spin relaxation time T_2, which reflects the local magnetic field resulting from the nuclear moments of neighboring nuclei. The T_1 and T_2 parameters provide information that can be converted into contrast differences in NMR images of tissue proton density.

In proton-rich structures such as myelinated nerves in the central nervous system, regions of demyelination can be sharply defined by NMR images based on the T_1 or T_2 relaxation parameters, as illustrated in Fig. 4(A). The development of demyelination disorders such as multiple sclerosis may therefore be detected with a greater sensitivity using NMR imaging than other contemporary imaging modalities. Proton magnetic resonance also shows promise as an effective imaging modality for the detection of malignancies.

In addition to its demonstrated value as a new medical imaging technique, magnetic resonance can be used as an in vivo spectroscopic method for studying the metabolism of high-energy phosphate compounds, ^{13}C-labeled metabolites, and a wide variety of other endogenous or injected compounds containing magnetic nuclei [132-136]. It has been demonstrated in various studies that ^{1}H, ^{13}C and ^{31}P chemical shift spectra can be obtained from living tissues. For example, ^{31}P signals provide a direct measure of the relative concentrations of ATP, phosphocreatine and inorganic phosphates during oxidative phosphorylation processes in organs such as the heart.

Biomagnetic measurements. Extraordinarily small magnetic fields ranging from 5 fT to 1 nT are produced by the bioelectric activity of living tissues and by the presence in tissues of trace amounts of magnetic materials. Initial attempts to measure the magnetic fields resulting from cardiac and CNS bioelectric activity were made in the 1960's by the use of detection coils that consisted of several million turns of copper wire wound on a ferrite core [137,138]. A major advance in biomagnetic measurements occurred in 1970 with the development of a SQUID (superconducting quantum interference device) magnetometer for detecting weak biomagnetic fields [139]. When combined with a gradiometer detection coil and filters to reduce interference from ambient magnetic noise, the SQUID magnetometer technique can achieve a sensitivity of

approximately 35 $fT/Hz^{1/2}$ in an unshielded environment. As demonstrated by a large number of studies during the last 15 years, the SQUID gradiometer technique provides quantitative information on the bioelectric properties of the heart, brain, eye and other tissues in both normal and pathological states [140,141]. In comparison with direct measurements of tissue electrical activity using electrodes, the external recording of biomagnetic fields offers several advantages illustrated in Fig. 4(B):

- the SQUID gradiometer technique provides remote, noninvasive sensing of electric current profiles in tissue;
- the recording of weak biomagnetic signals can be accomplished with a high sensitivity;
- the interpretation of biomagnetic signals does not require assumptions about tissue conductivity and electric field boundary conditions that must be introduced for the interpretation of direct electrical recordings;
- the location of current sources responsible for tissue bioelectric activity can, in general, be determined with greater precision from the resultant magnetic field than from the resultant electric field.

In addition to recording bioelectric signals, the SQUID gradiometer technique can be used to analyze small deposits in tissue of magnetic materials [142]. For example, substances containing iron can be detected with a high level of sensitivity within the lung airways and in the liver.

Several clinical studies have also demonstrated that biomagnetic measurements may provide a useful diagnostic technique. Three examples are the following:

- The accumulation of small quantities of asbestos within the lung can be detected magnetically as a result of the adsorbed magnetite carried by asbestos particles [143];
- biomagnetic measurements provide a sensitive method for studying

iron storage diseases, an example being the detection of an abnormally large quantity of iron within the liver in Thalassemia patients [144].

- SQUID gradiometer recordings from patients with local paroxysmal discharges of epileptic brain tissue revealed the existence of local spiking in the external neuromagnetic field profile; the measurement of these spikes provided information on the brain location, depth, orientation and polarity of abnormal electric currents underlying the paroxysmal discharges [145].

Electromagnetic blood flow measurements. As a result of magnetic induction, a conductive fluid such as blood will develop a transverse electrical potential when flowing in the presence of a magnetic field. In accord with the theoretical description of this phenomenon given earlier in this chapter (see Eq. 1), the induced blood flow potential (ψ) is a linear function of the blood flow rate (v), the vessel diameter (d), and the magnetic flux density (B). Magnetically-induced blood flow potentials were first used by Kolin[146,147] as the basis of a method for measuring blood flow rate without opening a vessel or introducing foreign substances such as dyes into the circulation. The original electromagnetic flowmeter employed a static magnetic field, which was later replaced by a time-varying magnetic field in order to avoid artifacts associated with polarization of the electrodes used to measure the induced potential. The flowmeter models that are now commercially available use time-varying fields with frequencies up to approximately 500 Hz. Fig. 4(C) shows a perivascular flowmeter and representative data on carotid artery blood flow rates.

The use of flowmeters with either perivascular or intravascular transducers has become a widely used clinical method for monitoring blood flow during surgical procedures [148]. This technique can be used for measuring

the rate of blood flow in major vessels such as the portal vein [149] and the coronary artery [150] with a precision of 1 to 2% over a period of several hours. Other useful applications of the flowmeter principle include the measurement of microscopic variations in vascular diameter [151] and the determination of blood flow through large segments of an organ such as the pancreas [152].

Pulsed magnetic field facilitation of bone fracture reunion. Several investigations carried out during the 19th century and the early part of the 20th century indicated that electrotherapy may provide a promising technique for the treatment of bone fractures [153]. Increased interest in this area arose during the 1950's and 1960's as the result of several demonstrations of the piezoelectric properties of bone [154,155]. Although some measure of success was achieved in treating bone nonunions by electrical stimulation, the use of direct currents produced by electrodes led to several undesirable side effects, including:

- surgical trauma and a risk of infection as a result of the implantation of electrodes in bone;
- the development of electrode polarization with time, which led to increased impedance and decreased current for a given applied voltage;
- osteogenesis was found to be increased near the negative (cathodic) pole, but decreased near the positive (anodic) pole.

These disadvantages of DC electrical stimulation were overcome by the recent introduction of pulsed magnetic field generators as a means of inducing ELF electrical currents into bone tissue [156]. Magnetic coils are placed about a limb and positioned such that the bone fracture lies along a line joining the centers of the coils, and hence along the magnetic field lines. This coil geometry and the types of pulsed magnetic field waveforms used for bone fracture therapy are illustrated in Fig. 5(A). Assuming the conductivity

of bone to be 0.01 S/m at ELF frequencies [157], the local current densities induced in bone by the pulsed magnetic field can be estimated to lie in the range of approximately 2 to 20 mA/m^2.

Following the initial demonstration of the efficacy of pulsed magnetic fields in achieving bone fracture reunion in experimental animals, several clinical trials have reported success in treating bone fractures and arthroses in humans by this method. In a four-year clinical trial involving more than 100 patients, Bassett et al. [158] reported an 85% success rate in the treatment of long-established pseudoarthroses. The successful use of pulsed magnetic fields in the facilitation of bone healing in human subjects has subsequently been reported by several clinical groups [159-163]. The importance of continuing these clinical trials, including the use of dummy stimulators in control subjects, has been emphasized by Barker and others [164,165].

The mechanism(s) by which the weak ELF electric currents induced in bone tissue by pulsed magnetic fields exert an influence on fracture repair is under investigation in a number of laboratories. Evidence from *in vitro* studies on osteoblasts and chondrocytes indicate that exposure to pulsed magnetic fields leads to a depression of the intracellular concentrations of calcium ions and cyclic AMP [166,167]. These effects, in turn, can significantly influence cellular metabolism and alter the biosynthesis of proteins such as collagen [167,168]. Studies by Hinsenkamp and Rooze [169] with *in vitro* cultures of limbs from mouse fetuses have demonstrated that electromagnetic stimulation leads to chondrocyte proliferation and an improved alignment of trabeculae and cartilage.

Magnetic separations. Paramagnetic and ferromagnetic biological materials can be separated from other constituents within a mixture by using strong magnetic field gradients. As discussed in an earlier section of this chapter (see Eq. 4) and illustrated in Fig. 5(B), the force exerted by a

magnetic field ($\vec{B}$) on a material with a net magnetic moment ($\vec{m}$) is equal to the negative gradient of the magnetic interaction energy ($U = -\vec{m}\cdot\vec{B}$). For the simple case of a linear magnetic field gradient, the net force is proportional to the magnetic susceptibility of the substance (χ), its volume (V), and the product of the magnetic flux density and the linear field gradient ($B\cdot dB/dz$). As a result of this force, paramagnetic and ferromagnetic materials will migrate along the direction of the magnetic field gradient.

A number of useful applications of magnetic forces have been made, including the targeting of drugs contained in magnetic microcarriers [170], the removal of microorganisms from water [171], and the magnetic separation of erythrocytes [172,173] and antibody-secreting cells [174,175]. The use of magnetomechanical forces to separate erythrocytes from whole blood is illustrated in Fig. 5(B). In this procedure, a magnetic field of approximately 2 T is used to magnetize a stainless steel wire mesh packed within a polyethylene cylinder, thereby creating local field gradients approaching 10^4 T/m near the wires. Blood is applied to the column after dilution in an isotonic solution that contains sodium dithionite to reduce the erythrocyte hemoglobin to its paramagnetic deoxyhemoglobin form. When the column is flushed with buffer solution while the magnetic field is being applied, elution of the nonerythroid blood cells occurs and the erythrocytes are retained on the magnetized wire mesh. The field is then switched off and the column is again flushed with buffer solution, producing a pure erythrocyte cell population in the eluant. Up to 70% of the total erythrocyte population can be retained in the column while the field is being applied, thereby producing a significant enrichment of the nonerythroid cell populations such as white blood cells and platelets.

Another interesting example of magnetic separation technology is the

demonstration that erythrocytes containing malarial parasites can be separated from uninfected erythrocytes in a strong magnetic field gradient [176]. The malarial parasite digests hemoglobin to produce high-spin haem products that are paramagnetic, whereas intact hemoglobin is diamagnetic in the oxygenated state. Paul et al. [176] have found that a 45-fold enrichment of parasitized erythrocytes can be achieved by the high-gradient magnetic separation technique.

Magnetic circular dichroism. A promising method for studying the conformation of nucleic acids *in vivo* is magnetic circular dichroism (MCD) spectroscopy. In this technique, conventional circular dichroism (CD) instrumentation is used in combination with a superconducting magnet capable of producing a field of several Tesla intensity within the sample. As a consequence of the Faraday effect, the plane of polarization of a beam of linearly polarized light passing through an optically active sample will rotate by an angle, ϕ, that is proportional to the magnetic field intensity. The value of ϕ is a function of the ellipticity, which is a measure of the circular differential absorption induced by the strong magnetic field. The circular differential absorption is expressed as a function of the difference in extinction coefficients for the left- and right-hand circularly polarized components of the light beam, $(\varepsilon_L - \varepsilon_R)$. The magnetic optical activity arises from a different set of molecular interactions than those that give rise to natural CD, and in isotropic media the MCD and CD spectra are additive.

In general, three types of interactions are responsible for the structure of MCD spectra obtained with polymers such as DNA [177]. Two of these, called the "A" and "C" terms in MCD spectra, are due to Zeeman splittings of ground or excited states. The third type of MCD contribution, called the "B" term, arises from the mixing of ground states with two or more excited

states. This third type of interaction is largely responsible for the MCD spectra of nucleic acids in the UV spectral range, since the bases have a low degree of symmetry and the terms involving Zeeman splitting of degenerate states are eliminated. The theoretical basis of the Faraday rotational strength for a polymer composed of N monomer units has been described by Tinoco and Bush [178].

Several advantageous features of MCD for studying the secondary structure of DNA contained within complex, heterogeneous biological structures was demonstrated experimentally by Gray et al. [179] in a study with bacteriophage. These investigators obtained CD and MCD spectra of nucleic acid polymers of varying length, of T2 and T5 bacteriophage DNA at various stages of heat denaturation, and of intact and broken bacteriophages. The results of these studies demonstrated that MCD spectra are strongly dependent on nucleic acid conformation, as shown by spectral changes that were a function of oligimer length, the extent of thermal denaturation, and the internal packing of DNA within the two strains of bacteriophage that were examined. The resulting data, illustrated in Fig. 5(C), also demonstrated that MCD measurements have an advantage over conventional CD for studying the conformation of biological macromolecules such as DNA because MCD is insensitive to the light scattering contribution of large chiral structures. In addition, the phage studies demonstrated that there is significantly less protein contribution to the spectra above 250 nm obtained by MCD relative to conventional CD. Although the instrumentation required for MCD measurements is complex, this method offers considerable promise as a technique for studying the secondary structure of DNA in living cells. It is also possible that MCD can provide a sensitive technique for examining the *in vivo* conformational changes in DNA that result from the interaction of perturbing agents such as chemical mutagens and ionizing radiation.

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Figure legends

Figure 1. Electrocardiogram (ECG) and intraarterial blood pressure records are shown for a *Macaca* monkey exposed to uniform static magnetic fields up to 1.5 Tesla. The ECG clearly demonstrates the increase in signal amplitude at the locus of the T-wave during magnetic field exposure. No measurable change occurred in the intraarterial blood pressure at field levels up to 1.5 Tesla. [Adapted from Fig. 1 of ref. 16]

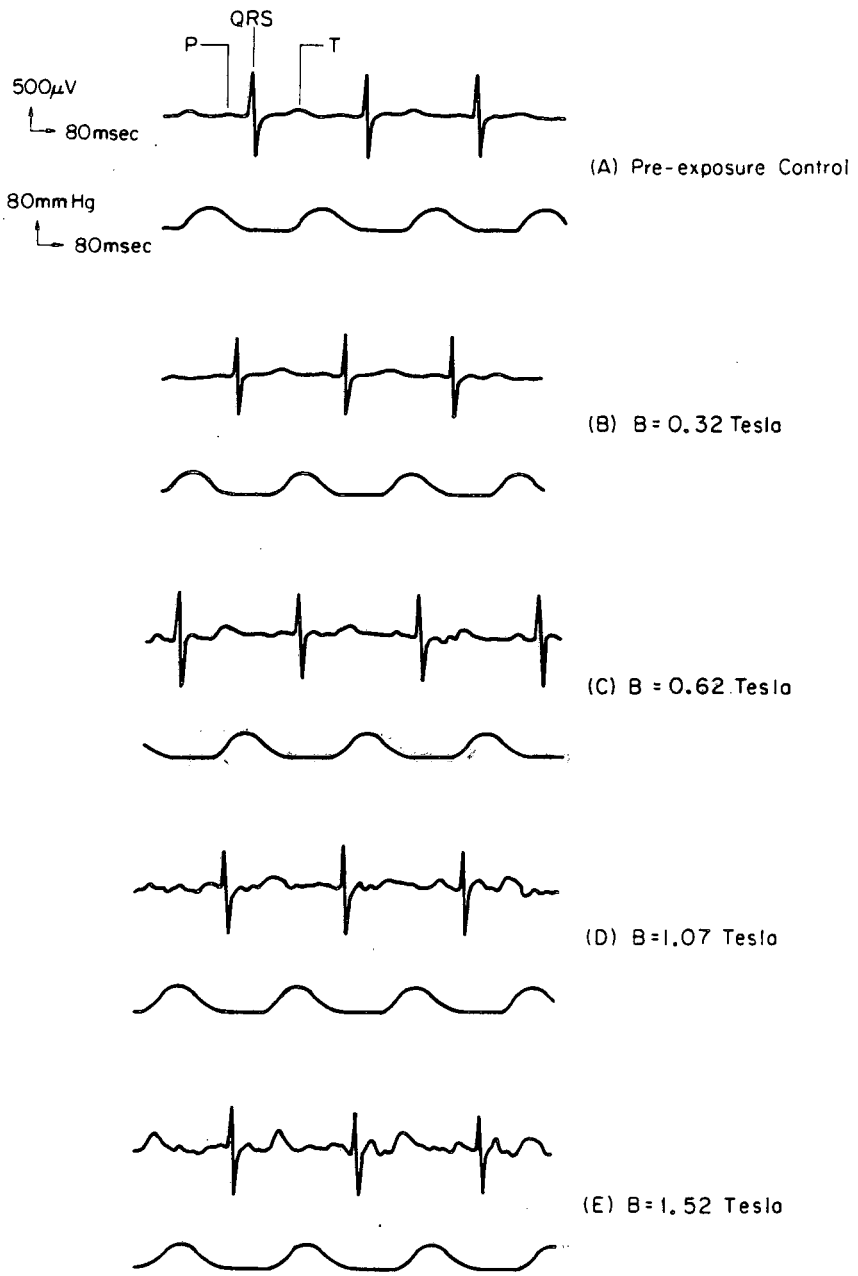
Figure 2. Threshold values of the magnetic flux density required to elicit magnetophosphenes are plotted as a function of the field frequency. Each data point represents the mean value $\pm$ 1 S.E. for 10 volunteers, all of whom were studied with a background white light level of 3 cd/m^2. [Adapted from Fig. 3 of ref. 79].

Figure 3. Electron micrograph of a magnetotactic bacterium (courtesy of Dr. T. F. Budinger), and illustrations representing the response of these bacteria to the geomagnetic field (adapted from Fig. 1 of ref. 105). The three sets of diagrams illustrate the response to a weak magnetic field (N = north magnetic pole) of magnetotactic bacteria contained in a water droplet. In the illustrations on the top two lines, the horizontal and vertical components of the geomagnetic field were reversed at the times indicated by dots on the U-shaped tracks. These tracks represent the direction of bacterial migration in response to the earth's field. In the illustrations on the bottom line, the polarity of the microbial magnets was reversed by applying a high-intensity, pulsed magnetic field ($\sim$60 mT, 1.75 μsec) at the time indicated by the dot on the U-shaped track. The reversal of magnetic polarity converts the "north-seeking" bacteria to "south-seeking" bacteria.

Figure 4. Illustration of three applications of magnetic fields for (A) nuclear magnetic resonance (NMR) imaging and *in vivo* spectroscopy, (B) the measurement of endogenous biomagnetic signals reflecting brain electrical activity, and (C) electromagnetic blood flow measurements. In (A) the arrows indicate the locations of demyelination defects in the brain of a patient with multiple sclerosis. In (B) the acronym SQUID represents "superconducting quantum interference device."

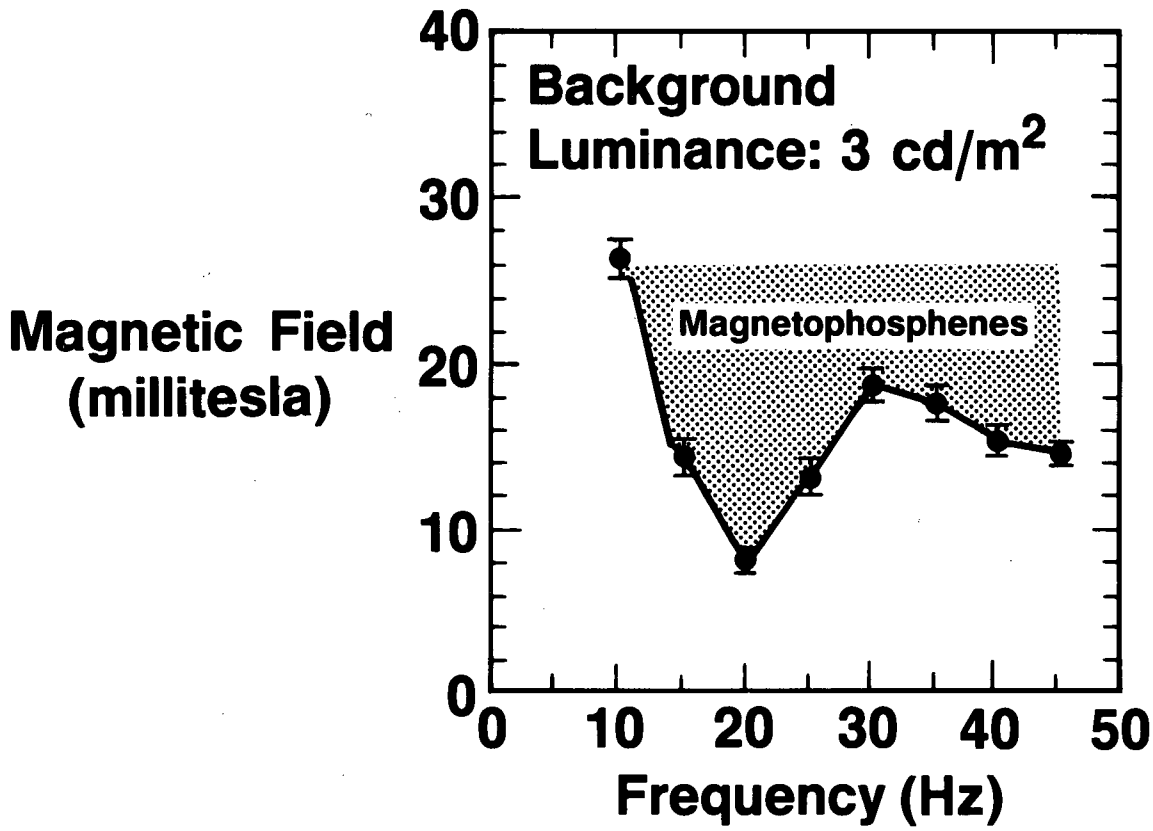
Figure 5. Illustration of applications of magnetic fields for (A) the facilitation of bone fracture reunion, (B) the separation of paramagnetic biological materials such as deoxygenated erythrocytes, and (C) magnetic circular dichroism spectroscopy studies on the conformation of biological macromolecules such as DNA.

MONKEY ELECTROCARDIOGRAM
AND BLOOD PRESSURE



XBL 819-4225A

FIGURE 1

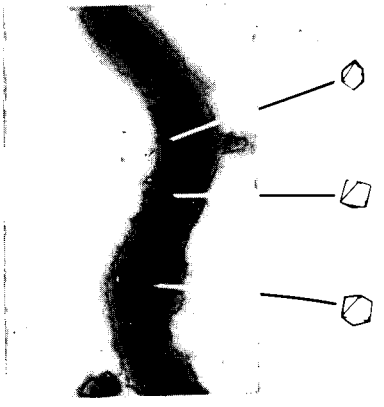


[From Lövsund et al.,
Acta Ophthalmologia 57: 812 (1979)]

XBL 848-7796

FIGURE 2

MAGNETOTACTIC BACTERIUM



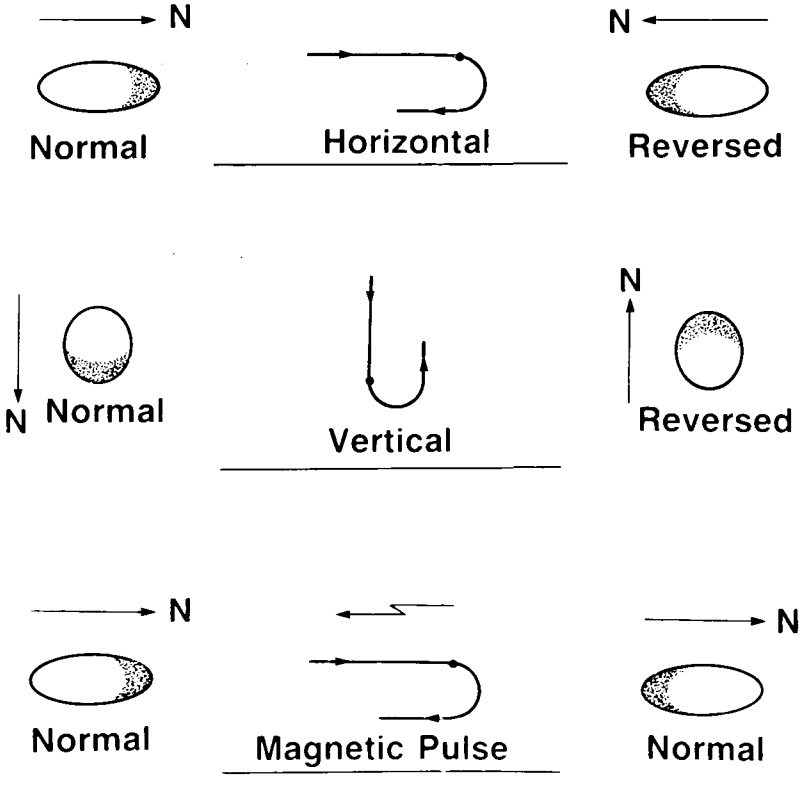


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FIGURE 3

APPLICATIONS OF MAGNETIC FIELDS IN MEDICINE AND BIOLOGICAL RESEARCH

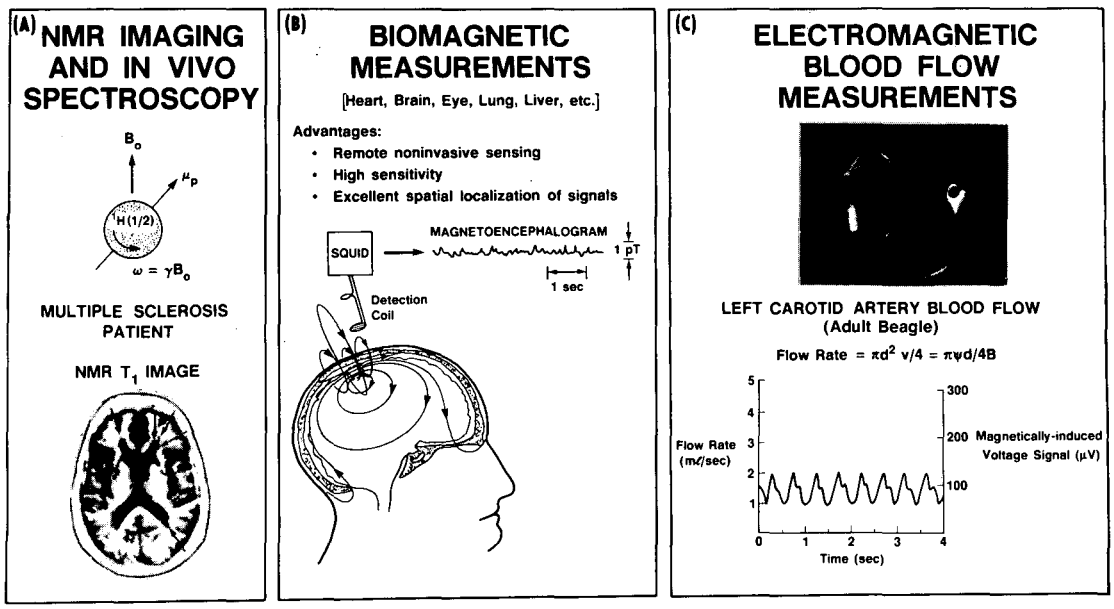

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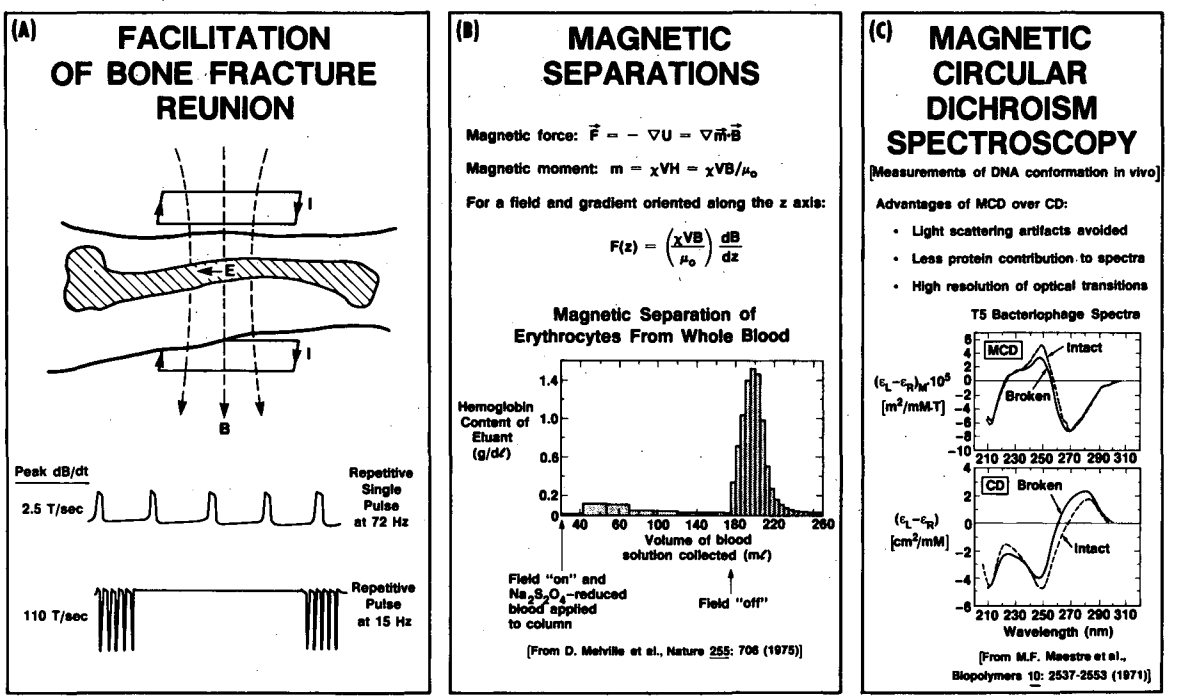
FIGURE 4

APPLICATIONS OF MAGNETIC FIELDS IN MEDICINE AND BIOLOGICAL RESEARCH



XBL 863-8682

FIGURE 5

This report was done with support from the Department of Energy. Any conclusions or opinions expressed in this report represent solely those of the author(s) and not necessarily those of The Regents of the University of California, the Lawrence Berkeley Laboratory or the Department of Energy.

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