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BIOLOGICAL EFFECTS AND PHYSICAL SAFETY ASPECTS OF NMR IMAGING AND IN VIVO SPECTROSCOPY

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CONTENTS:

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ABSTRACT

An assessment is made of the biological effects and physical hazards of static and time-varying fields associated with the NMR devices that are being used for clinical imaging and in vivo spectroscopy. A summary is given of the current state of knowledge concerning the mechanisms of interaction and the bioeffects of these fields. Additional topics that are discussed include: (1) physical effects on pacemakers and metallic implants such as aneurysm clips, (2) human health studies related to the effects of exposure to nonionizing electromagnetic radiation, and (3) extant guidelines for limiting exposure of patients and medical personnel to the fields produced by NMR devices. On the basis of information available at the present time, it is concluded that the fields associated with the current generation of NMR devices do not pose a significant health risk in themselves. However, rigorous guidelines must be followed to avoid the physical interaction of these fields with metallic implants and medical electronic devices.

INTRODUCTION

The primary objective of this chapter is to summarize the theoretical and experimental bases for judging the safety of human exposure to the static and time-varying fields associated with NMR imaging and in vivo spectroscopy. Unlike ionizing radiation, the interaction of these fields with living objects is generally subtle and frequently difficult to detect. A few exceptions include magnetically-induced potentials in the circulatory system, the induction of magnetophosphenes by extremely-low-frequency (ELF) magnetic fields, and tissue heating by radiofrequency (RF) fields with sufficiently high power densities. These phenomena, and the direct interaction of NMR fields with electronic devices and metallic implants, will be discussed within the context of established interaction mechanisms that can be characterized using elementary physical principles. A summary and critique will also be given of several human health studies that have been reported in the literature, with a particular emphasis on evaluating the soundness of the methodology used in these epidemiological surveys. Detailed discussions of these topics have also been given in several recent review articles and monographs.[1-16]

FIELDS ASSOCIATED WITH NMR DEVICES

The present generation of devices for NMR imaging and in vivo spectroscopy use static magnetic fields with flux densities less than 2.5 Tesla (1 T = 10^4 Gauss). Most of the existing machines for whole-body imaging contain large-volume superconducting magnets that produce highly stable, uniform fields of 0.6 T or less. Several of the newer whole-body imaging units use fields up to 2.0 T, and fields up to 2.5 T are currently used for in vivo spectroscopy. Higher field levels are being considered for future NMR units.

The magnetic field gradients that provide spatial information defining the location of magnetic nuclei are less than 10 mT/m, and generally lie in the range of 1-5 mT/m in the existing NMR devices. The rapid switching of gradient fields leads to a time variation of the magnetic flux density (dB/dt) which is less than 3 T/sec in the current imaging devices, with typical values in the range of 0.5-1.5 T/sec. Higher values of dB/dt are anticipated in future NMR units using faster rates of data projection.

The frequencies of the RF fields used in current NMR devices are a function of the static field strength and the Larmor frequencies of the magnetic nuclei being studied. For example, in a 1 T field the resonant frequencies of ^{1}H, ^{13}C, ^{23}Na, ^{31}P and ^{39}K are, respectively, 42.576, 10.705, 11.262, 17.235 and 1.987 MHz. Under the near-field imaging conditions used for in vivo NMR, the absorption of RF energy is primarily associated with the magnetic component of the field, which is typically on the order of 0.5 mT. As discussed in a later section of this chapter, the specific absorption rate of RF energy is a function of frequency, tissue conductivity and dielectric constant, geometric factors, and the NMR pulse characteristics used for imaging.

STATIC MAGNETIC FIELDS

Interaction Mechanisms

Although numerous mechanisms have been proposed through which static magnetic fields could potentially influence biological functions,[13] only three classes of physical interactions 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 charge transfer processes. Each of these physical interaction mechanisms, along with relevant experimental data, will be described in this section.

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 a local electric field $\vec{E} = -\vec{v} \times \vec{B}$, where v is the velocity of current flow and 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.

One 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.[17-19] 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.[20] 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.

A second example of electrodynamic interactions is the electric field resulting from 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:[13]

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

where Θ is the angle between $\vec{B}$ and the axial velocity vector, $\vec{v}$. This equation, which was first derived by Kolin, describes the physical principle upon which the electromagnetic blood flowmeter operates.[21-23] The induced blood flow potentials within the central circulatory systems of several species of mammals exposed to large static magnetic fields have also been characterized from electrocardiogram (ECG) records obtained with surface electrodes.[24-30] As demonstrated by the data shown in Fig. 1 for a Macaca monkey exposed to static fields up to 1.5 T, 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.[25-30] The opening and closing of the aortic heart value have been shown to correspond with the timing of the appearance and disappearance of the magnetically-induced potential at the locus of the T-wave.[31] 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.[29] For larger animal species such as dogs, monkeys and baboons, the threshold field level which induces a measurable potential is approximately 0.1 T.[27,30,31] 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 ψ on magnetic field strength and its variation as a function of animal orientation within the field [see eqn. (1)] have been experimentally confirmed.[27,29-31]

The linear dependence of a magnetically-induced blood flow potential on vessel diameter, as shown in eqn. (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

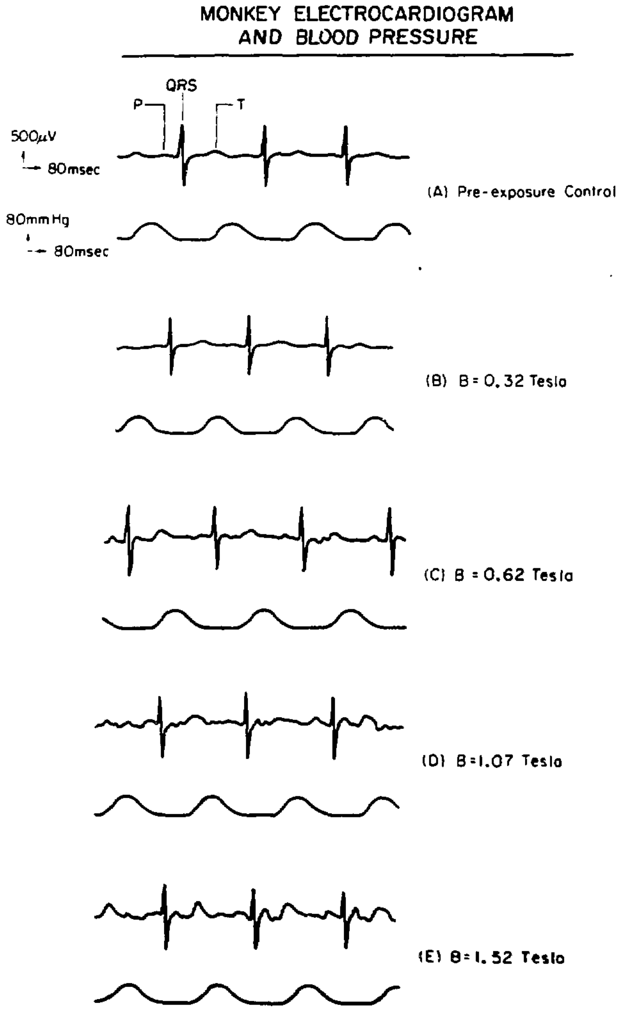

Fig. 1: Electrocardiogram and intraarterial blood pressure records are shown for a *Macaca* monkey exposed to uniform static magnetic fields up to 1.5 T. The ECG clearly demonstrates the increase in signal amplitude at the locus of the T-wave during magnetic field exposure. No measurable change occurred in the intraarterial blood pressure at field levels up to 1.5 T. [Adapted from Fig. 1 of ref. 30.] (XBL 819-4225A)

on eqn. (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.[14,27-31]

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:[31]

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

where R is the vessel radius and σ and η are, respectively, the electrical conductivity and kinematic viscosity of blood. From eqn. (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.[31] Also, as demonstrated by the intraarterial blood pressure measurements shown in Fig. 1, no hemodynamic alterations were observed during the exposure of three Macaca monkeys to a 1.5 T field.[30] Contrary to earlier speculations,[32-34] the extent to which magnetohydrodynamic interactions alter blood flow dynamics is therefore expected to be minimal even in relatively large magnetic fields.

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.[35,36] For example, it has been estimated that a 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.[35] The absence of a measurable interaction of a 2 T static field with the ionic currents of an isolated sciatic nerve is demonstrated by the action potential recordings shown in Fig. 2. In other studies with isolated nerves, 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.[37-39] 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 the relative refractory periods that follow the passage of an action potential.[39]

Magnetomechanical effects. 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 symmetry. The total interaction energy with the field, U, is obtained by integrating the tensorial product of the magnetic flux density, B, and the magnetic moment per unit volume, M, over the molecular volume, V. The resulting expression for U is:[13]

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

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

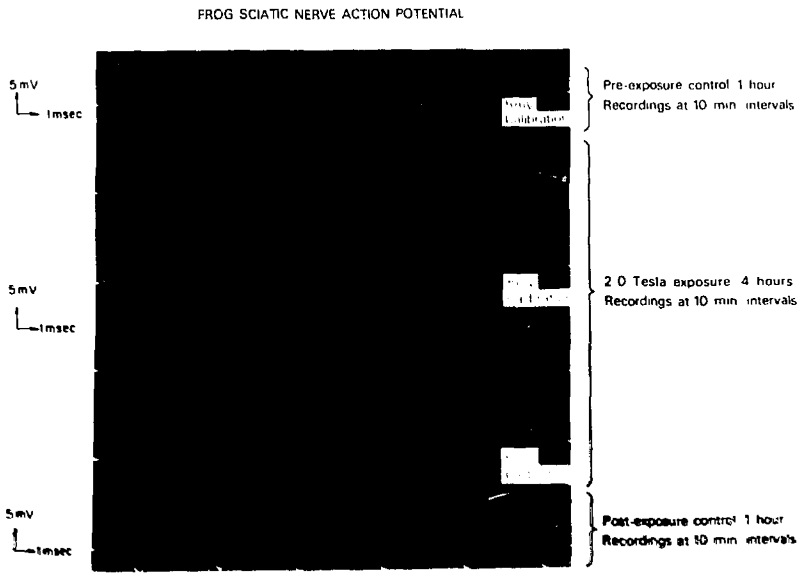

Fig. 2: Evoked action potentials in a frog sciatic nerve are shown before, during and after a 4-hr exposure to a uniform static 2.0-T field. The nerve axis was oriented parallel to the magnetic field lines, and there was no significant variation in the 20-mV amplitude of the maximal action potential during exposure to the field. [Adapted from Fig. 1 of ref. 39.] (XBB 809-10171B)

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 eqn. (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.[40] In contrast, there are several examples of macromolecular assemblies that can be oriented in fields of 1 T or less. 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 orient in fields of 1 T or less include retinal rod outer segments,[41-47] muscle fibers,[48] photosynthetic systems (chloroplast grana, photosynthetic bacteria and Chlorella cells),[49-53] and purple membranes of Halobacteria.[54] 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, 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 2 T. It is likely that a magnetic orientational torque has little influence on the strong structural matrix in which retinal rods are embedded within the intact retina.

There are also biological examples of cellular structures with permanent magnetic moments in which significant magnetic orientational effects occur. One example is the magnetotactic bacterium,[55] in which approximately 2% of the dry mass is iron contained in magnetite (Fe_3O_4) crystals.[56] These bacteria require a low oxygen tension for survival, and their net magnetic moments interact with the geomagnetic field to produce a downward directed motion that carries them into the bottom sediments of their aquatic environment. This fascinating survival mechanism requires that there be opposite polarities of the magnetic moments of these bacteria in the northern and southern hemispheres, and this feature of magnetotactic bacteria has been confirmed experimentally.[55,57,58]

Another 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 field with the long axis of the sickled cell oriented perpendicular to the magnetic flux lines.[59] 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:

$$F(z) = \frac{\chi VB}{\mu_o} (dB/dz) \qquad (4)$$

From simple energetic calculations it can be shown that extremely large magnetic fields and gradients must be used to produce a significant translation of individual paramagnetic molecules. A similar conclusion can be drawn for large collections of paramagnetic molecules such as the deoxyhemoglobin contained within a deoxygenated erythrocyte. This theoretical expectation is supported by experimental observations on the magnetic separation of erythrocytes from whole blood following conversion of the diamagnetic hemoglobin to paramagnetic deoxyhemoglobin. In order to achieve an efficient separation of the cells, they must be attracted to a wire mesh that is highly magnetized in a 2 T field to produce a gradient at the surface which exceeds 10^4 T/m.[60,61] Fields and spatial gradients of this magnitude are seldom encountered by man, even in the vicinity of high-field superconducting magnets.

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.[15,62,63] One well-studied example of such reactions which involves an important biological process is the photo-induced charge transfer reaction in bacterial photosynthesis.[64-69] 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 nanosec. 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.[67] Although these observations may have implications for naturally occurring biological processes, it should be emphasized that the magnetic field effects studied to date occur only when the photosynthetic system is placed in an abnormal state by chemical reduction of the electron acceptor molecules.

Static Magnetic Fields - Laboratory Studies

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, i.e., approximately 50 μT. It has been established experimentally that weak magnetic fields influence direction finding by elasmobranch fish[17-20] and the orientation and swimming direction of magnetotactic bacteria.[55-58] As discussed in the preceding section, the biophysical mechanisms underlying the magnetic field sensitivity of these organisms are well understood. In addition, evidence has been presented that the kinetic movements of mollusks,[70] the waggle dance of bees,[71] and migratory patterns of birds[72-75] are all influenced by weak static fields. The precise mechanism underlying the magnetic field sensitivity of these species has not been determined, although magnetomechanical effects leading to the stimulation of sensory receptors may be involved since small deposits of magnetite have been found in the tooth denticles of mollusks,[76,77] the abdominal region of bees,[78] and the cranium of pigeons.[79,80]

Studies of static magnetic field interactions with higher organisms have produced numerous contradictory findings, and the only effect that is well established at the present time is the induction of electrical potentials in the central circulatory system. Several detailed reviews of the literature on static magnetic field bioeffects have been published by the authors,[4,7,14] in which a number of examples were cited of recent experimental results that contradicted earlier claims of significant magnetic field effects at the cellular and animal levels. Several examples of the disparity between early and recent findings include: (1) the report[81] 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;[82] (2) numerous reports of alterations induced by static magnetic fields in the metabolism, respiration, and growth properties of normal and tumor cells[83-93] have not been successfully replicated;[94-102] (3) genetic and developmental changes in several animal species and lower organisms exposed to magnetic fields[84,103-116] have not been observed in more recent studies;[117-126] (4) adverse effects of static magnetic fields on sensitive target tissues such as the hematologic, immunologic and endocrine systems[85,86,127-149] have not been found in several recent studies;[150-153] (5) several reports of magnetic field effects on physiological regulation and circadian timing[154-161] have not been confirmed in carefully controlled studies with rodents.[14,162-164] One recent example of an effect that could not be replicated in another laboratory is the report that thermoregulation in rodents is influenced by strong magnetic field gradients.[165,166]

During the past decade a significant number of studies have been reported 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 this body of literature, the following important biological processes appear not to be influenced by static magnetic fields at levels up to approximately 2 T: (1) cell growth and morphology;[82,94-102] (2) DNA structure and gene expression,[120-123,125,126] (3) reproduction and development (pre- and post-natal),[118,119,124] (4) bioelectric properties of isolated neurons,[37-39] (5) animal behavior,[167] (6) visual response to photic stimulation,[168] (7) cardiovascular dynamics (acute exposures),[29,30] (8) hematological indices,[150-152,162] (9) immune responsiveness,[153] (10) physiological regulation and circadian rhythms.[14,162-164]

Although there is an increasing database which suggests that mammals experience no adverse effects from exposure to fields up to 2 T, 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;[169-172] (3) additional studies are needed to clarify whether adrenergic and cholinergic hormonal responses occur in exposed animals;[146-148] (4) cellular, tissue and animal studies will be required to assess the effects of static magnetic fields at the high intensities of 2 to 10 T that have been proposed for use in NMR in vivo spectroscopy.

TIME-VARYING MAGNETIC FIELDS

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:

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

In eqn. (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, eqn. (5) gives for the magnitude of the average electric field tangent to the loop surface:

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

If the magnetic field is sinusoidal with a frequency υ, then

$$E = \pi\upsilon RB \qquad (7)$$

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

$$\vec{J} = \sigma \vec{E} \qquad (8)$$

The rate of energy dissipation in tissue per unit time, P, is equal to:

$$P = \vec{J} \cdot \vec{E} = \sigma E^2 \qquad (9)$$

The metric units of B, E, J and P are Tesla, V/m, A/m^2 and W/m^3, respectively.

Electrical potentials can also be induced magnetically by fields that are static, i.e., not varying in time. One example is the induction of potentials in a moving electrolytic conductor such as blood, which was discussed earlier in this chapter. A magnetically-induced potential can also result from the application of a static field when the area linked by the lines of magnetic flux changes as a function of time. From eqn. (5) the resulting potential ϕ can be estimated as:[29]

$$\phi \simeq B f \Delta S \qquad (10)$$

where ΔS is the area change and f is the frequency of motion leading to the change in area and magnetic flux linkage. This type of induced potential results from changes in the area of the chest during breathing, and can be detected in the ECG of animals placed in extremely high fields. The magnitude of ϕ is small, typically being less than 25% of the magnitude of the induced aortic blood flow potential.[29]

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, which determine the maximum time rate of change of the field and hence the maximum instantaneous current densities induced in tissue.

Time-Varying Magnetic Fields -- Laboratory Studies

Four levels of biological effects from time-varying magnetic fields can be defined on the basis of the electrical currents induced in living tissues: (1) fields that induce current densities above 1 A/m^2 in tissue can be expected to produce rapid, irreversible effects such as cardiac fibrillation; (2) fields inducing current densities above 10 mA/m^2 lead to reversible visual effects (magnetophosphenes and changes in visually evoked potentials) during acute exposures; (3) the chronic application of fields that induce current densities in the range of 10-100 mA/m^2 can produce irreversible alterations in the biochemistry and physiology of cells and organized tissues, an example being the effects of bidirectional pulsed fields used to facilitate bone fracture reunion; (4) fields that induce current densities less than approximately 1-10 mA/m^2, which is the range of endogeneous current densities present in organs such as the brain and heart,[173,174] lead to few (if any) biological effects irrespective of the exposure duration.

Neuromuscular stimulation. In the first class of phenomena described above, direct neuromuscular effects result from large tissue currents induced by a time-varying magnetic field. Several investigators[175-182] 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,[181] 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 preparations. Using a 20 kHz sinusoidal field applied in bursts of 0.5 to 50 msec duration, Öberg[178] 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.[179,182]

The threshold current density required to produce ventricular fibrillation has been studied in several species of laboratory animals in which large currents were induced by sinusoidal voltages applied through contact electrodes.[183-194] From these data it can be estimated that the threshold current density required to produce ventricular fibrillation in the human heart is in the range of 2-10 A/m^2. For sinusoidal voltages, the minimum threshold current densities were observed in the frequency range of 20-200 Hz.[184] In experiments with dog hearts subjected to 60 Hz voltage stimuli it was found that the threshold current required to elicit fibrillation increased by a factor of approximately 140 as the stimulus duration was decreased from 1.6 sec to 16 msec.[189] Dalziel[195] has estimated that the stimulus strength producing cardiac fibrillation varies as the reciprocal square root of the shock duration over the range of exposure times from 8 msec to 5 sec.

The thresholds for several other forms of neuromuscular effects in laboratory animals and man, including the stimulation of seizures, extrasystoles and respiratory tetanus, have been estimated. From electroshock studies in humans it has been estimated that a current density of 30 A/m^2 must be induced for 300 msec to produce convulsive seizures.[196] The threshold current density for stimulation of extrasystoles was found in studies with guinea pig hearts to be 3-5 times lower than the threshold for eliciting ventricular fibrillation.[192,193] However, a prolonged stimulation of extrasystoles was found to ultimately lead to ventricular fibrillation. Based on limited studies with humans, it can be estimated that the threshold stimulus required to produce respiratory tetanus is approximately 10-15 times less than that which produces ventricular fibrillation.[197-199] This estimate suggests that induced current densities in the range of 0.15 - 1.0 A/m^2 could produce tetanic contractions of the muscles involved in breathing.

It is important to note that extremely large values of the magnetic flux density are required to elicit stimulatory effects on the neuromuscular system of animals when sinusoidal waveforms are used. As an example, consider a 60-Hz field that is axially incident on a circular loop of tissue with $R = 0.06$ m and $\sigma = 0.2$ S/m, comparable to the human heart. From eqns. (7) and (8) it can be calculated that the magnetic flux density must be 0.88 T to induce a current density of 2 A/m^2, which is the estimated lower threshold for inducing ventricular fibrillation. The corresponding time rate of change of the magnetic field and the induced electric field intensity are 330 T/sec and 9.95 V/m, respectively. ELF magnetic fields with this magnitude and time variation are seldom, if ever, encountered by man. However, some caution must be taken in assessing the effects of time-varying magnetic fields on potentially sensitive neuromuscular substrates, such as pacemaker cells. In a study with pacemaker neurons from the Aplysia abdominal ganglion, Wachtel[200] demonstrated that an ELF field with a frequency synchronized to the endogenous neuronal firing rate could alter the membrane electrical activity when the induced current density in the extracellular medium exceeded 20 mA/m^2.

Magnetophosphenes and other visual phenomena. One of the most extensively studied effects of time-varying magnetic fields is the induction of a flickering illumination within the visual field known as magnetophosphenes.[201-213] 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.[210] At this frequency the threshold magnetic field intensity required to elicit phosphenes is approximately 10 mT, as shown in Fig. 3. The corresponding time rate of change of the field is 1.26 T/sec. 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.[213] 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;[205] (2) pressure on the eyeball abolishes sensitivity to magnetophosphenes;[205] (3) the threshold magnetic field intensity required to elicit magnetophenes 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;[210] (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.[210]

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.[211] It was found that the average latency time for response of the ganglion cells to a photic stimulus increased by

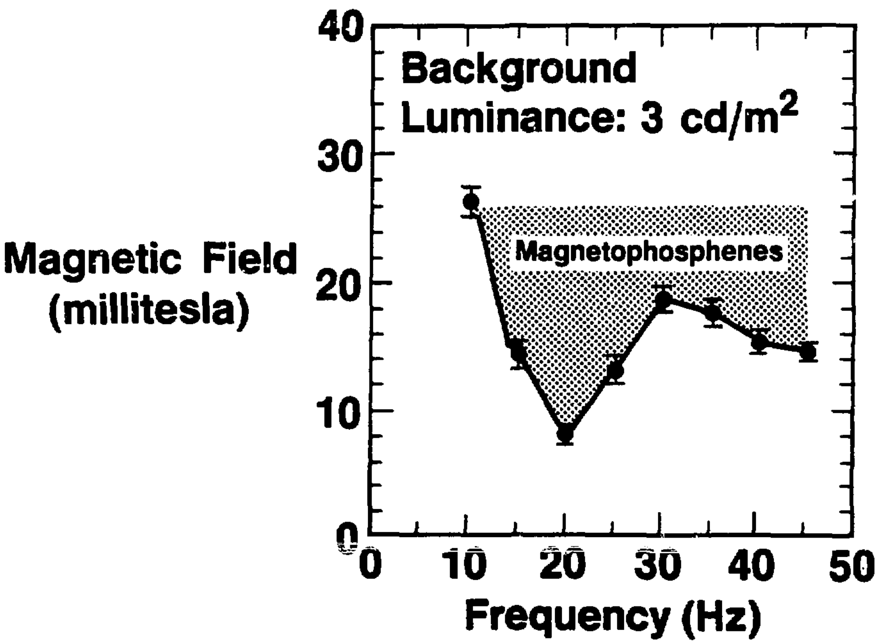

Fig. 3: Threshold values of the magnetic flux density required to elicit magnetophosphenes are plotted as a function of the field frequency. Each data point represents the mean value ± 1 S.E. for 10 volunteers, all of whom were studied with a background white light level of 3 cd/m^2. [Adapted from Fig. 3 of ref. 207.] (XBL 848-7796A)

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. 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.[214] 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) have also been reported to occur in sinusoidal ELF magnetic fields at intensity levels that are 5-10 times greater than those which produce magnetophosphenes.[214] 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.

Effects on cellular, tissue and animal systems. A large number of reports have appeared in the literature on the biochemical, physiological and behavioral effects of time-varying magnetic fields in the ELF frequency range.[167,215-284] The information gained in these studies is in many cases difficult to interpret for several reasons: (1) A wide range of field intensities, frequencies, waveforms, and exposure durations have been used. Many of the earlier studies utilized sinusoidal ELF magnetic fields, but recent research has focused increasingly on the effects of pulsed fields with complex waveforms. (2) Few of the findings of positive bioeffects have been verified by independent replication in different laboratories. (3) A number of apparent inconsistencies can be found among the reported behavioral and physiological effects of time-varying magnetic fields. For example, behavioral alterations were observed in a majority of studies with animals exposed to ELF sinusoidal fields that induced maximum current densities of less than 1 mA/m^2 in the cranium.[269-277] In contrast, no effects were noted in several behavioral studies conducted with magnetic fields that induced maximum intracranial current densities of 1 mA/m^2 or larger.[167,222,278-283] Another example of contradictory data are the reports that exposure to a low-intensity ELF magnetic field produced an elevation in serum triglyceride levels in human subjects,[221] but comparable effects were not observed in monkeys.[222]

Although many uncertainties exist in the interpretation of the existing laboratory data on the cellular, tissue and animal effects of time-varying magnetic fields, there is increasing evidence that several biochemical and physiological properties of cells and organized tissues are altered. Briefly summarized, these biological effects include: (1) altered cell growth rate,[229,233,241,245,246,266] (2) decreased rate of cellular respiration,[241-243] (3) altered metabolism of carbohydrates, proteins and nucleic acids,[228,231,236,237,243,248,256,263,264,268] (4) effects on gene expression and genetic regulation of cell functions,[240,251,259] (5) teratological and developmental effects,[219,220,250,261,262] (6) morphological and other nonspecific tissue changes in adult animals, frequently reversible with time following exposure,[216,223,247,249,252,255] (7) endocrine alterations,[217,224,230,232,236,249] (8) altered hormonal responses of cells and tissues, including effects on cell surface receptors,[254,257,260,265] (9) altered immune response to antigens and lectins.[215,225,258]

The results of these studies have been summarized schematically in Fig. 4, in which the observations of bioeffects from exposure to time-varying magnetic fields have been grouped according to estimates of the maximum value of dB/dt and the maximum induced current density in the target tissues that were examined. It is evident that alterations were observed at the cellular and tissue levels in the majority of studies in which the induced current densities exceeded 1 mA/m^2, which is a level typical of the endogenous current densities within living tissues. It should be noted in particular that the investigations in which either square waveforms or pulsed fields that induced tissue current densities greater than 10 mA/m^2 led to findings of positive bioeffects.[240,245,250,251,254,256-263,265,268] The suggestion has been made that these fields may exert electrochemical effects at the cell surface.[254,260] Such effects, in turn, could influence hormone-receptor interactions, adenylate cyclase activity, and the membrane transport and intracellular concentration of calcium ions. These membrane functions have been shown to exert a major influence on cellular metabolism and growth dynamics.

Several investigations using bidirectional pulsed magnetic fields have shown an enhanced synthesis of collagen, decr[illegible] intracellular cAMP, and altered synthesis of cell surface glycoproteins in cultures of fibroblasts and bone-forming cells.[256,263,265,268,284] These findings suggest biochemical and biophysical mechanisms through which the stimulation of bone growth may occur in response to pulsed magnetic fields. Beginning in the early 1970's, several clinical reports have indicated that the use of pulsed magnetic fields with repetition frequencies in the ELF range may provide an effective, noninvasive procedure for the treatment of bone nonunions and pseudoarthroses via electrical stimulation.[285-291] Current densities of approximately 20 mA/m^2 can be induced in bone by the pulsed field applicators that are presently used for fracture therapy.[16,292] Although the initial clinical trials yielded success rates up to 85% in achieving bone fracture reunion via magnetic stimulation, a recent report has suggested that prolonged immobilization of a patient wearing the magnetic field applicator may also be an important factor contributing to the success of this procedure.[293]

Time-Varying Magnetic Fields – Cell, Tissue and Animal Studies

- *Magnetophosphene and behavioral studies excluded*
- Combined electric and magnetic field experiments excluded
- Complete description of field and exposure conditions required
- Quantitative physiological and/or biochemical end points required

dB/dt (T/s)	Findings (+)	Findings (–)
<1	6	8
1→3	3	1
3→20	25	1
>20	9	1

J_{max} (mA/m^2)	Findings (+)	Findings (–)
<1	5	6
1→10	8	2
10→20	10	3
>20	20	0

Positive Effects Reported:

- Altered cell growth rate
- Decreased cellular respiration
- Effects on gene expression
- Developmental effects
- Altered immune response
- Endocrine alterations
- Altered metabolism of carbohydrates, nucleic acids and proteins

Mammalian systems:	42/54
Non-mammalian systems:	12/54
In vivo studies:	32/54
In vitro studies:	22/54
Sinusoidal fields:	39/54
Square-wave fields:	3/54
Pulsed fields:	12/54

Fig. 4. Experimental observations on the bioeffects of time-varying magnetic fields in the ELF frequency range are summarized on the basis of the estimated maximum values of dB/dt and induced current density in the exposed samples. The literature database used in preparing this summary is from refs. 215-268. Criteria employed in the selection of literature are stated at the top, and several of the observed bioeffects are listed on the right side of the figure. A summary is given at the bottom of the general characteristics of the biological systems studied and the magnetic field waveforms that were tested.

RADIOFREQUENCY FIELDS

Interaction Mechanisms

An established mechanism through which RF radiation produces direct cellular and tissue effects is through heating. As discussed in the following section, various nonthermal effects of RF radiation have also been reported. However, controversy still exists in regard to direct biological effects from induced currents and polarization effects (dipole orientation) produced by RF fields with incident power densities sufficiently low that no measurable temperature rise occurs in the exposed tissue.

In the RF frequency range below 100 MHz that is presently used in medical NMR, approximately 90% or more of the absorbed energy results from tissue currents induced by the magnetic component of the field.[294,295] The total energy dissipation is a function of the frequency, RF incident power density, exposure duration, coupling between the RF coil and the specimen, and several properties of the exposed tissue, including conductivity, dielectric constant, specific gravity, size, and orientation relative to the field polarization. Tissue heating is also influenced by the rate of heat loss via thermal conduction and convection mechanisms in the exposed subject.

Under the near-field geometric conditions present in NMR imaging devices, the energy dissipation is best expressed in terms of the specific absorption rate in W/kg, as opposed to the incident power density in W/m^2, which is commonly used for far-field (Fraunhofer) irradiation conditions. The specific absorption rate, SAR, is related to the average induced electric field, $E/\sqrt{2}$, the tissue conductivity, σ, the tissue density, ρ, and the duty cycle, D, of the applied RF field by the equation:

$$\mathrm{SAR} = \frac{\sigma E^2 D}{2\rho} \qquad (11)$$

The duty cycle $D = \tau/\delta$, where τ is the pulse duration and δ is the pulse repetition interval. Because the magnetic component of the field is dominant in the low range of RF frequencies used for medical NMR, the induced electric field can be calculated for a circular loop of tissue of radius R using eqn. (7), in which B is now understood to be the magnetic component of the RF field. In addition, the rotating component of the field, B_1, must satisfy the Larmor resonance condition. For a rectangular $\pi/2$ pulse,

$$B_1 = \frac{\pi}{2\gamma\tau} \qquad (12)$$

where γ is the gyromagnetic ratio (expressed as an angular frequency in units of Hz/Tesla). Noting that $B = 2B_1$ for conversion from a linear to a rotating field, and using eqns. (7) and (12), the SAR given by eqn. (11) becomes:

$$\mathrm{SAR} = \frac{\pi^4 \sigma \upsilon^2 R^2}{2\gamma^2 \rho\tau\delta} \qquad (13)$$

For proton NMR, the SAR in MKS units of W/kg is given by:

$$\mathrm{SAR} = \frac{(6.80 \times 10^{-16})\sigma \upsilon^2 R^2}{\rho \tau \delta} \qquad (14)$$

If the flip angle is π, the SAR is 4 times greater than the value given by eqn. (14). The SAR for an arbitrary flip angle, Θ, can be calculated from eqn. (14) using the multiplicative factor $4\Theta^2/\pi^2$. It is important to note for calculational purposes that the appropriate units of the parameters in eqn. (14) are σ = S/m, υ = Hz, R = m, ρ = kg/m^3 and τ and δ = sec.

The SAR predicted by eqn. (14) is plotted for a human torso model with R = 0.17 m in Fig. 5. The SAR at frequencies from 1 to 100 MHz is presented as a double logarithmic plot with $\tau \cdot \delta = \tau^2/D$ as the abscissa. It is evident that the SAR increases as the pulse repetition interval (δ) decreases and/or the duty cycle (D) increases. At 30 MHz the SAR in the torso model equals the average body basal metabolic rate (in the resting condition) when τ^2/D is approximately 10^{-5} sec^2. The quadratic dependence of the SAR on the loop radius as shown in eqn. (13) has been confirmed experimentally.[296,297]

It should be noted that the SAR given by eqn. (13) represents the peak surface SAR since the attenuation of the RF magnetic field in tissue is neglected. By comparing the results of SAR calculations using this simplified model with the results of a more precise calculation in which attenuation effects were taken into account,[294] Bottomley and Edelstein[298] concluded that eqn. (13) overestimates the true SAR by about 30% at frequencies in the range of 30 - 100 MHz. At lower frequencies a substantially better agreement is achieved.

The average SAR in a three-dimensional element of tissue can be obtained from a volume integration of the surface SAR for simple geometries such as spheres and cylinders with an axial orientation relative to the incident RF field. By this procedure it can be shown[299] that the average SAR in spherical and cylindrical elements of tissue are, respectively, 0.4 and 0.5 times the surface SAR predicted from eqn. (13).

Experimental measurements of SAR have been performed using a number of techniques, including infrared thermography and direct temperature measurements both in living specimens and in phantoms filled with saline or tissue-equivalent materials.[300-307] To determine the SAR associated with the RF fields used in medical NMR, the simplest method is to measure the change in Q (quality factor) of the coil upon introduction of the specimen.[308] For an unloaded coil, $Q_o = 2\pi\upsilon_o L/R_o$, where L and R_o are, respectively, the coil inductance and resistance. The effective resistance, R_s, which the presence of a sample adds to the resistance of the coil is equal to:

$$R_s = 2\pi\upsilon_o L(1/Q_s - 1/Q_o) \qquad (15)$$

In eqn. (15) Q_s is the Q value of the coil with the specimen in place. Using eqn. (15) the fraction of the applied RF power that is dissipated in the specimen can be calculated from the resistance ratio:

$$\frac{R_s}{R_s + R_o} = 1 - Q_s/Q_o \tag{16}$$

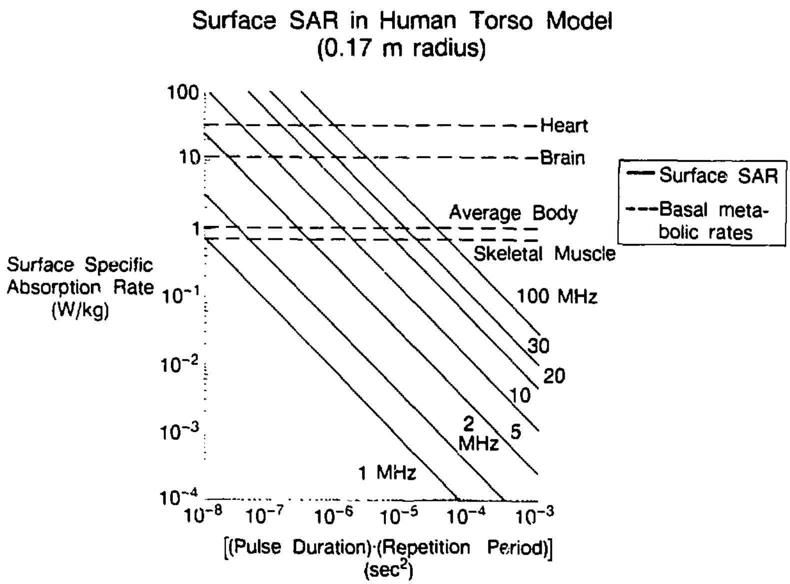

Fig. 5: The peak surface SAR in a human torso model is plotted as a function of the pulse duration (τ) times the pulse repetition interval (δ). Curves calculated from eqn. (14) in the text using conductivity values for muscle tissue are shown for RF field frequencies ranging from 1-100 MHz. Also shown are average basal metabolic rates for the whole body, skeletal muscle, brain and heart. [Adapted from Fig. 3 of ref. 298.] (XBL 856-8361)

A calculation of SAR can then be made using eqn. (16) in combination with information on the RF pulse characteristics and the specimen size.

A direct calculation of the expected temperature rise, ΔT, in tissue exposed to RF radiation for a time t (in sec), can be made from the equation:

$$\Delta T = \frac{(SAR)\cdot t}{C} \qquad (17)$$

where C is the heat capacity expressed in J/kg/^{o}C. It should be noted that eqn. (17) does not include terms to account for heat loss via thermal conduction and convection processes. An average value of the soft tissue heat capacity[306] is 0.83 kcal/kg/^{o}C = 3.47 kJ/kg/^{o}C. In the absence of heat loss mechanisms, eqn. (17) predicts that an SAR of 2 W/kg applied for 10 min would lead to a temperature rise of 0.35 ^{o}C. Experiments have been performed by one of the authors (T.F.B.) in which fiberoptic probes were used to determine temperature changes in the stomach and subcutaneous tissues during NMR imaging that produced an SAR at the 2 W/kg level.[309] No temperature change was observed in the stomach during a 10 min exposure, but an elevation occurred in the skin temperature as anticipated from the vasodilation response to thermal stress.

At the frequencies used in medical NMR procedures the deposition of RF energy in tissue is expected to be more uniform than that observed at frequencies above 100 MHz, where "hot spots" are theoretically predicted and experimentally observed.[300,307,310,311] Nevertheless, anisotropy and discontinuities in tissue electrical properties can lead to significant nonuniformities in RF heating profiles at frequencies well below 100 MHz.[312] Consideration must also be given to the local RF heating that can occur because of constrictions in the induced current pathways within anatomically thin regions that are not electrically insulated from large current loops, e.g., regions of ischemic tissue. Recent experiments using lucite and wood phantoms constructed to simulate this conditions have confirmed that geometric constraints on current pathways can produce excessive local heating.[297]

RF Fields — Laboratory Studies

Thermal effects. Tissue heating from exposure to RF radiation produces a series of physiological responses characteristic of stress, with a resultant onset of thermoregulatory mechanisms mediated through the neuroendocrine and cardiovascular systems.[5,313] Thermosensitivity and thermoregulatory responses are associated both with the hypothalamus and with thermal receptors located in the skin and internal regions of the body.[314,315] Afferent signals reflecting temperature change converge in the central nervous system and modify the activity of the major neuroendocrine control systems, thereby triggering the physiological and behavioral responses necessary for the maintenance of homeostasis. These responses have been studied extensively in several animal species, including rodents, dogs and nonhuman primates. In general, laboratory investigations have been conducted with RF radiation at frequencies significantly higher than those used in NMR devices, and with the subjects irradiated under far-field conditions. Nevertheless, tissue heating resulting from NMR imaging procedures can be expected to elicit a similar set of physiological responses.

Neuroendocrine responses to RF heating have been shown to alter the activity and the complex interactions of the hypothalamic, pituitary, adrenal and thyroid systems. At SAR values in excess of 3 W/kg, plasma corticosterone levels are elevated in rats and this endocrine response is dependent upon ACTH secretion by the pituitary.[316,317] Depressed thyroid hormone levels are observed under similar irradiation conditions, and this response has been associated with an inhibition of secretion of thyrotropin (TSH) by the pituitary.[318-321] In both cases, the alteration in hormone levels is reversible upon termination of the exposure.

Exposure of dogs to RF radiation at SAR values in excess of approximately 4 W/kg has revealed a characteristic pattern of thermoregulatory response in which the body temperature initially increases and then stabilizes following the onset of thermoregulatory mechanisms.[313,322-324] The early phase of this response was found to be accompanied by an increase in blood volume due to withdrawal of fluid from the extracellular space into the circulation, and by increases in heart rate and intraventricular blood pressure. These cardiodynamic changes reflect thermoregulatory responses that facilitate the conduction of heat to the body surface. Prolonged exposure of animals to thermalizing levels of RF radiation ultimately led to failure of these thermoregulatory mechanisms.

Several studies with rodents and monkeys have also demonstrated a behavioral component of thermoregulatory responses. It has been shown that rats will turn on a heat lamp less frequently when exposed to RF radiation at an SAR greater than 1 W/kg,[325] and a similar thermoregulatory behavior is exhibited by squirrel monkeys.[326,327] In these monkeys it has been found that altered thermoregulatory behavior commences when the temperature in the preoptic/anterior hypothalamic area increases by as little as 0.2-0.3 $^{\circ}$C.[328] This brain region is considered to be the control center for normal thermoregulatory processes, and its activity can be modified in response to a small temperature increase under conditions in which the colonic temperature remains constant.[328]

There have been numerous published reports of physiological and behavioral changes occurring as the result of exposure to RF radiation at levels that produce direct thermal effects. Briefly summarized, several of the cellular, tissue and animal responses that have been studied include: (1) alterations in neural and neuromuscular functions;[329-332] (2) increased blood-brain barrier permeability,[333-339] (3) operant behavioral changes;[340-343] (4) cutaneous thermal perception;[344-347] (5) auditory stimulation resulting from a thermoelastic interaction;[348-353] (6) ocular impairment (lens opacification and corneal abnormalities);[354-359] (7) stress-associated effects on the immune system;[5,360-366] (8) hematological alterations;[5,367-371] (9) effects on reproductive organs;[372-374] (10) teratogenic effects;[375-381] (11) effects on cellular morphology, water and electrolyte content, and plasma membrane properties.[382-393]

Although substantial evidence exists for direct thermal injury to cells and tissues exposed to RF radiation at high intensities, it should be noted that there have been many conflicting reports on the threshold field intensities that elicit effects and the relative potency of pulsed versus continuous wave radiation in many systems. Under conditions where the field frequency, waveform, intensity, and exposure duration are similar, the possibility must be considered that inadequate dosimetry may be the origin of divergent findings of positive and negative biological effects. As one example, there were several early reports of chromosomal alterations and genetic changes in cells exposed to RF radiation,[394-397] whereas subsequent research has not led to similar findings.[398-401] Recent studies with NMR fields at frequencies of 15-30 MHz have also shown no evidence for cytogenetic effects in cellular systems.[125,402-404] As emphasized by Michaelson,[405] variations in the exposure system, specimen sizes, and dosimetry procedures used for cellular samples could be the basis of many differing results described in the literature. He further states that several reported genetic effects from exposure to RF radiation at power levels that were presumed not to produce sample heating may in fact, have been the consequence of direct thermal damage.

Nonthermal effects. Beginning in the 1950's, an increasing body of evidence has been compiled by scientists in the Soviet Union and Eastern European countries that low-intensity RF fields in the microwave band can produce measurable alterations in the nervous, cardiovascular, endocrine, immune, and reproductive systems of mammals.[406-408] Although many of these reports conflict with data obtained by scientists in the United States and Western Europe, the possible existence of nonthermal effects of RF radiation remains an unresolved issue. As described by McRee,[408] U.S. and U.S.S.R. scientists working in collaboration have confirmed the existence of several metabolic and behavioral effects resulting from the chronic exposure of rats to low-intensity microwaves. There are also numerous examples of biological studies conducted by U.S. and Western European scientists in which nonthermal effects of RF radiation were observed, one example being the alteration of rat brain metabolic parameters.[409-411] Reviews of nonthermal RF radiation effects and possible interaction mechanisms have recently been prepared by Taylor[412] and by Postow and Swicord.[413]

An observation on nonthermal effects that has elicited considerable interest among U.S. scientists is the finding that alterations in calcium-ion binding to nerve cell surfaces occurs as the result of exposure to low-intensity RF radiation that is amplitude-modulated at ELF frequencies. In the first publication describing this effect, Bawin et al.[414] reported that the release of preloaded $^{45}Ca^{++}$ was accelerated by exposure of chick brain hemispheres to an amplitude-modulated 147-MHz field. The maximum increase in the release of calcium ions was 10 to 20 percent relative to control samples, and occurred at an ELF modulation frequency of 16 Hz. This finding was subsequently confirmed by Blackman et al.,[415,416] who further observed that the calcium efflux phenomenon was limited to an intensity window for the RF carrier wave that was centered around 0.8 mW/cm^2. Several other carrier frequencies, including 50, 147 and 450 MHz, have also been studied to assess the presence of intensity windows.[417-420] It was found that the intensity window observed with 16-Hz amplitude modulation of the different RF carrier fields shifted in a manner that gave an identical electric field strength within the exposed brain tissue.

Adey et al.[421] have reported that an increased release of preloaded $^{45}Ca^{++}$ can be produced in the cerebral cortex of an anesthetized cat by exposure to a 450-MHz field with an intensity of 3 mW/cm^2 and amplitude modulation at 16 Hz. In this in vivo study, no attempt was made to determine the presence of windows of sensitivity in either the frequency or intensity domains.

The observations of windowed phenomena described above have led to a number of interesting theoretical concepts concerning possible origins for nonthermal RF radiation effects,[412,413] and they provide a strong impetus for additional biological studies using RF field intensities that do not produce significant tissue heating. However, the implications of these effects for NMR imaging procedures are not clear at the present time. As demonstrated both in the original research on this subject, and in other recent studies,[422,423] ELF amplitude modulation appears to be essential for producing an RF field effect on calcium ion binding to brain tissue. Differences therefore exist in the waveforms that are effective in producing this effect relative to the RF fields used in present NMR imaging devices.

HUMAN HEALTH STUDIES

Static Magnetic Fields

A clinical study of Soviet workers in the magnet production and machine-building industries was reported by Vyalov.[424] The exposure group consisted of 645 workers whose hands were routinely exposed to static fields of 2 to 5 mT, and whose chest and head were in fields of 0.3 to 0.5 mT under normal working conditions. It was estimated that the magnetic field exposure levels were 10 to 50 times larger than the typical values during 10 to 15 percent of the workday. The control group in this study consisted of 138 supervisors in a machine-building plant who were not in contact with magnets. A number of subjective symptoms were reported among the exposed group, including headache, fatigue, dizziness, unclear vision, noise in the ears, and itching and sweating on the palms of the hands. Edema and desquamation on the palms of the hands were also reported. In addition, minor physiological effects including decreased blood pressure and changes in hematological parameters were noted in the exposed group. These studies were qualitative in nature and no statistical analysis was performed on the clinical data. There was also no effort made to assess the possible effects of stressful environmental factors such as high ambient temperature, airborne metallic particles, or the chemical agents used for degreasing and other procedures.

In contrast to the Soviet study, two recent epidemiological surveys in the United States failed to reveal any significant health effects associated with chronic exposure to static magnetic fields.

Marsh et al.[425] conducted a cross-sectional study on the health data of 320 workers in plants using large electrolytic cells for chemical separation processes. The average static field level in the work environment was 7.6 mT and the maximum field was 14.6 mT. The study included a control group of 186 unexposed workers. Among the exposed group, slight decreases were found in the blood leukocyte count and the percent of monocytes, while a small increase occurred in the lymphocyte percentage. However, the mean value of the white cell count for the exposed group remained within the normal range. There was also a slight tendency for elevated systolic and diastolic blood pressures among the black workers in the study. None of the observed changes in blood pressure or hematologic parameters was considered indicative of a significant adverse effect associated with magnetic field exposure.

A recently completed study characterized the prevalence of disease among 792 workers at U.S. National Laboratories who were exposed occupationally to static magnetic fields.[426] The control group consisted of 792 unexposed workers matched for age, race and socioeconomic status. The range of magnetic field exposures was from 0.5 mT for long durations to 2 T for periods of several hours. No significant increase or decrease in the prevalence of 19 categories of disease was observed in the exposed group relative to the controls. Of the 792 exposed subjects, 198 had experienced exposures of 0.3 T or higher for periods of 1 hour or longer. No difference in the prevalence of disease was found between this subgroup and the remainder of the exposed population or the matched controls. No trends were observed in the health data suggestive of a dose-response relationship.

Milham[427] recently reported that workers exposed to large static magnetic fields in the aluminum industry have an elevated leukemia mortality rate. The percentage mortality ratios (PMR) for all forms of leukemia and for acute leukemia among these workers were compared with general population values determined from 438,000 death records of adult males in the state of Washington during the period 1950-1979. The PMR values for all types of leukemia and for acute leukemia were reported to be 189 and 258, respectively, both of which differed significantly from the no-effect level of 100. Because of the large magnetic fields associated with the aluminum reduction process, which have been measured using a magnetic field personal dosimeter and found to be as high as 57 mT during anode changes on prebake cells,[428] Milham suggested that a correlation may exist between exposure to these fields and leukemogenesis.[427] The excess of leukemias observed in Milham's study was confirmed in a subsequent study involving 21,829 workers in 14 aluminum reduction plants.[429] In this second study, an excess incidence of pancreatic, genitourinary and benign tumors was also found among the aluminum workers.

Although these two epidemiological studies have demonstrated an increased cancer risk for persons directly involved in aluminum production, there is at present no clear evidence to indicate the responsible carcinogenic factors within the work environment. The process used for aluminum reduction creates coal tar pitch volatiles, fluoride fumes, sulfur oxides and carbon dioxide. The presence of hydrocarcon particulates, and perhaps other environmental contaminants, must be taken into account in any attempt to relate magnetic field exposure and increased cancer risk among persons working in the aluminum industry.

Time-Varying Magnetic Fields

Several laboratory studies have been conducted with human subjects exposed to sinusoidally time-varying magnetic fields with frequencies in the ELF range.[221,227,253] None of these investigations have revealed adverse clinical or psychological changes in the exposed subjects. Beischer et al.[221] observed an elevation in serum triglycerides at 24 and 48 hours post-exposure, but the subjects were not fasted prior to blood sampling and the change in triglyceride concentration could have resulted from differences in diet or physical activity. In a subsequent study with rhesus monkeys exposed to similar fields, no change in serum triglyceride concentration was observed.[222] The strongest field used in the various laboratory studies with humans was a 5-mT, 50-Hz field to which subjects were exposed for 4 hours by Sander et al.[253] In this investigation no field-associated changes were observed in serum chemistry, blood cell counts, blood gases and lactate concentration, electrocardiogram, pulse rate, skin temperature, circulating hormones (cortisol, insulin, gastrin, thyroxin), and various neuronal measurements including visually evoked potentials recorded in the electroencephalogram.

Recent concern over th possible health effects of time-varying magnetic fields has been raised by several reports of an apparent correlation between cancer incidence and exposure to power-frequency fields. The first publication on this subject appeared in 1979, and reported a correlation between the incidence of leukemia among children living in the Denver, CO, area and exposure to 60-Hz magnetic fields from high-current primary and secondary wiring configurations in the vicinity of their residences.[430] This finding was followed by 12 additional epidemiological studies during the period 1980-1985. Three of these studies involved the analysis of cancer incidence in relation to residential exposure to power-frequency fields.[431-433] In the other nine studies, cancer incidence was analyzed for groups of individuals in various electrical, electronic and telecommunication occupations.[427,434-441] As summarized in Table I, 11 of the 13 epidemiological surveys conducted to date have shown an apparent correlation between the incidence of various forms of cancer and residential and/or occupationsl exposure to power-frequency fields. In nearly all cases where a positive finding was obtained, the increased risk of cancer among the exposed group of individuals was small, generally less than a factor of two relative to a control group or the general population.

Despite the large number of positive findings that have been reported, it is not possible to conclude at the present time that a definite association exists between the exposure of individuals to ELF electromagnetic fields and their relative risk of contracting leukemia or other forms of cancer. This uncertainty arises from numerous methodological deficiencies in the epidemiological surveys

Table I. Epidemiological studies on the potential relationship of residential and occupational exposure to ELF electric and magnetic fields and cancer

Reference	Subjects	Correlation between increased cancer incidence and residential or occupational exposures
Wertheimer and Leeper, 1979 (Ref. No. 430)	Children (< 19 yr); residential fields [344 cases; 344 controls]	(+)
Fulton et al., 1980 (Ref. No. 431)	Children (< 20 yr); residential fields [119 cases; 240 controls]	(-)
Tomenius et al., 1982 (Ref. No. 432)	Children (< 18 yr); residential fields [716 cases; 716 controls]	(+)
Wertheimer and Leeper, 1982 (Ref. No. 433)	Adults; residential fields [1179 cases; 1179 controls]	(+)
Wiklund et al., 1981 (Ref. No. 434)	Adults; telecommunication workers [Swedish Cancer Registry with 385,000 cases, 1961-1973]	(-)
Milham, 1982 (Ref. No. 427)	Adults; male workers in 11 occupations involving electric and/or magnetic fields [Survey of 438,000 deaths in Washington State men from 1950-1979]	(+)
Wright et al., 1982 (Ref. No. 435)	Adults; male workers in 10 electrical/electronic occupations [Cancer Surveillance Program in Los Angeles County, 1972-1979]	(+)
McDowall, 1983 (Ref. No. 436)	Males aged 15-74; workers in 10 electrical/electronic occupations [Survey of occupational mortality in England and Wales, 1970-1972]	(+)

Table I (cont'd). Epidemiological studies on the potential relationship of residential and occupational exposure to ELF electric and magnetic fields and cancer

Reference	Subjects	Correlation between increased cancer incidence and residential or occupational exposures
Coleman et al., 1983 (Ref. No. 437)	Males aged 15-74; workers in 10 electrical/electronic occupations [South Thames Cancer Registry from 1961-1979]	(+)
Vågarö and Olin, 1983 (Ref. No. 438)	Males and females aged 15-64; workers in electrical/ electronic occupations [Swedish Cancer Registry with 385,000 cases from 1961-1973]	(+)
Pearce et al., 1985 (Ref. No. 439)	Adults; male workers in 8 electrical/electronic occupations [546 cases; 2184 controls]	(+)
Milham, 1985 (Ref. No. 440)	Adults; male members of American Radio Relay League in states of Washington and California [1691 male cancer deaths in these two states compared with U.S. age-specific white male death frequencies in 1976]	(+)
Lin et al., 1985 (Ref. No. 441)	Adults; white male workers in 3 electrical/electronic occupations [Brain tumor decedents in state of Maryland from 1969 through 1982]	(+)

conducted to date. Several specific problems are the following: (1) In all of the studies thus far reported, the electric and magnetic field dosimetry was at best qualitative. In studies of residential ELF fields, the neglect of local fields from appliances may have led to incorrect conclusions concerning the peak and average exposure of individuals to power-frequency fields and the harmonic frequencies that emanate from electrical devices used within the home. (2) The sample populations in many of the epidemiological studies were small, and the reported increases in cancer incidence by a factor of 2 or less might be expected to occur on the basis of chance alone. In these studies, it would have been informative if the authors had presented data on several nonexposed occupational groups in which the sample size was comparable to that of the exposed groups. (3) Control groups were frequently chosen in a nonblind manner involving subjective criteria, and the control population was often not matched with the exposed group on the basis of age, sex, race, socioeconomic class, or urban/rural residential status. (4) Several of the studies used weak statistical methods such as the calculation of proportionate mortality ratios, which can lead to extremely misleading conclusions for population subgroups in which the overall incidence of disease is low with the exception of one disease class such as cancer (or some specific form of cancer such as leukemia). (5) The existence of confounding factors such as smoking habits and exposure to industrial pollutants of known carcinogenic potential (e.g., aryl hydrocarbons) has been ignored in all of the epidemiological studies that have attempted to relate ELF fields and cancer incidence.

Radiofrequency Fields

There have been several epidemiological studies on military, industrial and foreign service personnel exposed to RF radiation. In a broad study involving Navy personnel who had served during the Korean War,[442] no evidence was obtained for increased illness or mortality rate among a "high-exposure" group (20,109 personnel involved in radar repairs) and a "low-exposure" group (20,781 personnel involved in operating radar equipment). Mortality was assessed from death certificates during the period 1955-1974, and morbidity from (1) "in-service" hospitalization during the period 1950-1959, (2) Veterans Administration hospital admissions during the period 1963-1976, and (3) disability compensation records for 1976. In another case-control study on World War II and Korean War veterans who had worked with radar units, no evidence was found for an elevated incidence of cataracts in the exposed population.[443] These studies of radar workers lacked sufficient dosimetric information to make assignments of exposure levels. However, accidental exposures of Navy personnel to RF power densities exceeding 100 mW/cm^2 have been documented, and some personnel may have been subjected to levels in excess of 10 mW/cm^2 on a routine basis.[444] In a study on adult males occupationally exposed to radar for a period of four years, Robinette et al.[445] also found no evidence for an effect on life span, morbidity or cause of death. A four-year medical surveillance program in the aircraft industry involving 355 employees exposed to radar failed to detect any abnormal change in the general health of these personnel.[446]

One epidemiological study suggested a possible link between microwave exposure and congenital abnormalities. In a case-control study on the incidence of Down's syndrome in Baltimore, MD, it was found that paternal exposure to radar during military service was weakly associated with an increased incidence of this disorder in their offspring.[447] However, further investigation did not confirm the existence of a correlation between radar exposure of fathers and the incidence of Down's syndrome in the offspring.[448]

Effects from controlled RF heating have been studied in the offspring of women treated with diathermy to relieve the pain of uterine contractions during labor. In studies involving 2000 diathermy patients, no adverse short-term or long-term effects on the fetus were observed.[449,450]

The effects of chronic exposure to low-intensity microwaves were studied in 1827 employees who had served in the U.S. embassy in Moscow during the period 1953 to 1976, during which time the embassy was irradiated at RF power densities up to 15 $\mu W/cm^2$. The morbidity and mortality rates among this study group were compared with the rates in a second group of 2561 U.S. employees who had served during the same time period at eight Eastern European embassies or consulates that were not irradiated with microwaves. Based on information gained from personnel records, mail questionnaires and telephone interviews, there were no untoward health effects found among the irradiated study group from the Moscow embassy in comparison with individuals in the unirradiated group.[451,452]

In contrast to reports from the U.S. and Western European countries, epidemiological studies carried out in the Soviet Union and Eastern European countries on workers exposed to RF radiation have led to findings of apparent effects on the nervous and cardiovascular systems.[453-456] The nervous system effects revealed in these studies were characteristic of the neurasthenic syndrome, and included headache, fatigue, irritability, loss of appetite, drowsiness, sweating, memory loss, depression and emotional instability. The cardiovascular effects that were reported among exposed workers included bradycardia and alterations in cardiac conduction properties. The significance of these apparent neural and cardiovascular effects is difficult to assess, especially in view of the fact that a similar symptomatology was generally not observed in U.S. studies on radar workers or in the study on irradiated Moscow embassy personnel.

One aspect of the potential health effects of exposure to RF radiation that has not been satisfactorily addressed in previous studies is the issue of possible carcinogenic risk.[452] In a recent investigation involving 100 rats chronically exposed for 25 months to pulsed 2450-MHz microwaves, a statistically significant increase in primary neoplasms was observed in the exposed group relative to a sham-exposed control group of equal size.[457] Although the investigators concluded that the biological significance of this study is questionable at the present time, it underscores the need for further investigations on the carcinogenic potential of chronic exposure to RF radiation.

NMR Clinical Experience

Because NMR imaging and in vivo spectroscopy are relatively new techniques, the opportunity has not been available for a long-term medical assessment of patients and volunteers subjected to the fields from NMR devices. Based on a six-month follow-up of 181 patients and 70 volunteers ranging in age from 2 to 83, Reid et al.[8] have reported that no unexpected changes in cardiac or neurological functions occurred as the result of imaging with a 0.04 T NMR unit. The cohort of patients included three with epileptic seizures and one with myocardial infarction. A total of 118 patients who received head imaging with the same NMR unit exhibited no visual or central nervous system dysfunctions subsequent to imaging.[458]

PHYSICAL SAFETY FACTORS IN MEDICAL NMR

Metallic Implants

Two types of physical hazard are associated with the interaction of metallic implants and the fields used in NMR imaging devices: (1) forces and torques are exerted on ferromagnetic materials by the static magnetic field, and (2) significant RF heating can occur in materials with a high electrical conductivity. New et al.[459] measured the magnetic forces and torques exerted on 21 hemostatic clips and various other materials such as dental amalgam. Of the 21 clips, 19 of which were aneurysm clips, 16 showed a deflection near the portals of two magnets operating at 0.147 T and 1.44 T, respectively. Five of the 16 magnetic clips exhibited slight deflections of less than 5° arc, and 5 others showed marked deflections greater than 45° arc. Of the remaining materials tested, only a shunt connector demonstrated significant ferromagnetic properties. The nonmagnetic materials were primarily composed of austenitic stainless steel, which has a high (10 to 20 percent) nickel content that stabilizes the iron in a nonmagnetic form. Clips composed of tantalum or titanium are also non-ferromagnetic.[460] Surgical clips composed of martensitic stainless steels are ferromagnetic and experience significant forces and torques in magnetic fields comparable to those used in NMR devices.[461] Barrafato and Henkelman[462] conducted a systematic study of 54 different types of surgical clips and characterized their magnetic properties based on the rotational torque experienced in a 0.15 T static field, and the force experienced when a 1.5 mT/m field gradient was imposed. These studies confirmed the nonmagnetic character of clips composed of tantalum and various austenitic stainless steel alloys and silver alloys.

A study has been carried out to determine heating effects in surgical clips and hip protheses exposed to rapidly time-varying magnetic fields and to RF fields at intensities greater than used in conventional NMR devices.[463] The maximum temperature rises recorded for copper and steel clips and for individual hip prosthetic devices were less than $1^{\circ}C$ under these exposure conditions, and it was concluded that no significant heating problem should be encountered during NMR imaging procedures. However, when two hip prostheses were joined together in a saline solution and subjected to the RF field, a temperature increase of several degrees was observed. The authors cautioned against the use of NMR imaging on patients with large implanted prosthetic devices until further research has been performed to assess the extent of possible RF heating problems.

Cardiac Pacemakers

An issue of particular concern is the malfunction of implanted cardiac pacemakers in response to the fields from NMR imaging devices. Because modern pacemakers contain a reed relay switch that can be closed by applying an external magnetic field in order to remotely test the battery strength, it is expected that implanted pacemakers will be influenced by static magnetic fields used for NMR imaging. Based on in vitro tests with demand pacemakers from six major manufacturers, Pavlicek et al.[464] found that fields of 1.7 to 4.7 mT produced closure of the reed switch, thereby resulting in a change from a synchronous to an asynchronous pacing mode. All six of the pacemakers studied were found to experience forces and torques when placed in NMR devices operating at fields up to 0.5 T. Two of the pacemakers experienced a torque that was judged on subjective criteria to be sufficient to cause significant movement within tissue.

A second aspect of pacemaker vulnerability to NMR imaging fields is the electromagnetic interference (EMI) that can result from signals introduced by the time-varying magnetic field or the RF field. Protection against RF fields is provided by a titanium casing and a low-pass input filter that discriminates against high-frequency EMI transmitted through the electrode leads. However, many brands of pacemaker are not protected against EMI in the ELF frequency range. The "unipolar" design of demand pacemakers, in which the cathode lead is implanted in the heart and the pacemaker case serves as the anode, is particularly susceptible to low-frequency EMI. This sensitivity results from the considerable physical separation of the anode and cathode, which thus provides a large antenna for the detection of EMI signals. The "bipolar" pacemaker design is much less sensitive to EMI because both leads are implanted within the heart at a small distance of separation. It has been estimated that among the 350,000 to 500,000 individuals in the United States with implanted pacemakers, approximately 50 percent have models with the unipolar electrode design.[465] It should also be noted that some manufacturers of pacemakers with the unipolar electrode configuration have overcome the problem of low-frequency EMI by incorporating a design feature that automatically decreases the sensitivity of the amplifier circuit when an interference signal is sensed. These specific pacemaker models thereby avoid reversion to an asynchronous mode in response to EMI.[466]

Pavlicek et al.[464] have found that a rapidly-switched gradient field with a time variation of 3 T/sec can induce potentials up to 20 mV in the loop formed by the electrode lead and the case of a unipolar pacemaker. This signal amplitude is sufficiently large to avoid rejection by the pacemaker's EMI discrimination circuitry, and it could therefore be mistakenly recognized as a valid cardiac electrical signal. A total of 26 pacemaker models were examined by Jenkins and Woody[467] for sensitivity to 60-Hz magnetic fields. Twenty of these units were found to revert to an asynchronous mode or to exhibit abnormal pacing characteristics in 60-Hz fields with amplitudes ranging from 0.1 to 0.4 mT. The average threshold field strength for inducing pacemaker malfunction was 0.2 mT, which corresponds to a dB/dt of 0.075 T/sec. This value of dB/dt is significantly less than the time variation of the switched gradient fields used in present NMR devices.

CLINICAL NMR EXPOSURE GUIDELINES

Exposure guidelines for NMR imaging and in vivo spectroscopy issued in the United States,[468] United Kingdom,[469] and the Federal Republic of Germany[470] are summarized in Table II. Recommended limits were given for the static magnetic fields, the time-varying magnetic fields, and the RF fields used in NMR devices. These guidelines are in close agreement on a limit for the static magnetic field of 2 to 2.5 T, but significant differences exist in the recommended exposure limits for time-varying magnetic fields and for

Table II. Exposure guidelines in clinical NMR

Source	B (Tesla)	Time-varying fields	RF fields
National Center for Devices and Radiological Health, DHHS: 1982	2.0	3 Tesla/sec	Specific absorption rate < 0.4 W/kg (whole body) or < 2 W/kg per g of tissue
National Radiation Protection Board, U.K.: 1983	2.5	20 Tesla/sec (r.m.s)for pulses > 10 msec; $2t^{-1/2}$ for pulses < 10 msec (t in sec)	Body temperature rise of < 1°C [specific absorption rate < 0.4 W/kg (whole body) or < 4 W/kg per g of tissue]
Federal Health Office, FRG: 1984	2.0	Induced current < 30 mA/m^2 or induced field < 0.3 V/m for pulses > 10 msec; induced current < 0.3/t mA/m^2 or induced field < 3/t mV/m for pulses < 10 msec (t in sec)	Specific absorption rate < 1 W/kg (whole body) or < 5 W/kg per kg of tissue (except for the eyes)

RF fields.

A limit of 3 T/sec for the time-varying field was recommended in the U.S./D.H.H.S. guideline[468] based on a review of the known interaction mechanisms and biological effects of time-varying magnetic fields.[4] In contrast, the U.K./N.R.P.B. guideline[469] was set at 20 T/sec (r.m.s.) based on the estimate that a time-varying magnetic field of this magnitude would induce a maximum current density of less than 0.3 A/m^2 (r.m.s.) in any part of the body.[471] This current density was judged to be safe on the basis that it is approximately one order of magnitude less than the threshold for producing cardiac fibrillation. The limit on dB/dt in the U.K./N.R.P.B. guideline is permitted to increase as the reciprocal square root of the pulse duration, i.e., 2/ t in units of T/sec (r.m.s.), for pulses shorter than 10 msec. This specification was based on various measurements of the stimulus strength versus duration relationship for human responses to electric current, as reviewed in an earlier section of this chapter. The F.R.G./F.H.O. guideline for time-varying magnetic fields is not extensively justified on the basis of laboratory data.[470] However, the recommended limits on induced current density and voltage gradient are reasonably consistent with the U.S./D.H.H.S. limit of 3 T/sec, since the maximum current density induced in the human body by a magnetic field with this time rate of change would be approximately 30 mA/m^2. The F.R.G/F.H.O. guideline also permits the induced current density limit to increase as the reciprocal of the pulse duration, i.e. 0.3/t in units of mA/m^2, for pulses less than 10 msec.

The recommended exposure limits for RF fields given in all three sets of guidelines are designed to avoid significant regional or whole-body heating. The maximum whole-body SAR value recommended in the U.S./D.H.H.S. guideline is consistent with recommendations by the American National Standard Institute,[472] whereas the F.R.G./F.H.O. limit is 2.5 times higher. In both sets of NMR exposure guidelines, the recommended limit for absorbed RF power in localized tissue regions is increased by a factor of 5 relative to the whole-body SAR limit. The U.S./D.H.H.S. guideline, however, specifies the local SAR per gram of tissue, whereas the F.R.G./F.H.O. guideline specifies this quantity per kilogram of tissue exclusive of the eyes. The U.K./N.R.P.B. guideline for the whole-body SAR limit is consistent with the U.S./D.H.H.S. recommendation, but the SAR limit per gram of tissue is twice that given in the U.S./D.H.H.S. guideline.

Both the U.K./N.R.P.B. and F.R.G./F.H.O. guidelines discuss the risks of imaging patients with implanted pacemakers, vascular clips, or large prosthetic devices. In addition, the U.K./N.R.P.B. guideline states that it would be prudent to exclude women in the first trimester of pregnancy from NMR imaging procedures.

The one recommendation that relates to staff members operating NMR equipment is the specification in the U.K./N.R.P.B. guideline that the Stanford Linear Accelerator limits on static magnetic field exposure[473] should be applied to these personnel. Under these limits, exposure of the whole body is not to exceed 0.02 T for prolonged periods, and exposure of the arms and hands is limited to 0.2 T. For short periods of less than 15 min duration, these exposure limits are increas' ' to 0.2 T for the whole body and 2 T for the arms and hands.

SUMMARY AND CONCLUSIONS

Based on the review presented in this chapter of interaction mechanisms, laboratory investigations, and human health studies, several summary statements and general conclusions can be drawn regarding biological effects of the static and time-varying magnetic fields and the RF fields used in the present generation of NMR devices:

- Static magnetic fields at levels up to 2 T have not been found to produce adverse behavioral or physiological changes in mammals. Electrical potentials induced within the central circulatory system of laboratory animals placed in fields up to 2 T do not significantly influence cardiac performance during brief exposures. Additional studies are needed to assess the effects of prolonged exposure to fields of this magnitude on the cardiovascular and central nervous systems. Future research should also address the issue of potential effects on cellular, tissue and animal systems resulting from exposure to ultrahigh fields in the range of 2-10 T. Little information exists on the response of biological systems to fields of this magnitude, which have been considered for use in future NMR devices.
- Time-varying magnetic fields that induce tissue current densities less than 10 mA/m^2 have not been demonstrated to produce harmful effects, although some laboratory findings of behavioral and physiological alterations have been reported. A time variation of 1 to 2 T/sec would induce maximum current densities of this magnitude in critical organs such as the heart and brain. Acute visual phenomena that occur in fields with a time rate of change exceeding 1.3 T/sec are completely reversible and produce no harmful long-term effects.
- It is well established that exposure to RF fields can lead to irreversible tissue damage if the regional or whole-body heating exceeds the normal thermoregulatory capacity of the body. Nonthermal effects of low-intensity RF fields have also been reported to occur in the cardiovascular and nervous systems, tissue metabolism, and a variety of other cellular and tissue functions. Windows of sensitivity in the frequency and intensity domains have been observed in studies on the influence of amplitude-modulated RF fields on calcium-ion binding to nerve cell surfaces. The maximum influence on calcium binding occurs when the RF field is amplitude modulated in the ELF frequency range, and theoretical calculations indicate that this effect cannot be attributed to a thermal interaction mechanism.[474] Further research is needed to elucidate the physical and chemical processes by which RF fields could exert nonthermal effects on living systems.
- Epidemiological studies on human populations exposed to large static magnetic fields and to RF fields have provided no consistent evidence for adverse health effects. Controversy currently surrounds the issue of elevated cancer risk among individuals exposed residentially and/or occupationally to ELF electric and magnetic fields above the normal ambient levels. A direct correlation between cancer risk and exposure to ELF fields has not been established, and numerous criticisms have been raised of the epidemiological

procedures used in the studies reported to date. Among the various methodological deficiences noted in these studies, the failure to account for confounding variables has been the most widely criticized.[475,476] At the present time, there are no direct implications of these epidemiological studies for the safety of patients or operational staff exposed to the time-varying magnetic fields of NMR devices. However, a long-term assessment of the health profiles of these individuals is advisable, and may lend further insight into the issue of potential carcinogenic risk from exposure to electromagnetic fields.

- A serious risk in NMR imaging procedures is associated with the forces and torques exerted by large static magnetic fields and magnetic field gradients on metallic implants such as vascular clips and prosthetic devices. Static magnetic fields greater than 1.5 mT and time-varying fields with dB/dt greater than approximately 75 mT/sec can alter the performance of implanted cardiac pacemakers. These physical interactions of the fields associated with NMR devices constitute a direct health hazard to patients and operational staff with implanted pacemakers, vascular clips, or prostheses.
- Clinical NMR exposure guidelines issued in the U.S. U.K., and F.R.G. impose a reasonable limit of 2 to 2.5 T on the static magnetic field level, and the various RF exposure limits are adequate to protect patients against excessive thermal stress. A 3 T/sec limit recommended in the U.S./D.H.H.S. guideline on the maximum time variation of rapidly-switched gradient fields appears reasonable on the basis of available information from laboratory studies, including several clinical investigations on human subjects. The F.R.G./F.H.O. limits on induced current density and voltage gradient are reasonably consistent with the 3 T/sec limit imposed by the U.S./D.H.H.S. guideline. From available laboratory information on cellular, tissue and animal systems, the 20 T/sec (r.m.s.) limit recommended in the U.S./N.R.P.B. guideline appears to be excessive.

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