Review

Invited

Safety of Strong, Static Magnetic Fields

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Issues associated with the exposure of patients to strong, static magnetic fields during magnetic resonance imaging (MRI) are reviewed and discussed. The history of human exposure to magnetic fields is reviewed, and the contradictory nature of the literature regarding effects on human health is described. In the absence of ferromagnetic foreign bodies, there is no replicated scientific study showing a health hazard associated with magnetic field exposure and no evidence for hazards associated with cumulative exposure to these fields. The very high degree of patient safety in strong magnetic fields is attributed to the small value of the magnetic susceptibility of human tissues and to the lack of ferromagnetic components in these tissues. The wide range of susceptibility values between magnetic materials and human tissues is shown to lead to qualitatively differing behaviors of these materials when they are exposed to magnetic fields. Mathematical expressions are provided for the calculation of forces and torques. J. Magn. Reson. Imaging 2000;12:2–19. © 2000 Wiley-Liss, Inc.

Index terms: magnetic bioeffects; safety of MRI; magnetic forces; diamagnetism; magnetotherapy; susceptibility

THE POSSIBILITY THAT some hazard may be associated with exposure to the strong magnetic fields required to perform MRI has been of concern since the introduction of this technique in the late 1970s. Although MRI studies require that patients be exposed to strong static magnetic fields throughout the duration of the examination, there is good reason to believe in the inherent safety of these procedures. Informal market research studies suggest that more than 150,000,000 diagnostic MR studies were performed worldwide between the onset of clinical MRI in the early 1980s and the end of 1999. These studies also indicate that more than 20,000,000 examinations are performed worldwide each year (more than 50,000 each day). The vast majority of these examinations are, of course, performed without any sign of patient injury.

Concerns for patient safety have been raised in regard to each of the three distinct fields used in MRI: the radiofrequency transmitter field, B_1, the time-dependent gradient fields, and the static field, B_0. These fields are essential features of the scanner operation, and each of them interacts with every component of the patient's body. The safety aspects of the radiofrequency (RF) and gradient fields are easier to quantify than are those of the static field. The reason is that for RF and gradient fields clear-cut physical phenomena establish upper limits for safe patient exposure (Table 1).In contrast, as long as proper precautions are taken, such as ensuring the absence of magnetic materials and avoiding rapid patient motion, neither theoretical nor experimental studies have demonstrated an upper limit for safe exposure to intense static fields. At the present time, therefore, the limits on the strength of the static fields used in MRI are set by technical, regulatory, and cost factors and not by the ability of patients to tolerate them safely.

Although there are few, if any, rigorously established magnetic effects on human biology, the topic is the subject of a vast literature that began several centuries ago and that has recently grown rapidly because of the widespread success of MRI as a clinical imaging modality. Several bibliographies of the earlier literature (1–4) and a recent historical summary (5) are available. A complete bibliography of the field at the present time is not possible, but a representative listing of books (6–20), reviews (21–24), and research reports (25–88) is included in the references. As will be discussed below, the absence of direct harmful effects of strong static magnetic fields on human health can be attributed to the absence of ferromagnetic components in human tissues and to the extremely small value for the magnetic susceptibility of these tissues.

Deaths attributed to MR scanning are extremely rare. Exact quantification is not possible as there is no uniform reporting mechanism of adverse events for this modality, which is heavily utilized worldwide, and the possibility of underreporting of severe adverse events must be considered. However, a brief literature review in 1998 found reports of seven deaths attributed to MR scanning (89–91). These incidents included one death during examination for cerebral infarction, one involving a ferromagnetic cerebral aneurysm clip, and five related to inadvertent scanning of patients with cardiac pacemakers. The role of the MRI examination in the fatal outcome was not certain in several of these reports. This small group, however, underscores the importance of efforts to avoid the scanning of patients with

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Table 1
Comparison of the Physical Effects of the Various Fields Applied to Patients During MRI

Type of field	Physical limitation on human exposure
Switched gradient fields	Peripheral nerve stimulation[a,b]
Radiofrequency B_1 fields	Tissue heating[a]
Static B_o fields	Not known

[a]The origin of both these effects can be attributed to the electric field that accompanies all time-dependent magnetic fields and not the magnetic field itself.
[b]Both the rate of change of the field and the duration of the change must be above threshold values for stimulation to occur.

ferromagnetic foreign bodies or implanted electronic devices.

The large numbers of trouble-free studies attest to the high level of safety that has been achieved in this modality. The much smaller number of serious complications is a reminder of the importance of continued vigilance.

HISTORICAL REVIEW OF HUMAN MAGNETIC FIELD EXPOSURE

All human beings are continually exposed to the magnetic field of the earth, which is approximately 0.5 G or 5×10^{-5} T. This field is weak and unobtrusive and, except for the use of magnetic compasses, people are generally unaware of its existence. Naturally occurring magnetic minerals, such as magnetite, also known as lodestone (Fe_3O_4), have been known for several thousand years (1). As early as the first or second century AD, the Greek medical writer Dioscorides is said to have claimed a therapeutic role for magnetic minerals in treating arthritis and other diseases. Mineral magnets, made from naturally occurring magnetite, are quite limited in the strength and spatial extent of the magnetic fields they can produce. A fully magnetized sphere of magnetite produces a peak field of about 0.4 T and this only over a small region near its north and south poles. Using metallurgy to produce artificial iron or steel magnets can produce fields perhaps three times stronger than this. The introduction of electromagnets in the early 19th century made it possible to produce strong fields over larger regions, but these were limited by the available power supplies and the heating of the current-carrying coils. Only after the discovery of high-field (type 2) superconductors in the mid 20th century (92) did it become technically possible to achieve the intense whole-body field strengths currently used in MRI.

Even after it became possible to produce strong magnetic fields, however, only a relatively small number of people involved in specific professions, such as experimental high-energy physics and electromagnetic ore extraction, actually came in contact with them. Therefore, the routine use of whole-body magnets at strengths up to 1.5 T in clinical MRI, which began in the early 1980s, introduced a new degree of human exposure to magnetic fields.

Popular attitudes toward magnetic field exposure are to some degree affected by the association of magnets with hypnotism and magnetotherapy. Therefore, these topics are briefly reviewed here. Magnetotherapy is the use of magnets or coils to apply a magnetic field, usually much smaller than those used in MRI, to a patient's body for therapeutic purposes. For centuries it has been proposed in one form or another as a magical method of treating diverse conditions such as headache, seizures, and asthma. As discussed below, even though the magnetic forces on tissues are in all likelihood far too small to really produce any such effects and no objective evidence has been provided for its effectiveness, magnetotherapy has been an impressively resilient form of folk medicine since ancient times. There has also been a fairly constant polarization of attitudes toward its effectiveness with one relatively small, but often vocal and highly popular, group of advocates opposed by a more mainstream scientific group of opponents who found the technique implausible and dismissed it as a form of quackery or self-deception. This was evident in the 16th century with the flamboyant German physician and alchemist Paracelsus (Theophrastus von Hohenheim) promoting the therapeutic powers of powdered magnetic iron oxides opposed by the famous English physician William Gilbert, who ridiculed the idea of using magnets for therapeutic purposes (5). In particular, Gilbert pointed out that grinding a magnetic lodestone into a powder for medical purposes, as recommended by Paracelsus, randomizes the magnetic effects of the individual grains and weakens the overall magnetic influence to the vanishing point.

The Viennese physician Anton Mesmer (1734–1815) began practicing in Paris in 1778. His therapeutic use of magnetism became sensationally successful, and by 1784 he was perhaps the most famous and controversial physician in Europe (13). He came to believe that the curative powers did not originate in the mineral magnets themselves but in a universal force, analogous to gravitation and called animal magnetism, which he personally was capable of concentrating and transmitting for therapeutic effect. The turbulent therapeutic sessions conducted at his upscale Parisian clinic became controversial to the point of scandal, and a royal commission was appointed that year by Louis XVI to evaluate Mesmer's technique. This commission was composed of some of the most famous physicians and scientists of this pre-Revolutionary period including, among others, Benjamin Franklin, Antoine Lavoisier, and Joseph Guillotine (81). They compared the results obtained using the so-called magnetized therapeutic devices with those of sham substitutes and concluded that the positive results obtained were the results of the power of suggestion acting in naïve subjects, that "magnetism without imagination produces nothing," and that "this nonexistent fluid is without utility."

Mesmer was followed in the 19th century in both Europe and North America by practicing "magnetizers" who for the most part were probably simple quacks. However, another line of investigation prompted by animal magnetism explored the power of suggestion. These studies led to concepts such as hypnotism, magnetic sleep, and alternate states of consciousness and therefore have a direct ancestral relation to modern psychotherapeutic practice (18).

In the late 19th and early 20th century American entrepreneurs such as Dr. C. J. Thatcher, Gaylord Wilshire (for whom Wilshire Boulevard in Los Angeles is named), and Dr. Rodney Madison made heavy use of mail-order merchandising and radio advertising to promote magnet garments and devices that were claimed capable of curing an almost limitless array of diseases (78,85). These devices, sold under names such as Theronoid and I-on-a-co, were investigated by the American Medical Association (AMA) bureau on medical fraud, the Federal Trade Commission (FTC), and the Better Business Bureau; the FTC banned advertising of the Theronoid as a therapeutic device in 1933 (28).

Macklis (78) suggests that after the American Civil War the newly industrialized farm belts of the rural Midwest, with few well-trained physicians and a history of self-doctoring, were fertile grounds for the merchandising of magnetic salves, liniments, and boot insoles. It is interesting, however, that at the end of the 20th century, in a well-educated country with many well-trained physicians that is much less rural than it was 100 years ago, magnetotherapy appears to have at least as high, if not higher, degree of popular acceptance as a mode of alternative medicine in America than at any previous time. Furthermore, although this treatment modality still lacks a convincing theoretical and experimental rationale to justify its use, there does not seem to be any organized governmental or professional effort to regulate or investigate the business practices associated with it. In this sense the present era seems more gullible, or at least less critical, than preceding generations. Widely distributed mail order gift catalogues routinely advertise mattresses with magnetic pads sewn into them that are claimed to provide various health benefits and that sell for up to $1000. There are estimates that such products currently have sales on the order of $1 billion a year (84). A popular, physician-authored book published in 1998 states that magnets can be used to provide relief from arthritis, menstrual cramps, carpal tunnel syndrome, and many other disorders (20).

In the 1960s the onset of the space program led to a series of studies concerned with possible magnetic field-related safety problems for astronauts (33,34). It was thought these might arise either because the astronauts would not be exposed to the ordinarily ubiquitous earth magnetic field while in space, or because proposed magnetohydrodyamic propulsion and cosmic ray shielding techniques might expose them to unusually intense fields. At about the same time additional studies were undertaken to address safety concerns about the strong magnets being utilized in high-energy physics laboratories (38).

HISTORY OF MAGNETIC FIELD EXPOSURE DURING MRI

The introduction of MRI as a clinical imaging modality in the early 1980s led to the design, fabrication, and wide dissemination of new forms of large and powerful magnets and to a large increase in the level of human exposure to strong magnetic fields. MRI magnets are characterized by their large size and the highly homogeneous fields at their centers. These magnets are normally large enough to surround large, adult humans, although smaller magnets designed to image only the head or limbs are sometimes used. The central field is intense and has a homogeneity on the order of 10 ppm or better over spherical volumes approximately 50 cm in diameter. Most commonly the magnets used in MRI are cylindrically symmetric superconducting devices, although resistive, permanent, and hybrid magnets are also utilized.

Table 2 provides information on the time of introduction of scanners of various field strengths (93–101).It is not the purpose of this table to provide a rigorous historical record of priority, but rather to give the reader a feeling for the pace at which new levels of field strength have become available and accepted in clinical medicine and MRI research. The substantial financial and technical barriers experienced when developing whole-body machines of ever higher field strength is attested to by the 11-year period that elapsed between the introduction of the first 4-T whole-body scanners and the introduction of the first 8-T machine at Ohio State University in 1998 (88).

Human imaging has now been reported for field strengths from 0.02 (66) to 8.0 T, and specific advantages have been found for scanners operating over a wide range of field strengths. However, Bell (102) has estimated that more than 60% of the scanners operating in the United States in 2000 will be at field strengths of 1.0, 1.5, or 2.0 T. Up to the present time scanners operating at 3 T and higher have been utilized largely for research purposes, but a more widespread usage of these very high field units is likely in the next few years.

As indicated in the introduction, a huge number of diagnostic clinical scans have been completed without incident. This strongly supports the view of earlier authors (25–27) that the magnetic interactions with normal tissues are within the bounds of safety up to the highest fields now in use for MRI. However, in the presence of ferromagnetic materials, a number of authors have noted the danger associated with ferromagnetic objects either implanted in the patient or located in the fringing field of the magnets (Fig. 1) (47,52,53,56,73).

ASSESSMENT OF THE LITERATURE ON MAGNETIC FIELD EXPOSURE

A bibliographic review published in 1962 (2), well before the introduction of MRI, found 393 published reports dealing with biological effects of magnetic fields, and there have been many additional reports since that time. Of course, many of these reports do not address issues of pathological or therapeutic magnetic effects. The portion of this literature that does deal with the alleged pathological or therapeutic effects of magnetic fields is contradictory and confusing. Often basic information, such as the field strength and its variation over the organism studied, is not provided. Generally, these studies do not describe the dose-response characteristics of the effect, that is, the dependence on field strength and the duration of the exposure. Few, if any, have been replicated, and in most cases no plausible

Table 2
Historical Development of MRI Magnetic Field Strength.*

Field strength (T)	Date of introduction	Institution	Type	Comments
0.05–0.10	1977	State University of New York, Brooklyn	Superconducting	This machine produced an early thoracic image.
0.7	1977	University of Nottingham	Iron core electromagnet	This machine, with a 13-cm gap, produced an early wrist image.
0.04	1980	Aberdeen	Air core electromagnet	This machine was used for the first clinical MRI studies.
0.35	1981	Hammersmith, Diasonics	Whole-body, superconducting	These machines were the first whole-body superconducting scanners.
1.5	1982	General Electric	Whole-body, superconducting	Whole-body magnets at 1.5 T have been in widespread clinical use since the mid-1980s.
4	1987	Siemens, General Electric, Philips	Whole-body, superconducting	During the late 1990s 3-T and 4-T scanners became widely available at research institutions.
8	1998	Ohio State University	Whole-body, superconducting	This is the highest field whole-body MRI scanner currently operating.

*Data from refs. 63, 65, 76, 77, 93–101.

physical mechanism is put forward to explain the proposed effect. In other cases a mechanism is proposed but is not verified to be quantitatively large enough to explain the proposed effect. Several studies undertaken to look for harmful effects of magnetic fields have yielded negative results (25–27,45,49,50,76,77,79).

Responding to many earlier claims for the therapeutic effectiveness of magnets, in 1892 Peterson and Kennelly (26) collaborated on studies of magnetic field exposures at the laboratories of Thomas Edison. They used the largest magnet available to them at that time (approximately 0.15 T) to carry out whole-body exposures of a dog and a young boy. They found no positive results and concluded that, "The ordinary magnets used in medicine have a purely suggestive or psychic effect and would in all probability be quite as useful if made of wood."

In 1921 the Harvard physiologists Drinker and Thompson (27) investigated possible health consequences of the exposure to magnetic fields of industrial workers. They focused on the use of powerful separator magnets in the manganese industry and performed numerous experiments on nerve-muscle preparations and on living animals. Again, they found no effects of the magnetic fields and concluded that, "it seems certain that the magnetic field has no significance as a health hazard."

In many cases, efforts to reproduce positive findings are unsuccessful. For example, in a series of publications in the 1950s it was reported that magnetic field exposure in mice led to retardation of overall growth rate, tumor growth rate, and white blood cell counts (29,30). However, attempts to replicate these finding by Eiselein et al (32) produced completely negative results. In another example it was reported that the brainstem auditory evoked potential was delayed after exposure to a 0.35-T magnetic field (54). Several subsequent studies failed to confirm this finding (68,69,74).

Certainly many factors are at work to account for the many contradictory findings in the literature. It is often difficult to isolate the effects due to the applied magnetic field from other confounding factors that are present. In one recent case a finding of scientific misconduct has been made (103–106). The power of suggestion is operative in many cases involving the subjective evaluation of magnetic field effects. It is likely that anxiety caused by the presence of a large and somewhat intimidating superconducting magnet can influence perceptions of vague discomforts. Erhard et al found that, when studied after exposure to a 4-T superconducting magnet, 45% of subjects responded positively to the query, "Did you experience any unusual sensations while in the magnet?" even though the magnet was not energized (79). Irving Langmuir (107,108) has suggested the term pathological science for situations in which experiments studying low-level phenomena repeatedly fail to be replicated.

The current situation seems to be as summarized in 1981 by Budinger (43), who wrote "From the vast literature on cell cultures, animals, and man, no experimental protocol has been found that, when repeated by other investigators, gives similar positive results." Because of the difficulty in establishing a negative conclu-

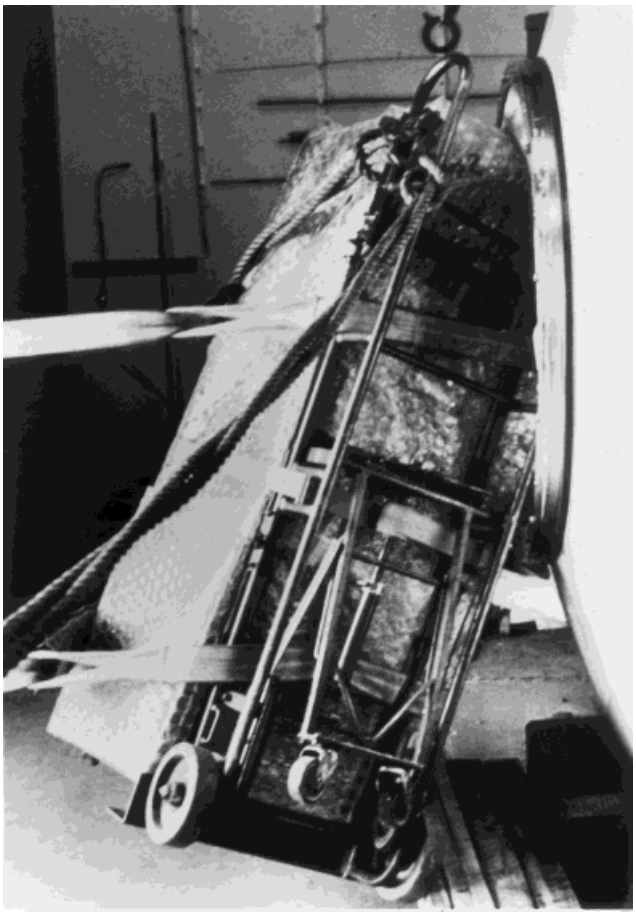

Figure 1. Magnetic field accident. The powerful and insidious nature of magnetic forces acting on ferromagnetic materials with very large magnetic susceptibilities are demonstrated in this accident. An RF power supply was being moved in the vicinity of an unshielded 1.5 T superconducting magnet. The magnetic forces depend on the field strength and gradient and vary extremely rapidly with position. In this case, over a very short distance, the magnetic forces went from being imperceptible to a level at which the workmen moving the power supply were unable to restrain it. (Photo courtesy of Dr. W. A. Edelstein. From Reference 80, with permission).

sion, it should not be concluded that it has been proved that there are no significant biological effects of static magnetic fields. However, it does appear correct to say that the work performed to date has yet to provide a single example of a scientifically sound and rigorously verified pathological effect of such fields. The steadily increasing capability of producing ever stronger magnets gives reason to believe that such effects will eventually be established, but probably at field strengths well above those currently used in MRI.

QUALITATIVE REVIEW OF POSSIBLE STATIC MAGNETIC FIELD EFFECTS ON HUMAN TISSUES

Several physical mechanisms of interaction between tissues and static magnetic fields could theoretically lead to pathological changes. Quantitative analysis of each of these indicates that they are below the threshold of significance. These effects are summarized below.

Magnetic Forces and Torques

Tissue components that are permanently magnetized or that have magnetic susceptibilities that are positive with respect to that of water are drawn toward high field regions and vice versa (109,110). Theoretically, this could lead to sorting of tissue components, with the more paramagnetic components moving to high field regions. However, as shown below for red blood cells, this effect is very weak in practice and not of practical significance in living tissues even in very intense static fields. Human tissues do not contain permanently magnetized components. When such materials are introduced through accident (as in shrapnel emplacement) or through surgical intervention they represent serious hazards that must be carefully controlled and may represent absolute contraindications for MR scanning.

Permanently magnetized materials tend to rotate such that their magnetic moment comes into alignment with the magnetic field. Soft magnetic materials, whose magnetization is proportional to the applied field, tend to rotate such that the long axis of the object is parallel to the applied field. As discussed below for magnetic foreign bodies these effects represent an even greater potential hazard than the translational forces on such materials. Paramagnetic materials whose susceptibilities vary with the direction of the magnetizing field (anisotropic susceptibility) tend to orient with the axis of most positive susceptibility aligned with the field. Diamagnetic materials tend to rotate such that the axis of least negative susceptibility aligns with the field. This effect can be demonstrated in vitro but, as shown below, is too Zeak to be operative within tissues.

Geim and his associates (109,110) have recently managed to use the very weak repulsive forces operating between magnets and diamagnetic materials such as living tissues to suspend small frogs and other diamagnetic objects against the pull of gravity in the space above a vertical small-bore magnet operating at 16 T. Interestingly, this dramatic exposure to strong magnetic fields did not produce any visible harm to the frogs.

Flow and Motion-Induced Currents in Tissues

In a truly static electric field the electric current density, $\mathbf{J}$, in tissues is determined by $\mathbf{J} = \sigma\mathbf{E}$, where σ is the tissue's electrical conductivity and $\mathbf{E}$ is the electric field. Under normal circumstances these electric fields result from processes such as the depolarization of the heart tissue. In this case the resulting current density produces the electrocardiogram (ECG). If the tissue moves with a velocity $\mathbf{v}$ relative to the static field, there is an additional term in the expression for the current density, $\mathbf{J} = \sigma(\mathbf{E} + \mathbf{v} \times \mathbf{B})$, with the term $\mathbf{v} \times \mathbf{B}$ acting as a motion-induced electric field.

Therefore, tissue motion, such as bulk physical movements (eg, rapid movement into or out of the magnet or rapid head turning) or internal movements (eg, blood flow), in strong static fields can produce additional physical effects beyond those directly associated with permanent magnetism and magnetic susceptibility. Measurement of the body surface potentials produced by blood flow in a magnetic field was long ago

proposed as a form of electromagnetic flow meter (111,112).

In the 1960s it was shown that the ECGs of subjects (originally monkeys) located in strong magnetic fields displayed field-induced changes, particularly T-wave abnormalities (34). It was originally suggested that this might indicate a magnetic field effect on the repolarization process in the myocardial tissues. However, a simpler effect, based on the electromotive force (EMF) developed in blood flowing in a magnetic field, was subsequently shown to explain these changes (113,114). As indicated above, when an electrically conducting fluid, such as blood, flows in an applied magnetic field a transverse EMF is developed. This leads to a small induced current density in the tissues, which in turn leads to a small electric voltage on the body surface, which, like the conventional ECG, can be detected by the use of metal electrodes on the skin. This effect is now easily demonstrated in clinical scanners and contributes to the difficulty in obtaining good ECGs during MR scanning.

This induced EMF is proportional to the velocity of blood flow and to the magnetic field strength. This effect has recently been studied in humans at field strengths as high as 8 T (88). At the highest field strengths currently available the flow-induced current densities are below the threshold levels to cause nerve or muscle stimulation effects (115). However, at some level of magnetic field strength it seems likely that the flow-induced currents surrounding blood vessels would reach levels capable of causing extraneous nerve or muscle excitation. This theoretical effect may eventually become the limiting factor in the ability of humans to tolerate extremely high magnetic fields. (77,86).

Magnetic Effects on Chemical Reactions

The proper metabolic functioning of tissues requires the continual operation of a huge number of chemical reactions. There are situations in which an applied static magnetic field might alter the rate or equilibrium positions of such reactions (116–123). For example, if the products of a chemical reaction are more paramagnetic than the reactants, the presence of a magnetic field should shift the reaction equilibrium to increase the concentration of the products. The dissociation of molecules consisting of oxygen bound to hemoglobin (which are diamagnetic) into separate molecules of oxygen and hemoglobin (each of which is paramagnetic) is an example of this possibility. In this case an applied field should lower the energy barrier for the dissociation of the bound pair and favor the production of the paramagnetic products. However, calculations indicate that, even in an applied field of 4 T, the free energy barrier to dissociation (about 64,000 J/mol) in this reaction is changed by only about 1 J/mol. This small energy shift will have less effect on the reaction equilibrium than a temperature change of 0.01°C (77).

Although a static magnetic field, acting on small differences between the susceptibilities of the products and the reactants, does not significantly affect the equilibrium position of chemical reactions, there is another mechanism that has been shown to allow magnetic fields to alter somewhat the dynamics of certain chemical reactions. Specifically, this refers to the dissociation of a binary molecule, AB, present in some solvent, where A and B are joined by a nonmagnetic electron-pair bond, into two radicals, A and B. In the bound state the two electrons have opposite spins so that together they form a singlet state with total spin equal to zero. If AB spontaneously dissociates, because of thermal agitation, into separate radicals A and B, each radical can, for a short time, be considered as residing within a cage of surrounding solvent molecules that impedes the complete separation of the radicals from one another. If A and B recombine before separating from one another, the process is called geminate recombination, and the so-called cage product, AB is formed. On the other hand, if they ultimately diffuse apart an escape product, A and B, is formed.

If an applied magnetic field is present, and if the magnetic moments are not the same for the two radicals, the spins of the two separating radicals will precess at somewhat different rates. Geminate recombination is only possible if the two radicals are still in a singlet state (total spin of zero) when they reencounter one another. If the differing rates of spin precession have given the total spin wave function a significant portion of triplet character, the probability of bond reformation will be reduced and the yield of escape products increased.

A complete discussion of this effect is beyond the scope of this article. However, there is experimental evidence for an effect of static magnetic fields on the yields of some photochemical and organic chemistry reactions involving free radical intermediates. In general the effects are not large, and effects on reactions of biochemical significance have not been reported. These effects depend on field strength in a complicated way. Certain reaction paths are enhanced, and then retarded, as the field strength is increased (117–123). The field effect on the yield of these reactions is small and is not linearly proportional to field strength. This effect has not been demonstrated in biochemical reactions, and its relevance to magnetic field safety is uncertain. It does not appear that the cage mechanism would be relevant to enzyme-mediated reactions.

Possible Ferromagnetic Tissue Components

The inherent weakness of the interaction of diamagnetic tissue components with external magnetic fields is a consequence of the extremely small susceptibility values of these materials. This conclusion would need reexamination if human tissues were found to contain significant amounts of ferromagnetic or strongly paramagnetic materials (124–129). Small amounts of some paramagnetic, but not ferromagnetic, substances are natural tissue components. For example, 70-kg adult humans have about 3.7 g of iron in their tissues. However, this iron is not present in a bulk ferromagnetic form but is distributed in various chemical compounds, such as hemoglobin, ferritin, and hemosiderin, which are only weakly paramagnetic and do not interact

strongly with applied fields. The concentrations of these paramagnetic substances is not large enough to convert the overall susceptibility of any tissue (including blood) from diamagnetic to paramagnetic (80).

Small amounts of particulate magnetite have been found in the lungs and other tissues of people such as coal miners who are occupationally exposed to rock dust, and contamination with magnetite and other iron oxides can result from tattooing (124–128). It has also been shown that small particles such as these can spread within the body (62). No evidence has been presented for a biological function of ferromagnetic particles or of a related pathology associated with their exposure to strong magnetic fields.

Electron microscopy evidence from autopsy studies (129) has been presented for the presence of extremely small magnetite particles, less than 500 Å in diameter, in human brain and other tissues. Possible functional roles for such particles were also presented. As with other such studies, additional confirmation and studies to rule out an exogenous source for these particles is desirable. Such small particles cannot produce MR imaging artifacts, at least using conventional pulse sequences, and if ferromagnetic particles much larger than this were present it is likely they could be detected in this way. Such artifacts are not observed.

Local edema and tissue swelling as well as localized image artifacts have been noted during MRI of patients with tattooing or permanently implanted eye shadow. This effect has been attributed to an interaction of the radiofrequency field with electrically conducting components of the implanted pigments (55,58,60–62). However, the B_1 field does not produce significant local heating interactions with small metallic implants such as surgical hemostasis clips and is unlikely to do so with relatively poorly conducting oxides. A more likely explanation is that the implanted pigments contain irregularly shaped magnetic iron oxide particles and these particles twist such that their long axis is aligned with the applied field when the patient enters the magnet. The magnetic fields of these particles lead to the observed image artifacts, and the twisting may produce local tissue irritation causing the edema formation. Any patient motion while in the magnetic field would tend to exacerbate this tissue irritation.

Magnetoresistance and the Hall Effect

The motion of electrons and ions in solution is altered in the presence of a strong magnetic field, and it has been conjectured that this could lead to a field-dependent modification of the depolarizing currents that are responsible for the propagation of the nerve and muscle action potentials. If the mean free path of the current carriers and the time between collisions is sufficiently long, the effective resistivity is increased and transverse electric fields are generated (Hall effect) when a conductor is placed in a magnetic field. However, the action potentials of nerve and muscle tissue are dependent on ionic currents. These ions have extremely short mean free paths ($\sim$ 1 Å) and collision times (10^{-12} seconds) and therefore magnetic fields will have negligible effects on the currents associated with action potentials (50).

Magnetohydrodynamic Forces and Pressures

Currents flowing in tissues experience a body force, $\mathbf{J} \times \mathbf{B}$, and the resulting pressures and forces are transmitted to the tissues. These forces can be substantial in flowing liquid metals such as mercury. However, flowing physiological fluids such as blood have much lower electrical conductivities than mercury, and magnetohydrodynamic (MHD) forces on flowing blood are very small compared with the naturally occurring hemodynamic forces in the vascular system. Therefore, contrary to early speculations, there is no requirement for increased heart activity to maintain the cardiac output in the presence of a magnetic field (59,71). On the other hand, very small MHD forces operating on the endolymphatic tissues of the inner ear may be the source of the sensations of nausea and vertigo sometimes reported at higher field strengths (76,77).

Magnetostriction

Ferromagnetic materials change their size and shape slightly when exposed to strong magnetic fields (130). However, these changes are very small, and human tissues do not normally contain ferromagnetic materials. Any effect in human tissue would be very small compared with the naturally occurring forces of thermal expansion and mechanical stresses.

QUANTITATIVE ASPECTS OF STATIC FIELD EFFECTS

To proceed from a qualitative to a quantitative analysis of the magnetic responses of tissues, the concept of magnetic susceptibility will be introduced and its consequences explored. An important goal of this analysis is to emphasize that the quantitative difference between the magnetic properties of ferromagnetic materials and those of plant and animal tissues is so great that in many cases there is a qualitatively different character to their response to applied magnetic fields. A common error in predicting the response of tissues to applied fields is to extrapolate from familiar experiences with ferromagnetic materials, whereas tissue components will not necessarily conform to these expectations. The approach is to introduce the concept of magnetic susceptibility and then to relate this to the magnetic energy forces and torques that determine the response of tissues to applied magnetic fields.

Magnetic Susceptibility and the Classification of Magnetic Materials

Permanently magnetized materials, such as bar magnets and compass needles, can be extremely hazardous in the MR environment and, in the exceptional situations in which they are required in MRI work, they must be rigorously controlled. Ordinarily, they should be excluded from these locations, and they will not be further discussed in this paper. All materials that are not per-

manently magnetized are characterized by a physical parameter called the magnetic volume susceptibility or just the susceptibility (80). The physical basis for the apparent lack of responsiveness of biological tissues to applied magnetic fields is primarily due to the very small values of their magnetic susceptibilities.

In this paper SI or MKS units will be used exclusively, and bold face symbols will be used to designate vector quantities. Most material objects are not spontaneously magnetic in the sense that they do not create a magnetic field in their environment unless they are exposed to an external magnetic field. Such external fields are usually generated by permanently magnetized materials or by electric currents. The response of the materials when placed in an external field that has been generated by some means is to develop a magnetic polarization that is measured by the magnetization or magnetic dipole moment per unit volume. The strength of the induced magnetization is proportional to the magnetic field and the susceptibility, χ, In SI units χ is dimensionless and is defined by the equation $\mathbf{M} = \chi\mathbf{H}$. Here **M** is the magnetization at the point in question, and **H** is the local value of the magnetic field strength. At each point these fields are related to **B**, the magnetic flux density, by the formula $\mathbf{B} = \mu_O(\mathbf{H} + \mathbf{M})$. The electromagnetic constant, μ_o, is referred to as the permeability of free space. The magnetization of the sample becomes the source of a second, or induced, magnetic field. The interaction of the applied and the induced fields leads to interactions between the magnetized object and the permanent magnets or currents that created the originally applied field. When we need to distinguish between the total field **B** and the applied field at a point we will use the symbol $\mathbf{B}_o$ for the applied field.

In most materials the induced magnetization is parallel to **H** and in this case **M**, **B**, and **H** all point in the same direction. In this common situation the materials are referred to as isotropic, and χ is a scalar quantity. In some cases the material magnetizes in some directions more easily than in others. In this case the magnetization is not necessarily parallel to the magnetic field, the material is anisotropic, and χ is a symmetric tensor. Except for a brief discussion of the weak torques present in certain biological crystals, this paper will assume that the materials under discussion are isotropic. Note that the field **H** used in the definition of χ is the sum of the applied and induced fields at the point in question. Therefore, for materials with large susceptibilities, it is necessary to determine the magnetization of an object self-consistently by accounting for the effects of the induced as well as the applied field. This will be done below for ellipsoidal objects through the use of demagnetizing coefficients. On the other hand, the fields induced by the magnetization of objects, such as biological materials, with very small susceptibilities are feeble compared with the applied fields and may often be neglected. In this important case the magnetization is determined entirely by the applied field. If the material is isotropic, **M** will be parallel to **H** and **B**, and, as discussed below, there will be no torques attempting to align the object with the local fields. More precisely, we can say that in this situation any such torques that are present are so small as to be negligible in comparison with other biological forces acting on the tissue component.

All nonpermanently magnetized materials have nonzero values of χ and are to some extent magnetic. Materials may be classified into three large groups based on their susceptibility values. Energy considerations show that χ values less than -1.0 are not possible, while any value of $\chi > -1$ is possible (132). Materials with negative susceptibilities, that is, with $-1.0 < \chi < 0$ are called diamagnetic. They magnetize in the direction opposite to the local magnetic field and are repelled from regions of strong magnetic fields. All materials have diamagnetic tendencies and will be in this class unless they also contain some components, such as magnetic ions of the transition elements, that provide an overriding positive contribution to χ. Materials with positive values for χ are referred to as paramagnetic and are attracted to regions of strong magnetic fields. Materials in which $|\chi| <$ approximately 0.01 or so are not overtly responsive to casual testing with hand-held magnets and are often considered nonmagnetic. This class includes the vast majority of common materials and, with rare exceptions such as magnetotactic bacteria, all living tissues. The third group of materials has $|\chi| >$ approximately 0.01 and is referred to in this paper as ferromagnetic or magnetic. These materials can respond very strongly to an applied magnetic field and can present real dangers if present in the vicinity of an MR scanner (Fig. 1). In contrast to permanent magnets or hard magnetic materials, these materials are also referred to as soft magnetic materials as their magnetic properties are not manifest until they are exposed to an external field.

Figure. 2 illustrates a fundamental physical fact—the enormous range of susceptibility values that occur in nature (80). The vast majority of materials have susceptibility values much less than 0.001; for such materials magnetic forces are quite weak and require special efforts to demonstrate them. In particular, the vast majority of biological tissues have susceptibilities in a narrow range of about $\pm 20\%$ from the susceptibility of water, $\chi_{H_2O} = -9.05 \times 10^{-6}$ in SI units. If it were not the case that biological tissues all have similar susceptibility values, MR imaging would be severely limited or impossible because of the strong local field variations and, therefore, position-dependent variations in the Larmor frequency, that would be produced by local variations in χ.

The forces involved with diamagnetic repulsion are normally so small as to be negligible. It is true that when a patient is moved into an MRI scanner the magnet exerts a small force to oppose this motion, but this force is so small as to be unnoticeable. The materials commonly thought of as magnetic, on the other hand, can have susceptibility values of 1000 or more and respond forcefully to applied magnetic fields. As discussed further below, this huge quantitative variation in susceptibility values leads to qualitatively differing responses of ferromagnetic and "nonmagnetic" materials to applied fields.

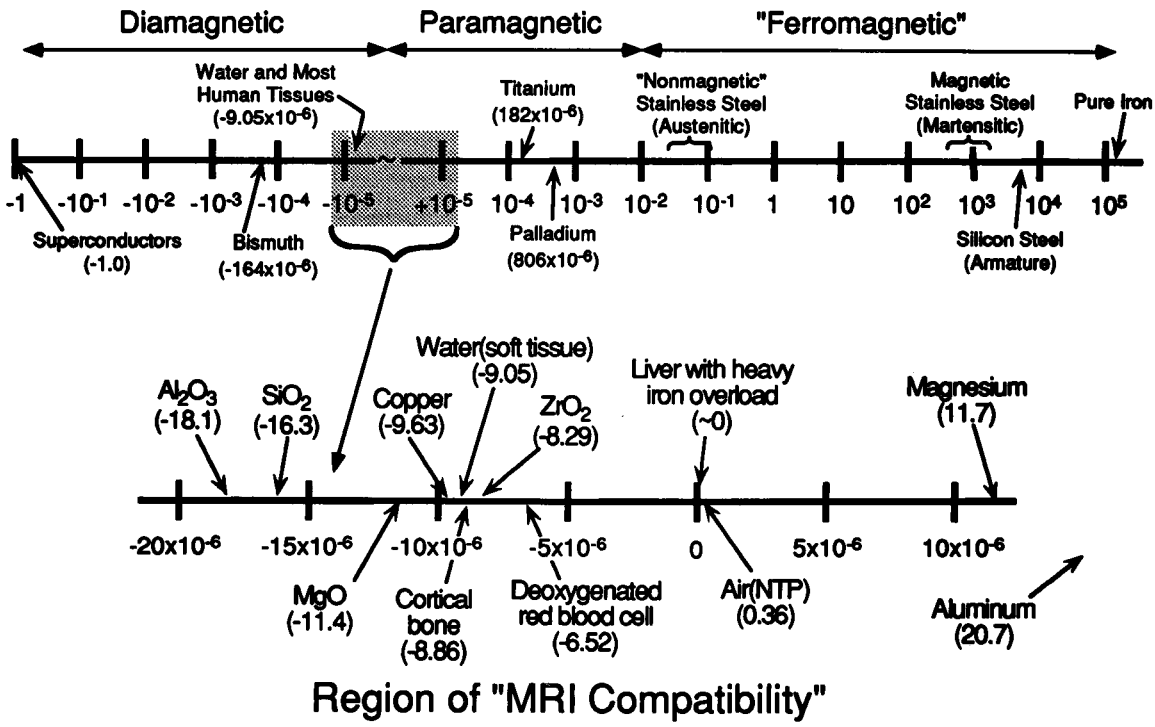

Figure 2. Spectrum of magnetic susceptibilities. The upper diagram uses a logarithmic scale to indicate the full range of observed magnetic susceptibility values: it extends from $\chi = -1.0$ for superconductors to $\chi > 100{,}000$ for soft ferromagnetic materials. The bottom diagram uses a linear scale (in ppm) to indicate the properties of some materials with $|\chi| < 20$ ppm. The susceptibilities of most human tissues are in the range from -7.0 to -11.0 ppm. (from Reference 80, with permission).

Magnetic Field Energy

When an object such as a human body, a red blood cell, or an aneurysm clip is placed in a magnetic field, it experiences forces that cause it to tend to move relative to the field and torques that tend to rotate it with respect to the direction of the field. These forces and torques depend on the nature of the material and the strength of the field and can range from absolutely negligible to potentially lethal values. To understand whether these forces and torques will be at a significant level in a given situation, it is necessary to have mathematical expressions that can be used to calculate them.

Once a magnetic potential energy function, U, is available to relate the magnetic energy of the object to its location, orientation, and material properties, standard techniques of physics (virtual work) can be used to generate the necessary expressions for the forces and torques. The dipole moment is the integral of the magnetization, $\mathbf{M}$, over the volume, V, of the object. If the magnetization is uniform over the object, $\mathbf{m} = \mathbf{M}\,V$. If a material with a permanent dipole moment $\mathbf{m}$ is brought to a point P within a magnetic field, it acquires an energy $U = \mathbf{m} \cdot \mathbf{B}_0$. If an object that has a magnetic moment proportional to the applied field is brought to P and thereby acquires an induced moment, $\mathbf{m}$, its energy is $U = \frac{1}{2}\mathbf{m} \cdot \mathbf{B}_0$. In both cases, $\mathbf{B}_0$ is the field existing at P prior to the introduction of the material, and it is assumed that the sources of this field are kept constant when the material is introduced into the field. The factor 1/2 accounts for the fact that, in the second case, as the material is brought into the magnetic field, its moment gradually increases from zero to $\mathbf{m}$, rather than being at the value $\mathbf{m}$ along the entire path.

Thus the magnetic energy is determined by the strength of the dipole moment, the strength of the magnetic field, and the angle between these two vector quantities (131–134). The magnetic field exerts forces and torques on the object that have the effect of increasing the magnetic energy. As shown below, the effect of the forces is to attract paramagnetic materials toward regions of stronger field strength and to push diamagnetic materials toward regions of weaker field strength. The effects of the torques are to turn the object such that $\mathbf{m}$ is brought into alignment with $\mathbf{B}_0$.

Writing $\mathbf{F}$ for the force and $\mathbf{T}$ for the torque we have

$$\mathbf{F} = \nabla U \text{ and } \mathbf{T} = \frac{\partial U}{\partial \theta}\,\mathbf{u} = \mathbf{M} \times \mathbf{B}_o,$$

where θ is the angle between $\mathbf{M}$ and $\mathbf{B}$ and $\mathbf{u}$ is the unit vector perpendicular to the plane of $\mathbf{M}$ and $\mathbf{B}$.

In many texts (eg, ref. 133), the expressions above for U, $\mathbf{F}$, and $\mathbf{T}$ all have a minus sign in front of the term on the right-hand side of the equation, that is, the definitions are $U = -\mathbf{m}\cdot\mathbf{B}_o$, $\mathbf{F} = -\nabla U$ and $\mathbf{T} = -\frac{\partial U}{\partial \theta}\,\mathbf{u}$. This sign is determined by whether or not the energy required to maintain the magnetic field at a constant level as the dipole is moved is included in the definition

of the magnetic potential energy (131–133). The choice of this convention does not affect the final formulas for the force and torque on the dipole. If an object has volume V and susceptibility χ,

$$\mathbf{m} = \mathbf{M}V = \chi V\mathbf{H}_o = \frac{\chi}{\mu_o} V\mathbf{B}_o$$

and

$$U = \tfrac{1}{2}\,\mathbf{M}\cdot\mathbf{B}_o = \frac{\chi V}{2\mu_o} B_o^2.$$

This formula assumes that the absolute value of the susceptibility is much less than 1 and that the particle is sufficiently small that B_0 does not change significantly over it.

Demagnetizing Factors

To make use of the formulas for the force and torque on materials that do not have a fixed dipole moment but that instead have a magnetization induced by the applied field, it is necessary to determine the field-induced dipole moment. In general this is a complicated process, but it can be simplified in the case of ellipsoids and the results for ellipsoids, such as spheres, plates, and cylinders, can be used in many cases to get an adequate idea of the behavior of less symmetric objects. If a field is applied along a principal axes of an ellipsoid and the susceptibility is isotropic, the induced internal field is parallel to the applied field and is given by $\mathbf{H}_{dm} = -D\mathbf{M}$ where D, the demagnetizing factor, is a shape-dependent number with a value between 0 and 1 (80,130). A general ellipsoid has three distinct principal axes, and the sum of the three demagnetizing factors is always equal to one: the three principal axes of a sphere are equivalent and, therefore, the demagnetizing factor for any direction must be 1/3. For cylinders transverse to the applied field, $D = 1/2$; and for long cylinders parallel to this field, $D = 0$. The total internal field $\mathbf{H}$ is uniform and is the sum of the applied field, $\mathbf{H}_0 = \mathbf{B}_{0/\mu_0}$, and the demagnetizing field, $\mathbf{H}_{dm}$. Using $\mathbf{M} = \chi\,\mathbf{H}$ and $\mathbf{B} = \mu_0\,(\mathbf{H} + \mathbf{M})$, the total internal fields are given in terms of the applied field $\mathbf{B}_0$ by

$$\mathbf{B} = \mathbf{B}_o(1 + \chi)/(1 + D\chi),$$

$$\mu_o\mathbf{H} = \mathbf{B}_o/(1 + D\chi), \text{ and}$$

$$\mu_o\mathbf{M} = \mathbf{B}_o\chi/(1 + D\chi).$$

Here it is assumed that $\mathbf{B}_0$ is in the direction of one of the principal axes and D is the demagnetizing factor for that axis. If $\mathbf{B}_0$ is not along a principal axis, it may be resolved into components along these axes and the resulting fields summed to get the total fields. An examination of these formulas shows how the shape of an object (acting through D) and the magnetic properties (acting through χ) interact with $\mathbf{B}_0$ to establish the magnetic response of the object to an applied field. A general ellipsoid has three independent principal axes and three different demagnetizing factors, but it is simpler and often sufficient to consider only ellipsoids of revolution: they have two equivalent principal axes and, therefore, two of the demagnetizing factors are equal.

These equations show that to first order for strongly magnetic materials, with $\chi >> 1$, the internal $\mathbf{B}$ field and the magnetization are *independent of the susceptibility* and are determined only by the shape of the object. Conversely, for $|\chi| << 1$, $\mathbf{M}$ is parallel to the applied field, is equal to $\chi\ \mathbf{B}_0/\mu_0$, and is *independent of the shape of the ellipsoid.* An immediate consequence is that the forces and torques experienced by a ferromagnetic object in a magnetic field depend crucially on the object's shape, while the forces and torques on a biological object with a very small susceptibility are essentially independent of the object's shape.

Comparison Risks from Translational Forces and Torques

Table 3 provides a summary of the expressions for the magnetic energy, force, and torque that act on ellipsoids of revolution and emphasizes how the limiting forms of these expression for large and small values of the susceptibility predict qualitatively differing behavior in these two cases.The demagnetizing factor along the axis of symmetry is D_a, and the radial demagnetizing factor is D_r. Therefore $D_a + 2\ D_r = 1$. For a long, needle-like ellipsoid, $D_a \to 0$ and $D_r \to ½$. For a sphere, $D_a = D_r = 1/3$. For a flat, disk-like ellipsoid, $D_a \to 1$ and $D_r \to 0$. Expressions for demagnetizing factors for the full range of ellipsoids of revolution are given in ref. 80. The applied field and the axis of symmetry are in the x,z plane and the angle between them is θ. A patient with an implanted magnetic object, such as a surgical clip, is at risk from both the tendency of the object to move into the magnetic field as a result of translational forces and the tendency of the object to twist into alignment with the magnetic field. The relative strength of these two effects depends on the shape and susceptibility of the object and on its position in the field of the magnet.

It will now be shown that in many situations the torque represents a greater hazard than the translational force. To simplify the analysis, regions near the central axis of a cylindrical magnet are considered. If the object is spherically symmetric only translational forces are present as the induced magnetization is parallel to the applied field, and there is no torque and no tendency for the it to rotate. However, if the object is long and slender, ie, needle-like, or thin and flat, ie, plate-like, very substantial torques may be encountered. Needle-shaped objects will tend to turn their long axis parallel to the field direction, and plate-like objects will tend to turn their flat surfaces parallel to the field lines.

For a needle-like object ($D_a << D_{ra}$) located on the z-axis of the magnet, the maximum translational force will with the needle aligned with the field ($\theta = 0$) and at the z-location where the product $B_z\frac{\partial B_z}{\partial z}$

Table 3
Magnetic Properties of Ellipsoids of Revolution

	Full Expression	Soft Magnetic Materials $\chi D_a, \chi D_r \gg 1$	"Non-Magnetic" Materials $\lvert\chi\rvert \ll 1$
U	$\frac{\chi V B_o^2}{2\mu_o}\left[\frac{\cos^2\theta}{1+\chi D_a} + \frac{\sin^2\theta}{1+\chi D_r}\right]$	$\frac{V B_o^2}{2\mu_o}\left[\frac{\cos^2\theta}{D_a} + \frac{\sin^2\theta}{D_r}\right]$	$\frac{\chi V B_o^2}{2\mu_o}$
F_z	$\frac{\chi V}{\mu_o} B_o \frac{\partial B_o}{\partial z}\left[\frac{\cos^2\theta}{1+\chi D_a} + \frac{\sin^2\theta}{1+\chi D_r}\right]$	$\frac{V}{\mu_o} B_o \frac{\partial B_o}{\partial z}\left[\frac{\cos^2\theta}{D_a} + \frac{\sin^2\theta}{D_r}\right]$	$\frac{\chi V}{\mu_o} B_o \frac{\partial B_o}{\partial z}$
M_x	$\frac{\chi B_o}{\mu_o}\left[\frac{D_r - D_a}{(1+\chi D_a)(1+\chi D_r)}\right]\cos\theta \sin\theta$	$\frac{B_o}{\mu_o}\frac{D_r - D_a}{D_a D_r}\cos\theta \sin\theta$	$\frac{\chi^2 B_o}{\mu_o}(D_r - D_a)\cos\theta \sin\theta$
M_z	$\frac{\chi B_o}{\mu_o}\left[\frac{\cos^2\theta}{1+\chi D_a} + \frac{\sin\theta}{1+\chi D_r}\right]$	$\frac{B_o}{\mu_o}\left[\frac{\cos^2\theta}{D_a} + \frac{\sin^2\theta}{D_r}\right]$	$\frac{\chi B_o}{\mu_o}$
T_y	$\frac{\chi^2 V B_0^2}{\mu_o}\left[\frac{D_a - D_r}{(1+\chi D_a)(1+\chi D_r)}\right]\cos\theta \sin\theta$	$\frac{V B_o^2}{\mu_o}\frac{D_a - D_r}{D_a D_r}\cos\theta \sin\theta$	$\frac{\chi^2 V B_o^2}{\mu_o}(D_a - D_r)\cos\theta \sin\theta$

The first column gives the complete expression for the magnetic potential energy (U), force (F_z), magnetization (M_x and M_z) and torque (Ty) for an ellipsoid of revolution in a magnetic magnetic field along the z-axis. The symmetry axis is in the x-direction and θ is the angle between this axis and the magnetic field. The second column gives approximations appropriate for soft magnetic materials and the third column gives approximations appropriate to materials, such as biological tissues, with very small susceptibilities. For objects inside a medium of uniform susceptibility, such as water or tissue with $\chi = \chi_{H_2O}$, χ should be replaced by $\Delta\chi = \chi - \chi_{H_2O}$. It is assumed that B_z is the only non-zero component of $\mathbf{B}_o$ at the location of the object and that the spatial derivatives of the transverse components, $\frac{\partial B_x}{\partial x}$, $\frac{\partial B_y}{\partial x}$, etc. are all zero. This is the case along the central axis of the magnets commonly used in MRI. At other points in the field there may be non-zero force components in addition to F_z, but the qualitative physical principles are unchanged.

is at a maximum. Note that near the center of imaging, magnets the field is constant (although large) and $\frac{\partial B_z}{\partial z}$ meaning that there is no translational force, even on strongly magnetic objects, in this location. The function $B_z\frac{\partial B_z}{\partial z}$ is therefore zero both well outside the magnet and near its center. This product goes through a maximum near the opening to the bore for most magnets, and at this location the attractive translational force will be at its maximum. This maximum will tend to be stronger and more localized for unshielded than for shielded magnets. The maximum translational force for a needle-like object on the magnet's axis is

$$F_{trans}^{\max} = \frac{V}{\mu_o D_a}\left[B_z\frac{\partial B_z}{\partial z}\right]_{\max}.$$

We define the F_{torque} as the strength of the force couple applied to either end of the symmetry axis that would be required to prevent the ellipsoid from turning into alignment with $\mathbf{B}_0$. Along the z-axis the maximum torque will occur at the center of the magnet and for $\theta = \pi/4$. Taking the total length of the ellipsoid as 2 L and using absolute values for the force

$$F_{torque}^{\max} \approx \frac{V}{2\mu_o L D_a} B_z^2|_{\max}. \text{ Then}$$

$$\frac{F_{torque}^{\max}}{F_{trans}^{\max}} = \frac{1}{2L} B_z^2|_{\max} \Big/ \left[B_z\frac{\partial B_z}{\partial z}\right]_{\max}.$$

For one unshielded magnet where these values have been published (76), $B_z^{\max}$=4T and $\left[B_z\frac{\partial B_z}{\partial z}\right]_{\max}$ =8.8 T^2/m. For most superconducting cylindrical magnets, whatever their field strength, it is expected that the ratio

$$B_z^2|_{\max} \Big/ \left[B_z\frac{\partial B_z}{\partial z}\right]_{\max}$$

will be approximately of the same order of magnitude, 1.8/m, as in the current case. However, this ratio will be smaller in shielded magnets. In the current example, if L = 1 cm = 0.01 m,

$$\frac{F_{torque}^{\max}}{F_{trans}^{\max}} = 90.$$

This calculation illustrates the important fact that for nonspherical magnetic implants the body tissues may be required to exert substantially more force to prevent them from twisting in place than is required to prevent them from undergoing translational motion. Therefore, an implant such as an aneurysm clip that is substantially longer than its width is much more likely to injure a patient by twisting than by undergoing translational motion. This can be readily verified by carefully moving a paper clip or similar small magnetic test structure around in the bore of a magnet. A relatively mild attractive translational force will be found and it will be a maximum near the opening into the scanner. It will vanish well inside the magnet near the region of imaging. A much stronger force will be required to twist the paper clip out of alignment with the field. This torque will be greatest near the magnet center and for the axis of the paper clip at 45° to the z-axis. To avoid the possibility of injury, of course, care should be taken not to lose control of the paper clip, and this experiment

should not be attempted with anyone inside the bore of the scanner.

An interesting result in Table 3 is that the torque on a object, such as a tissue component, with $|\chi| << 1$ is proportioal to χ^2. It is sometimes thought that diamagnetic and paramagnetic materials tend to line up differently in a uniform magnetic field. This result shows that the alignment torque is independent of the sign of χ and that both types of materials tend to align with the long axis parallel to the field. More importantly, however, this also shows that for very small values of χ. this shape-dependent alignment tendency is negligibly small. This is an example of how magnetic materials and materials with very low susceptibilities can exhibit qualitatively different responses to applied fields. For example, a flat plate-like magnetic object, such as a washer, has a very strong tendency to align itself with its face parallel to the field. It is sometimes said that red blood cells, which also have an approximately plate-like geometry, tend to align with their flat side parallel to the applied field. However, since $\chi^2 \simeq 10^{-10}$, for these cells the shape-dependent alignment torque is completely negligible.

Torque Caused by Anisotropic Susceptibility

It has just been shown that the shape-dependent torque on biological materials is negligible because of the presence of a χ^2 factor in the expression for the torque. However, another source of field-dependent has been observed on several occasions in biological samples and can be explained by anisotropic susceptibility. This is normally observed when a cluster of macromolecules or cells are bound together in a crystalline or quasi-crystalline structure so that they all present the same orientation to the applied magnetic field. In this way the torques on individual elements are summed over all the molecules or cells in a volume *V*. Suppose that the susceptibility in one direction in this volume is χ_1 and that the angle between this direction and the applied field is θ. Also assume that, for simplicity, in both orthogonal directions the susceptibility is χ_2 and that $|\chi_1|, |\chi_2| << 1$. Then the magnetic energy is given by

$$U = \tfrac{1}{2} V \mathbf{M} \cdot \mathbf{B}_o = \frac{V B_o^2}{2\mu_o} [\chi_1 \cos^2\theta + \chi_2 \sin^2\theta]$$

and the torque is given by

$$T = \frac{\partial U}{\partial \theta} = \frac{V B_o^2}{\mu_o} (\chi_2 - \chi_1) \sin\,\theta\,\cos\,\theta.$$

Normally, for biological materials, both χ_1 and χ_2 will be negative and of the order of -10^{-5}. The object will try to orient itself such that the axis with the least negative value of χ is aligned with the field. It is found that the magnitude of $\Delta\chi = \chi_1 - \chi_2$ can can be on the order of 1%–10% of the average susceptibility, $(\chi_1 + 2\,\chi_2)/3$, or in the range of 10^{-7} to 10^{-6}. This factor is much larger than the factor 10^{-10} calculated above for the shape-dependent torque. This is one reason why anisotropy-dependent torques have been demonstrated in biological materials while shape-dependent torques have not. Also important in the above expression for the torque is the volume, *V*. This factor shows that the torque can be enhanced by aggregating more anisotropic molecules or cells together.

Some time ago Murayama (35,36) demonstrated that the red blood cells (RBCs) of sickle cell anemia can be aligned in vitro by a field of 0.5 T. The explanation for this is that the hemoglobin molecules in normal RBCs are free in solution and randomly oriented, which leads to an isotropic susceptibility for normal cells. In sickle cell RBCs the hemoglobin S molecules tend to aggregate and polymerize to form fibers and gel-like structures with many equivalently oriented hemoglobin molecules bound together. This structure amplifies the anisotropy of the individual molecules and leads to the anisotropy-dependent orientation discovered by Murayama. Although this effect is easily demonstrated in the test tube environment, the red cells of sickle cell patients are not aligned by magnetic fields. This is because the shear forces present in flowing blood are orders of magnitude larger than is required to overwhelm the forces of magnetic orientation (51,64,67,75).

A similar orientation effect has been observed in fibrin gels, retinal rod cell preparations, and nucleic acid solutions (135–140). Again, these effects are observed *in vitro* and would probably be too small to affect the orientations of the equivalent structures *in vivo*. However, the equation above shows that the orienting torque is proportion to B_0^2 and going to ever higher field strengths may lead to an observable in vivo effect. A step in this direction has recently been reported by a group who have used a 16-T magnet to orient the cleavage planes of the developing frog embryo (141). The investigators have attributed this result to the anisotropy-dependent alignment of tubulin molecules (142). If this effect is confirmed, it may become one of the first repeatable magnetic field effects on biological tissues.

Field-Induced Alignment of Water Molecules

One argument sometimes proposed to provide a rationale for magnetotherapy is that the application of magnetic fields can cause a local alignment of water molecules that results in significant alterations in tissue biological and physiological processes. Therefore, it is of interest to determine how much alignment of water molecules can be produced in this way. In water the molecules have a random range of orientations, which leads to $\chi = -9.05 \times 10^{-6}$. The asymmetry of the water molecule leads to about a one- percent variation in χ along the principal axes of the molecule (143). The magnetic alignment energy of a water molecule may be estimated as follows. The susceptibility of water is $\chi = -9.05 \times 10^{-6}$, and the magnetization in an applied field of 1 T is

$$M = \chi H = \frac{\chi}{\mu_o} B = -\,7.2\text{A/m}.$$

There are 3.34×10^{28} water molecules per cubic meter, which gives an average dipole moment per water molecule in a 1-T field of $m = -2.16 \times 10^{-28}$ J/T. Using the 1% value for the anisotropy of the molecular magnetization gives a maximum magnetic energy change as the molecular orientation changes of $\Delta E = 2.16 \times 10^{-30}$ J. At 37°C, $kT = 4.28\ 10^{-21}$ J, which gives for an applied field of 1 T,

$$\frac{\Delta E}{kT} = 5.0 \times 10^{-10}.$$

Therefore, it would require a field approaching 450 T to achieve a deviation of 0.01% from a random orientation, and the alignment to be expected in fields of normal strength is totally negligible. This is consistent with the lack of observation of any magnetic field-induced alignment of water molecules at the field strengths currently used in MRI.

Field-Induced Translational Forces in Tissues

In a nonuniform magnetic field, those tissue components that are less diamagnetic than the average will tend to move toward the higher field regions and vice versa. It might be thought that even a very small differential force on tissue elements might disturb some delicate biological process and lead to tissue injury. It is possible to make a quantitative argument that in the normal course of events biological structures contend with much greater internal forces than are produced by susceptibility variations among the tissue components (24,77) Tissue components must have mechanisms that prevent them from being disrupted by the gravitational and acceleration forces that are continually experienced during normal activity, and these same mechanisms are expected to resist the smaller magnetic forces.

The approach is to show that even under extreme conditions in a very high field magnet, the differential magnetic forces are much smaller than the differential gravitational forces, which are themselves too small to have physiological consequences. The RBCs in blood are again used as an example. These cells are slightly denser than the surrounding plasma and therefore continually tend to sink in it. This phenomenon taking place in a test tube is the basis of the erythrocyte sedimentation rate (ESR) study, which is a well-known test for blood protein abnormalities. This gravitational separation is very slow, however, and in the body this tendency for blood cells to sink is completely overwhelmed by the hemodynamic forces present in flowing blood. The presence of iron atoms in hemoglobin makes the red blood cells slightly less diamagnetic than plasma; as a result, RBCs have a tendency to move relative to the plasma toward regions of strong magnetic fields. From Table 3 this force is seen to be

$$\frac{(\chi_{rbc} - \chi_{plasma}) V_{rbc}}{\mu_o} B_o \frac{\partial B_o}{\partial z}.$$

In an unusually strong (4 T) clinical imaging magnet the maximum value of

$$B_o \frac{\partial B_o}{\partial z}$$

is about 8.8 T^2/m, Accounting for the four paramagnetic iron atoms per molecule of deoxygenated hemoglobin gives a $\chi_{RBC} = -6.53 \times 10^{-6}$, and the susceptibilty of plasma is taken equal to that of water, or -9.05×10^{-6}. The mass density differences that lead to the ESR are given by $\rho_{RBC} = 1.093$ g/cc and $\rho_{plasma} = 1.027$ g/cc. The ratio of the magnetic and gravitational forces is given by

$$\frac{F_m}{F_g} = \frac{1}{\mu_o g} B_o \frac{\partial B_o}{\partial z} \frac{\chi_{rbc} - \chi_{plasma}}{\rho_{rbc} - \rho_{plasma}} = 0.027$$

where $g = 9.8$ m/s^2 is the acceleration of gravity. Even in this case with an unusually strong magnetic field, the maximum magnetic force tending to separate the RBCs from the plasma is less than 3% of the gravitational forces and these, themselves, have negligible effects in living organisms. Although many magnetic effects on tissue are not precisely zero, they are very small in comparison with other familiar stresses that are easily resisted by the cohesive and stabilizing forces present in tissues.

SENSORY EFFECTS IN MAGNETIC FIELDS

Mild, low level sensory effects associated with motion in strong magnetic fields (eg, refs. 34, 38, 70, and 76). The reports are transient and not harmful. Care must be taken in assessing these reports because of the subjective nature and the low level of the observed effects. It has been shown that reports of field-induced sensory effects in the vicinity of superconducting magnets can be elicited even when the magnets are turned off (79). However, when efforts have been made to distinguish between the responses of subjects exposed to 1.5 and 4 T, a higher incidence of positive reports has originated from those subjected to the 4-T field (76). This finding supports the concept of field-dependent sensory effects. Statistically significant ($P < 0.05$) evidence was found for sensations of nausea, vertigo, and metallic taste at the 4-T field strength. Statistically significant evidence was not found for other effects such as headache, tinnitus, hiccuping, vomiting, and numbness that have sometimes been attributed to magnetic field exposure.

At 4 T evidence was also found for magnetophosphenes which are sensations of brief flashing lights when the eyes are moved rapidly while in the field. The observation of this effect required the room to be darkened (76). Each of these positive effects can be plausibly ascribed to the activation of highly sensitive sensory tissues by very weak electrical currents induced in tissues by motion of the body through the magnetic fields. Sensations of nausea are probably the result of extraneous excitation of motion sensations by weak magnetohydrodynamic forces in the semicircular canals of the

inner ear and the resulting conflict between the position sensing apparatus of the vestibular and visual systems. It is also possible that these forces could arise from a diamagnetic anisotropy of the inner ear receptors. Even mild levels of extraneous sensory effects can be disconcerting. Therefore, patient comfort at very high field strengths will be enhanced by moving patients in and out of the magnet slowly and by minimizing their motion while they are within the magnet.

REGULATORY CONSIDERATIONS

The US Food and Drug Administration (FDA) has regulated the use of MRI since the late 1970's. Similar regulatory activities have been carried out in the United Kingdom by the National Radiological Protection Board (NRPB) and in the European Union by the International Electrotechnical Commission. The regulatory positions of these three agencies are generally consistent, although they differ somewhat in detail. (144–154).

MRI became the first major imaging modality required demonstrate safety and efficacy as required by the Medical Devices Act as passed by the US Congress in 1977. During the 1980s several manufacturers sought approval to market MR scanners in the United States, and their applications were considered on a case-by-case basis. With the availability of substantial positive clinical experience, the FDA reclassified MR scanners operating below 2 T as nonsignificant risk devices in 1987. Further experience led the FDA in 1996 to designate all field strengths below 4 T as nonsignificant risk. Currently in the United States the exposure of research subjects to fields above 4 T requires the informed consent of the subjects and the approval of the research protocol by an Institutional Review Board.

OCCUPATIONAL CONSIDERATIONS

Some groups of workers may experience a more or less chronic exposure to strong magnetic fields in their working environment. These groups include researchers in experimental high energy physics and hospital technologists working with MRI. Several attempts have been made to provide regulatory guidelines for the chronic exposure of people occupationally required to work near strong magnets. These guidelines customarily take the form of limits on the integrated field exposure over the course of an 8-hour working day. An example is the time-weighted-average field exposure of 0.20 T per 8-hour day proposed by the NRPB of the United Kingdom. The use of this guideline would mean that a worker could be in a 2000-G (0.2-T) field for the entire working day or in a field of 1.6 T for 1 hour. In common with several other guidelines, the NRPB exposure guidelines permit substantially higher average field (2 T/day) if the extremities only, but not the head or trunk, are exposed to the field.

Other than injuries related to ferromagnetic forces, the literature does not contain a scientifically confirmed harmful effect of static field exposure and, therefore, it does not provide a scientific rationale to serve as a basis for designating a particular magnetic field strength as unsafe. In particular, it follows that there is no confirmed experimental evidence for any cumulative harmful effect of magnetic field exposure. A related difficulty is the rapid spatial variation of the magnetic fields typically found in workplace environments. A magnet is rated typically by the magnetic field strength at its center. However, the field falls off rapidly with distance away from the magnet and, except in unusual circumstances, the exposure of workers to environmental magnetic fields as they move about performing their responsibilities is not characterized by a single value that can be readily averaged over a period of time.

Although there are experiments and theoretical analyses to support the belief that the proposed mechanisms of tissue injury are not harmful at the field strengths currently available, the literature also does not contain extensive controlled studies demonstrating the absolute safety of prolonged magnetic field exposure. It is therefore prudent and logical to take reasonable precautions against casual and readily avoidable exposure to intense fields and to provide guidelines based on the best available information for the exposure of workers whose duties require working in the vicinity of magnetic fields. It is also important and desirable that additional data be collected and analyzed to provide improved confidence in the safety of magnetic field exposure as a function of field strength and exposure duration.

SUMMARY

Almost all of the more than 100,000,000 clinical MRI studies performed since the early 1980's were completed without any evidence of harm to the patients from the static field. The few cases of injury have been attributed to the inadvertent presence of ferromagnetic materials or cardiac pacemakers. Results on humans in fields up to 8 T and on animals up to 16 T indicate that there is a substantial margin of safety remaining above the highest fields now in clinical use in the range of 3–4 T. This safety margin, of course, is no indication that efforts should not continue to search energetically for signs of unexpected field-related health issues. In particular, there is a need for improved techniques to protect patients from injuries caused by the occult presence of ferromagnetic foreign bodies. It may be some time before whole-body MRI magnets operating above 8 T become available to study the human ability to withstand even stronger fields. However, small-bore magnets designed to permit NMR chemistry studies at frequencies approaching 1 GHz may soon be available in the range of 20–25 T, and these will no doubt be used to see whether small animals can tolerate fields of this strength (155,156).

There have been many reports of potentially harmful biological effects of magnetic fields on cells, tissues, or organisms, none of these has been thoroughly verified and firmly established as a scientific fact. Given this experience, it seems reasonable to require the replication of any experiment claiming to demonstrate a biological effect of static fields before it is accepted as the

basis of a regulatory standard. The lack of serious effects of the magnetic fields in current use on tissues is attributed to the very weak diamagnetic susceptibility of these tissues. At very high field strengths there is considerable evidence for mild sensory effects such as vertigo, metallic taste, and magnetophosphenes, but there is no evidence that these effects are at all harmful. These effects, vertigo in particular, can be reduced by moving patients slowly while they are in regions of very strong fields.

There a need for additional studies to support the belief that extended exposure to magnetic fields during interventional MRI and related activities is not harmful. Although there is no evidence for a cumulative effect of magnetic field exposure on health, further studies of the exposed populations will be helpful in establishing rational guidelines for occupational exposure to magnetic fields.

It is of interest to speculate on the physical process that will provide the ultimate upper limit on the ability of humans to withstand intense magnetic fields. Some effects, such as the field-induced alignment of water molecules, are so ineffective that they are unlikely to ever to be observed. On the other hand, as higher field strengths become available, it is likely that either flow-induced EMF or diamagnetic anisotropy will eventually become a truly limiting factor. However, it appears that substantial safety margins still exist and high-field MRI will remain a fertile area for exploration and that, with proper precautions, human subjects will safely tolerate whole-body fields considerably higher than any yet experienced.

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