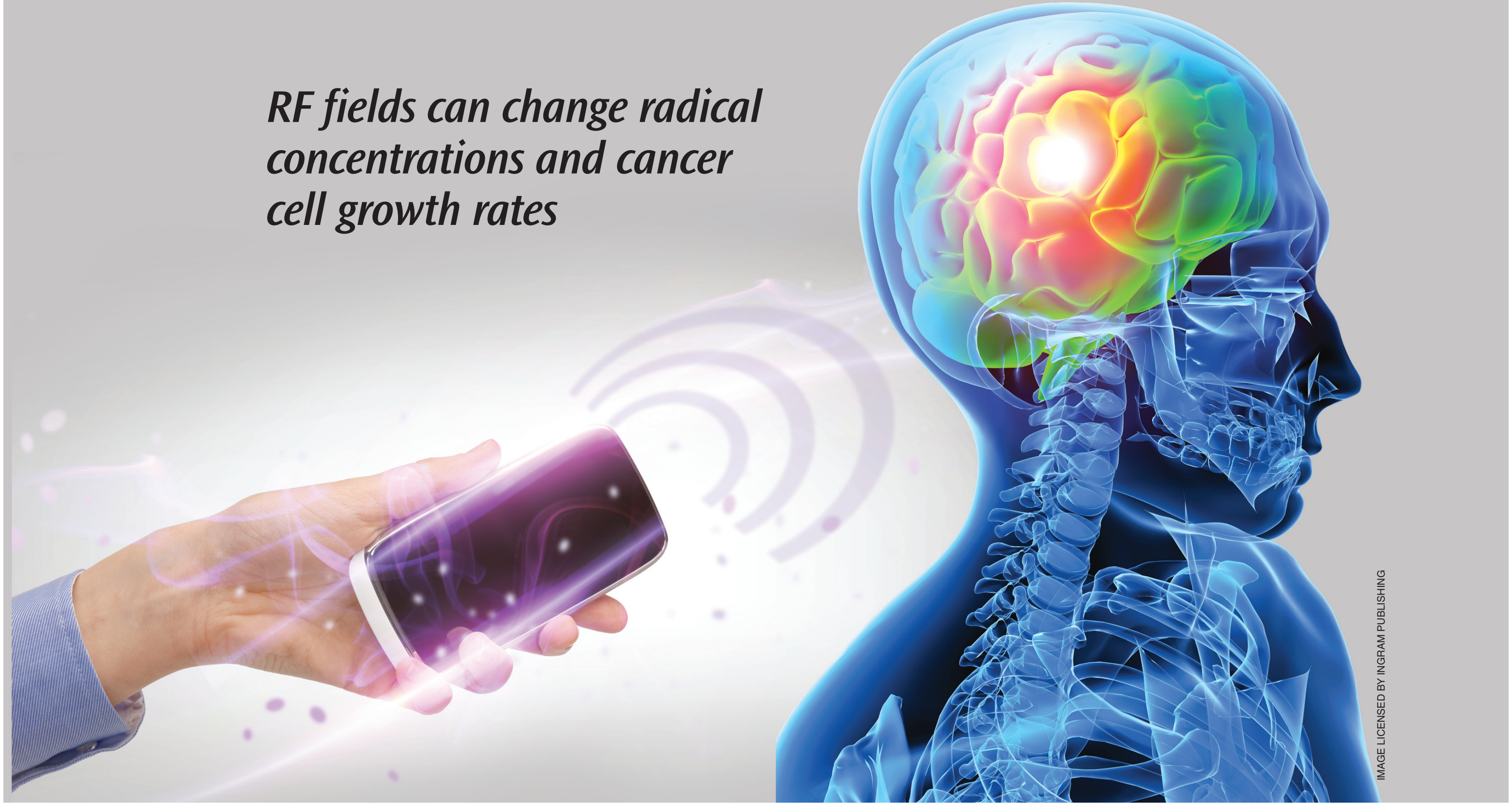
Some Effects of Weak Magnetic Fields on Biological Systems

RF fields can change radical concentrations and cancer cell growth rates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by Frank Barnes and Ben Greenebaum

Concerns have been raised about the possible biological effects of nonionizing radiation since at least the late 1950s with respect to radar, other radio, and microwave sources. More recent concerns have arisen about the potential effects of low-intensity fields, including low-frequency fields from the electric power generating, transmission, and distribution system and the devices it energizes, as well as intermediate, radio-frequency (RF), and higher-frequency radiation from devices such as cell phones, broadcast antennas, Wi-Fi, security monitors, and so forth. These are concerns about the direct effects of radiation on humans or other organisms. They are distinct from the electromagnetic compatibility issues that concern interference by the fields from one device with the function of another, though human health can be indirectly affected by electromagnetic interference with the function of medical devices, including hospital equipment or pacemakers.

Because of the difficulties in establishing the direct biological effects of long-term low-level exposures, the lack of an understood mechanism, and difficulties in obtaining reproducible results, the guidelines for exposure limits have

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been set based on relatively short-term exposures (minutes) that show clear-cut damage with the addition of a substantial safety factor. The current guidelines from the U.S. Federal Communications Commission (FCC) for limiting exposures in free space to the general public for the frequency range 100 kHz–100 GHz are given in Table 1. These guidelines are based on American National Standards Institute (ANSI) and IEEE recommendations. For cell phones, the specific absorption rate (SAR) is limited to 1.6 W/kg averaged over 1 g of tissue. These limits have been set based on providing a significant safety factor over exposure levels known to cause damage, where the primary damaging mechanism is heating and an increase in temperature. At low frequencies, the limits are based on induced current densities that would excite nerve firing, and the permissible exposures recommended by IEEE C95.6 are shown in Table 2. The International Commission on Nonionizing Radiation Protection (ICNIRP) sets electric field exposure limits at 50 Hz to 5 kV/m and magnetic flux density limits at 100 μT. It also sets guidelines for general public exposures in the frequency range 3 kHz–10 MHz at E = 83 V/m, B = 27 μT and a whole-body SAR = 0.08 W/kg, and 1.6 W/kg over 1 g.

In general, environmental exposures at any frequency do not exceed these guidelines, especially for the general public. Instances of occupational exposures approaching or exceeding the guidelines are less uncommon [1]. However, the time constants for cell growth cycles and many other growth phenomena are often hours or days. The most favored proposed mechanism for effects from low-level, long-term exposures involves radicals, such as super oxide O_2^{-*}, NO_x, and H_2O_2, which is readily converted into the radical OH^-, molecules with unpaired electron spins that are highly reactive. These molecules are both signaling molecules and molecules that can cause damage to important biological molecules, such as lipids and DNA. Damages, such as aging, cancer, and Alzheimer's, are associated with radical concentrations that are elevated for extended periods of time [2]. In this article, we present the possible theoretical mechanisms and experimental data that show long-term exposures to relatively weak static, low-frequency, and RF magnetic fields can change radical concentrations. As a consequence, a long-term exposure to fields below the guideline levels may affect biological systems and modify cell growth rates, while an organism's built-in mechanisms may compensate for these changes.

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Background

Much of the public concern dates from epidemiological studies that show small, though statistically significant increases in childhood leukemia for children living near power lines and possible increases in brain tumors for heavy use of cell phones. The early study by Wertheimer and Leeper [3] has shown an increase that was just statistically significant in childhood leukemia for children living near power lines. Of the many additional studies since then,

Table 1. The FCC limits for maximum permissible exposure (MPE).

(A) Limits for Occupational/Controlled Exposure

Frequency Range (MHz)	Electric Field Strength (H) (V/m)	Magnetic Field Strength (H) (A/m)	Power Density (S) (mW/cm^2)	Averaging Time $\|H\|^2 \cdot \|H\|^2$ or S (min)
0.3–3	614	1.63	(100)*	6
3–30	1842/f	4.89/f	$(900/f^2)$*	6
30–300	61.4	0.163	1	6
300–1,500			$f/300$	6
1,500–100,000			5	6

(B) Limits for General Population/Uncontrolled Exposure

Frequency Range (MHz)	Electric Field Strength (H) (V/m)	Magnetic Field Strength (H) (A/m)	Power Density (S) (mW/cm^2)	Averaging Time $\|H\|^2 \cdot \|H\|^2$ or S (min)
0.3–1.34	614	1.63	(100)*	30
1.34–30	824/f	2.19/f	$(180/f^2)$*	30
30–300	27.5	0.073	0.2	30
300–1,500			$f/1{,}500$	30
1,500–100,000			1	30

f = Frequency in MHz

*Plane-wave equivalent power density

Source: OET Bulletin 56, 4th edition, 08/1999, FCC

Table 2. IEEE C95.6 environmental electric field MPEs, whole body exposure.

General Public		Controlled Environment	
Frequency Range (Hz)	*E*–rms* (V/m)	Frequency Range (Hz)	*E*–rms* (V/m)
1–368 [c]	5,000 [a,d]	1–272	20,000 [b,e]

[a] Within power line rights of way, the MPE for the general public is 10 kV/m under normal load conditions.

[b] Painful discharges are readily encountered at 20 kV/m and are possible at 5–10 kV/m without protective measures.

[c] Limits below 1 Hz are not less than those specified at 1 Hz.

[d] At 5 kV/m induced spark discharges will be painful to approximately 70% of adults (well-insulated individual touching ground).

[e] The limit of 20,000 V/m may be exceeded in the controlled environment when a worker is not within reach of a grounded conducting object. A specific limit is not provided in this standard.

*rms = root mean square

about half show small correlations with proximity to power lines and/or weak magnetic fields, and about half do not [4]. However, the possibility that there may be a cause and effect for a long-term exposure to low levels of low-frequency electromagnetic fields has led to the classification by the International Agency for Research on Cancer (IARC), an agency of the World Health Organization (WHO), as a possible cause of cancer. However, this classification has not been included in the International Committee on Electromagnetic Safety or ICNIRP reference levels because of conflicting results and a lack of physical mechanisms by which weak magnetic fields could be expected to modify biological systems. The IARC has published an extensive review of the research epidemiological and laboratory research used in its determination concerning cancer [5]; the WHO has previously published a similar monograph concerning low-frequency field effects and various diseases, including cancer [6].

Although the earliest questions about exposure to high-frequency fields predate the concerns arising from power frequencies, these were generally related to higher-intensity exposures of military personnel or industrial workers. Concerns about more widespread exposures of the general public arose with the advent of the cell phone. Similar to the situation with power frequency fields, there have been many epidemiological studies on RF exposures and, particularly, cell phone use [7]. Among the largest of these is the Interphone study [8]. There have been many challenges to interpretations of the results of this study that no increase in risk of glioma or meningioma was observed with the use of mobile phones. Another view is that the data definitely show an increased risk of brain cancers for individuals with long-term, heavy cell phone use. This report also shows a slightly reduced incidence of cancers for light users. Many challenges to the various conclusions are associated with possible selection bias and the accuracy of the exposure data. Roosli [9] provides detailed discussions of the weaknesses of many epidemiology studies. However, the net result of a review of many epidemiology studies is that there is epidemiological evidence for an association of small increases in cancer rates with long-term exposures to magnetic fields, and the IARC has also classified RF exposure as a possible carcinogen. It has also published a volume summarizing the epidemiological and laboratory RF research related to this finding [10]. The WHO published a 1993 monograph on RF exposure effects and disease [11] and is expected to publish a revision in the near future.

While public concern about the field effects is primarily about adverse health effects, there is also considerable interest in the potential of using either low- or high-frequency fields beneficially. At present, medical uses of electromagnetic fields involve relatively high intensities. For example, RF fields are used for their heating effect in diathermy and ablation of tissues, and pulsed lower-frequency magnetic fields have entered medical practice to encourage healing of recalcitrant bone fractures. A long-term goal of research in this area is to find reliable field effects at lower levels that could be used as noninvasive diagnostic or treatment tools or as research probes of underlying biological processes.

It has long been known that magnetic fields can change chemical reaction rates and radical concentrations. Most of these studies were done with relatively large magnetic fields, 1 mT or greater. Reviews of much of this work have been done by Grissom [12] and Steiner and Ulrich [13]. These reviews show that both changes in nuclear spin states and changes in the angular momentum for electrons in a molecule occur with variations in the magnetic field and affect chemical reaction rates. Some of the earliest work on the effects of nuclear polarizations states on chemical reaction rates of alkyl radicals is described in [14]. This work is followed by numerous papers showing the effects of nuclear polarization and nuclear spin states on chemical reaction rates, including Kaptein [15], Charlton and Bargon [16], Den Hollander et al. [17], and Buchachenko [18]. Woodward et al. [19], among others, find many RF absorption spectra lines in the range 1–160 MHz. Reviews of dynamic spin chemistry by Nagakura et al. [20] and by Hayashi [21] present detailed descriptions of the theory for the conversion of singlet to triplet states for radical pairs and the resulting changes in radical concentrations as a function of magnetic field strength, orientation, and the viscosity of the medium.

Radicals perform a wide variety of biological functions. Reactive oxygen species (ROS), such as super oxide, O_2^{-*}, and nitrogen species, such as NO_x, are used both as signaling molecules and to attack bacteria and other pathogens. O_2^{-*} is released by neutrophils to as part of the immune systems response in killing bacteria. NO can activate guanylate cyclase, which results in a rise in cyclic guanosine monophosphate in smooth muscle tissue and vasorelaxation. It is also involved in the activation of macrophages [22]. In addition, the

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ion-radical mechanism for the phosphorylation of a very large number of biological molecules is affected by magnetic fields, and phosphorylation is an important step in many biological signaling systems and the activation of biological processes [23].

Our work in this area was triggered by the observation that reducing the Earth's magnetic field to less than 1 μT inhibited the growth of fibrosarcoma HT1080 cells [24] and the theoretical and experimental work by Batchelor et al. [25]. Data from one such experiment involving radicals are shown in Figure 1, and additional work is summarized by Brocklehurst and McLauchlan [26].

A peak value for the concentration of the radical near the Earth's magnetic field with a magnetic flux density range below 1 mT is shown in Figure 1. This result, along with the results given in Figure 2 from [19], shows a large number of resonances in the radical spectra throughout the RF spectrum, provides the theoretical bases by which weak magnetic fields can change radial concentrations.

It is clear from these results that changes in magnetic fields on the order of tens of microtesla can change the concentrations of radicals. We have elaborated on these results to show that one can expect to change radical concentration when magnetic fields are applied at frequencies corresponding to resonances and at level crossings [27]–[29]. Some of these resonances may have narrow line widths corresponding changes in nuclear spin states [30]. In addition, as the static magnetic field (SMF) is varied in

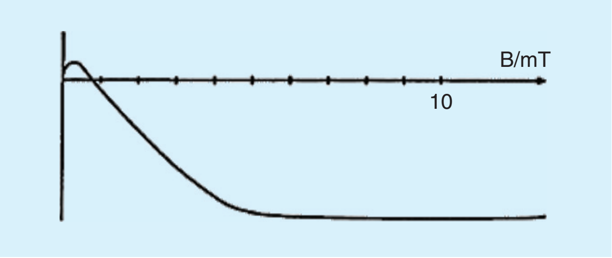

FIG 1 A schematic representation of the experimentally observed field effect in the pyrene/1,3-dicyanobenzene system. At the lowest low-field values, including that of the geomagnetic field, the effect of the field is to increase the proportion of radicals, which survives the geminate period and diffuses into the surroundings, but at high field, the reverse happens. The schematic presentation is used, since the actual published results measured the derivative of the curve, and to display them would introduce an unnecessary complication [25].

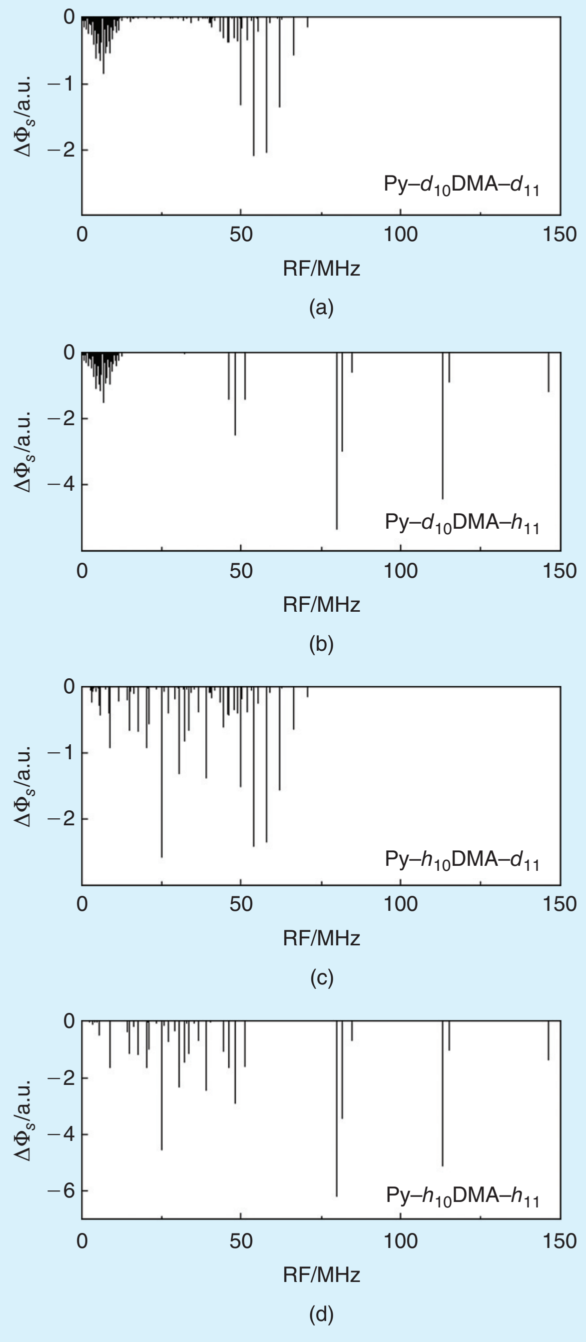

FIG 2 (a)–(d) The RF spectra for pyrene^{+}-N,N-dimethylaniline^{++}(DMA^{++}) [19].

intensity and as the angle between the static and ac magnetic field changes, the recombination rates between the fragments of a radical pair will change [30]. More recent work shows a quantum limit for the detection of weak magnetic fields by changes in chemical reactions using radicals to be on the order of tens of nanotesla [31].

Hypothesis

The proposed hypothesis, which is based on extensive work by others, e.g., [2], [18], [19], [26], and, extended by some of our own [27], is that weak magnetic fields change the rate of recombination for radical pairs that are generated by the metabolic activity in cells, which, in turn, change the concentration of radicals such as O_2^{-*} and molecules such as H_2O_2. Most of the time, the signaling properties of these molecules generate antioxidants and other radical scavengers so that damaging health effects are not seen, and, in some cases, positive effects, such as the activation of the immune system, may be observed. However, long-term exposure to elevated magnetic fields can lead to elevated radical concentrations and an association with aging, cancers, and Alzheimer's. This hypothesis is supported by some theoretical and experimental results. However, because biological systems contain a lot of feedback, feedforward, and repair processes, changes in radical concentrations will often have no observable effects. There is much work that needs to be done to illuminate the conditions in which magnetic fields can lead to either positive health effects or negative health effects, and observable effects may only occur when the exposures are combined with other biological stresses.

Some Theoretical Observations

Radicals are created during many biological reactions, including the metabolic processes in mitochondria. Figure 3 shows a schematic for the formation of a radical pair in either a singlet (S) state, where the spins are aligned with electron spins with opposite spins, or a triplet (T) state, with the spins parallel.

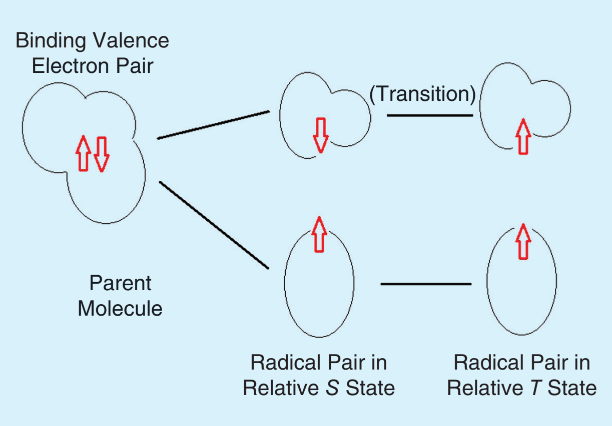

FIG 3 The vector representations of the components of the electron spin, electron angular momentum, and the nuclear spin with respect to the applied magnetic field.

In the singlet state, these pairs recombine with typical lifetimes between 10^{-6} and 10^{-10} s. In the triplet state, they are not allowed to recombine, and the opportunity for them to diffuse away increases so that they can react with other molecules. The coupling between the unpaired electrons and the nuclei in each fragment of the radical pair is different and, typically, can be described by magnetic fields in the range 10 μT–3 mT [26]. For many radicals, this is stronger than the Earth's magnetic field flux density of about 50 μT so that the quantum numbers describing the state of each fragment are determined by the sum F of the electron angular momentum and electron spin J and the nuclear spin I (see Figure 4).

The unpaired electrons in the outer orbit of each of the radical pair fragments can be thought of as rotating about their nuclei at different rates, so the net magnetic

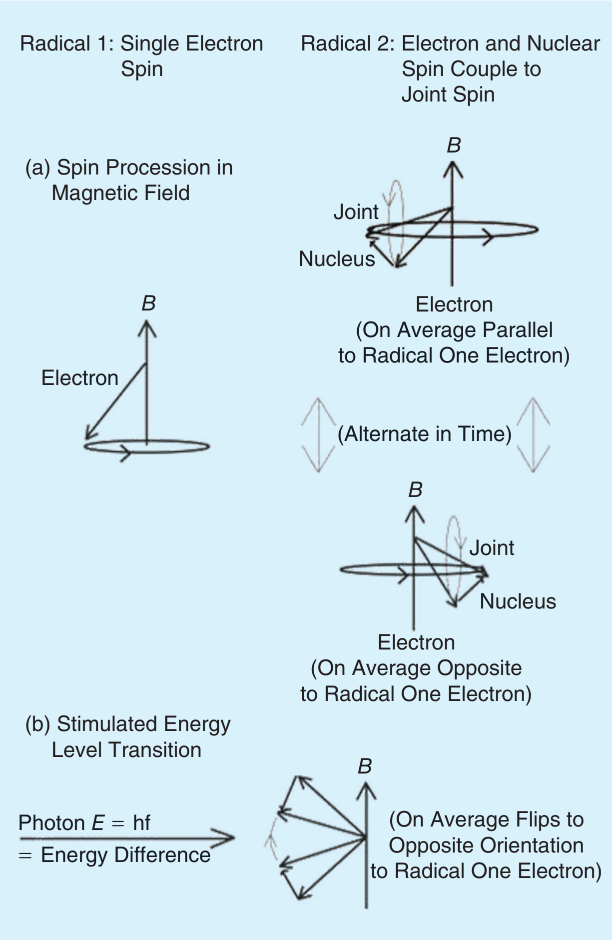

FIG 4 A schematic diagram of evolution of spins of two members of a radical pair, one with only an electron spin and the other with both an electron and a nonzero nuclear spin, illustrating changes between relative *S* and *T* states under two sets of conditions. (a) Precession of spins in an external magnetic field. (b) Stimulated transition by absorption of photon of energy corresponding to energy difference between levels in one radical. A photon must also carry angular momentum corresponding to the difference between levels.

moments for the two fragments switch from an S to a T state and back [26]. The rate at which this happens is perturbed by the external magnetic field. The energy levels in each fragment are shifted by different amounts by the external magnetic fields [see Figure 4(a)].

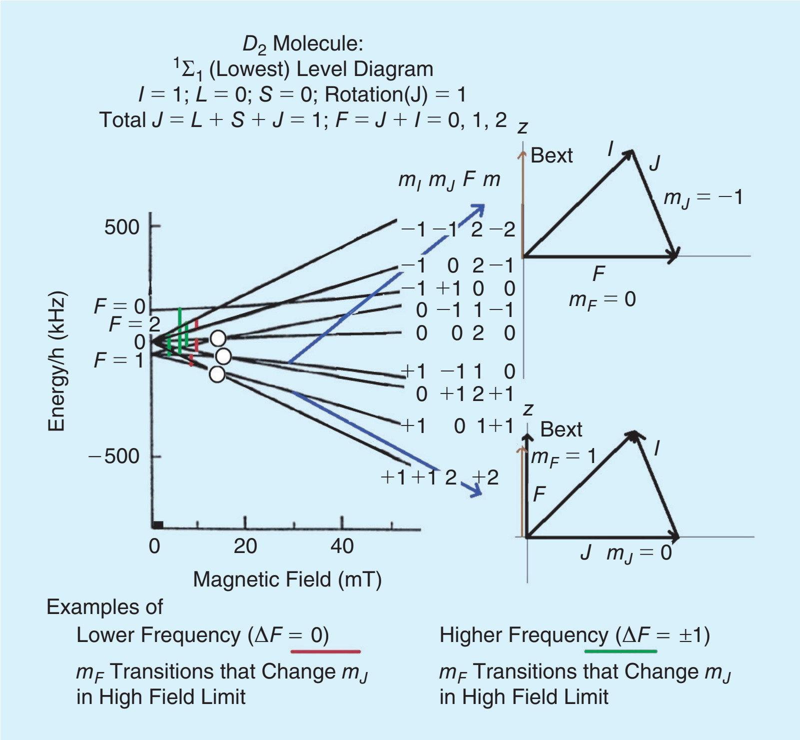

FIG 5 The energies of D_2 molecule states as a function of magnetic field with low field (F, m) and high field (J, m_J, I, m_I). Quantum number labels m_J and m_I are the projections of the electron angular moment and nuclear spin on the external magnetic fields. Note the linearity of curves in low-field region, where $F = J + I$ is a good quantum number, and curvature as well as crossovers as field increases (after Ramsey [29]). Vertical lines (left diagram) indicate allowed transitions. Relative orientations of one transition's upper and lower state angular momenta are shown (right upper and lower diagrams). In the left diagram, circles indicate the examples of possible level-crossing transition points and box on horizontal axis indicates the region of possible zero-field transitions.

Changes in the applied magnetic field shift the size of the energy barrier for the recombination and the recombination rate. Nuclear magnetic spectra may have very narrow absorption lines with bandwidths of a few cycles with corresponding lifetimes for excited states of seconds or longer. Magnetic fields at the frequency corresponding to differences in the energy levels can drive molecules between energy levels of different nuclear spin states and change the concentration in these energy levels, which, in turn, can change the recombination lifetimes for radial pairs [27], as shown in Figures 4(b) and 5. Note that these narrow line widths can lead to saturation effects with magnetic fields in the range $10^{-8} - 10^{-9}$ T [32]. With large molecules that contain many atoms with nuclear spins, the calculations of the recombination rates are very complex as the contributions to the magnetic field seen by the electron that is active is dependent on the nuclear spin of each atom, its distance from the electron, and the shielding by other electrons in different orbits. For examples, see the calculations in [19], [25], [26], [28], and [33]. For our purposes, we will assume that the sum of these fields is large enough so that coupling can lead to relatively sharp resonances, and the nuclear spin states are important in determining the recombination rates for the radical pairs. Nuclear resonance spectroscopy at radio frequencies shows that nuclear spin states may have lifetimes of seconds or longer and corresponding resonant line widths of a few cycles [30]. We postulate that, in weak magnetic fields, where the magnetic coupling between the active electrons and the nuclei in the radicals is stronger than the perturbing external field, that we will also see shifts in radical concentrations that are frequency and amplitude dependent with relatively narrow line widths [27], as shown in Figure 5. This figure also gives an explanation for effects seen when the ambient magnetic is shielded [37], for then level energy differences are below the natural line widths and spontaneous transitions can occur.

Experimental Results

The experiments that most clearly show that weak magnetic fields affect biological processes and radical concentrations are those that involve changes in the SMF. The fact that birds, salmon, and other animals can sense small changes in the Earth's magnetic field and use them for navigation says that biological systems can sense small changes in these fields. Experiments in vitro that show changes in the growth rates of cells are more relevant to potential health effects. The results in reference [24] have shown a reduction in the growth rate of *E. coli* by reducing the SMF below 18 μT. It has also been shown that we can reduce the growth rates of HT1080 fibrosarcoma cells by 20–30% by reducing the SMF to less than 1 μT, while normal fibroblast cell are reduced by less than 10%.

In addition, we have data that show that changes in magnetic field change the growth rate of cancer cells more than normal cells of the same type. Typically, the interior of a a quiescent normal cell is more negative with respect to the exterior than growing cells or cancer cells of the same type. For example, a normal fibroblast cell might have a membrane potential of −70 mV and a fibrosarcoma −30 to −35 mV [34]. Radicals have been shown to modify the channel currents of Na^+, K^+, and Ca^{++} [35]. Preliminary data on fibrosarcoma cells in our lab show both changes in oxidative stress and

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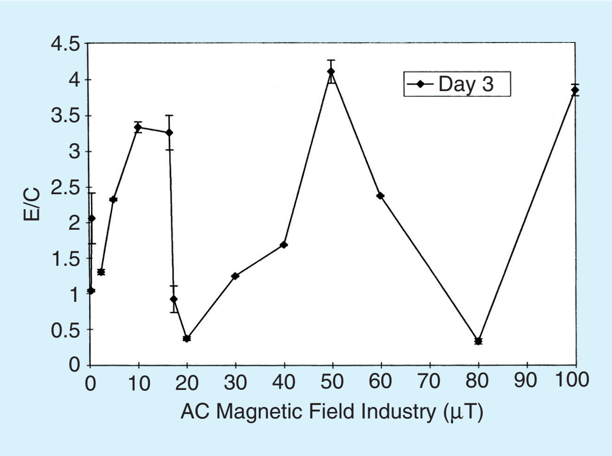

FIG 6 Normalized mastocytoma cell growth at 60 Hz and $B_{dc} = 38\ \mu T$ [38].

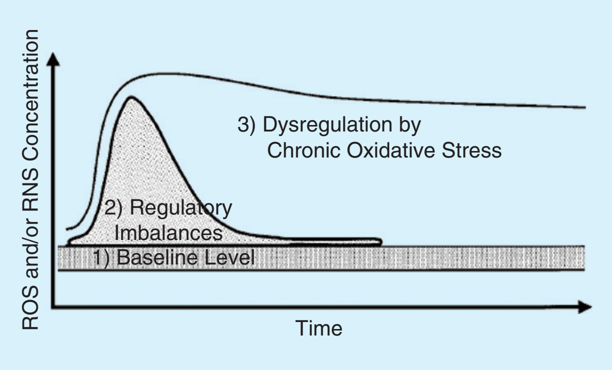

FIG 7 The regulatory events and their dysregulation depend on the magnitude and duration of the change in ROS or reactive nitrogen species (RNS) concentration. ROS and RNS normally occur in living tissues at relatively low steady-state levels. The regulated increase in superoxide or nitric oxide production leads to a temporary imbalance that forms the basis of redox regulation. The persistent production of abnormally large amounts of ROS or RNS, however, may lead to persistent changes in signal transduction and gene expression, which, in turn, may give rise to pathological conditions [2].

membrane potential for changes in magnetic fields from 45 to 100 μT and 200 μT (unpublished results).

At low frequencies, the magnetic fields can both increase and decrease the growth rates of cells. Zmyslony et al. [36] have shown changes in the number of free oxygen radicals in rat lymphocytes in vitro upon the application of weak 50-Hz magnetic fields. Prato et al. [37] have shown a reduction in the pain sensitivity upon exposure to 33 nT at 30 Hz. Bingham [38] has shown both increases and decreases in the growth rates of mastocytoma cells at 60 Hz, as shown in Figure 6. Note that the location of the peaks shift with changes in the SMFs and also with the induced electric fields and the corresponding induced current densities.

Usselman et al. [39] have shown that for rat pulmonary arterial smooth muscle cells, enhanced cell proliferation was observed with continuous applied 45 μT SMF and 7 MHz at 10 μT_{RMS} magnetic fields compared with the control group with only 45 μT SMF. The RF magnetic fields enhanced cellular proliferation by up to 40% on day two and 45% on day three in proportion to the SMF control group, and at three days, it led to a decrease of 45% in O_2^{-*} and an increase in H_2O_2 of 50%. Note that the calculated SAR is estimated to be approximately 0.12 W/kg. Other results [40] have shown that the exposure of HT1080 fibrosarcoma cells to 45 μT SMFs oriented vertical to the plane of growth or to SMFs combined with weak 5- and 10-MHz RF magnetic fields of 10 μT_{RMS} perpendicular to the static field inhibits the growth rate. Cell numbers were reduced up to 30% on day two for the cells exposed to the combination of SMF and a 10-MHz RF magnetic field compared with the SMF control cells. In addition, cells exposed to 10-MHz magnetic fields for 8 h increased H_2O_2 production by 55% [40]. The results demonstrate an overall magnetic-field-induced biological effect that shows elevated H_2O_2 levels with accompanying decrease in cellular growth rates. These effects are time dependent, and different cells can respond in opposite directions. Both the forgoing results are believed to occur through the interaction of the RF fields with hyperfine transitions between energy level associate with the generation or absorption of the radicals in the cells.

In addition, exposure at 1 mW and an estimated SAR of 0.76 W/kg for 10 h have been shown to reduce the growth rate of *E. coli* by a more than a factor of two while doing very little to *B. subtilis* [41].

Discussion

We have shown that both a theoretical base and the experimental results exist, demonstrating that weak static, low-frequency, and/or high-frequency magnetic fields can affect the concentration of radicals. There are also results that indicate that weak magnetic fields can change the growth rate of cells. However, there are many experiments where no changes are seen. This, we believe, is due to the many feedback and repair processes in the body. Droge [2] has shown in Figure 7 how extended elevations of ROS and nitrogen oxide species lead undesired biological effects, such as aging, cancer, and Alzheimer's.

> ***The question becomes: What does all this mean for people designing wireless power-transfer systems?***

The question becomes: What does all of this mean for people designing wireless power-transfer systems? Typical systems have been designed so that the fringing fields meet current safety standards that have been set on relatively short-term exposures. For example, a system for charging car batteries using capacitive coupling at 6.78 MHz has a calculated maximum electric field of 33 V/m at 0.25 m from the charging plates, and the magnetic flux density is expected to be less than a few microtesla. A 6.6-kW system being developed under contract through Oak Ridge National Labs for charging car batteries using two coils separated 160 mm at 22–26 kHz with 85% efficiency has fringing magnetic fields of less than 6.125 μT and fringing electric fields less than 87 V/m at 0.8 m.

These values are moderately close to the ICNIRP standards of 83 V/m and 27 μT. However, the magnetic flux density is only a little less than 10 μT, which has been shown to change a smooth muscle cell growth rate over a period of days. As people are not likely to stand next to their car for days, long-term effects are not likely to be important. However, there may well be other situations where designers may need to be concerned about the possible effects of long-term exposures.

Conclusions

We think that there are now both the theoretical bases and sufficient experimental results for further consideration of the possibility that long-term exposures to magnetic fields can lead to both useful applications in treating diseases and to undesired health effects. It is expected that these effects are frequency, amplitude, and time dependent. They will also be dependent on other biological conditions that can lead to changes in radical concentrations. In short, we have only begun to scratch the surface, and there is a lot of exciting research to be done before we can understand the ways in which low levels of magnetic fields can be used to control biological systems.

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