

Magnetoreception and Electromagnetic Field Effects: Sensory Perception of the Geomagnetic Field in Animals and Humans

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This chapter reviews numerous discoveries that have been made during the past 15 years concerning the ability of living organisms to respond to the geomagnetic field. These include (1) the magnetotactic response of bacteria and protozoans, (2) magnetic effects on homing and navigational behavior by migrating animals, (3) the discovery of magnetically influenced signals in nerve fibers from the trigeminal system in birds and fish, and (4) the testing of two biophysical hypotheses for the magnetoreception mechanism (biogenic magnetite and optical pumping). A final discussion concerns possible biological effects of environmental electromagnetic fields on the basis of the energy required to rotate the small crystals of biogenic magnetite that have been discovered in various human tissues.

THE QUESTION OF WHETHER SOME LIVING ORGANISMS might be sensitive to the Earth's magnetic field has been one of the most controversial topics in the behavioral and neural sciences for more than a century. Earlier reports of magnetic effects on animals were criticized properly by biologists because of the difficulty of replication and by physicists who could not think of a plausible biophysical mechanism by which animals could detect the weak magnetic field of

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the Earth (e.g., 1, 2). However, this situation changed radically during the past 15 years by developments in three separate areas.

First came the discovery of many highly reproducible magnetic effects on behavior. These effects include the magnetotactic response of bacteria and protozoans, magnetic effects on homing and navigational behavior by migrating animals, and the development of some robust psychological magnetic conditioning techniques. Apparently, two separate magnetic sensory systems exist in higher animals: a directional compass and a magnetointensity sense.

Second, at least two plausible biophysical mechanisms are now known through which the Earth's magnetic field can be transduced to the nervous system. These mechanisms include use of the ferromagnetic mineral magnetite (Fe_3O_4), which is a biochemical precipitate in virtually all groups of higher organisms, including humans. In several groups of vertebrates it forms chainlike structures ideally suited for responding to magnetic fields (3-6). Optical pumping is another potential transduction mechanism (e.g., 7-9) by which Earth-strength magnetic fields could influence charge-transfer reactions in organic molecules. Both mechanisms have received support from laboratory-based experiments, as discussed in this chapter. A third mechanism, electrical induction, is not a plausible transduction hypothesis for terrestrial organisms (e.g., 10).

Finally, two separate groups obtained clear records of magnetically influenced signals in single nerve units connecting magnetite-bearing tissues with the brain, and these signals suggest strongly that the magnetite-bearing tissues of the ethmoid sinus contain a magnetoreceptor. The ophthalmic branch of the trigeminal nerve appears to be the main conduit of magnetic intensity information to the brain; the origin of the compass is as yet unknown.

A brief review of each of these three important developments will be presented, followed by a review of the past work on magnetoreception in humans.

Experimental Evidence for Magnetoreception

Directional Compass Effects. Microorganisms. Magnetotactic bacteria and algae provide the clearest examples of a directional compass response in any living organism (11, 12). When observed under the microscope, living cells swim in straight lines parallel to a magnetic field, and their swimming directions can be changed instantly by using a small hand magnet. Each cell contains between 0.5 and 2% by weight magnetite or greigite (Fe_3S_4), and the arrangement of crystals into chains provides each cell with magnetic moments large enough to align the organism passively like a compass needle in the geomagnetic field.

Why is magnetotaxis useful for these microorganisms? In the Northern hemisphere, the magnetotactic bacteria swim to the North, or toward the South pole of a magnet, whereas in the Southern hemisphere they do precisely the opposite (13). In both cases, the inclination of the Earth's magnetic field leads them down, back to their natural environment at the mud-water interface. Most

of these bacteria do not like a high concentration of oxygen in the water, so using the geomagnetic field to stay near the surface of the mud, which has a low oxygen concentration, is convenient for them. Hence, the geomagnetic field is very important to their survival. On the geomagnetic equator (or in environments where the magnetic field is parallel to the mud-water interface), the population density of magnetotactic bacteria is reduced by several orders of magnitude (14). The magnetotactic behavior of the algae is more complex, as they respond to other environmental clues.

Invertebrate Magnetic Compass Effects. Of all terrestrial invertebrates that have been examined for magnetic field sensitivity, the honeybee (*Apis mellifera*) stands out as having the most extensive and reproducible behavior. Table I shows a summary of the known magnetic effects, as well as the independent attempts to replicate them. Of the nine basic effects, six have been replicated by independent groups, and three by two or more groups. We know of no attempts to replicate these effects that were not eventually successful (some apparently took practice). Effects 2, 3, and 8 from Table I all demonstrate that honeybees have a very good directional magnetic compass sensitivity. These data have been reviewed extensively by Towne and Gould (15), Kirschvink (16), and Kirschvink et al. (17).

Table 1. Summary of Magnetic Effects on Honeybee Behavior

Effects	Original Reports	Similar Reports
1. Misdirection in the waggle dance influenced by weak magnetic fields	Lindauer and Martin (90) Lindauer and Martin (91) Martin and Lindauer (92)	Hepworth et al. (95) Towne and Gould (15) Kilbert (96)
2. Dances on horizontal comb align with points of magnetic compass	Lindauer and Martin (91) Martin and Lindauer (92)	Brines (97) Gould (98) <i>see also</i> Kirschvink (99)
3. Magnetic orientation of comb building	Lindauer and Martin (91) Martin and Lindauer (93)	De Jong (100) Towne and Gould (15)
4. Time sense of bees influenced by geomagnetic variations	Lindauer (94)	partially by Gould (98)
5. Extinction test conditioning experiment	Walker and Bitterman (37)	Kirschvink and Kobayashi-Kirschvink (41)
6. Two-choice threshold conditioning experiment	Walker and Bitterman (38)	Kirschvink et al. (42)
7. Small magnets on anterior dorsal abdomen interfere with conditioning experiments	Walker and Bitterman (39)	No attempts reported
8. Pulse remagnetization converts North-seeking into South-seeking bees	Kirschvink and Kobayashi-Kirschvink (41)	No attempts reported
9. Two-choice conditioning to ELF magnetic fields up through 60 Hz	Kirschvink et al. (42)	No attempts reported

NOTE: ELF is extremely low frequency.

Phillips and Sayeed (18) have reported recently that males of the fruit fly (*Drosophila melanogaster*) also display a magnetic compass response when released into an eight-arm radial maze. This finding is an exciting development, as numerous genetic mutants exist for *Drosophila* that should aid in the localization of the receptor cells, as well as aid in the elucidation of the transduction mechanism. The experimental protocol appears to be simple and straightforward. If the results prove to be reproducible, the fruit fly could replace the honeybee as the organism of choice in magnetic studies, as it is much easier to maintain and work with.

A directional magnetic compass response also appears to be present in some marine mollusks, particularly *Tritonia diomedea* (19). Using intracellular electrophysiological recording techniques, Lohmann et al. (20) found that the large cells of the left and right pedal (lPe5 and rPe5) alter their firing patterns consistently (although slowly) in response to a rotation of the magnetic field direction. The ability to identify these discrete, magnetically sensitive brain cells offers hope that neurological staining techniques may ultimately locate the actual receptor cells and help clarify the transduction mechanism.

Vertebrate Magnetic Compass Effects. Magnetic compass effects have been reported in all five classes of vertebrates, including fish (21), amphibians (22), reptiles (23), numerous birds (e.g., 24–26), and mammals (27).

Wiltschko and Wiltschko (26) first recognized that the magnetic compass response in European robins was insensitive to the polarity of the field. Reversing the vector direction of the local magnetic field (by inverting both the horizontal and vertical components) yields no change in the directional preference. On the other hand, inversion of the vertical component alone yields a 180° shift, and tests in horizontal fields (vertical component canceled) yield random directional preferences. Apparently, the animals are responding to the axis of the field relative to horizontal, and hence this behavior is generally referred to as an inclination compass. Numerous studies have shown that this pattern of response is a general characteristic of birds, and it has been reported in amphibians and reptiles as well [newts (22) and loggerhead turtle hatchlings (23)]. However, migrating salmon fingerlings (28) display a polar compass, as do migrating newts (22) and mole rats (29a). Unfortunately, very few reports of magnetic compass responses in animals include tests to distinguish axial from polar compass mechanisms, so the phyletic consistency of these observations is unknown.

The inclination compass is also interesting because the behavioral response combines sensory information from two separate systems: gravity and magnetism. This behavior unfortunately complicates attempts to elucidate the biophysical mechanism(s) underlying magnetoreception, as some important features that might be present at the receptor level (e.g., polarity sensitivity) could be eliminated in the complex sensory processing leading to the behavioral response.

Magnetointensity Perception. Most of the pre-1980 literature on magnetic sensitivity dealt with tests of various sorts on the ability of animals to

obtain directional information from the geomagnetic field (e.g., “compass” information), and this type of response has been difficult sometimes to replicate in subsequent attempts (e.g., 29b). However, numerous reports in the literature deal with the effects of weak fluctuations in the background intensity of the magnetic field, with little change in the vector direction of the field itself. Examples include the release of homing pigeons at magnetic anomalies (30, 31), the preferential stranding of cetaceans at local magnetic minimum (32–34), the tendency of cetaceans to avoid high fields and field gradients while at sea (35), and virtually all of the successful attempts to condition animals to magnetic fields (36–42). The data suggest that migrating and homing animals derive useful information from magnetic variations that can be as weak as only a few tenths of a percent of the background field. Although many magnetic features, such as the marine magnetic lineations, and regional geomagnetic variations could be rich sources of position information for animals, the change in the vector direction of the magnetic field associated with them is rather small. For example, a 50-nT magnetic anomaly in the ~50- μ T geomagnetic field could at most produce a directional change of 0.06°. As moving animals are not known to keep track of their spatial orientation better than this, the animals are thus probably monitoring some scalar component of the magnetic vector field (e.g., 43).

Walker and Bitterman (38) report a remarkable measurement of the threshold level of static magnetic intensity perception in the honeybee (effect 6 of Table I). They first developed a two-choice training paradigm using two sucrose–water feeder assemblies mounted on a vertical window frame. Each assembly had a pair of double-wrapped coils that could either produce a sharply focused magnetic anomaly or a matching null-field anomaly, but with the same thermal effects. Individual foraging bees were trained via a reward–punishment scheme to feed preferentially from the feeder paired with the magnetic anomaly, and usually within 10 or 20 repeat visits they would learn to land at the feeder with the magnetic anomaly and avoid the nonmagnetic one. By starting with a moderately strong anomaly (3 mT) and by reducing the amplitude of the anomaly in small exponential steps, the threshold sensitivity could be determined by the point at which the bees were no longer able to discriminate correctly. Of nine bees run through the procedure, the median threshold was 250 nT in the presence of the Earth’s field, a relative sensitivity of 0.6%. As shown in Figure 1, the best bee lost the ability to discriminate in fields below 25 nT (0.06% of background). Similar, but less direct, estimates of the magnetic sensitivity of bees were obtained from both the misdirection and circadian rhythm experiments (effects 1 and 4 of Table I).

In a previous study, we reported (42) the replication of this basic conditioning technique for strong fields and used it to obtain a first-order look at the frequency response of the honeybee magnetoreceptor system. Bees are able to discriminate oscillating magnetic fields at frequencies at least up through 60 Hz. Subsequently, we ran a series of bees through the Walker and Bitterman threshold procedure at 60 and 10 Hz in an attempt to measure the weakest power-line-frequency magnetic field they can perceive (44a); preliminary results are shown

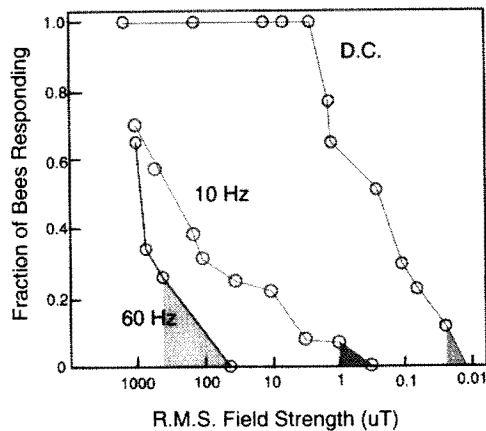


Figure 1. Measurement of the threshold sensitivity of honeybees to weak direct current (DC), 10-Hz, and 60-Hz magnetic anomalies. In each case, an individual bee is first conditioned to discriminate the presence or absence of a moderately strong magnetic anomaly using the two-choice paradigm of Walker and Bitterman (38). After reaching performance criterion, the field level is reduced to a lower value, and the bee is tested to determine if discrimination can be reestablished. This figure shows the proportion of bees able to discriminate the given field stimulus. Data for the nine bees exposed to the DC field are from Walker and Bitterman (38), and those from 15 bees tested at 10 Hz and 11 bees tested to a 60-Hz stimulus are from Kirschvink et al. (44a). All of the bees were initially able to detect the DC stimulus and were able to maintain discrimination through a reduction of 3 orders of magnitude. On the other hand, bees did far worse at detection of the 60-Hz stimulus, a result that is consistent with the viscous damping model of an elongate magnetosome chain (17, 42). RMS is root mean square.

in Figure 1, compared with the results for static fields of Walker and Bitterman (38). Apparently the threshold sensitivity at 60 Hz is reduced by over 3 orders of magnitude compared with that at 0 Hz, with the 10 Hz value in between. As discussed below, this finding is consistent with the biophysical predictions of a magnetoreceptor that employs a linear magnetosome chain for detecting the magnetic field (17, 42).

Vertebrate Neurophysiology.

This most important development involves the discovery of magnetically influenced signals in nerve fibers that ramify in the magnetite-bearing tissues of the ethmoidal region. The ophthalmic branch of the trigeminal nerve is the one that connects tissues in the ethmoid region to the brain, so this nerve is the most likely one with which to begin the electrophysiological search. Within the past 4 years, two groups have had spectacular success at making direct electrophysiological recordings of magnetically mediated signals in this nerve. The first report (44b) was recorded from cells in

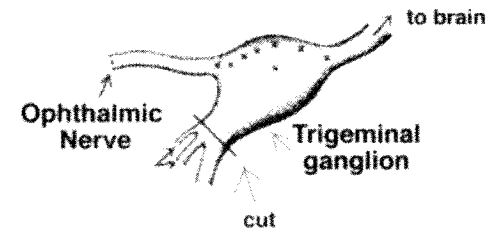


Figure 2. Schematic drawing of the bobolink trigeminal ganglion showing the nerves and recording locations (indicated by x) of cells responding to magnetic stimulation. The line indicates where mandibulomaxillaris nerve was severed (Adapted from reference 44b, courtesy of R. Beason.)

the trigeminal ganglion of a small migratory bird, the bobolink (Figure 2). In this report, about 21% of the fibers in the ophthalmic nerve and 9% of cells in the trigeminal ganglion responded to small changes in the intensity of the applied magnetic fields (Figure 3), including neurons that fired in response to changes in the field as weak as 200 nT (4% of the background geomagnetic field). The roughly logarithmic increase in firing frequency of the nerve with stimulus intensity is a pattern observed in many other sensory systems. Similar results were obtained by Walker et al. (44c) in New Zealand on the brown trout (a relative of the salmon). In both the bird and fish, no other sensory nerve fibers have yet been found to convey magnetic signals.

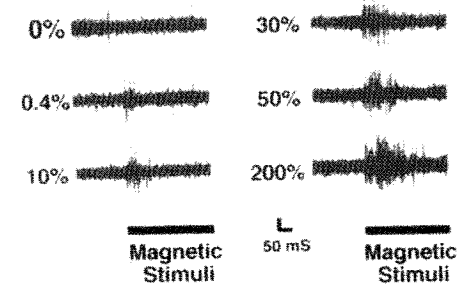


Figure 3. Electrophysiological recordings of magnetically mediated signals in a bobolink, showing the response of one ganglion cell to different vertical magnetic field intensity changes. On each of the six horizontal traces, the number with the % symbol indicates the size of the magnetic intensity increase compared with the background (static) field level, which was 50 μ T. 0% is an example of the spontaneous activity of this neuron, 0.4% was with a stimulus of 200 nT, 10% was with 5 μ T, 30% was with 15 μ T, 50% was 25 μ T, and 200% was 100 μ T. The stimulus onset is indicated by the bar below each series. Horizontal scale is 50 ms; vertical scale is 2 mV. (Adapted from reference 44b; data courtesy of R. Beason.)

Human Magnetoreception. The question of whether humans also have a magnetic sensitivity is perhaps one of the most controversial areas in this entire field. Humans make magnetite in many tissues and have an ophthalmic nerve in their trigeminal system. However, most humans do not claim to perceive consciously the Earth's magnetic field, and magnetoreception is not listed among the five major senses (vision, hearing, smell, taste, and touch). Therefore, if magnetoreception exists in humans, it must either be buried deeply in our subconscious or masked in some other fashion. One research group in England has claimed for the past 13 years that humans do indeed have a subconscious magnetic compass sense like many other animals (45–53). However, no independent research group has yet claimed success at replicating any of these results, (e.g., 54–57).

Two more recent developments indicate that now may be a good time to reinvestigate this human magnetoreception question. First, Bell et al. (58) obtained evidence from surface-based electroencephalogram recordings that environmental magnetic stimuli are somehow having an influence on neurological activity in the human brain. Second, Dobson et al. (59, 60; see also reference 61) report that a 1–2-mT static magnetic field applied through the head of epileptic patients was able to elicit epileptiform (epilepsy-like) activity, as recorded by electrodes implanted directly in the hippocampus. The ability to induce epileptiform activity on command led to the successful localization of the epileptic foci in several patients who otherwise had been difficult to treat. However, in one study (60) the induced activity developed into a full-blown epileptic seizure in one patient.

At present, the evidence suggests an intensity “window” for eliciting this response, as static fields below 0.9 mT do not work, and apparently no claims exist of epileptic seizures being triggered by exposures to the strong (1.5-T) magnetic fields of clinical magnetic resonance imaging (MRI) machines. This feature is as yet poorly understood. The only other report of a behavioral intensity window for a vertebrate is in birds (26), and it was centered on the geomagnetic field strength.

All of these more recent observations are consistent with the hypothesis that external magnetic fields are being transduced into neurological activity in humans. If so, some form of sensory transduction must be operating for this hypothesis to be true, as all known inputs to the nervous system arise ultimately in cells specialized to convert external stimuli into coded bursts of action potentials (e.g., 62). Hence, the investigation of human magnetoreception is an area that needs much additional work.

Biophysics of Magnetoreception

The Ferromagnetic Transduction Hypothesis: Biogenic Magnetite. Theory and Occurrence. The simplest possible method for a living organism to respond to magnetic fields as weak as that of the Earth's is to use a

permanent magnet, much as human navigators do today. However, most materials found in organisms are generally thought of as nonmagnetic, that is, either diamagnetic (repelled weakly from a magnetic field, like water and most fatty substances) or paramagnetic (weakly attracted to a magnetic field, like the deoxyhemoglobin in red blood cells). For materials of these types, the direct physical influence of the Earth's magnetic field is extraordinarily weak, with the energy of magnetic interaction being many orders of magnitude below that of the background thermal energy, kT (where k is the Boltzmann constant and T is the absolute temperature). However, another category of materials, termed ferromagnetic, interacts very strongly with the Earth's magnetic field. Unlike diamagnetic and paramagnetic substances, quantum mechanical interactions acting on unpaired electrons within ferromagnetic materials force the electron magnetic moments (Bohr magnetons) to form long-range alignments. The magnetic moments from each Bohr magneton within such a crystal are added vectorially, and in some materials a crystal of only a few tens of nanometers in size will have magnetic interaction energies with the geomagnetic field greater than the background thermal energy (kT). Motion of this material in response to external magnetic fields can in principle account for a variety of magnetic effects at the cellular level, such as the opening of mechanically sensitive transmembrane ion channels (Figure 4; references 17 and 63) or the biophysical transducer in a cell specialized to detect the magnetic field (e.g., a magnetoreceptor; 17, 43).

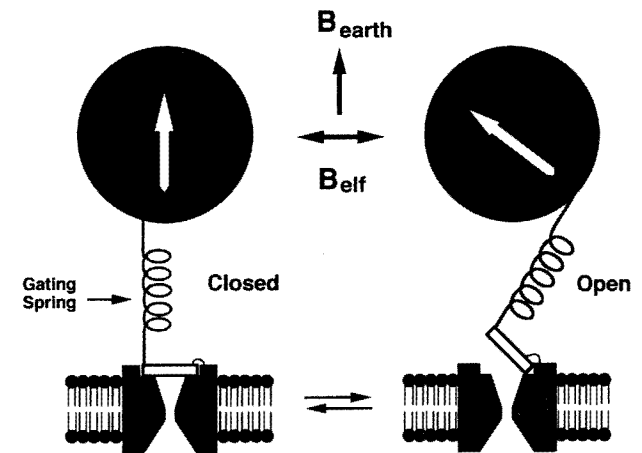


Figure 4. A schematic diagram for how a magnetosome might act to open or close a mechanically sensitive transmembrane ion channel. A magnetosome connected to an ion channel gate via a cytoskeletal filament (a “gating spring”), adapted from reference 88 but not drawn to scale as the magnetosome should be larger than shown. The geomagnetic field, B_{Earth} , is perpendicular to the plane of the membrane, whereas the extremely low frequency (ELF) magnetic field component, $B_{ELF} \cos(\alpha)$, is parallel to it (17).

At present, 12 iron minerals have been identified in organisms (64) although only three of these have been found so far as biochemical precipitates in vertebrates. These three are ferrihydrite ($5\text{Fe}_2\text{O}_3 \cdot 9\text{H}_2\text{O}$), which is the mineral in the core of the ferritin molecule, normally the chemical precursor of magnetite, and the substance often referred to in the medical literature as hemosiderin; goethite ($\text{Fe}_2\text{O}_3 \cdot n\text{H}_2\text{O}$); and magnetite (Fe_3O_4). Of these materials, ferrihydrite is paramagnetic above 240 K and goethite is antiferromagnetic, whereas magnetite has a variety of ferromagnetism termed "ferrimagnetism". These magnetic properties make magnetite interact over 10^6 times more strongly with external magnetic fields than does any other biological material. Magnetite crystals are permanently and spontaneously magnetized bar magnets, which cannot be demagnetized under physiological conditions.

In 1962 Heinz Lowenstam (65) first discovered that magnetite was the major mineral in the teeth of a primitive marine mollusk (the chitons, class Polyplacophora, Figure 5). Magnetite crystals in chiton teeth range from superparamagnetic to multidomain in size, implying that they have not been selected for on the basis of their magnetic properties. The chitons clearly use magnetite because it is much harder than any other biogenic mineral, not because it is magnetic. In contrast, all of the magnetite crystals that have been found subsequently in other living organisms are single domains, suggesting that the magnetic properties of these crystals have important biological functions. Numerous studies earlier in the 1980s revealed that virtually every group of vertebrates possessed anomalously high concentrations of magnetite in tissues in the vicinity of the ethmoid sinus (4).

An impressive variety of organisms are now known to biomineralize magnetite, including insects (66), birds (67), bacteria (68), fish (69), protozoans (12), and more recently humans (70). This list includes representatives of three of the five kingdoms of living organisms (bacteria, protists, and animals) and all five classes of vertebrates (fish, amphibians, reptiles, birds, and mammals). Only fungi and higher plants are not yet known to make it. Work by our group and others during the past decade has also shown (e.g., 14, 71) that magnetite crystals formed by the magnetotactic bacteria are preserved in oceanic sediments as magnetofossils. By extracting magnetofossils from older and older sediments, we now know that the magnetotactic bacteria evolved at least by two billion years ago, about the same time as the appearance of the first eukaryotic cells. Hence, as shown on Figure 6, the biochemistry of magnetite formation quite possibly evolved only once in the magnetotactic bacteria, and all other groups inherited it from them. Magnetite biomineralization appears to be a common trait among most living organisms.

All of the magnetotactic bacteria when examined with the transmission electron microscope (TEM) contain chains of similarly sized magnetite or greigite crystals (around 30–50 nm) that span the bacterial cell (Figure 7). Under very high magnification (Figure 8), the crystal lattice can be imaged directly. The uniform fine stripes that cross the crystal are produced by successive layers of Fe atoms in the lattice. The high uniformity and structure of these fringe patterns are typical of biologically formed crystals. At present the biochemical

pathways that form magnetite with such perfect, defect-free structures are unknown. Similar biogenic magnetites are also present in higher animals.

Largely due to the construction of a magnetically shielded clean laboratory at the California Institute of Technology, Kirschvink et al. (4) and Mann et al. (5) were able to demonstrate that the ethmoid tissues of the salmonoid fish

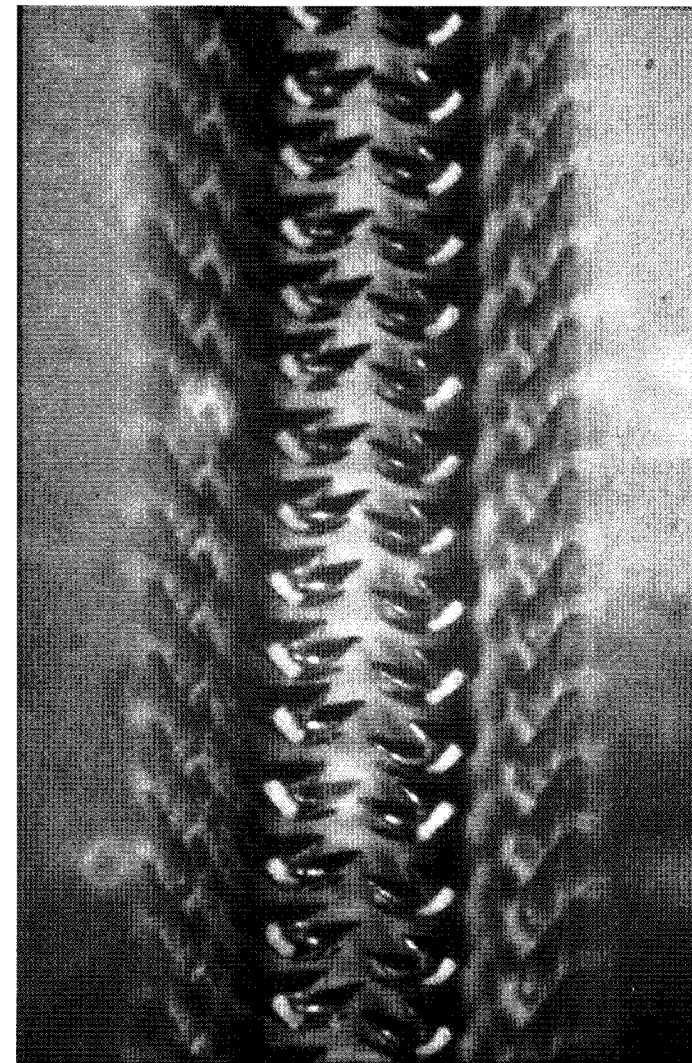


Figure 5. Chiton teeth. Length of one tooth is about 0.5 mm. Dark areas are covered with a thin ($\sim 10 \mu\text{m}$) layer of magnetite. Red areas are made of other type of ferrihydrite, and their composition depends on the species. (Photo by H. Lowenstam. Reproduced with permission of California Institute of Technology.)

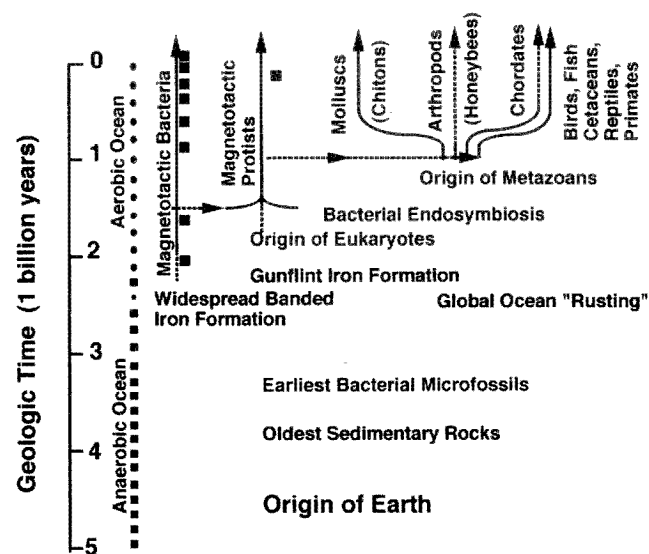


Figure 6. Evolution of magnetite biomineralization. Because biogenic magnetite has been discovered in three of the five kingdoms of living organisms, with a fossil record reaching back nearly 2 billion years, it probably shares a common descent in higher organisms. Presumably, the magnetotactic protists acquired this ability through an endosymbiotic relationship with a magnetotactic bacterium, and other groups of eukaryotes inherited it from them. (Adapted from reference 14.)

contained chains of single-domain magnetite crystals (Figure 9), identical in morphology to those used for magnetotactic responses in bacteria and protists. These magnetites were discovered using a sensitive magnetometer, based on Superconducting Quantum Interference Devices (SQUIDs), which were designed originally to measure the direction and intensity of the magnetism of rock samples for geophysical studies. We modified these techniques for finding ferromagnetic minerals in frozen animal tissues. From these measurements, we located the largest concentrations of magnetite in the frontal regions of the head, particularly in the vicinity of the ethmoid-sphenoid sinuses (or their anatomic equivalents). By the fall of 1982, this pattern was demonstrated clearly in a variety of fish, birds, and mammals and was shown for amphibians shortly thereafter.

In a series of papers published between 1984 and 1988, Walker, Kirschvink, and others demonstrated (4, 5, 69) that extracts from the ethmoid tissues of pelagic fish (tuna and salmon) contained linear chains of single-domain magnet-

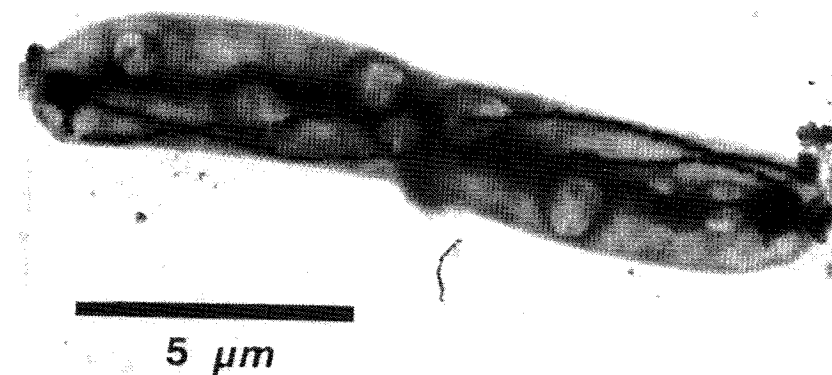


Figure 7. Transmission electron microscope photo of an unusually large magnetotactic organism from a depth of 44 m in the Ammersee, 50 km south of Munich. The 15- μm -long organism has two magnetosome chains and a total of about 180 crystals. These crystals are unusually large (170 \times 80 \times 80 nm), with magnetic-to-thermal energy ratios in the geomagnetic field of about 6 per particle, giving the entire cell a ratio of 1100 (assuming both chains are magnetized in the same direction). Crystals near the central portion of the chains are much smaller than average; this size is typical of immature grains near the growing end of magnetosome chains in other bacteria (e.g., reference 73). This oversized organism may be in the initial stage of division. Scale bar is 5 μm . (Reproduced with permission from reference 89. Copyright 1991 Plenum.)

ite crystals, and the crystal shapes and structures are very similar to those found in magnetotactic bacteria. Furthermore, high-resolution TEM studies demonstrated that the {111} crystal axes of the magnetite were aligned along the chain length, as they are in most magnetotactic bacteria. This configuration yields a slightly higher magnetic moment per gram of magnetite (e.g., 72) and is most easily explained as the result of natural selection for the magnetic properties, or as the result of new crystals growing in the strong magnetic fields at the end of a magnetosome chain (73). These are clearly "biological bar magnets". However, the ultrastructural localization of the magnetite in the tissues is not a trivial problem, as the maximum concentration in the ethmoidal tissues is still only a few parts per million, and the search for the magnetite-containing cells is not easy.

Even if we do not know the biological function of magnetite in humans, its presence in our tissues could have important implications for other biological effects of magnetic fields. Unfortunately, tissues associated with the human ethmoid sinus are not easy to study using the SQUID magnetometers, and the magnetite found in them in an earlier report (74) was contamination from a band-saw blade (75). For this reason, we focused instead on the soft tissues of the human

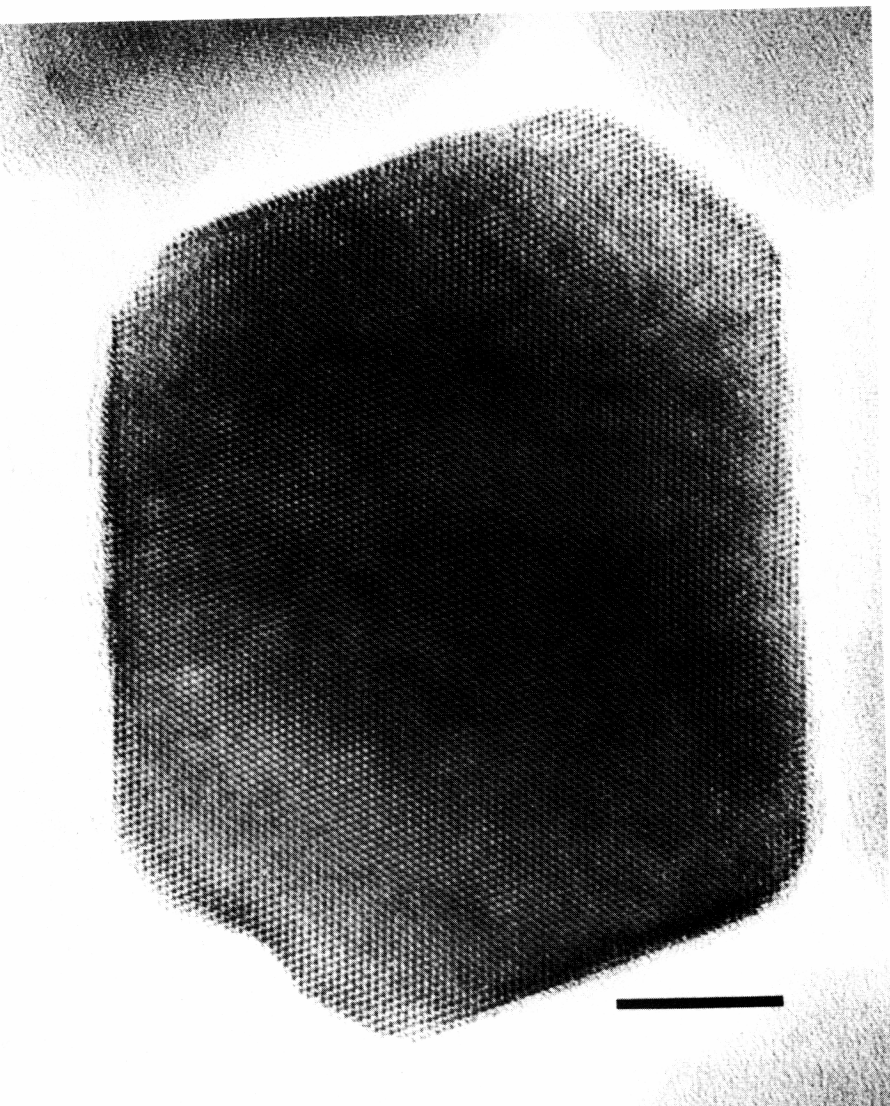


Figure 8. TEM images of single-domain magnetite extracted from the magnetotactic bacterium, *Aquaspirillum magnetotacticum*. The scale bar is 10 nm. The high-resolution TEM (300-kV) image of the bacteria magnetite shows several sets of crystal lattice fringes (thin stripes) that correspond to three sets of $\{111\}$ planes spaced a distance of 4.8 Å apart. (Photo by A. Kobayashi.)

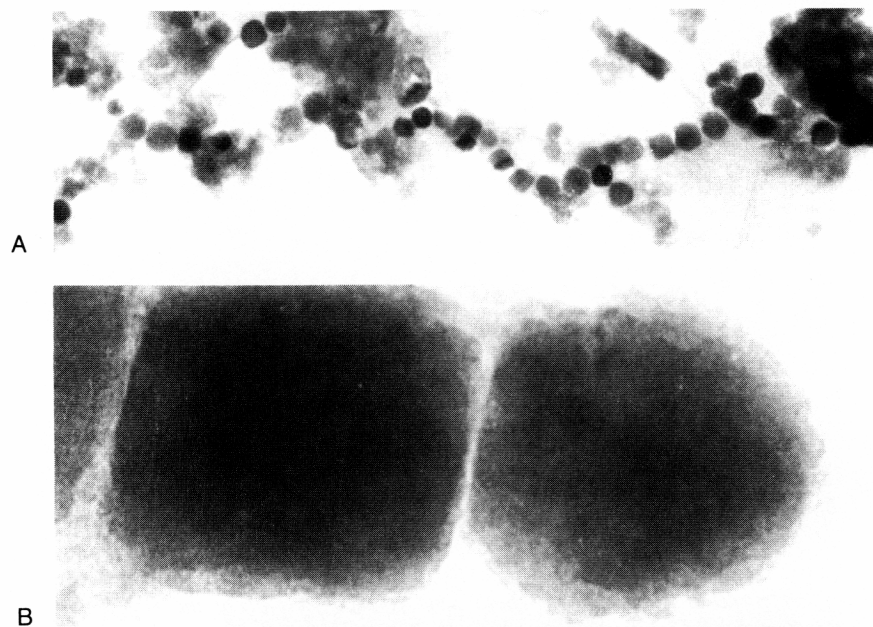


Figure 9. a: Magnetic extract from the ethmoid tissue of sockeye salmon showing a chain of ~50 nm electron-dense particles associated with organic material. (Reproduced with permission of S. Mann). b: Lattice images of two adjacent magnetite crystals showing the preferential crystallographic orientation of both crystals such that the $\{111\}$ lattice planes (4.8-Å separation) lie perpendicular to the chain axis. (Reproduced with permission from reference 5. Copyright 1988 Company of Biologists Ltd.)

brain, as this organ is the best studied tissue of any organism, both human and animal. Although in 1989 our initial SQUID measurements quickly demonstrated the presence of something ferromagnetic in the brain tissues, the absolute concentrations were rather minute: only a few parts per billion, much less than the concentrations of magnetite in the ethmoidal tissues mentioned already (Figure 10). After several more years of hard work extending our clean-lab extraction techniques, we were able to view the magnetic material high-resolution TEM (Figure 11a) using electron diffraction (Figure 11b). Almost perfect lattice fringe patterns were present, with many of the crystal shapes very similar to the magnetosome of the bacteria and fish (70). These features imply that humans also have the process of magnetite biomineralization. Recently, Dunn et al. (76) reported an independent replication of the brain magnetometry work with similar results.

Experimental Evidence for Magnetite-Based Magnetoreception. Why is biogenic magnetite present in such a diverse set of living things? In all organisms except chitons, the particle sizes, shapes, orientation of crystal axes, and

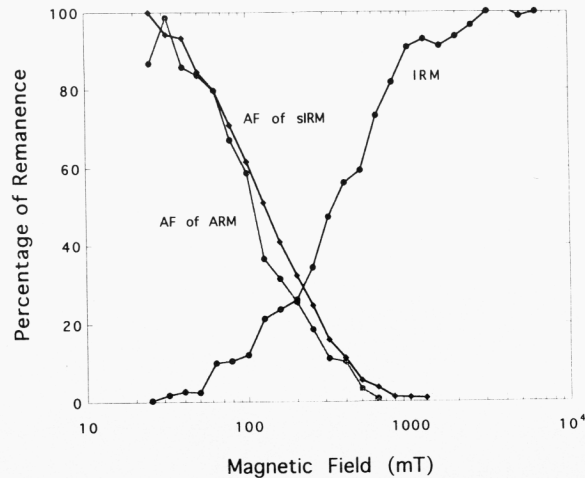


Figure 10. The curve labeled IRM (isothermal remanent magnetization) shows the relative magnetic moments remaining in the samples of human brain cortex after a brief exposure to a magnetic pulse of the indicated strength. The tendency of the curve to flatten at high field level is characteristic of the magnetite-maghemite solid solution series; most other ferromagnetic iron minerals saturate in fields >1 T. The curve labeled AF of sIRM shows the progressive alternating-field demagnetization of the saturation IRM, and that labeled AF of ARM shows the similar demagnetization of an anhysteretic remanent magnetization. The magnetic field value at which these two curves cross is the best measure of the average coercivity. The ordinate of the intersection point for noninteracting particles occurs at the 50% value; a depression or shift in this position is an indication of particle clumping effects.

their alignment in chains act to produce single magnetic domains and to maximize their total magnetic moments. These observations suggest that the magnetic properties of the crystals are important biologically. Evidence that magnetite is used by organisms to respond to magnetic fields is very strong in bacteria, algae, honeybees, and in two groups of vertebrates, birds and fish.

A simple experiment first done by Kalmijn and Blakemore (77) demonstrates that this magnetotactic response is based on ferromagnetism. Single-domain ferromagnetic crystals, if slightly elongate or held in a chain, can be magnetized in one of only two stable orientations, either parallel or antiparallel to their length. A strong but brief magnetic pulse can cause the direction of the magnetic moment to jump from one stable state to the other, reversing the polarity of the crystal. A North-seeking compass would then point toward the South. (This principle is the same as that used to hold data on magnetic tapes and computer disks.) When applied to these magnetotactic microorganisms, a magnetic pulse actually causes them to reverse their swimming direction permanently. We

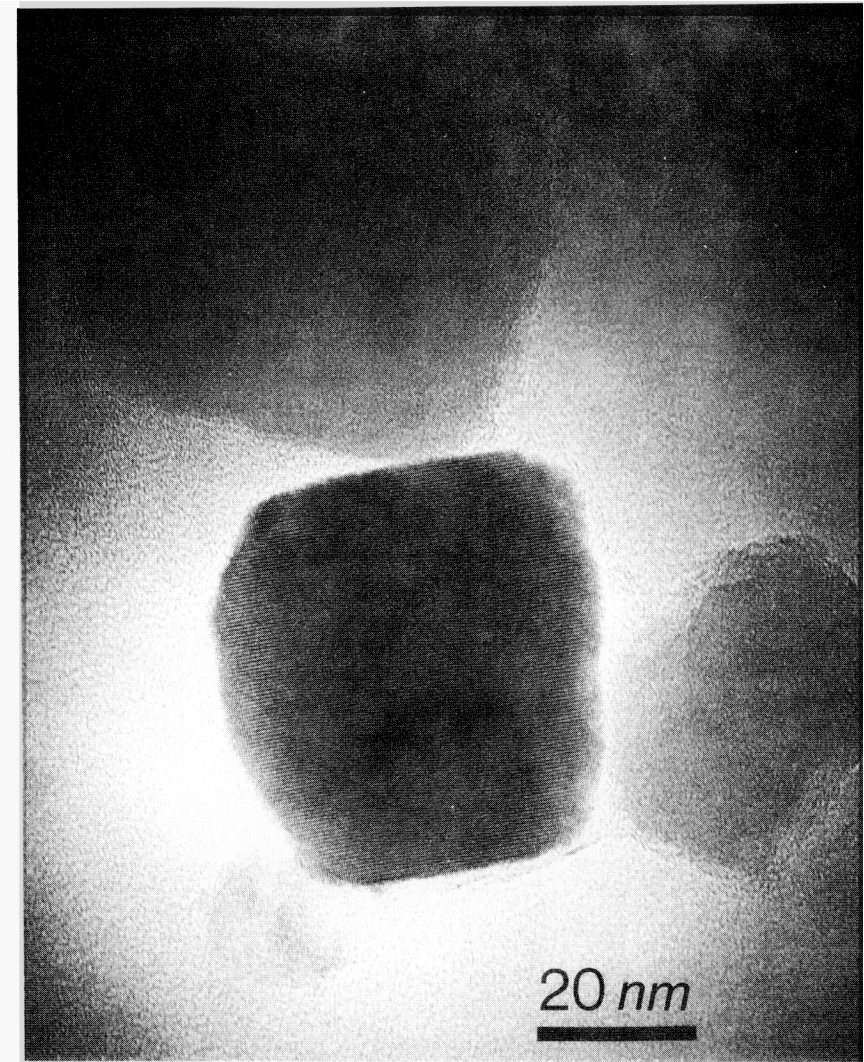


Figure 11a. TEM images of representative magnetite and maghemite crystals from the human cerebellum. High-resolution TEM image of the maghemite crystal shows the pattern of intersecting $\{111\}$ and $\{022\}$ fringes, with particle elongation in the $\{111\}$ lattice direction. (Photo by A. Kobayashi).

(78) used this technique to isolate strains of magnetic bacteria with different particle sizes. The ability of a short magnetic pulse like this one to change behavior permanently is unique proof that a single-domain ferromagnetic material is responsible for the ability to detect the magnetic field. Similar pulse effects have been reported (12) on the magnetotactic algae.

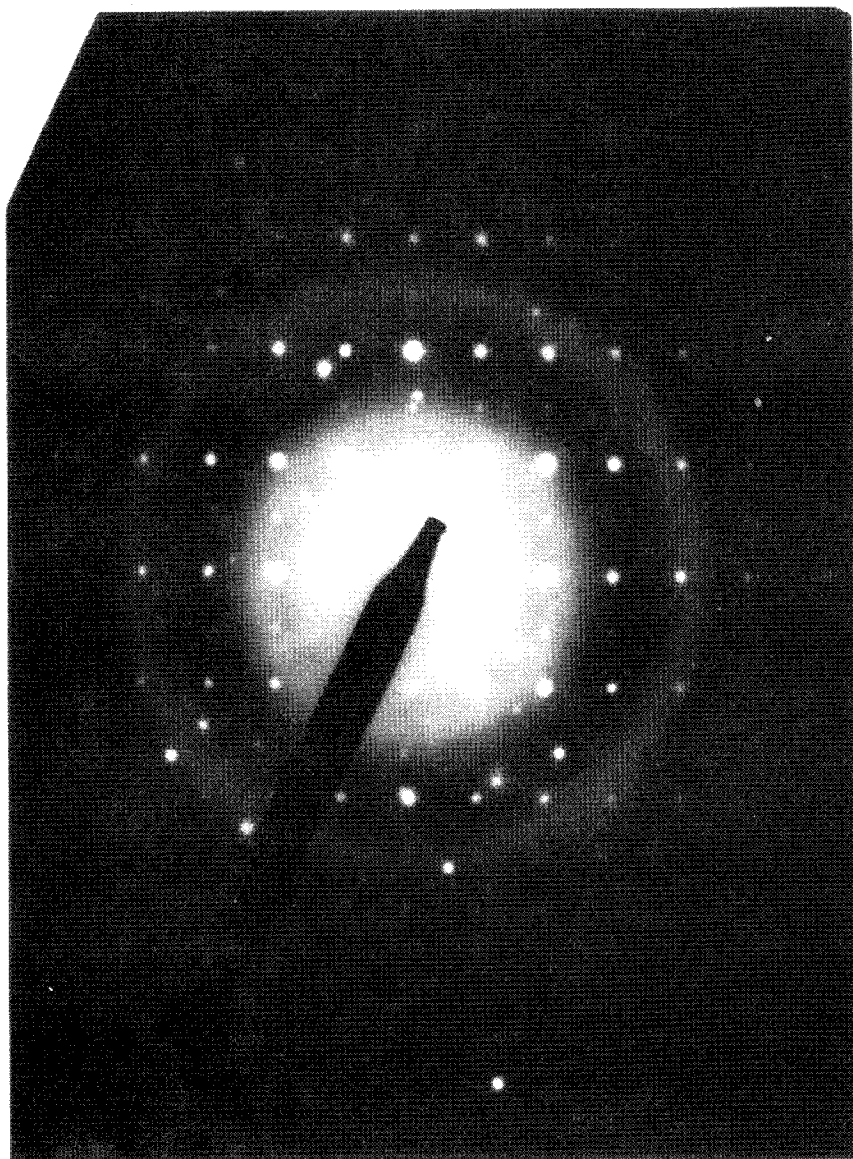


Figure 11b. The indexed selected-area electron diffraction pattern of this crystal, taken in the $\{211\}$ zone. (A few miscellaneous spots are also present from the adjacent crystals seen in part a, and the faint row of spots midway between the bright rows are $\{011\}$ and equivalent reflections that indicate the oxidation to maghemite) (Photo by A. Kobayashi). (Reproduced with permission from reference 70. Copyright 1992.)

Considerable support also exists for the hypothesis of magnetite-based magnetoreception in higher animals. Biogenic magnetite in honeybees is located primarily in the anterior dorsal abdomen (66), and small magnetized bits of wire glued over this location interfere with the bee's ability to learn to discriminate magnetic anomalies in conditioning experiments (effect 7 of Table I). Control bits of nonmagnetic wire, and magnetized wire placed elsewhere on the bees, do not interfere with the bee's ability to discriminate the magnetic cues. Hence, whatever the transduction mechanism, the magnetoreceptors must be in the anterior dorsal abdomen where the bulk of the magnetite is located. Furthermore, preliminary experiments with the pulse-remagnetization technique on bees trained to exit from a T-maze suggest that North-exiting animals can be converted to South-exiting ones, in a fashion similar to that for the magnetotactic bacteria (41).

In vertebrates, evidence for magnetite-based magnetoreception is slightly more circumstantial. As noted earlier, linear chains of magnetite crystals have been extracted from the vicinity of the ethmoid sinus in fish and birds, and nerves of the trigeminal system, parts of which ramify in the magnetite-bearing tissues, convey magnetic information to the brain. Unfortunately, the widespread existence of the axial magnetic compass ought to limit the ability to perform the pulse-remagnetization experiment on them. In theory, this type of experiment should be possible in mole rats (29a), salmon fry (21, 28), or newts (22), all of which display a polar compass response. However, despite the presence of the axial compass in birds, Wiltschko et al. (79) tried this experiment anyway and found a dramatic but temporary deflection in orientation. This finding implies that magnetite is indeed involved in the sensory system, but whether it is in the compass or intensity receptor is not clear.

Optical Pumping. Theory. Optical pumping is another potential biophysical mechanism that might enable organisms to transduce the geomagnetic field to the nervous system. This concept dates back to a suggestion by Leask (7), which was extended and developed further by Schulten (8) and Schulten and Windemuth (9). The model in its more current form centers on the fact that chemical reactions can be influenced by two fundamentally different methods. The first method is to alter the energy levels of the reactants, intermediates, and products, and these steps are all governed by the well-known rules of statistical mechanics and thermodynamics. On the other hand, quantum mechanical constraints can also affect reactions, such as preventing two electrons with parallel spins from forming a bond. Such effects can easily block entire reaction pathways. As magnetic fields as weak as 0.1 mT can lead to significant hyperfine splits in orbital energy levels, the magnetic fields needed to produce this type of effect are much weaker (by factors of 1000) than those required to break the kT barrier with diamagnetic or paramagnetic effects. Numerous such reactions have been reported, some of which have even found commercial application, like increasing the molecular mass of polystyrene by photopolymerization in an applied magnetic field [reviewed by McLauchlin (80)].

As a simple example, Schulten (8) discussed a situation in which the energy from a photon could lead to the breaking of a chemical bond, forming a pair of energetic electrons in a singlet state. As the spins in this electron pair would remain antiparallel immediately after the adsorption event, the back reaction (reforming the original covalent bond) is still permitted. However, because the singlet and triplet states of the pair are not in direct contact, the exchange interaction is negligible. Under these conditions, perturbation energies on the order of $10^{-8} kT$ can promote one of the spins to flip (or to evolve into one of the triplet states), thereby inhibiting the back reaction. This biochemical difference in subsequent reaction rates could then form the base of a magnetoreceptor function.

Experimental Evidence for Optical Pumping. Testing the optical pumping hypothesis is not such a simple matter, mainly because apparently no equivalent of the pulse remagnetization experiment, like that discussed earlier for the magnetite system, exists that could uniquely isolate optical pumping as the mechanism. However, the evidence presented so far is suggestive. First, an optically pumped system should yield an inclination compass, as has been observed in many groups of vertebrates. Second, using electrophysiological recording techniques, Semm and Demaine (81) found cells in the retina of pigeons that fired in response to magnetic stimuli. Third, behavioral studies in newts, migratory birds, and fruit flies (18, 82, 83) demonstrate that light of wavelengths that correspond to different receptor pigments has a strong influence on the compass orientation response, often shifting the mean orientation directions dramatically or abolishing the response completely.

On the other hand, the visual system exerts an extraordinary influence on many aspects of animal behavior, and all of the reports published to date could be explained by the interaction of the visual system with a separate magnetic sense. Similarly, the Semm and Demaine (81) preparations were done *in vivo*, and the vertebrate retina is known to receive inputs from elsewhere in the nervous system. Hence, the magnetic signals could have come from magnetoreceptors elsewhere in the bird, or, as magnetite has also been detected in vertebrate retinal tissue (84), the signals could arise from an occasional magnetite-based cell within the eye.

Two other problems further limit the viability of the optical pumping mechanism. First, it does not seem to be capable of accounting for the magnetointensity sense described earlier. At best it could give an organism the axial direction of the field, and as such it cannot account for the polar compasses of honeybees, salmon fingerlings, newts, and mole rats. Second, it would have trouble functioning in the dark, and good evidence suggests that a broad spectrum of animals do not need light to perceive the magnetic field direction [e.g., bees (41), salmon (21), beetles (85), mollusks (19), turtles (86), and mole rats (29a)]. A chemically based "dark" reaction probably could not supply the energetic electrons necessary for this process to operate, as the chemical reactions needed for this process require access to molecular oxygen (87). Oxygen and highly toxic compounds are usually sequestered within the mitochondria, far

away from the ordered membranes where the photopigments reside. Such a dark reaction should also produce an obvious side effect, as some of the electrons that were pumped up to higher energy levels would have the chance to decay spontaneously to their ground state, emitting visible photons in the process. Bioluminescence of this sort has not been reported in any vertebrate eye.

Discussion: Electromagnetic Field Effects, Biogenic Magnetite, and Magnetoreception

The preceding discussion indicates that the subject of magnetic field sensitivity (e.g., magnetoreception) in terrestrial organisms has evolved over the past two decades from a set of "fringe science" observations to one of serious scientific pursuit, and it now includes a body of highly reproducible effects. A variety of exciting and innovative experiments ranging from the behavioral, ultrastructural, and neurophysiological sciences have narrowed the range of potential transduction mechanisms, weeding them down to two major contenders: magnetite and optical pumping. In terms of the biological effects of environmental electromagnetic fields (EMFs), no other area of investigation appears to have such a solid foundation. For this reason, the biophysics of magnetoreception ought to be used as a starting point in any analysis of potential mechanisms for any reported biomagnetic effect, whether in whole animals or cells grown in tissue cultures. In particular, the discovery that magnetite biomineralization occurs in human tissues, even in structures that have no conceivable sensory role, argues that ferromagnetic bases for many deleterious EMF effects should be considered. This mechanism certainly raises far fewer objections about the thermal noise problem than virtually any other proposal.

Even though we as yet do not understand the function for all of the biogenic magnetite found in tissues, its mere presence has interesting implications for at least two areas of biomedical research. These include aspects of magnetic resonance imaging (MRI) and the possible health risks associated with low-frequency magnetic fields. MRI is one of the fastest growing fields in medical diagnosis. How and why the images show contrast between tissue types is a major field of investigation, but all MRI biophysical analyses so far have not considered the effect of biogenic magnetite. However, because a major component of the contrast is a function of the square of local magnetic field perturbation in a tissue, a simple calculation shows that the trace amounts of magnetite should play a significant role in providing this contrast.

Unfortunately, all past biophysical assessments of possible health effects from exposure to magnetic fields have assumed that human tissues did not contain ferromagnetic materials. In MRI, for example, the strong magnetic fields (which will soon reach up to ~ 5 T in clinical instruments) are often said to be too weak to break chemical bonds in diamagnetic or paramagnetic materials, and hence they cannot produce permanent physiological effects. This statement is completely untrue for a magnetosome, however, as its potential energy in an MRI instrument is over 1000 times the strength of the carbon-carbon bond en-

ergy and nearly 10,000 times more than hydrogen bonds. The million or so magnetosomes present per gram of brain tissue will rotate into alignment as a patient is inserted into the MRI instrument, and this rotation does have at least the potential to do cellular damage. (Translational forces due to the magnetic gradients are negligible.) On the other hand, most biological membranes act like flexible structures when they are deformed slowly, with time constants of about 10 Hz. Because strong magnetic fields of the sort used in MRI instruments act at very low frequencies, no permanent damage should result. Evidence suggests that they are certainly much safer than imaging techniques based on X-rays, which are known to initiate cancer.

At frequencies above about 10 Hz, however, biological membranes and other structures tend to behave in a more rigid, brittle fashion, and ultrastructural damage and other biological effects may be possible. Figure 4 shows a simple biophysical model of a magnetosome floating in the cytoplasm of a cell and connected to an ion channel; this model can be used to predict what frequencies and field strengths are necessary to produce an effect. The simplest biological effect that the motion of a magnetosome might produce is the opening of an ion channel in a membrane. These channels control the diffusion of ions and molecules into, out of, and within cells, and in turn these are fundamental regulators for many cellular processes. Many ion channels are also mechanically activated; applying enough tension to a cytoskeletal filament can cause them to open. They actually have little "gates" that open like trap doors to allow molecules to pass through. From detailed studies of these ion channels in hair-cell mechanoreceptors (88), we know that the little doors move through a gating distance of about 4 nM, and the opening force needs to be about 1 pN. The energy associated with opening the gates, a force times a distance, is $\sim 4 \times 10^{-21}$ J, which is $\sim kT$, the background thermal energy.

The problem is to determine which combinations of field strength and frequency will move a magnetosome enough to just barely open an ion channel. Two factors compete to influence this motion. On the one hand, the magnetic force on the magnetosome produced by an external oscillating magnetic field is trying to force the crystal to twist back and forth like a torsional pendulum. Resisting this torque are the viscous drag of the cytoplasm and the restoring torque of the static geomagnetic field. The resulting motion of the magnetosome and the attached ion channel is given by the solution of a fairly simple but nonlinear differential equation. These results show that we need 50- or 60-Hz oscillating magnetic fields of about 100 μ T to contribute ~ 1 kT of energy to an ion channel from an individual magnetosome.

How does this result scale in biological systems, and how can we compare it to the alternating magnetic fields found in a modern, industrialized society? Two factors are important. First, the energy in a system responding to the magnetic field generally increases as the square of the field strength, that is, $\Delta E \sim B^2$, where ΔE is the energy change and B is the magnetic field strength. Second, the relative biological effect generally follows an Einstein-Boltzmann relationship, or $\sim \exp(\Delta E/kT)$. Hence, if we double the threshold field in our magnetosome

model, the energy ΔE increases by a factor of 4 and the biological effect increases by e^4 or by a factor of ~ 54 . Similarly, for fields below the threshold, the relative energy quickly falls below thermal noise, and magnetic effects will be difficult to detect (unless some special form of signal averaging occurs).

We can now compare this threshold level for biological effects with the measured extremely low frequency (ELF) EMFs produced by man-made objects in our environment, as summarized in Figure 12. Most of the magnetic fields produced by electrical power transmission and distribution lines are much weaker than the threshold levels discussed already, unless one approaches very close to them. On the other hand, electrical appliances like hair dryers, electric razors, and electric blankets do expose parts of our anatomy like our hands, fingers, and skin to alternating fields well above these thresholds. A 1-mT, 60-Hz magnetic field, for example, can give enough energy to a magnetosome to break covalent bonds (~ 100 kT). Because of the small size of most household appliances and the rapid decay of the field strength with distance, the actual volume of tissues that are exposed to these strong fields is usually quite small.

This discussion leads naturally to the important question of whether alternating magnetic fields actually produce harmful effects such as cancer in hu-

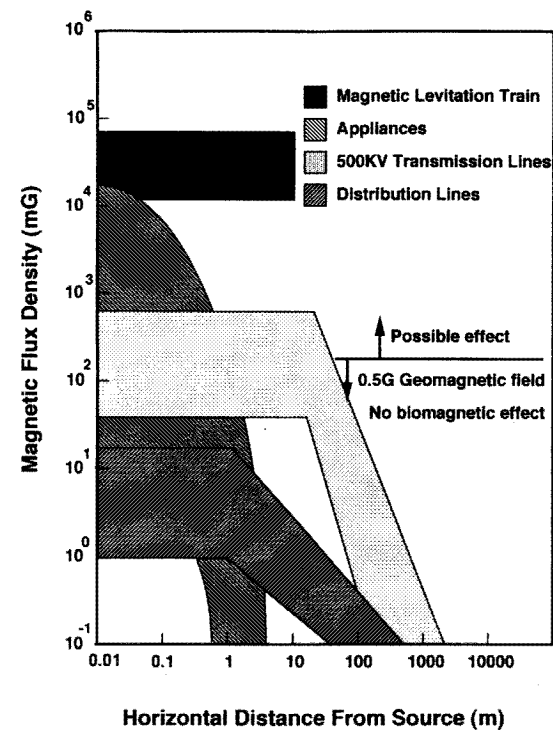


Figure 12. Magnetic field exposure depending on the distance and type of equipment.

mans; this topic is now extremely controversial in the United States and Europe. The assessment of medical risk generally falls into two major categories of research, including animal experimentation and epidemiology. Although numerous studies of magnetic fields on mice and other laboratory animals have been done in the past 200 years, surprisingly little research has been done using continuous magnetic exposure systems on large numbers of animals to assess the effect on rare diseases. These studies are expensive, particularly when experimental controls are done properly. Several epidemiological studies have implicated slight increases of diseases such as childhood leukemia and brain tumors with electromagnetic exposure, but the underlying mechanisms are unknown, and the results need to be confirmed by replication. However, as a precautionary measure all electric blankets now sold in the United States have been designed to minimize external fields, and magnetic shielding materials are being incorporated into many electrical appliances. New power lines are being routed away from populated areas or buried in shielded cables. In 1992, the U.S. Congress authorized the National Institutes of Health and the Department of Energy to spend \$65 million for research on magnetically related health effects over a 5-year period. We hope this new work will help us to understand the basic biophysical mechanisms through which magnetic fields interact with life at the cellular level.

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