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INSIDE

3 Resonance Solutions to the kT Problem

5 Biological Magnetite

6 Magnetically Sensitive Chemical Reactions

7 Membrane Transport of Oscillating Ions

8 The Sodium Channel

9 Further Reading

Recent Research

10 Weak Cancer Link Seen in German Cellular Phone Epidemiology Study

12 UK Research Group Replicates Low Intensity 50-Hz Magnetic Field Effect

15 Canadian Study Suggests a Basis for EMF Hypersensitivity

15 *Abbreviations*

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A New Twist on an Old Mechanism for EMF Bioeffects?

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While there is no generally accepted mechanism to explain how weak EMFs can produce biological effects, several classes of possible mechanisms have been advanced. All these proposed mechanisms have deficiencies, which is why a theoretical article by a group of researchers at the University of Athens in Greece is of interest. Panagopoulos and colleagues postulate that alternating electric fields vibrate all ions inside and outside cells in tune with the intensity and frequency of the field, and when the displacement of this ocean of ions (charged molecules) reaches a critical value it trips the switch for opening or closing the channel in cell membranes through which ions such as calcium or sodium move in or out of cells. This process may either allow or prevent the passage of these critical ions, thereby disrupting the cell's integrity and function in very weak fields, like those associated with power lines. This article reviews three major theories of EMF bioeffects mechanisms and discusses Panagopoulos' new theory.

The Mechanism Problem: For at least some investigators and critics of EMF research, lack of a plausible mechanism for low-level EMF bioeffects causes them to doubt the validity of experimental evidence of effects, even those reported by more than one group of investigators. Writing in the journal *Reports on Progress in Physics,* Yale University physicist Robert K. Adair, a long-time skeptic regarding low-level EMF effects, summed up his argument as to why the bulk of the reported research results should be disregarded. After calculating the minimum fields required to satisfy various proposed mechanisms, he disavowed the possibility of any effects from power frequency magnetic fields smaller than 500 mG. How to explain reports of lower level effects? He characterizes the body of research supporting weaker magnetic field effects (some 200 reports by his count) as "pathological science," analogous to the several hundred experiments supporting cold fusion. He suggests that there is a passion in science to discover new patterns that displace older ideas. Because of this, he suggests that funding agencies may encourage investigators to enthusiastically report errors and outliers while penalizing careful work that ends with a negative, especially when the research touches health and welfare areas that are the special responsibility of government bodies that fund research.

Based on unassailable rules of physics and some plausible biological mechanisms as well, Adair sees no reason to doubt high intensity magnetic field effects like the induction of magnetophosphenes (light flash images produced in the retina by fields with a threshold of

Continued on page 2

100 G at 20 Hz), or the clinical use of magnetic fields in bone and soft tissue repair (requiring induced currents of 1 mA/m or more, which requires magnetic fields on the order of 2 G that change intensity over a period of 200 microseconds). As Adair sees it, lower intensity field effects challenge the rules of physical plausibility and therefore the experimental evidence suggesting otherwise simply must be in error.

Many scientists are skeptical about the existence of low-intensity non-ionizing EMF bioeffects based on the low energy levels available for delivery to cells during exposure. First, the energy of non-ionizing radiation in itself is insufficient to break chemical bonds, an action that would be necessary in order to produce the carcinogenic effects of known mutagens and ionizing radiation (damage to genetic material or other important biological molecules in the cell by direct action). At radio and microwave frequencies, high intensity EMF readily penetrates tissues and vibrates molecules to produce the well-known heating effects exploited by microwave ovens. This can clearly produce cell damage, but usually of a nonspecific and potentially fatal nature. As intensity levels decrease and become too low to produce any detectable heating, EMF exposures may still generate tissue electric fields that are capable of stimulating nerves and muscles. Below this intensity level, the reliability of observed bioeffects and the physical mechanisms that cause them become more uncertain. At the other end of the EMF spectrum, the extremely low frequencies used for electric power transmission and distribution, the electric field component does not penetrate tissues easily and most weak electric field effects are limited to the body surface. While extremely low frequency magnetic field components pass through tissues with minimal attenuation, they do not produce much heating. They can induce substantial tissue electric fields if they are of sufficient intensity. However, energy levels actually reaching the interior of the body from environmental levels of extremely low frequency EMF exposure usually induce electric fields in the body that are well below the levels of fields produced by the normal functions of nerve and muscle. Consequently, there is no generally accepted mechanism based on standard physiology and physics to explain how such very low-intensity EMF might exert a biological effect.

As Adair sees it, lower intensity field effects challenge the rules of physical plausibility and therefore the experimental evidence suggesting otherwise simply must be in error.

Below the threshold established by endogenous nerve and muscle electrical impulses, there is a level of random molecular motion and electrical noise in biological membranes that establishes what may be an absolute limit for any possible EMF bioeffects. Thermal "noise" reflects the natural energy background of randomly moving ions and other biological molecules whose magnitude depends on the temperature. This establishes a limit where an imposed EMF introduces no more energy than background heating at biological temperatures. This is often called the "kT limit" because of terms used to denote thermal noise in equations (Boltzmann's constant times the absolute temperature).

Thermal "noise" reflects the natural energy background of randomly moving ions and other biological molecules whose magnitude depends on the temperature.

It seems fundamental that kT must be exceeded if a cell is to be able to detect, let alone respond to, an externally imposed EMF. However, depending on how it is calculated, this kT limit can be a factor of ten or more greater than some of the low level EMFs reported to produce biological effects like altered cell growth patterns, changes in levels of gene expression, or enhanced calcium ion flux through the cell membrane. Explaining such bioeffects requires some means of circumventing the kT limitation of physical theory.

While total energy levels of typical EMF exposures

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are generally considered to be too low to be discerned by a cell against such a background, a different picture emerges if you think in terms of the "information content" of the EMF. By analogy with the way a relatively subdued conversation can be understood by the participants against a noisy background or a weak radio station signal is picked up from the airways and selectively amplified, some scientists working on EMF research have suggested that EMFs deliver a message that is detectable by the cell despite the noise level. Ross Adey, a longtime investigator of neurophysiological EMF effects, has characterized this informational content, with particular reference to the endogenous electric

Basically the various suggestions of EMF informational content can be summarized in the concept that an external man-made EMF can "fool" cells by presenting them with a signal that is in some way analogous to normal cell-controlling signals for which they have built-in responses.

fields produced by cells in the brain that are measured in an electroencephalogram, as "whispering between cells." Adey suggests that these fields are not just random, but form part of the regulatory mechanism in neural tissue. Basically the various suggestions of EMF informational content can be summarized in the concept that an external man-made EMF can "fool" cells by presenting them with a signal that is in some way analogous to normal cell-controlling signals for which they have built-in responses. The imposed EMF taps into an existing signal pathway. This leads to initiation of a cascade of amplifying events that are normally associated with the mimicked signal, and which finally produce biological effects. What is the original mimicked signal? Considerable research effort has gone into looking for such a mechanism. A number of potential types of mechanisms have been proposed of which we will discuss three here and then look at the new theory by Panagopoulos and coworkers

Among the most plausible theoretical interaction mechanisms are those that depend on special resonance conditions, combinations of static and alternating magnetic fields that are tuned to make the electrically charged forms (ions) of specific elements such as calcium or potassium resonate. These ions enter or leave the cell through gated channels in the cell membrane, the gates opening or closing in response to the resonating

MECHANISM KEY

- ❶ **Resonance Solutions to the kT Problem**
- ❷ Biological Magnetite
- ❸ Magnetically Sensitive Chemical Reactions
- ❹ Membrane Transport of Oscillating Ions

ions. Another proposed mechanism involves magnetic particles within cells that respond to external magnetic fields, but it is unclear how this response could serve as a generalized mechanism rather than one specifically involved in direction finding, the process where it was discovered. A third class of mechanism postulates that the rates of specific chemical reactions are significantly altered by changes in orientation of magnetically sensitive reactant molecules.

❶ Resonance Solutions to the kT Problem

Several classes of mechanisms have been advanced to overcome the kT limit objection. Since many of the experimental results indicating effects from weak EMFs show that the imposed EMFs must occur in a limited

Among the most plausible mechanisms are those that depend on special resonance conditions, combinations of static and alternating magnetic fields that are tuned to make the electrically charged forms (ions) of specific elements such as calcium or potassium resonate or move in an orderly fashion.

range of specific frequencies, intensities, and/or duration in order to have an effect, a number of the explanations evoke resonance mechanisms. Among the most plausible mechanisms are those that depend on special resonance conditions, combinations of static and alternating magnetic fields that are tuned to make the electrically charged forms (ions) of specific elements such as calcium or potassium resonate or move in an orderly fashion. Calcium and potassium ions enter or leave the cell through gated channels in the cell membrane, and the gates open or close in response to the resonating ions. By analogy, resonance operates like a person pushing a child on a swing. If a slight push is applied at the right time, just after the child passes the point of maximum upward travel and starts to descend again, even a series of gentle pushes can make the child swing higher and higher. Pushes applied at the wrong time, such as before the child reaches the apex of a swing, will not make the

Continued on page 4

child swing higher and can even slow the swing down. Resonance, then, provides a situation where a small input of additional energy has a strong ultimate effect, but only if the specific timing (frequency) requirements are met.

One major class of proposed resonance mechanisms involves altered movement of calcium ions across cell membranes. There is much experimental evidence to support this, although the findings also have significant inconsistency. Calcium has an important function in cells as a "second messenger," participating in biochemical pathways that ultimately exert profound effects on cellular metabolism. Alterations in calcium flow could provide just the type of signal with far reaching consequences that is required for substantial EMF bioeffects.

Ions do not move easily through the lipid portion of cell membranes and special mechanisms (channels) are required to move critical ions and other water-soluble compounds through the membrane.

Movement of ions across biological membranes requires special features. A biological membrane is typically composed of a double layer of fatty molecules (a lipid bilayer), which is relatively impermeable to water-soluble, and especially to electrically-charged water-soluble, materials. For this reason, ions do not move easily through the lipid portion of the membrane and special mechanisms (channels) are required to move critical ions and other water-soluble compounds through the membrane. For ions there are two well-established mechanisms: active transport pumps that require a continuous supply of energy and operate against concentration gradients, and voltage gated channels (leak channels) that open or close in response to electrical signals to allow passive movement (leakage) of ions. It is the latter that concern us here. To affect the cross-membrane flow of an ion like calcium, the EMF must be a signal that mimics the one to which the gate normally responds. But the question remains -- what is this original EMF signal? Electrically charged particles will resonate when exposed to a magnetic or electric field that is alternating at an appropriate frequency, in the same way that sound of a particular frequency can cause objects to vibrate when their physical properties are in tune with that frequency. Some available experimental evidence suggests that certain biological effects may only be produced by specific combinations ("windows") of EMFs tuned to the resonance of calcium or some other ion. A number of types of resonance conditions have been suggested, and each has its adherents and has found both support and contradiction in various experimental studies undertaken to test them. The detailed mathematical mechanisms proposed are often complex but entirely plausible.

Ion Cyclotron Resonance: At least some of the reported experimental results for weak EMF bioeffects fit specific parameters that establish conditions of resonance, called ion cyclotron resonance, for specific ions of biological importance. The experiments establishing resonance are not without their detractors as contradictory results have often been obtained when research groups attempt to reproduce resonance results reported by others. Nevertheless, cyclotron resonance has remained the best possible explanation for at least some low-level bioeffects since the idea was first introduced in the mid 1980s.

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Ion cyclotron resonance, the earliest and most widely investigated resonance theory, occurs when a charged particle in a constant (static) magnetic field is also subjected to a time-varying magnetic field. Under the right conditions, the ion will follow a circular or helical path (depending on the angle between the particle and the field) whose radius depends upon the ion's intensity, mass, and charge. This situation will occur if the ratio of the frequency of the time-varying field to the intensity of the static field equals the charge-to-mass ratio of the particle. With the earth's static magnetic field at about 0.5 G in midlatitudes, most of the biologically important ions such as calcium, potassium, and sodium will respond to frequencies of 10-300 Hz; it is about 38 Hz for calcium. A proviso is that hydration of the ion (association with molecules of water, which is a common occurrence) will affect the resonance conditions by reducing the resonant frequency because of the increase in mass due to the associated water molecules. Another problem with this ion-cyclotron-resonance picture is that the energies involved are below thermal energy levels, making such a mechanism not feasible for free-floating ions in the cytoplasm or outside the cell. Cyclotron resonance conditions are also hard to visualize in the real world since ions in solution and in biological systems are generally not free to move in the large circular paths predicted by physical models based on free-space parameters. On the other hand, within the cell membrane and in the channels specific for the transport of various ions, cyclotron resonance conditions can, on theoretical grounds, be maintained to force ions into traversing these channels in single file along a helical pathway. Channel opening is governed by changes in the local transmembrane potentials in the vicinity of the gated channels. This is related to periodic increases and decreases in local calcium concentrations brought about through a cellular oscillator system, which involves release of calcium intracellularly by proteins inside the internal cell membrane system and into the extracellular medium by the active calcium pump in the boundary membrane of the cell that operates when levels of the ion inside the cell reach a threshold value. Further propagation of the effects of changes in calcium concentration are mediated through such other components as the protein calmodulin to which calcium binds.

An important feature of such ion resonance theories is that they permit interactions to occur between extremely low frequency (ELF) alternating fields and the earth's geomagnetic field.

An important feature of such ion resonance theories is that they permit interactions to occur between extremely low frequency (ELF) alternating fields and the earth's geomagnetic field. The ions involved play major roles in controlling the cell membrane through osmotic forces, participating in a range of cellular metabolic processes and helping to create the electric potential across the membrane. Such a resonance mechanism also seems appropriate as a basis for several clinical applications such as the use of resonance-tuned EMFs to stimulate bone growth in situations where healing of fractures is much delayed or does not occur (see "Electromagnetism and bone repair," *EMFHR* Jan/Feb'01:1-7). However, it is hard to see how findings such as the association of residential EMF exposures (mainly at 50 or 60 Hz) with childhood leukemia seen in a number of epidemiologic studies can meet the exacting criteria necessary for these very specific resonance conditions for any significant length of time. Unlike experimental systems or clinical situations, people do not remain for substantial periods of time in a precise position such that the static and time-varying magnetic fields are correctly aligned and at the right frequency and intensities.

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❷ **Biological Magnetite**
❸ Magnetically Sensitive Chemical Reactions
❹ Membrane Transport of Oscillating Ions

❷ Biological Magnetite

A second class of mechanisms depends upon the fact that cells from the whole range of organisms from bacteria to humans contain minute crystals of magnetite, an iron-containing magnetic material (Fe_3O_4). These crystals are enclosed within double-layered lipid structures termed magnetosomes that are often strung together in linear chains. These structures can be regarded as tiny biological bar magnets that respond to the earth's magnetic field by twisting so as to align with the field. Initially discovered in magnetotactic bacteria and in the specialized organs of higher organisms, including birds and insects that use the earth's magnetic field to provide directions for migration or foraging, magnetosomes provide a mechanism for transducing magnetic information into a biological response. The energy of magnetosome interaction with external fields can theoretically exceed that of thermal noise at low field intensity, so providing a sort of sensitive antenna for weak fields. Magnetosomes also respond to applied man-made fields, as has been shown in experiments in which birds that normally orient in the earth's magnetic field became disoriented and lost their sense of homing direction as a result of exposure to artificial magnetic fields. Human brain tissue also contains magnetite equivalent in amount to several million magnetosomes per gram, so that, even with less than 0.1% of human brain cells containing magnetite, there are a large number of potentially EMF-sensitive cells. Nothing is

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Continued on page 6

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known yet of magnetite's function in humans, but magnetic material has been found in the hippocampus, a region of the human brain which is known to be involved in memory, learning, and sensory processing, and a region which has been shown to be sensitive to applied magnetic fields.

One hypothetical process that might occur is the formation of pores in the cell's double layered lipid membrane by means of energy transfer from the rotational motion of magnetic particles that are coupled to the cell membrane.

One hypothetical process that might occur is the formation of pores in the cell's double-layered lipid membrane by means of energy transfer from the rotational motion of magnetic particles that are coupled to the cell membrane. The result would be a significant change in molecular transport into and/or out of a cell exposed to a magnetic field pulse. However, there are energetic constraints on possible pore formation through association of magnetic particles with pore structures in cell membranes because the energy required for pore creation is much larger than thermal noise. Pore creation involves the rearrangement of membrane molecules within a region much larger than the pore's aqueous interior. For this to happen, a rather intense magnetic field would be needed. To barely satisfy the energetic constraints, an effective pulse would need to be approximately 200 to 500 G for extremely short periods. This means that while pore creation involving individual magnetosomes is theoretically possible, energy requirements impose significant constraints on this mechanism, which could not operate at the level of magnetic field intensity (below 50 mG) involved in typical human exposures. As with the resonance concept, theories based on mediation by magnetite have come under critical analysis. Adair in particular has concluded that the interaction of 60-Hz magnetic fields weaker than 50 mG with biological magnetite will always be masked by thermal noise, but his analysis did not rule out biological effects from more intense 60-Hz fields.

Despite having the potential to respond to a wide range of magnetic stimuli, the magnetosome appears to be a structure adapted to a very specialized role rather than a mechanism suited to play a generalized role in picking up and converting EMF signals to biological effects. It should be pointed out, however, that there have been a number of reports of densely aggregated magnetite that is quite different from the coherent chain-like organization of the magnetosomes involved in sensory processes. Its presence suggests that there may be some other as yet unknown way for magnetic material in cells to interact with external fields. Alternatively, there could be some other functional explanation for this magnetite, such as a role as an intracellular iron storage molecule. A final caution regarding intracellular magnetic particles was provided by Kobayashi *et al.* who noted ubiquitous contamination of cell culture medium with ferromagnetic particles that are actively ingested by cells.

Magnetic detection could be accomplished using a biochemical reaction if the rate of product formation from that reaction depends on the magnetic field strength, and there is some detection mechanism to register the resulting field-dependent differences in product concentration.

❸ Magnetically Sensitive Chemical Reactions

A third potential mechanism postulates effects on chemicals and chemical reactions that are magnetically sensitive. This approach follows from the dependence of many chemical reactions on the orientation of reacting molecules. It assumes that among such chemical reactions there are some whose rates are affected by changes in the orientation of the reacting molecules brought about by a magnetic field. James Weaver and colleagues at the Massachusetts Institute of Technology have shown that such sensitivity could form a plausible basis for magnetic detection by brain tissue, postulating a chemically based biological compass. Magnetic detection could be accomplished using a biochemical reaction if the rate of product formation from that reaction depends on the magnetic field strength, and there is some detection mechanism to register the resulting field-dependent differences in product concentration. These investigators looked into the limitations of this method and concluded that a field variation of 1 to 10 mG could be detected with a minimum detector volume of a few cubic millimeters, so that the amount of brain tissue involved in this perception is very small. Significant temperature variations will not overwhelm the magnetic anomaly if the temperature coefficient for alterations in the reaction rate is low. This is probably

In theory, the rate of any reaction that involves free radicals, molecules that have unpaired electrons, will be sensitive to magnetic fields.

achievable given natural selection for refinement of the detection process. With regard to animal navigation, it should be noted that some animals have been proved to detect anomalies in the earth's magnetic field as small as 1 mG, a 0.2% variation.

Although the authors of this theory were concerned with its significance as the basis for a specific sensory function, detection of a minute change in magnetic intensity as part of an animal's navigation system, the same concept could have wider application. In theory, the rate of any reaction that involves free radicals, molecules that have unpaired electrons, will be sensitive to magnetic fields. Many biological reactions involve such free radical intermediates. Free radicals are highly reactive due to the unpaired electrons they possess. Free radicals form as matched pairs and will tend to recombine with the radical they just split from as long as the electron spins still match: however, the spin of unpaired electrons is redirected by magnetic fields. Thus, a known effect of magnetic field exposure is to extend the free radicals' usually very short lifetimes, which are normally terminated by rapid recombination. During their brief existence, free radicals that do not recombine may react with biologically important molecules through chain reactions in which more free radicals are regenerated. These chain reactions can rapidly cause significant damage to molecules such as DNA. Extension of the natural life span of the free radicals would allow increased amounts of damage to occur. Adair also presented a theoretical evaluation of this possible mechanism for overcoming the swamping of low-energy EMF signals by thermal noise. By his calculation, a 500-mG field may have small but significant effects on the free radical recombination rate, but only under a narrow range of circumstances. The restrictions are such that weak fields on the order of 50 mG, at the upper range of most environmental exposures, would be unable to alter

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the radical recombination rate by even as much as 1%. The implication is that environmental magnetic fields would not be expected to affect biological systems by modifying radical pair recombination rates.

❹ Membrane Transport of Oscillating Ions

Since current theories all face objections on the grounds of energy levels and other issues, a recent theoretical discussion written by Dimitris J. Panagopoulos and colleagues from the laboratory of Lukas H. Margaritis at Athens University in Greece, is

Since current theories all face objections on the grounds of energy levels and other issues, a recent theoretical discussion written by Dimitris J. Panagopoulos and colleagues from the laboratory of Lukas H. Margaritis at Athens University in Greece, is of great interest.

of great interest. Their approach has four features. First, they focused their attention on electric fields in contrast to most ELF EMF research, which has focused on magnetic fields. Of the two EMF components, the electric field is attenuated both by external objects and on penetrating the body, while the magnetic field can permeate the body without significant attenuation and is therefore generally considered to be the component more likely to have a biological impact. However, several lines of evidence suggest otherwise. This evidence includes the poorer correlation of childhood leukemia risk with measured magnetic fields than with wiring configuration or powerline proximity associated with high voltage/current in certain residential epidemiologic studies. In a few occupational epidemiologic studies that measured or estimated electric field exposure, results indicated that the electric field component was an important risk factor in some cancers. Second, the model proposed by these researchers would apply to a wide range of alternating electric fields down to the ELF range, and at those low frequencies even relatively weak fields would show an effect. Third, the simple hypothesis proposed is that an external electric field will

Continued on page 8

exert a force on all free ions existing on both sides of cell membranes leading to vibrational displacement without specific resonance requirements. Lastly, the site of the interaction is, as in ion cyclotron resonance, the gated channel for transport of critical ions. Most of the discussion will refer to the sodium channel, which has been more intensively studied than the gated channels for other ions. Gated channels may differ significantly in details of their operation. For example, the potassium channel differs in its inactivation control and takes significantly longer to activate. However, many other features of the calcium or potassium gates are similar.

As the positions of the free ions change with respect to the fixed charges on the passive transport gate molecules there will be a periodically varying interaction between them.

If the external electric field is alternating, it will force each free ion to oscillate at the same frequency as the field. The amount by which a free ion is displaced in both directions from its starting position during each oscillation is inversely proportional to the frequency of the applied electric field. In contrast, the fixed charges on the gates of the ion transport channels cannot vibrate to a significant extent because of the much larger mass of these structures. As the positions of the free ions change with respect to the fixed charges on the passive transport gate molecules, there will be a periodically varying interaction between them. Voltage sensors determine the open or closed status of the ion channel gates for ions like calcium, sodium and potassium. These sensors consist of four symmetrically arranged positively charged helical-shaped proteins termed S4, which are part of four sub-unit gate structures that extend completely across the membrane (see side bar, "The Sodium Channel"). At a point at which the electrostatic force on the channel voltage sensors resulting from interaction between S4 and the transmembrane voltage exceeds a set value, the channel switches between the closed and open states. In the open state the S4 unit projects outwards into the extracellular space.

Normally, there is a potential difference across the cell membrane of the order of 100 mV; this is what is known as the membrane potential, and corresponds to an electric field intensity of 10,000 kV/meter across the thin membrane. It is maintained by a combination of factors: the operation of the passive ion transport channels, the sodium-potassium pump that actively exchanges these ions, other ion pumps, and the negatively charged

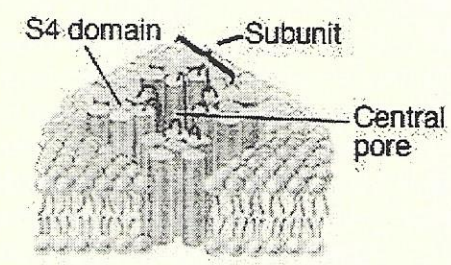
The Sodium (Na^+) Channel

The Na^+ channel is composed of four subunits, each comprised of six transmembrane protein domains, S1-6. There are two gates, the inactivation gate consisting of an amino acid loop connecting two subunits of the Na^+ channel, and the activation gate whose nature is unknown. The activation gate opens when the membrane depolarizes staying open on average about 0.7 milliseconds. The inactivation gate is open as long as the activation gate is closed, but when the latter opens, the inactivation gate closes after a short time, closing the channel again. After repolarization the activation gate closes and the inactivation gate opens.

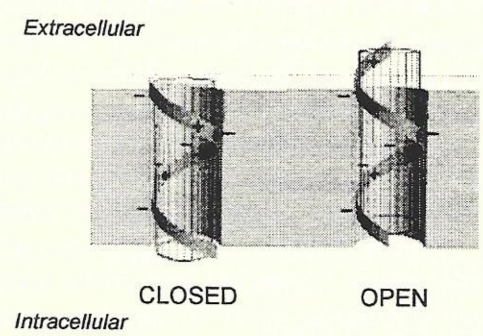
The central S4 domain appears to be the voltage sensor, and opening of the channel may result from its actual physical movement. When the membrane is depolarized, S4 moves so as to project extracellularly. This is probably due to changes in affinity of positive charges that are associated with the S4 protein for the interior face of the membrane as it depolarizes. Movement of S4 appears to open up the channel but it is not understood how this occurs, nor exactly how there is an interaction with external ions.

Presumably either a build up in ion concentration, or synchronized displacement of ions as proposed by Panagopoulos *et al.*, will destabilize the interaction between S4 and the channel membrane.

The Sodium Channel in the Bilayer Plasma Membrane of Cells



Movement of the S4 Domain



Sodium channel graphic adapted from Paul Patton, University of Illinois at Urbana Champaign, http://soma.npa.uiuc.edu/courses/bio303/Ch5b.html
S4 graphic adapted from College of Pharmacy at University of Texas Austin, http://www.utexas.edu/depts/pharmacology/gonzales/channel.html

lipid molecules on the inner membrane surface. Experimental studies in nerve and muscle fibers have shown that a minimum change in membrane potential of about 30 mV is needed to cause the gates to open and permit the exchange of sodium and potassium ions across the membrane. Model calculations show that the synchronous movement of the oscillating ions in the vicinity of S4 induced by an external applied field can give an

Model calculations show that the synchronous movement of the oscillating ions in the vicinity of S4 induced by an external applied field can give an electrostatic interaction with the gate that is of a similar order of magnitude to that given by a physiological change in membrane potential.

electrostatic interaction with the gate that is of a similar order of magnitude to that given by a physiological change in membrane potential. Panagopoulos and colleagues proceeded with mathematical proof that displacement of a single positively charged ion by four billionths of a millimeter from its normal position, easily induced by a moderate electric field, can generate the same electrostatic interaction as a 30 mV change in membrane potential. This will cause the gates to switch between closed and open states for ions already in the channels. They discussed potential problems due to thermal motion of the ions, pointing out that in contrast to the coherent motion of all the ions in phase induced by an electric field, thermal motion is a random process with no net overall directional displacement of the cloud of ions. Furthermore, thermal motion has never been shown experimentally to play any major role in affecting the operation of the gated channels.

In contrast to theories based on ion resonance, in this theory many combinations of frequency and field intensity can cause biological effects on cells. A crucial point is that at ELF frequencies (*i.e.*, those below 1,000 Hz) even very-low-intensity electric fields of a few V/m can alter the configuration of the ion channel gate and cause biological effects. Above about 1,000 Hz, there is a linear relationship between the minimum intensity needed for the biological effect and frequency. As a result, in order to alter the gate status and have a biological effect through this particular mechanism, the intensity must be at least 100 kV/meter for a 100-MHz radiofrequency field and at least 10 megavolts/meter for a 10-GHz microwave field. Of course, biological effects of high frequency fields of such intensity are known and they result from a quite different mechanism, namely heating and damage to tissues, and it is these thermal effects that have led to the establishment of exposure limits for these extremely high frequency EMFs.

The irregular gating of ion channels by the mechanism proposed by Panagopoulos and fellow researchers could affect the electrochemical balance of a cell's boundary membrane. Through this mechanism, ELF-EMF exposure in particular could have significant consequences for such cellular functions as exchange of calcium and other ions, and the signaling mechanisms that are dependent on them. Sodium and potassium

The mechanisms depend upon some measure of interference with the channels that exist for the passive movement of ions across biological membranes, both the cell membrane and the membranes of structures within the cell such as the mitochondria and the nucleus.

exchange is critical for balancing out the charges on the cell membrane and maintaining its electrical properties and its integrity. Looked at from the perspective of ion transport, the mechanism proposed by these researchers falls into the same general category as the ion resonance theories. All depend upon some measure of interference with the channels that exist for the passive movement of ions across biological membranes, both the cell membrane and the membranes of structures within the cell such as the mitochondria and the nucleus. Further, the proposed mechanism would not rule out the possibility that displacement due to ion resonance would be *superimposed* at the specific resonance frequency, leading to greater displacement and an increased biological effect. However, this new wrinkle on an old mechanism appears to be free from some of the constraints that apply to other versions. It also emphasizes the electric rather than the magnetic component of the EMF as the generating force for ion motion. Whether it will stand up to theoretical and experimental challenge remains to be seen. ❁

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Continued on page 10

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Dr. William A. Creasey holds a D.Phil. degree in biochemistry from the University of Oxford for thesis research on the effects of ionizing radiation and received postdoctoral training in pharmacology as applied to oncology at Yale University. Dr. Creasey has published approximately 100 original articles and reviews and three books of which he was sole author, including *Cancer: An Introduction*, published by Oxford University Press, and *Diet and Cancer*, published by Lea and Febiger. A prior *EMFHR* article by Dr. Creasey, entitled, "Can power-frequency electromagnetic fields be mutagenic?" appeared in the March/April 2000 issue.

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Recent Research

CELL PHONE CANCER EPIDEMIOLOGY

Weak Cancer Link Seen in German Cellular Phone Epidemiology Study

The few epidemiologic studies of cellular phone users that have been published to date generally give no indication of increased cancer risk (see "Two cellular-phone studies for Christmas." *EMFHR* Nov/Dec'00:1-6). These results have been welcomed as comforting indications of phone safety, but widespread heavy cellular phone use is still a relatively recent phenomenon and the study authors themselves readily admit that their results can say little about possible effects of long-term,

The researchers noted an increase in uveal melanoma (UM), a rare form of intraocular malignancy with a European incidence rate of up to 1 per 100,000 person-years, associated with exposure to radiofrequency (RF) EMF.

high-level cellular phone exposures. Known chemical carcinogens act with a characteristic "latency period" that must elapse after exposure before a cancer appears. If there are any similar adverse effects from cellular phones, it is likely that they will only be detected by closely monitoring many individuals who have already integrated heavy cellular phone use into their daily personal and work life. For this reason, even statistically insignificant indications of possible risk increases are scrutinized closely. As scientists, we know these are more likely to be chance associations than true adverse effects, but since the human experiment of cellular phone use is already underway, we do not want to overlook even dubious indications of hazards.

A provocative cancer association emerged early this year in published results of a German population-based case-control study conducted between 1994 and 1997 on occupational risk factors for 8 rare malignancies. Andreas Stang and coworkers from the Epidemiology and Ophthalmology Departments at the University of Essen noted an increase in uveal melanoma (UM), a rare form of intraocular malignancy with a European incidence rate of up to 1 per 100,000 person-years, associated with exposure to radiofrequency (RF) EMF. To