reported in next week's *Science*.) In keeping with the idea that activation of the receptor leads to aggressive tumor growth, the researchers find that the peptides are made just by cells from invasive breast tumors.

Several of the growth factors made by breast cancer cells, including the new ones identified by Lippman's group, act on the cells they came from. But others, including the fibroblast growth factors (FGFs), may act on other cell types.

The FGFs contribute to tumor growth by stimulating the formation of the blood vessels needed to nourish expanding tumors. They are therefore another potential target for cancer therapy. In fact, Lippman reported at the Cold Spring Harbor meeting that experiments done with Anton Wellstein, also at Georgetown, have shown that pentosan polysulfate, a carbohydrate related to the natural anticoagulant heparin, blocks the growth of mammary and other tumors in nude mice. The substance works, Lippman says, by binding to the FGFs.

Pentosan polysulfate is already used in Europe as an anti-anticoagulant and has so far shown little toxicity, Lippman says. In any event, the Georgetown group will be starting a clinical trial of the drug in patients with advanced breast and other types of cancers in the next week or two.

At least one other group has already begun a clinical trial of a therapy aimed at depriving a cancer of the growth stimulation it needs. Thomas Waldmann and his colleagues at the National Cancer Institute have chosen as their target the receptor for interleukin-2 (which is also known "T cell growth factor"). The gene encoding the interleukin-2 receptor has so far not been found to be a classical oncogene, but the rationale for the Waldmann group's therapy is essentially the same as that employed by the other researchers—use an antibody or other agent to stop a growth factor from stimulating cancer cell growth.

The interleukin-2 receptor is a good target for such therapy, Waldmann says, because it is present only on the surfaces of actively dividing cells, including those of several leukemias and lymphomas. Waldmann and his colleagues have treated 20 patients with one of those cancers, adult T cell leukemia, with a monoclonal antibody that recognizes and binds to one of the two proteins that together make up interleukin-2 receptor. Although the leukemia has proved refractory to other treatments, seven of the 20 who received the antibody have gone into remission, four of them complete.

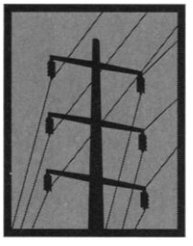
The treatment did not appear to cause toxic side effects, but there were other problems. Most of the remissions lasted only 5 to 8 months, Waldmann says, apparently because the patients eventually mounted an immune response to the therapeutic antibody, which was of mouse origin. And although the antibody could inhibit tumor cell growth by binding to the interleukin-2 receptor, it did not kill the cells. "It knew where to go, but didn't know what to do when it got there," as Waldmann puts it.

So now Waldmann and his colleagues are trying to develop new and improved antibodies that can overcome these problems. Cary Queen of Protein Design, Inc., in Palo Alto is "humanizing" the mouse monoclonal by substituting human antibody sequences for all portions of the molecule except those that bind the receptor. In addition, the NCI group is combining the antibody with toxins or radioactive isotopes that might be able to kill cells bearing the interleukin-2 receptor after the antibody binds.

The hope is that the oncogenes and the other growth regulators that have been so helpful to researchers in probing the biology of normal and malignant cells will also be reliable guides to cancer therapy. What will happen in the planned clinical trials remains to be seen. But if they should not prove successful, it's nice to known that there are many more genes that could also be potential targets for therapy. ■ JEAN MARX

Electromagnetic Fields: The Biological Evidence

Researchers now accept that even relatively weak EMFs have biological effects, but the evidence for health effects remains "iffy"



The second in a series.

OVER THE PAST FEW YEARS, epidemiological studies that seem to show links between exposure to electromagnetic fields (EMFs) and cancer—especially leukemias, lymphomas, and brain cancer—have generated headlines and prompted public concern about the hazards of living near power lines and operating electrical equipment. But while these studies are suggestive, they are sometimes contradictory and often lack statistical significance, and that has led most scientists to decide that the epidemiological data by themselves are inconclusive (see *Science*, 7 September, p. 1096). A recent draft report on EMFs and cancer, prepared by the Environmental Protection Agency, concludes, for example, that there is not enough evidence to classify the fields as "probable human carcinogens."

So researchers are studying how the body reacts to EMFs at the cellular level, in the hope that this will shed some light on the epidemiological findings. After more than a decade of laboratory experimentation, there is still no direct evidence that EMFs cause or promote cancer in lab animals. But during that time scientists have discovered a number of ways EMFs can affect biological functions, including changes in hormone levels, alterations in the binding of ions to cell membranes, and the modification of biochemical processes inside the cell, such as RNA transcription and protein synthesis.

Could any of these biological effects explain how EMFs might increase the risk of cancer? Some scientists think it's possible. Calcium ion concentrations in the cell, for instance, plays a major role in cell division, which in turn has an important part in cancer promotion. And recently, researchers at Battelle Pacific Northwest Laboratory in Richland, Washington, have come close to showing a direct EMF-cancer link in rats. They have found that EMFs suppress levels of the hormone melatonin, something that other researchers have shown makes female rats more susceptible to chemically induced breast tumors.

Despite these possible connections, "it's still not clear whether these biological effects translate into health effects," says Imre Gyuk, who manages the EMF research program at the Department of Energy. The Battelle work, for instance, hints at an EMF–breast cancer connection, but the epidemiological evidence pointing toward breast cancer is weaker than for leukemias, lymphomas, and brain cancers. Many of the laboratory experiments have been done at EMF intensities thousands of times higher than those people normally encounter at home or at work. And little of the data has been independently replicated by researchers in separate labs. As a result, Gyuk says, many of the results are still "iffy."

To some researchers, it is amazing that the

Breast cancer connection? *Bary Wilson's melatonin work is suggestive.*

EMFs produced by power lines and electric appliances have any effect on the body at all. In the early and mid-1970s, most scientists thought that because these fields have low frequencies—and thus low energies—they would be far too weak to have biological effects. The energy carried by photons of 60-hertz electromagnetic radiation is too meager to break chemical bonds, as x-rays do, or even heat up things in their path, as microwaves do. So how could EMFs have any biological effects?

The answer to that question, it now seems, may lie in the fact that low-frequency EMFs induce weak electric fields inside the body. Low-frequency EMFs—such as those produced by the 50- and 60-hertz electric currents in power distribution systems—behave as if they consist of independent electric and magnetic fields, each of which interacts with the body in its own way. An external electric field induces a much smaller electric field inside the body—usually about one ten-millionth the size of the applied field—and this induced field accelerates ions, creating electrical currents in and around cells. An oscillating magnetic field, such as from a 60-hertz power line, also creates an induced electric field and currents.

If these oscillating fields do affect cells, "the cell membrane is where the interaction is likely to be," says Jim Weaver, a physicist at the Massachusetts Institute of Technology who studies the effects of physical stimuli on biological systems. The EMFs may alter something on the membrane, perhaps the conformation of receptors on its surface; these changes in turn appear to modify signals that are sent through the membrane into the interior of the cell; and the final result is a change in some aspect of the cell's biochemistry, such as protein synthesis.

The problem with this model, though, is

Face to Face with EMFs

Standing in the grasp of an intense electric field is a spooky experience. You see nothing and hear nothing, but suddenly the hairs on the back of your neck are standing on end. As the field increases, the sensation spreads across your body. "You can feel a pulsing," says Charles Graham, who runs an electric field exposure test facility at Midwest Research Institute in Kansas City, Missouri. "It's a creepy, crawly feeling, like bugs crawling across your skin."

A magnetic field is harder to detect, but one that is 200 times as strong as the earth's magnetic field and oscillating at 20 times a second does the trick. Under those conditions, the magnetic field interacts directly with the retina and becomes palpable as waves of faint light that ripple across the visual field.

The fields that produce these dramatic sensations are stronger than anything a person normally encounters, even standing directly under a high-tension power line. In fact, most electromagnetic fields (EMFs) outside the laboratory are imperceptible. But imperceptibility does not imply the lack of an effect, and researchers who study how humans and other primates respond to EMFs have found that physically undetectable fields can produce physiological and behavioral changes. So far, however, none of these whole-body changes have been linked to specific health effects.

In the mid-1960s, Russians scientists reported that workers in a high-voltage power switchyard were suffering from headaches, fatigue, and decreased libido, and there have been anecdotal reports of various physiological effects of EMFs since then, but most of the observations have been poorly characterized. MRI's Graham is trying to change that. He has exposed human volunteers to 60-hertz EMFs of slightly higher intensities than those directly under a high-voltage transmission line: electric fields of up to 12 kilovolts per meter and a magnetic flux of as much as 300 milligauss. At these levels, the subject cannot sense the EMFs, Graham says, but the fields are strong enough to produce consistent changes in both heart rate and test performance.

"The heart rate slows within 3 or 4 minutes after you turn the field on or off," Graham reports, each time returning to its normal rate within a few minutes. The average drop in heart rate is about three beats per minute. Graham has also found subtle changes in brain activity, as well as a slight slowing of reaction time and a minor deterioration in performance on time-related tests, such as estimating the passage of time. All of the changes disappear after the field is turned off.

At the molecular level, Graham says, "We checked out umpteen different biochemical tests, and we haven't found anything"—no changes in hormone levels and no differences in the blood cell counts. That may be because the 24- and 36-hour periods over which the tests were done were too short, he notes. It might take weeks or even years for some effects to appear, but no one wants to try that on humans.

Baboons are a different matter, however, and Walter Rogers at the Southwest Research Institute in San Antonio has exposed these animals to intense electric fields for weeks at a time. The apes can sense fields as low as about 12 kV/m—approximately the same as the perception threshold in humans—and they accept fields up to 66 kV/m without pain. In one experiment, Rogers exposed the baboons to a 30-kV/m field for 12 hours a day, and looked for effects on learning activities and social behavior. "On the first day of exposure, the monkeys don't do anything—they look slightly sedated," Rogers reports. But by the beginning of the third day, they're all performing tasks just like the baboons in the control group, who get no EMF exposure. "There is something interesting [to the baboons] about the first exposure," Rogers says. "Maybe the apes are just responding to a new sensation, getting used to it, and then deciding to act as normal." Social behavior among the exposed baboons is noticeably different at first, too, he says. During the first week, there is more passiveness, more tension, and more grooming and scratching than in the control group, but after another week, their behavior returns to normal.

Like Graham, Rogers ran a battery of biochemical tests on his subjects and found nothing. Nor is there evidence that the baboons' exposures led to the simian equivalent of headaches or fatigue. Although he couldn't ask the apes how they felt, Rogers says that because there was no noticeable difference between the controls and exposed group, it seems unlikely that the fields made the baboons feel worse. The combination of human and ape data seems to imply that whatever effects EMFs may have over periods of years, they do little or nothing obvious over the short run. ■ **R.P.**

that no one knows how the rather weak fields and currents induced by EMFs could make their presence felt in the midst of the electrical activity that naturally takes place inside the body all the time. Cells maintain electric fields across their outer membranes, for instance, that are billions of times larger than the electric fields induced by EMFs from power lines. And the electric signals of the heart induce currents in the tissue surrounding the heart that are as high as 10 to 100 milliamperes per square meter—100 to 1000 times as intense as the currents induced by EMFs from power lines.

Several researchers, including Weaver, have suggested ways in which the small signals from EMFs could be detected by cells, but they are all rather speculative. At this point, the only thing that appears certain is that cells do manage somehow to respond to EMFs no larger than those commonly found in the environment.

One such response that has been replicated many times is a modification of melatonin production by the pineal gland. Melatonin is a regulatory hormone whose levels have been linked to various cancers, especially breast and prostate, as well as to the functioning of the immune system. At Battelle Pacific Northwest Laboratory, a series of studies has shown that 60-hertz electric fields of about 2 kilovolts per meter reduce the amount of melatonin in the rats' pineal glands at night, when melatonin levels are normally at their peak. And at the University of Texas Health Science Center in San Antonio, Russel Reiter has found that by quickly turning on and off magnetic fields of 0.8 gauss—twice the strength of the earth's field—he can reduce rats' nighttime melatonin levels by 30 to 50%.

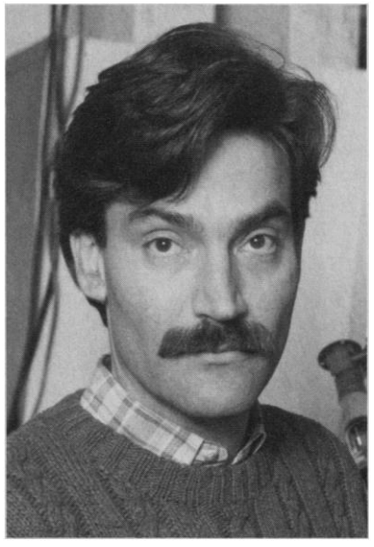
The melatonin studies may be one experiment away from finding a direct link between EMFs and cancer. Bary Wilson at Battelle notes that other researchers have found that lower melatonin levels leave the rats vulnerable to chemically induced mammary tumors. Rats whose pineal glands have been surgically removed are more likely to develop tumors, and will develop more tumors on average, than rats with intact pineal glands; on the other hand, rats whose pineal glands have been removed but that are given melatonin injections are no more likely to develop tumors than the controls.

Battelle scientists plan to attempt to reproduce the results with EMF exposure in place of the pinealectomy. They hypothesize that the EMFs will lower melatonin levels, leaving the rats more prone to developing tumors. Preliminary, unpublished data do show an effect, Wilson says, but it was necessary to put together data from two groups of animals to get statistical significance, weakening the overall results. He now plans to perform the experiment on a larger group of animals in hopes of getting statistical significance from a single data set.

The melatonin work has also received support from a recent epidemiological study. In 1987, Richard Stevens at Battelle reasoned from the laboratory evidence to suggest that EMFs might promote breast cancer, although at the time there was no epidemiological evidence of that. He pointed out that since melatonin suppresses sex hormones, lower levels of melatonin would lead to higher levels of estrogen and prolactin, which are known to be associated with increased risk of breast cancer.

In June, epidemiologist Paul Demers at the Hutchinson Cancer Research Center in Seattle released a report that seems to have borne out Stevens' prediction. The study found that male electricians, utility linemen, and power plant workers had six times as great a chance of developing breast cancer as males who worked in jobs with no EMF exposure. Now Stevens and workers from the Hutchinson Center are putting together a proposal to look for a link between female breast cancer and EMF exposure. Two earlier studies have looked for such a link with conflicting results, Stevens notes. One saw a correlation between EMF exposure and female breast cancer, and the other didn't, but neither result had a high statistical significance. No laboratory data, however, yet bears on the childhood leukemias and brain cancers that the epidemiological work has most frequently linked to EMF exposure.

Although the melatonin studies at Battelle and the UT Health Science Center show that EMFs can have measurable biological effects, they say nothing about how. But a series of experiments at other labs is slowly assembling a picture of the ways in which EMFs interact with individual cells.



EMFs and calcium flow. *Robert Liburdy's magnetic fields alter the uptake of calcium ions.*

The first clear, reproducible evidence of EMFs affecting biological tissue was the observation of a change in how calcium atoms leave the cell membrane. In 1976, Suzanne Bawin and Ross Adey at the Space Biology Laboratory at the University of California, Los Angeles, took the brains from freshly killed chicks, cut them in half, put them in solution, and exposed one half to an electric field and used the other half as a control. They found that the brain cells exposed to the electric field held onto much more calcium than the unexposed cells. Carl Blackman, a researcher at the Environmental Protection Agency and current president of the Bioelectromagnetics Society, has also seen a modification in the binding of calcium to the membrane, although he uses a different type of EMF exposure and his results generally show less calcium binding in the exposed cells rather than more. Blackman is one of the few researchers who reports seeing effects at EMF levels comparable to normal background in homes.

At Lawrence Berkeley Laboratory, Robert Liburdy has recently completed a series of experiments in which he altered calcium uptake in rat lymphocytes with magnetic fields comparable in intensity to some occupational exposures. He found that, in undisturbed cells, EMF exposure did not affect how much calcium the cells took in from a surrounding solution, but when he first dosed the cells with a mitogen—a substance that triggers cell division—the EMFs' exposure did increase calcium uptake. The increase varied from 20% to 200%, he says.

"This could explain how cell proliferation and division could be altered by signals at the cell membrane," Liburdy says. Once the mitogen binds to the cell membrane, it sends a signal to the interior of the cell that eventually triggers cell division. Calcium flow through the membrane is an important part of this signal, and the increased calcium uptake is an indication that the mitogen's signal is somehow being amplified by the EMFs, Liburdy says. Since cancer growth is dependent on cell proliferation, these findings might offer a way that EMFs could promote cancer, Liburdy adds, but the connection is rather tenuous.

At the University of California, Riverside, biochemist Richard Lubin is also trying to trace the path of EMF-induced effects on the cell membrane and into the cell. He works with osteoblasts, the specialized cells that produce bone. For more than 15 years, orthopedic surgeons have used strong, pulsating magnetic fields to speed the healing of fractures that have not joined by themselves, but no one understands why the

fields trigger the bone healing. Lubin now thinks he is close to an answer.

Once again, the EMFs appear to be modifying a signal that passes across the membrane—this time a signal triggered by parathyroid hormone, a substance that stimulates the breakdown of bone and inhibits bone growth. Magnetic fields, Lubin says, seem to block the action of this hormone. To test the effects of high-intensity magnetic fields on the receptor for parathyroid hormone, he did a series of experiments using monoclonal antibodies designed to recognize various parts of the receptor. Turning on a magnetic field doesn't alter the binding of monoclonal antibodies designed to mimic the hormone, Lubin says, "but the monoclonal antibodies that recognize the signal transduction region are being affected." His conclusion: "The induced electric fields are changing the pattern of charges on the surface [of the membrane] so that the receptor is not in the best configuration to transmit its signal."

Inside the cell, the result is a decrease of up to 80% in the amount of cyclic adenosine monophosphate (cAMP) , an important regulator of cell metabolism. The decrease in cAMP somehow causes an increase in bone synthesis, but that part of the picture is still out of focus.

Researchers have identified several other functions inside the cell modified by EMF exposure. Some have reported that pulsed magnetic fields can alter DNA synthesis. And in a series of experiments at Columbia University in New York City, Reba Goodman and Ann Henderson have modified RNA transcription—the process of making molecules of messenger RNA from the DNA template—and protein synthesis. Working with both 60-hertz magnetic fields and the complicated pulsed fields used to facilitate bone healing, they found that their cell cultures produced more than the normal amount of some proteins and less of others.

On the other hand, a number of experiments have shown that low-frequency EMFs apparently do not cause mutations in the cellular DNA. This is consistent with theory. Since low-frequency EMFs have too little energy to damage molecules.

So does any of the laboratory evidence point toward a connection between EMFs and cancer in humans? As with the epidemiological data, the laboratory data remains maddeningly inconclusive. The most suggestive evidence—the melatonin work—points toward breast cancer, which is not one of the types of cancer with the most epidemiological data behind it. For now, says Gyuk at DOE, what is known about the biological effects of EMFs makes it at least possible that the fields could promote cancer. But whether "possible" ever turns into "probable" depends on the results of further research. ■ **Robert Pool**

Eternal Plague: Computer Viruses

Can there ever be an all-purpose vaccine against an ever variable late 20th-century plague? No, we're not talking about AIDS here, but about computer viruses. And the answer seems to be no. Short of total isolation, there is no way to protect a computer against all possible viral attacks. That, at least, is what William Dowling finds in the September issue of the *Notices of the American Mathematical Society*.

Dowling is a computer scientist at Franklin Electronic Publishers in Mount Holly, New Jersey. His finding is an illustration of some elementary but far-reaching techniques in mathematical logic, techniques he applied to show that the existence of computer viruses is "an inevitable consequence of fundamental properties of any computing domain."

That's not to say programs designed as computer virus vaccines don't work. On the contrary, once a particular virus has been identified, it's relatively easy to combat. What is futile, Dowling's work shows, is to look for a single "magic bullet" that will eradicate all conceivable computer viruses.

Dowling considers two basic types of computer virus and shows that neither can be eradicated without severely restricting a computer's capacities. The first kind of virus simply reproduces: it is a program whose output is always a copy of itself. If a programming language is powerful enough to permit programs that interpret the language and manipulate other programs as input, then, Dowling demonstrates, those programs are inevitably open to attack by a self-reproducing virus.

The second type of virus is a program that infects and alters an operating system—the larger "environment" that programs run in but normally don't affect. In this case, Dowling finds, no single program can correctly identify all viruses unless the operating system is unalterable. Indeed, computers that store their operating system in read-only memory are impervious to this type of virus, but most computers are vulnerable, because their operating system is stored in the main, writable memory.

Dowling's second argument hinges on diagonalization, a familiar technique in mathematical logic. Diagonalization lies at the heart of Kurt Gödel's famous incompleteness theorem and Alan Turing's pioneering work on the theory of computing. Roughly speaking, diagonalization is a way of creating paradoxes out of seemingly sensible statements by making them self-referential. For example, the statement "all the statements in the *Encyclopedia Britannica* are true" is unproblematic: it may be true or false, but it is not self-contradictory.

On the other hand, the proposition "this statement is false" poses a logical puzzle: if false, it's true, and vice versa. What makes this pertinent to computer science is that computer programs, which are normally thought of as instructions for turning input into output, are themselves a kind of input. Hence they can operate on themselves and on each other in a way that is somewhat analogous to self-reference—and analogous paradoxes emerge.

For example, in the case of Dowling's second type of virus, you rapidly run into a quandary if you assume that there is a detection program that can correctly identify all such pathogens. The argument (a bit tortuous, to be sure) runs something like this. A universal virus-detection program is equivalent to one that says "yes" if a program P is safe to run with input X and "no" if running P with input X would alter the operating system. But this opens the door for a new program that can take other programs as input. The new program runs harmlessly if the detection program says "no" to program P with P itself as input, but otherwise it alters the operating system. The contradiction occurs when you ask the virus detector if this new program is safe to run with itself as input. The detector can't correctly answer "no," because then the new program would do nothing. But if the answer is "yes," then the new program would proceed to tamper with the operating system. Arriving at this contradiction implies that it is not possible to formulate such a virus-detectable program.

In practical terms, Dowling's results imply that new computer viruses will continue to appear and new vaccines will be needed. "People writing detection programs will never be out of business," he says. Alvin Thaler, program director for computational mathematics in the division of mathematical sciences at the National Science Foundation, says Dowling's demonstration gives computer virologists a sense of what they're up against. "The good news about viruses," says Thaler, "is that they're written by humans and not by nature. All you have to do [to defeat a virus] is find a smarter or more patient human, and that's easy to do." ■ **Barry Cipra**