**Biologically Based Epidemiological Studies of Electric Power and Cancer**

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As societies industrialize, the health profile of the population changes; in general, acute infectious disease declines and chronic disease increases. Use of electricity is a hallmark of the industrialization process, but there has been no suspicion that electricity could increase the risk of cancer. Recently, however, a number of epidemiologic studies have suggested that electromagnetic fields (EMF) may do just that. Although few cancer experiments have been done yet, there are a number of biological effects of EMF reported in the literature that might provide bases for designing cancer experiments and epidemiologic studies. These include effects of EMF on: a) DNA transcription and translation, b) calcium balance in cells, and c) pineal production of melatonin. Alterations in DNA transcription and translation could have pleiotropic effects. Disruption of calcium homeostasis has many implications including oncogene activation, promotional activity via protein kinases and ornithine decarboxylase (ODC), and increasing oxidative stress. Reduction of melatonin suggests a possible increased risk of cancers of hormone-dependent tissues such as breast and prostate. The idea that a cancer-causing agent must either be an initiator or a promoter should be discarded; indeed, the phenomenologic meaning of these two terms has become confused with imputed mechanistic necessity in recent years. Agents that affect division of normal cells or of fully transformed cells can play an important role in clinical cancer development quite apart from initiation or promotion. Epidemiologic studies of EMF and cancer should attempt to take account of other products of electric power (e.g., light at night) or factors associated with occupational EMF exposure (e.g., toxic chemicals) that may increase cancer risk and therefore act as cofactors or confounders. Epidemiologic and laboratory studies should act synergistically in determining if there is a problem and identifying mitigation strategies if needed. — Environ Health Perspect 101(Suppl 4):93–100 (1993).

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**Introduction**

Industrialization is associated with changes in the health status of a population. There are large differences among countries in the rates of cancer of specific sites (1). The ratio of colon cancer incidence in Connecticut (high rates) to that in Nigeria (low rates) is 10; the ratio of breast cancer incidence in Canada (high rates) to that in the non-Jews in Israel (low rates) is 7. Total cancer incidence varies by about 3-fold among countries. Migrants from one area take on the cancer rates of their new homes, and there are known, or strongly suspected, causes of some of the most common cancers in each society such as hepatitis B virus and liver cancer in Taiwan, and cigarette smoking and lung cancer in the United States. These observations suggest racial factors do not account for the large variations in cancer risk around the world. Rather, lifestyle is believed to play a major role in cancer occurrence. However, it is not clear how much of the variation in risks can be accounted for by specific lifestyles. At one extreme is the confidence that cigarette smoking accounts for 90% of lung cancer in high risk societies; at the other extreme is the lack of understanding of societal differences in stomach cancer risk and why it has declined in the industrialized world. Understanding of breast cancer lies somewhere in the middle. Although major risk factors have been identified for breast cancer, they do not appear to account for the observed international variation in breast cancer rates (2). The reason for the large differences in risk among countries remains a mystery.

Until recently there was no suspicion that any aspect of the use of electric power might play a role in explaining cancer differences among societies. Motivated by the seminal, although limited, observations of Wertheimer and Leeper (3,4) and by recent emerging evidence for biological effects of electromagnetic fields (EMF) from the laboratory (5), interest in the possible role of electric power in cancer risk has increased dramatically.

This paper is deliberately speculative and suggests new avenues for epidemiologic inquiry. Biological effects of EMF are described then reexamined after a presentation of the two-stage model for cancer (6) in order to determine how the biology might relate to carcinogenesis. Implications for timing of exposure, cancer types, cofactors (effect modifiers), and confounders in epidemiologic studies are suggested.

**EMF Biological Effects**

The biophysical mechanisms of interaction of EMF with biological systems is the subject of intense interest, but is beyond the scope of this paper (7–10). Many biological effects of EMF have been reported in the literature over the years and it is not possible here to evaluate each fairly as it might affect cancer risk. Many of these are single reports that have not yet been assessed in other laboratories. However, several biological effects that do have such implications are discussed as they might relate to cancer risk and as they might be accommodated in the design of epidemiologic studies. The following discussion is selective and brief.

**DNA Mutation**

There is evidence that EMF does not damage DNA directly (11,12), although there is one report of increased micronuclei production by 50-Hz electric field exposure (13). Effects of EMF on chromosome segregation might lead indirectly to mutation, although this possibility is in the very early stages of evaluation. In addition, there has been very little study of possible effects of EMF on DNA repair (12).

**DNA Transcription and Translation**

Although direct DNA damage from EMF has not been demonstrated, there have been reports of altered mRNA and protein synthesis (14,15). Goodman et al. (16) reported increased RNA transcription in diptheral salivary gland cells after exposure to a magnetic field. Alterations in protein synthesis have also been observed, and there is a shift to proteins of lower molecular weight with a higher net charge. These results are consistent with...
a model in which translation of protein from mRNA is interrupted (17). Such an interruption of protein synthesis would be interesting in light of the emerging theory of cell cycle regulation by a complex interplay of Rb, the protein product of the retinoblastoma oncogene, with a series of other nuclear proteins (18). If the interaction of Rb with other proteins can be disrupted by EMF due to shortening of the polypeptides and consequent changes in conformation, then effects on cell cycle regulation would be expected.

**Calcium**

Since the report by Bawin and Adey (19), there has been growing interest in the role of EMF in calcium balance in cells and in ion flow in general (20). A window of effect that depends on frequency and amplitude seems to determine whether EMF will affect calcium balance (21). This idea was tested by Smith et al. (22) who reported that diatom mobility, which is dependent on calcium concentration in the growth medium, can be affected by EMF at specified frequency-intensity windows. Reese et al. (23) replicated this result with considerably more variability in response.

Electromagnetic stimulation has been used clinically to improve bone healing. Luben et al. (24) examined the biological mechanisms for this and suggested that the effects are mediated at the plasma membrane either by interference with hormone binding to osteoblasts or by blocking receptor-cyclase coupling in the membrane. They further speculate that Ca$^{2+}$ movement may be involved. Lyle et al. (25) reported that a 13.6 Hz magnetic field with a peak intensity of 20 $\mu$T doubled uptake of normal lymphocytes and of a lymphoma cell line. These researchers point out that calcium concentration and intracellular distribution affects many cellular functions, in particular the protein kinase C, which is important to lymphocyte activation and proliferation.

**Ornithine Decarboxylase**

Ornithine decarboxylase (ODC) is required for polyamine biosynthesis, and levels of it are high in rapidly dividing cells. Tumor promoters such as 12- O-tetradecanoxyphorbol-13-acetate (TPA) rapidly increase ODC activity in cells. Byus et al. (26) reported that a 1-hr exposure of several different cell lines to a low-intensity (10 mV/cm) 60-Hz electric field increased ODC activity (although still far below the levels induced by TPA). They also reported that in Reuber H35 hepatoma cells, 3 hr of exposure first led to an increase, then to a decrease in ODC activity. The monotonically increasing dose--response that might be expected from a toxic chemical model is not evident. Instead, a 1-hr exposure to 10 and to 0.1 mV/cm increased activity, and 5 and 1 mV/cm had no effect.

**Immune Function**

Lyle et al. (27) reported that exposure to a 450-MHz field amplitude modulated at 60 Hz inhibited the toxicity of T-lymphocytes by 20%. The carrier wave had no effect, and amplitude modulation higher (up to 100 Hz) and lower (down to 3 Hz) showed less inhibition than at 60 Hz. Exposure to a 60-Hz electric field yielded similar results (28). Effects of EMF on intracellular calcium concentration might account for this inhibition (29). Experiments in animals have not shown effects of EMF on immune function (30). In humans, however, there is a report of impaired immune function in aluminum reduction plant workers who have had magnetic field and volatile aliphatic hydrocarbon exposures (30). The study was undertaken because five cases of B-cell lymphoma occurred over a 7-year period in an aluminum plant in Washington state when only 0.2 were expected. Among 23 apparently healthy volunteers from this plant, there was a significant increase in mean T8 and T4 levels, and there was a significant alteration in T4/T8 ratios in ten of the subjects due to disproportionate elevations of the T8 subpopulation. Another investigation, from Yugoslavia, reported that workers occupationally exposed to microwaves had greater numbers of micronuclei and other genomic abnormalities in a sample of their peripheral lymphocytes than controls (31).

**Pineal Function**

The pineal gland is a neuroendocrine transducer that produces a hormonal signal synchronized to the daily light and dark cycle (32). Melatonin, the principal pineal hormone, exerts a generally suppressive action on other endocrine glands. Reduced circulating concentrations of melatonin can result in increased prolactin release by the pituitary and increased estrogen and testosterone release by the gonads (33,34). Production of melatonin is suppressed by light perceived by the retina. Hence, circulating melatonin concentrations are low in daylight and higher at night (35).

Cohen et al. (36) suggested that reduced pineal melatonin production might increase human breast cancer risk because lower melatonin output would lead to an increase in circulating estrogen levels and would stimulate the proliferation of breast tissue. Indeed, early menarche, late menopause, and nulliparity are each associated with an increased risk of breast cancer (37), and all result in a longer period for proliferation of the breast epithelial stem cells at risk (38).

A number of investigators have reported that EMF, under some circumstances, can reduce or suppress melatonin production by the pineal gland (39–45). These observations provided a natural framework for postulating that EMF may influence risk of certain cancers, in particular breast and prostate cancer (46-47). Melatonin inhibits the growth of Dunning prostatic cancer cells transplanted into rats (48), is oncostatic to human breast cancer cells in vitro (49), and inhibits chemically induced breast cancer in rats (50). Light at night (LAN) suppresses melatonin production (34,51). Thus, two products of electric power, EMF and LAN, may reduce melatonin in humans and influence risks of breast and prostate cancers.

Two groups have reported experiments in rats in which a 50-Hz magnetic field increased chemically induced mammary cancer yield (52,53). Beniaivili et al. (52) used a 20-$\mu$T magnetic field, whereas Mevlisen et al. (unpublished data) used a 100-$\mu$T magnetic field. Should these findings be replicable in other laboratories they will be important.

**Two-Stage Model for Carcinogenesis**

The term carcinogenesis is meant to convey the entire process from a beginning with normal cells in a healthy tissue to an ending with a diagnosed malignant tumor. The terms initiation and promotion were originally defined on strictly phenomenological grounds: an initiator is an agent that alone does not produce tumors, yet when followed by a promoter yields many tumors. A promoter is an agent that alone yields no tumors, yet when preceded by an initiator yields many tumors. A promoter followed by an initiator also yields no tumors. The tumors on mouse skin originally used to define initiator and promoter were not in fact cancer; they were benign lesions, many, if not most, of which regressed upon cessation of the promoter. In the last two decades, the terms initiator and promoter have come by some to be used as if they offer deep insight into the process of carcinogenesis, as if a cancer-causing agent is either one or the other, and as if both must be necessary for cancer to occur. An alternative view is that the original definitions of these agents offer evidence on the process of carcinogenesis, but do not define it. The following paragraphs present a model for cancer and a specific interpretation of what initiators and promoters are and how they fit into the larger scheme of carcinogenesis according to this model.

Offering a definition of cancer in quantitative or even qualitative terms runs the risk of ignoring some or many of the myriad characteristics of cancer that have been reported.
However, without a model it is difficult to formulate meaningful studies that might contribute new understanding. Figure 1 is adapted from Stevens et al. (54) and depicts the two-stage model for cancer developed by Moolgavkar and Knudson (6). This model is biologically simple without, so far, being shown to be simplistic; it is currently the most parsimonious model consistent with the body of knowledge on cancer. It provides an appealing framework within which to evaluate the potential carcinogenicity of a putative cancer-causing agent, and to design studies based on specific mechanisms.

According to the model, the drivers of cancer appearance are mutations to DNA and the growth kinetics of normal, intermediate, and cancer cells. A normal cell divides with growth rate $A$ to maintain healthy turnover of a normal tissue. With low probability $\mu_1$, a normal cell may divide and produce a normal cell and an intermediate cell that has suffered one of the two DNA mutations required for malignant transformation. This intermediate cell divides with growth rate $B$ to form an intermediate lesion. An intermediate cell may also divide with low probability $\mu_2$ to yield an intermediate cell and a malignant cell that has suffered the second necessary mutation to DNA. A normal cell may suffer both DNA mutations at a single division with very low probability, $\mu_1$ times $\mu_2$. Malignant cells can divide with growth rate $C$ to form a malignant tumor (i.e., progression). After clinical diagnosis, behavior of the tumor is affected by the clinical treatment as well as all the endogenous factors previously affecting its growth.

Within the context of the two-stage model, an initator is a mutagen delivered at low dose, thus increasing mutation rates $\mu_1$ and $\mu_2$, and the probability of mutating both of the two genes necessary for malignant transformation is low. A promoter is an agent that increases the proliferation of intermediate cells, B (and perhaps normal cells, A). This increases the chance that the second mutation will occur by, for example, mitotic recombination if the two events must occur in both homologous of the same gene (e.g., an antioncogene, also known as a tumor-suppressor gene), or by mutation of a second necessary gene (e.g., a second protooncogene). A complete carcinogen is either a mutagen delivered at high dose or an agent that is both mutagenic and mitogenic. An intermediate cell may not be subjected to a promoter but may still suffer the second mutation to become malignant (depicted by the diagonal arrow leading from the single intermediate cell to the single malignant cell in Figure 1). A premalignant lesion is a proliferation of intermediate cells that are heterozygous for an antioncogene, or that have only one of two different and necessary protooncogenes activated. A malignant tumor is a proliferation of malignant cells which have both necessary mutations. At present, behavior of a malignant tumor is not addressed in the two-stage model. In particular, there may be further genetic alterations necessary for the ability to metastasize. It must be noted that cancer can arise in the absence of application of a promoter since normal cell turnover will still allow for mutation of DNA by a mutagen. Cancer can also arise in the absence of a mutagen since spontaneous DNA mutations do occur.

A prediction based on the two-stage model is that application of a low dose of a mutagen to a benign tumor will greatly increase malignant conversion of the tumor [so-called initiation-promotion-initiation (6)]. Experiments have confirmed this prediction (55). It must be stressed that agents that increase proliferation of normal or intermediate tissue will increase cancer risk apart from any direct effect on DNA. Such proliferation stimulating agents (promoters are one class) may account for a greater proportion of cancer cases than strictly genotoxic agents in the environment (56).

The darkness of the arrows in Figure 1 provides a very rough sense of the relative probabilities of the respective pathways leading to cancer. There is growing evidence that cancer arises from the malignant conversion of a single cell (57). If this is true, then although the probability of transformation of a particular cell is extremely low, the probability that at least one cell of a tissue becomes transformed is much higher. The darkest arrow leads from a normal cell to a normal tissue since this is the normal process. The probability that at least one normal cell will become malignant at a single cell division cycle is the product of $\mu_1$ and $\mu_2$. Typical mutation rates are approximately $10^{-7}$ per cell per division (58), so that even with approximately $10^{10}$ cells in a given tissue, the chance of a cancer cell arising is very low. However, the chance that an intermediate cell will arise is not so low. Intermediate cells divide as do their normal counterparts, and they may have a growth advantage, as when a promoter is applied and an intermediate lesion appears. Within an intermediate lesion, the chance that a malignant cell will arise depends on the second mutation rate and the rate of division of the cells of the lesion.

Some hereditary cancer syndromes can be equated to a germ-line mutation with inheritance of all cells in the intermediate stage. Retinoblastoma is the model for this growing list of cancers (59). The Rb gene confers a 100,000-fold increased risk for retinoblastoma in those who inherit one absent or defective homolog. Whereas the probability that a particular cell will suffer the second mutation and become malignant is very low (and therefore the syndrome is recessive at the cellular level), the probability that at least one cell of the tissue will suffer the second
mutation over the life of the individual is extremely high, approaching one (and therefore dominant at the level of the tissue).

**Epidemiological Study Considerations**

Consideration of biological effects of EMF suggests particular design features for epidemiologic studies (Table 1). Within the context of the two-stage model described above, temporal sequence of exposure, interaction with other agents, and confounding factors depend on how EMF is hypothesized to affect cancer risk.

The lack of direct effects on mutation suggests that if EMF increases cancer risk, it is not by increasing $\mu_1$. However, if the accurate functioning of mitosis is affected, EMF might indirectly lead to mitotic recombination, and the fixation of an oncogene if one is involved; an intermediate cell may yield a normal and a malignant progeny. In this way, $\mu_2$ may be affected and not $\mu_1$.

**Time of Exposure**

Tamarkin et al. (50) investigated the effect of melatonin on chemically-induced mammary cancer in rats. Sixty female Sprague-Dawley rats received 15 mg of dimethylbenzanthracene (DMBA) in peanut oil by intragastric intubation at age 50 days. Following the DMBA administration, 30 rats received daily injections of melatonin and 30 received vehicle injection. Ninety days after DMBA administration, 50% of the vehicle-treated rats had developed tumors, whereas none of the melatonin-treated group had tumors. Melatonin was discontinued in the latter group at this time, and tumors began to appear later. Their next experiment examined the effect of reducing melatonin. Thirty-six pinealectomized and 36 sham-operated rats received 7 mg of DMBA administered as before. Two months after DMBA was administered, 48% of the pinealectomized rats had mammary tumors, whereas none of the sham group had tumors. By day 240 (termination of the experiment), 88% of the pinealectomized rats had tumors, whereas only 22% of the sham group had tumors. These experimental observations showed that melatonin suppresses mammary tumorigenesis in rats, and lack of melatonin increases tumor formation.

Despite the animal and in vitro evidence, it is not clear that alterations in melatonin affect risk of breast cancer in humans. However, if suppression of melatonin does raise human breast cancer risk, then the mechanism by which it acts has important implications for the conduct of epidemiological studies of electric power. As shown in Figure 2, if a mechanism of action is by virtue of a general stimulation of estrogen production, then the increased turnover of the normal breast epithelial stem cells at risk could increase cancer risk. Past exposures to agents such as EMF or light-at-night (LAN) that might suppress melatonin would be important. This can be viewed in Figure 1 as EMF increasing $A$, the growth of normal cells. Exposures as early as puberty might be crucial. EMF exposure many years in the past should be assessed if stem cell turnover is thought to be affected.

However, if suppressed melatonin production increased breast cancer risk by virtue of releasing estrogen-receptor positive (ER+) breast cancer cells from a quiescent state (i.e., progression (60)), then very recent exposures could be crucial. This would be an increase in $C$ in the two-stage model. Similarly, direct effects of EMF on immune cell function (27) also might increase $C$. Very recent EMF exposures should be assessed if cancer-cell growth is thought to be affected (61). Perhaps even exposure within one year of diagnosis should be assessed.

**Table 1** Speculative table of how bioeffects of electromagnetic fields might be related to cancer site, time of relevant exposure, cofactors, and confounders.

| Site | Time* | Cofactors (effect modifiers) | Confounders |
|------|-------|-----------------------------|-------------|
| Transcription/translation | Calcium | Acute nonlymphocytic leukemia, oxygenated tissue (e.g., lung) | Promotion | Ionizing radiation; body iron stores | Toxic chemicals |
| Ornithine decarboxylase | | | | | Free radical producing toxic chemicals |
| Pineal | Cancer cells | Estrogen receptor breast | Progression | | Chemical promoters |
| | Stem cells | All breast/prostate | Prior to initiation | | | |
| | Immune | Non-Hodgkin's lymphoma | | | Shift work, alcohol, light-at-night |

*When time is prior to initiation, then exposures in the distant past are likely to be important; when time is progression, then very recent exposures, perhaps even less than 1 year, are likely to be important.

![Figure 2](image-url) Two possible mechanistic explanations for the observation of Tamarkin et al. (52). In the first, reduced melatonin leads to an increase in estrogen and/or prolatin that leads to an increase in the breast epithelial stem cells at risk. This results in increased DMBA-induced cancer cell production. The second mechanism postulates reduced melatonin leading to the release of existing DMBA-induced cancer cells from their quiescent state. Melatonin also may affect the immune function.
Effects of EMF on calcium balance that might influence promotion via increased oxidative stress or disrupted signal transduction might affect the growth of intermediate cells, B. In studies of these possible mechanisms, time of exposure, cofactors, and cancer types are all influenced (see below). Similarly, effects on ornithine decarboxylase (ODC) might affect B. Effects on promotion predict a time frame for relevant exposure that lies between the distant past and the very recent past, perhaps 2 to 10 years prior to cancer diagnosis.

Cancer Types

Certain leukocytes, such as neutrophils and macrophages, generate oxygen radicals in order to kill foreign cells (62). In contrast, cell-mediated killing by lymphocytes (e.g., cytotoxic T-lymphocytes) appears to depend not on oxidative bursts but rather on the calcium-dependent release of a pore-forming protein that perforates the membrane of the target cell (63). On this basis, nonlymphocytes that use oxidative bursts for their function may be more susceptible to the disruption of their own oxidative defence mechanisms than other cell types. Intracellular calcium concentration and distribution modulate cellular oxidative activity, degranulation, phagocytosis, and mobility (64). Therefore, EMF-induced disruption of calcium balance and increased oxidative stress may affect these nonlymphocytes more than other hematopoietic tissues (65). The observations of increased nonlymphocytic leukemia in occupational studies of EMF and cancer (66) are consistent with this possibility. A study of residential EMF exposure and acute nonlymphocytic leukemia (ANLL) did not find evidence for an association (67); however, occupational exposures were not assessed. Although carefully done, this study was small and does not, by itself, offer strong evidence against a role for EMF in adult leukemia.

Calcium is an important second messenger for gene expression; Morgan and Curran (68) reported that c-fos protooncogene expression in PC12 cells is induced by either receptor–ligand interaction or by alterations of voltage-dependent calcium channels. There is a report that exposure of human polymorphonuclear leukocytes to a static magnetic field of 0.1 T dramatically increased degranulation in a time-dependent manner; the effect was inhibited by calcium-channel antagonists (69). A case–control study of acute nonlymphocytic leukemia in adults that takes account of both residential and occupational exposures should be performed.

There have been three biological effects of melatonin investigated that might influence cancer risk (2) and account for the experimental observations of Tamarkin et al. (50), which showed melatonin inhibited DMBA-induced mammary carcinogenesis in rats. There is evidence that melatonin can a) stop the growth of hormone-dependent cancer cells, b) suppress production of sex hormones (e.g., estrogen, testosterone), and c) augment immune function. These three mechanisms have different implications for cancer types that might be affected (Fig. 3). If EMF or LAN suppresses melatonin and the first mechanism applies, then risk of hormone-dependent tumors could be increased (e.g., ER+ breast cancer). If the second mechanism applies, then risk of cancers of tissues that are dependent on hormones for growth could be increased (e.g., all tumors of breast and prostate). Compromise of immune function was long assumed to increase risk for cancer in general and for all sites. However, recent evidence shows a clear and large increased risk only of non-Hodgkin’s lymphoma, particularly of the brain. There also may be an elevation of some mesenchymal tumors and perhaps melanoma. It is significant to this discussion that the evidence is against a role for immunologic suppression in the etiology of most common cancers such as breast and colon cancer (70).

Among 370 patients diagnosed with malignant melanoma who were followed prospectively, a second primary cancer of breast later developed at a rate six times that expected (71), which suggests a common etiology for melanoma and breast cancer that may involve reduced melatonin. Melatonin has been reported to slow the growth of transplanted melanoma cells in athymic mice (72). Thus, studies of breast cancer and of malignant melanoma in females and in males and of prostate cancer in males should be performed.

Cofactors (Effect Modifiers)

Calcium is important in many aspects of cellular physiology, and it plays an important role as an intracellular messenger for the activation of genes and in intercellular communication. Calcium homeostasis also is important for protection from oxidative stress (73,74). EMF-induced disruptions of calcium balance that might lead to increases in free radicals may inhibit a cell’s ability to protect itself from some other oxidative attack such as a toxic chemical or ionizing radiation. Many tumor promoters are agents that increase radical production in cells (75); this may then provide a mechanism for EMF promotion or copromotion. A proposed test of whether EMF can increase oxidative stress is based on a hepatocyte toxicity assay. It was long speculated that the final event in the death of hepatocytes after exposure to toxins was the influx of extracellular calcium. However, Smith et al. (76) reported that incubation of freshly isolated hepatocytes in a calcium-free medium greatly increased their susceptibility to damage from carbon tetrachloride and other hepatotoxins. The calcium-free medium was not toxic in the absence of the chemical toxins. Reed and Faris (77) speculated about these results and suggested that the calcium-free medium led to a disruption of intracellular calcium, which led to increased oxidative stress and susceptibility to the toxins. If EMF can disrupt intracellular calcium balance and lead to increased oxidative stress, then EMF may increase the toxicity of carbon tetrachloride to freshly isolated hepatocytes (65).

Subtle effects of EMF on calcium homeostasis that might lead to an increase in oxidative stress could go entirely undetected unless they occurred in conjunction with another agent. By this mechanism, EMF may stress a cell not to the point of damage but to the point of increasing susceptibility to other agents. This reasoning leads to the speculation that EMF, under some circumstances, might be a radiosensitizer by increasing oxidative stress and reducing the cellular compliment of reducing equivalents (65).

Increases in oxidative stress could promote or copromote by increasing B, the growth rate of intermediate cells. Balcer-Kubiczek and Harrison (78) used a transformation assay of C3H/10T1/2 cells to determine the interactions of an X-ray, TPA, and a 2.45-GHz microwave pulse modulated at 120 Hz. They found that the microwave alone had no effect and did not increase the effect of the X-ray. However, the microwave...
significantly increased transformation when used in combination with the X-ray and TPA as compared to the X-ray plus TPA without microwave. In addition, microwave and TPA together increased transformation in the absence of the X-ray: neither increased transformation alone. Stuchly et al. (79) have reported copromotion by magnetic fields in the mouse skin.

Ady (80,81) suggested a synergism of EMF with chemical tumor promoters that leads to autonomous cell growth via disruptions of intercellular communication. Recent data in support of this speculation (82) showed that intermittent exposure to a 1-G, 60-Hz magnetic field significantly increased the expression of transformation by TPA of C3H/10T1/2 fibroblasts.

Another possible cofactor for oxidative stress resulting from effects on calcium balance is body iron stores. There is evidence that high body iron stores increase cancer risk (83), and the role of iron in catalyzing oxygen radicals is one possible mechanism (65). Phillips et al. (84) reported that exposure to a 60-Hz magnetic field or to a combined electric and magnetic field produced constitutive expression of transformin receptors on human colon cancer cells in vitro.

Finally, EMF-induced loss of iron from its intracellular storage protein, ferritin, might increase oxidative stress. Therefore, higher iron might increase the effect of any EMF increases in oxidative stress due to disruption of calcium, and, in contrast, EMF itself may increase reactive iron availability within the cell and cause further oxidative stress. There is a need for a study of EMF effects on susceptibility to radiation-induced cancer and cancer induced by chemicals that increase oxidative stress. Body iron stores also should be assessed in these studies.

**Confounding**

The group of confounders that are based on increased oxidative stress from disruption of calcium balance would include chemicals associated with occupational exposure to EMF. These would be chemicals that are known or suspected to derive their toxicity in whole or in part from generation of free radicals. These chemicals may also be cofactors (effect modifiers) as opposed to confounders.

In studies of leukemia, detailed information on exposure to agents that might increase oxidative stress should be gathered. If possible, biomarkers of exposure to these agents should be used in these studies.

If EMF is thought to increase cancer risk via an effect on pinéal function, then possible confounders include LAN, shift work, alcohol consumption, and any other factor that has been shown to affect pinéal function. These factors should be taken into account in epidemiological studies of EMF.

Also, in studies of breast and prostate cancers, other agents that affect pinéal function should be assessed.

**Future Directions**

Epidemiology can be conducted fruitfully in the absence of a biological rationale. Without much understanding of what was bad about cigarette smoke, early studies of smoking and lung cancer made great contributions to understanding people's health and eventually improving it. However, a biological rationale can aid in designing epidemiological studies, particularly in an area such as electric power and cancer, because the design is so challenging. In studies of smoking, it is simple and relatively inexpensive to gather data, because the answer to a question can yield good exposure information. There are also biomarkers of recent exposure to cigarette smoke. However, it is very difficult to assess exposure to EMF (even if there were consensus on what constitutes a relevant exposure); questionnaires are of limited use, and there is no identifiable biomarker of exposure. Therefore, biological considerations enable focused epidemiological studies of specific hypotheses.

There is a place for both epidemiological and laboratory studies in most research programs into the causes of cancer; there should be synergy between the two. Epidemiology can address directly the question of whether increased risk of cancer is associated with some aspect of the human environment such as exposure to EMF. These studies are necessarily crude and can rarely determine precisely what component of the exposure is the culprit because pure, single-agent exposures in human populations are virtually non-existent. EMF is too broad a definition of exposure in epidemiological studies to be very helpful in mitigating exposure, and there is no doubt that electricity will continue to be used whether or not a consensus eventually emerges from epidemiology that EMF increases cancer risk. However, laboratory studies can address what can be done about a problem of increased cancer risk by isolating what component of exposure causes the problem. If laboratory studies could isolate successfully a particular feature of exposure to EMF that accounted for an increased risk of cancer, then mitigation of exposure to that feature might be feasible. The reverse also is true: Laboratory studies can identify previously unsuspected cancer-causing agents that should be investigated epidemiologically.

Biological considerations for epidemiological studies are illustrated in Table 1. This table is speculative and selective. It is not intended to exclude any ideas on possible EMF studies. Rather, it is intended to provide an example of the kind of reasoning that might go from biological rationale to epidemiological design.

Suggested new avenues for study include hormone-dependent cancers and cancers of hormone-dependent tissues, increased susceptibility to radiation-induced cancer, and increased susceptibility to free-radical-producing toxic chemicals.

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