AN INVESTIGATION OF THE BIOLOGICAL EFFECTS OF ELECTROMAGNETIC FIELDS AND RISK ASSESSMENT OF MAGNETIC RESONANCE IMAGING SYSTEMS

by

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S. M. (M I T)

SUBMITTED TO THE DEPARTMENT OF NUCLEAR ENGINEERING IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF NUCLEAR ENGINEER

at the

MASSACHUSETTS INSTITUTE OF TECHNOLOGY

February 1994

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A B S T R A C T

This investigation pertains to the biological effects of electromagnetic fields and risk assessment of magnetic resonance imaging systems. It looks at the question of risk associated with conventional and non-conventional magnetic resonance imaging in terms of acute and chronic exposure, biologically based risk assessment models, risk of carcinogenesis, a biological model based epidemiological study design for cancer risk assessment, synergistic laboratory study of nerve and immune systems, risk assessment of special hazards associated with imaging patients with implanted devices, and the questions/issues relating to electric and magnetic field exposure criteria for patient safety and suggestions for research to resolve outstanding issues.

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1. INTRODUCTION

A time varying magnetic field has the potential for inducing circulating electrical currents within conducting objects. In the case of magnetic resonance imaging (MRI) procedures the induced current in the human body is a by-product that can be caused by conventional magnetic resonance (MR) imagers is well below levels needed to stimulate excitable tissue. Recent developments in fast imaging techniques (non-conventional) are driving technology towards rapidly switched gradients of such an high intensity that nerve and heart stimulation is a distinct possibility. Consequently, the design and operation of future MR imaging devices may include certain constraints if one wishes to avoid excitatory responsees in the exposed subjects.

In this investigation the question of risk associated with conventional and non-conventional MR imaging is addressed in terms of acute (patients who undergo diagnostic examination) and chronic (operators of MR imaging equipment) exposure to static and time varying magnetic fields and radiofrequency radiation. Certain well defined risks such as risk of flying projectiles, cardiac pacemaker and defibrillator malfunction due to static magnetic fields and tissue heating and burns due to radiofrequency field radiation, are known. however the question of nonthermal risks analogous to stochastic risks produced by low doses of ionizing radiation, are yet to be fully studied and issues arising remain to be resolved.

The stochastic risks (cancer mortality) associated with the use of ionizing radiation in radiologic diagnostic and treatment procedures have been historically extrapolated from large populations exposed to ionizing radiation at high doses and different dose rates. The risks inferred are based on epidemiological studies. We are faced with same problem when it comes to using non-ionizing radiation in MR imaging. Epidemiological studies of population exposed to extremely low frequency and low frequency electromagnetic fields

have shown a small increase in cancer risk (10^-4). Such electromagnetic fields are being used in conventional and non-conventional MR imaging. Therefore, this investigation of the biological effects and risk assessment of MR imaging systems was undertaken. An assessment of the biological effects of electromagnetic fields (EMFs), risk of carcinogenesis, patient safety, epidemiological and laboratory studies, and the questions/issues relating to the electric and magnetic field exposure criteria for patient safety and safe operation of MRI equipment are major issues of discussion. Lastly, suggestions are given for research investgations tailored to resolve many issues of concern.

2. BIOLOGICAL EFFECTS OF ELECTROMAGNETIC FIELDS

A number of epidemiological studies during the last two decades have suggested that EMFs may increase the risk of cancer. Biological effects of EMFs reported in the literature might provide a basis for designing cancer experiments and biological model based studies. These include effects of EMFs on:

1. DNA transcription and translation,

2. Calcium balance in cells,

3. Pineal production of melatonin,

4. Mechanical stress on cell structure, and

5. Anatomical link between nerve cells and immune cells.

Alterations in the DNA translation and transcription could have pleotropic (multiple

phenotypic expression or gene) effects. Disruption of calcium homeostasis (relative state of stable equilibrium) has many implications including oncogene activation, promotional activity via protein kinases and ornithine decarboxylase (ODC), and increasing oxidative stress. Reduction of melatonin may result in a possible increased risk of cancer of hormone dependent tissues, such as of breast and prostate. Cellular stretching and stress after exposure to time varying magnetic fields may be the missing link in many unexplainable problems in biology. Recent reports that neurons in the skin form physical links with key immune cells and coat them with neurotransmitters and nerve-cell-produced hormones known to affect the cell function, demonstrartes that an anatomical connection exists among nerve cells, an immune-modulating nerve product and immune cells.

The idea that to cause cancer, an agent must either be an "initiator" or a "promoter" is open to question now. Any agent that affects the division of normal cells can play a vital role in the clinical development of cancer apart from being an "initiator" or a "promoter".

2.1 DNA Mutation

There is evidence that EMFs do not damage DNA directly (1). The effects of DNA on chromosome segregation might lead indirectly to "mutation". This possibility is in the early stages of evaluation. Also, there has been very little study of possible effects of EMFs on DNA repair.

2.2 DNA Transcription and Translation

Goodman et al(2) reported increased RNA transcription in dipteran salivary gland cells after exposure to magnetic fields. Alteration in protein synthesis has also been observed. There seems to be 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.

2.3 Calcium

There has been a growing interest in the role of EMFs in calcium balance in cells and ion flow in general (3). A "window" of effect that depends on frequency and amplitude seems to determine whether EMFs will affect calcium balance (4). Lyle et al (5) point out that calcium concentration and intracellular distribution affects many cellular functions, in particular protein kinase C which is important to lymphocyte activation and proliferation.

2.4 Ornithine decarboxylase

Ornithine decarboxylase (ODC) is required for polyamine biosynthesis, and the levels are high in rapidly dividing cells. Tumor promoters such as (T-P-A) rapidly increase ODC activity in cells.

2.5 Immune Function Experiments in whole animals have not shown effects of EMFs on immune function (6). In humans there is a report of impaired immune function in aluminum reduction plant workers who have high magnetic fields and volatilized aromatic hydrocarbon exposures (7). The study was initiated because 5 cases of B-cell lymphoma occurred over a seven year period in an aluminum plant in Washington state when only 0.2 were expected. Recent reports by Hosol et al (8) of a direct anatomic link between nerve cells and immune system cells points to an interesting research area where further experiments to study the effects of EMFs on nervous and immune system cells may explain the aberrant immune system behavior and various diseases relating to the immune system.

2.6 Pineal Function

A number investigators have reported that EMFs under some circumstances, can produce or suppress melatonin production by the pineal gland (9). These observations have provided a framework for postulating that EMFs may influence the risk of certain cancers, in particular breast or prostate (10). Also light at night suppresses melatonin. Therefore a combination of EMFs and light at night may reduce melatonin in humans and thus influence risks of breast and prostate cancer.

3. MULTISTAGE MODEL

Carcinogenesis is a general term used to describe the development of neoplasia. Carcinogenesis can be induced by exposure to exogenous agents or it can occur spontaneously without external intervention. It can be actively induced by chemicals, radiation, infectious biological agents,transgenesis, or selective breeding. Many carcinogens alter the structure of the DNA resulting in carcinogenesis but a significant number of carcinogens do not appear to act through this mechanism. When actions of specific carcinogens can be considered in relation to the stages of cancer development, initiation, promotion and progression; the mechanism of induction of carcinogenesis by DNA-reactive agents that alter genomic structure can be reconciled with those agents that do not act in this manner. The final stage of carcinogenesis, progression, can occur spontaneously, enhanced by formation and propagation of genetic errors due to increased cellular proliferation associated with the promotion stage.

The development of cancer occurs in stages. The multistage concept of cancer development has been demonstrated during carcinogenesis in a variety of tissues during the last decade.

3.1 Initiation

The stage of initiation that occurs first reflects a permanent and irreversible change in the initiated cell (11). The efficiency of initiation is related to cellular replicative DNA synthesis and cell division (12). DNA synthesis is probably required for the fixation and thus the irreversibility of the initiated state (13). The stage of initiation can be altered by exogenous and endogenous factors. For example, a variety of chemicals in several tissues can inhibit the metabolism of chemicals to their ultimate forms, therby blocking initiation (14). The presence or absence of a threshold, or no effect level for initiating agents has been evaluated only by extrapolation in most studies (11).

3.2 Promotion

The principle characteristic of promotion is in its operational reversibility. Promotion may be continually modulated by a variety of environmental factors, including frequency with which the promoting agent is administered, age of test animal and composition and amount and diet. The dose-response curve of promoting agents exhibits a threshold or no effect level as well as a maximal response. In the absence of experimentally induced initiation, promoting agents increase the risk of cancer development by increasing the proliferation rate of normal cells and enhancing the likelihood of propagating a genetic error. Selective increase in the growth of passively initiated cells can result in tumorigenesis from exposure to promoting agents. Continuous exposure to promoting agents in the humans, like in the experimental animals, can result in malignancy as a result of passive (spontaneous) occurrence of the stage of progression in one or more cells in the stage of promotion.

3.3 Progression

The characteristic of the stage of progression in its kariotipic instability and evolution, and the devlopment of irreversible, aneuploid malignant neoplasms distinguishes it from both initiation and promotion. The alterations in the structure of the genome of the neoplastic cell during this stage are directly related to the increased growth rate, invasiveness, metastatic capability, and biochemical changes in the malignant cell. These changes continue to evolve (progress) during the stage of progression in a variety of different neoplasms, such as multistage epidermal carcinogenesis, leukemias and lymphomas, and multistage hepatocarcinogenesis.

3.4 Passive (Spontaneous) Occurrence of Individual Stages of Carcinogenesis

Passive carcinogenesis as synonimous with spontaneous carcinogenesis is a well recognized phenomenon both in the experimental animal (15) and humans (16). The passive (spontaneous) development of the stage of progression from cells in the stage of promotion most likely results from kariotipic changes that occur spontaneously in the mitotically active population of cells in the promotion stage. The passive development of the progression stage resulting from increased cell proliferation has been proposed as a significant mechanism whereby non-DNA-reactive chemicals can cause development of the malignant disease (10). Therefore, an expanded population of cells in the stage of promotion, actively proliferating under the influence of promoting agent, serves as a reservoir for the passive development of the stage of progression and cancer.

4. TWO STAGE MODEL FOR CARCINOGENESIS

The term "Carcinogenesis" is meant to fully describe the entire process from beginning with normal cells in a healthy tissue to an ending with a clinically diagnosed malignant tumor. The term"initiation" and "promotion" were originally defined on phenomenological grounds: an "initiator" is an agent that alone does not produce tumors on mouse skin, but

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" yields no tumor. The tumors on mouse skin originally used to define "initiator" and "promoter" were not in fact cancer: they were benign lesions, some of which regressed on cessation of "promoter"(17). For the last two decades, the terms "initiator" and "promoter" has been used as if they offer a deep insight into the process of carcinogenesis, and that a cancer causing agent is either one or the other and both must be necessary for cancer to occur. Another view is that the original definitions of these agents offer evidence for the process of carcinogenesis, but do not define it. A model for cancer and a specific interpretation of what "initiators" and "promoters" are and how they fit into the larger context of carcinogenesis, is described as follows.

Figure 1 is adopted from Stevens et al (17) and depicts a two stage model for cancer devloped by Moolgavkar and Knudson (18). This is currently the most careful model consistent with the body of knowledge available on cancer. It provides a framework within which to evaluate the potential carcinogenicity of an existing or commonly accepted cancer causing agent and to design studies of mechanism of biological effects and biological models based epidemiological studies of the EMFs as used in MRI.

According to the model, a normal cell divides with growth rate "A" to maintain a healthy tunover of a normal tissue. With low probability "μ 1", a normal cell may divide to give a normal cell that has suffered one of the two DNA mutations, required for malignant transformation. The intermediate cell divides with growth rate "B" to form an intermediate lesions. An intermediate cell may also divide with low probability "μ 2" to yield an intermediate cell and a malignant cell that has suffered the second mutation to DNA. A normal cell may suffer both DNA mutations at a single division with a low probability, "μ 1" time "μ 2". Malignant cells divide with growth rate "C" to form a malignant tumor (i. e. "promoter"). Within the context of a two stage model, an initiator is a mutagen delivered

at low dose thus increasing mutation rates "μ 1" and "μ 2". The probability of mutating both 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 second mutation will occur by mitotic recombination if two events must occur in both homologues of the same gene (for example antioncogene, a.k.a. tumor suppressor gene) or by mutation of a second necessary gene (for example a second protooncogene). A "complete carcinogen" is either a mutagen delivered at high dose or an agent of two different and necessary protooncogenes activated. "A malignant tumor" is a proliferation of malignant cells which have both necessary mutations. 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 abscence of a mutagen since spontaneous DNA mutations do occur. Experiments (20) have confirmed a prediction based on two stage model that application of a low dose of a mutagen to a benign tumor (so called "initiation-promotion-initiation" (19)) results in a malignant tumor. The agents that increase the proliferation of normal or intermediate tissue will increase cancer risk apart from any direct effect on DNA. Such proliferating-stimulating agents (promoters are one class) may in fact account for a greater proportion of cancer cases than strictly genotoxic agents in the environment.

There is growing evidence that the cancer arises from the malignant conversion of a single cell (20). 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 in Figure 1 leads from a normal cell to a normal pathway since this is the normal tissue, the chance of a cancer cell arising is very low. However, the chance that an intermediate cell arises is not so low. Intermediate cells divide as their normal counterparts, and may have a growth advantage when a promoter is applied and an intermediate lesion appears.

5. CARCINOGENESIS RISK ASSESSMENT OF MRI

5.1 Epidemiological and Laboratories Studies

In the research programs for the study of causes of cancer there is room for both epidemiological and laboratory studies, I believe there should be synergism between the two. Epidemiology can directly address the question of whether the increased risk of cancer is associated with some aspect of the human environment such as exposure to EMFs. These studies generally speaking are crude and rarely determine precisely what component of the exposure is the culprit. This is because pure, single agent exposures are non-existent. However, laboratory studies can better address a specific problem of increased cancer risk by isolating that component of the exposure which causes the problem. If laboratory studies could successfully isolate a particular feature of exposure of EMFs that accounted for a bioeffect, the that specific modality should be investigated epidemiologically.

5.2 Epidemiological Studies

The design features for epidemiological studies should take into consideration the biological effects of EMFs. Within the context of two stage model described above (17) temporal sequence of exposure, interaction with other agents, and confounding factors depend on how EMFs are hypothesized to affect cancer risk.

The lack of direct effects on mutation suggests that if EMFs increase cancer risk, it is not by increasing "μ 1". However if the accurate functioning of the mitosis is affected, EMFs might indirectly lead to mitotic recombination, and the fixation of an antioncogene if one is involved; an intermediate cell may yield a normal and a malignant progeny. In this way "μ 2" may be affected and not "μ 1".

The following are some specific suggestions for epidemiological studies which may help in carcinogenesis risk assessment of MRI systems:

1. Assess EMFs exposure many years in the past if stem cell turnover is thought to be affected. In the two stage model direct effects of EMFs on immune cell function might increase "C" (Figure 1).

2. Assess very recent EMF exposure, if cancer cell growth is thought to be affected, perhaps exposure within one year of diagnosis. Effects of EMFs on calcium balance that might influence "promotion" via increased oxidative stress or disrupted signal transduction might affect the growth of intermediate cells "B".

3. Effects on promotion predict a time frame for exposure that lies between the distant past and the very recent past: perhaps 10 to 2 years prior to cancer diagnosis.

   In the case of conventional MRI, patients and operators have been exposed to EMFs for about 10 years. Similarly for non-conventional MRI, the two population groups, patients and operators, have been exposed to MRI for at least two years. An epidemiological study can yield valuable information.

4. Perform a case-control study of acute non-lymphocytic leukemia in adults that takes account of both residential and occupational exposures.

5. Perform studies of breast cancer and of malignant melanoma in females and males, and of prostate cancer in males.

6. Study the effects of EMFs on radiation-induced cancer by chemicals that increase oxidative stress. Assess body iron stores in these studies.

EMFs 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. EMF itself may increase reactive iron availability within the cell, causing further oxidative stress.

5.3 Design of an Epidemiological Study

It is now more than a decade that conventional MRI is being used as a diagnostic modality. A large population of patients have been exposed to static and time varying magnetic fields and radiofrequency radiation while undergoing the procedure. Likewise, a large population of operators of MRI equipment exposed to low level EMFs is available for an epidemiological study. This would investgate the establishment of a causal link between EMF exposure and a large number of cancers and diseases of the immune system thought to be caused by exposure to EMFs.

The design of a typical study is as follows:

OBJECTIVE: To investigate the effect of EMFs on the risk of malignant melanoma, breast cancer, leukemia, in men and women and prostate cancer in men; exposed to EMFs while undergoing MRI procedures and operating MRI equipment.

DESIGN: Retrospective cohort study (years 1984-1994)

SETTING: A number of MRI sites in the United States

ENROLLMENT: Men and women selected for this investigation will be drawn from the poulation groups 1) patients and 2) operators of equipment at MRI sites.

ASSESSMENT OF EXPOSURE: Questionnaires are mailed to obtain information on risk factors to ascertain whether medical events have occurred.

ASSESSMENT OF OUTCOME: All incident cases of malignant melanoma, leukemia and breast cancer in men and women and prostate cancer in men are outcomes under investigation. For incident cases, permission to review relevant hospital and cancer registry records is requested to confirm self-reported diagnosis.

The following variables are examined as potential effect modifiers, confounders and risk factors: malignant melanoma, breast cancer, leukemia and prostate cancer, and the other outcomes of interest.

GENERAL DATA: Age, weight, height, smoking, alcohol use, diet, use of vitamin supplements(anti-oxidants), exercise, education, employment(x-ray exposure)

FAMILY HISTORY: family history of malignant melanoma, breast cancer, leukemia and prostate cancer.

MEDICAL HISTORY: Benign breast disease, all breast and prostate cancer, non-Hodgkin'slymphoma, major illnesses, use of medications.

OBSTETRIC HISTORY: Age of menarche, age of first birth, parity, breast feeding, use of oral contraceptives, age of menopause, type of menopause.

JUSTIFICATION: The use of conventional and non-conventional MRI as diagnostic modality is becoming increasingly popular. The potential benefits must be balanced against possible risks of malignant melanoma, breast cancer, leukemia and prostate cancer.

This study would eliminate selection and recall bias associated with case control studies. The retrospective nature of the study would allow the assessment of relationship between EMF exposure and various forms of cancer. Epidemiological and laboratory studies would act synergistically in determining if there is a problem and it would help identify mitigation strategies if needed.

5.4 Laboratory Studies

5.4.1 Immune and Nervous Systems

Several observations have suggested interaction between the immune and nervous systems. Psoriasis may worsen with anxiety and has been associated with anaomalus neuropeptide regulation. Neurotransmitters affect lymphocyte function. Calcitonen gene-related peptide (CGRP) is a neuropeptide and vasodilator that modulates some macrophage functions, including antigen presentation in vitro. CGRP is associated with langerhans cells (LC) in esophageal mucosa, particularly during inflammation, is present in epidermal nerves and is associted with Merkel cells. In functional assays (8) CGRP has inhibited LC antigen presentation.

The findings indicate that CGRP may have immunomodulatory effects in vivo and suggest a locus of interaction between the nervous system and immunological function. There has also been reports of individuals with unusual sensitivity or adverse symptoms when exposed to EMFs from power lines. EMFs are known to affect nerve cells. Since nerve

cells and immune cells are linked anatomically, adverse effects on nerve cells might affect immune cells. Laboratory studies into the biological effects of EMFs on nerve and immune cells will give a better insight into the aberrant immune system response. Such a study might explain some individual's unusual sensitivity and adverse symptoms when exposed to power line EMFs. Experiments on nerve and immune cell preparations with low frequency EMFs used in MRI might give information about adverse health effects on patients suffering from psoriasis and other skin disorders.

6. RISK ASSESSMENT OF SPECIAL HAZARDS ASSOCIATED WITH IMAGING PATIENTS WITH IMPLANTED DEVICES

The Safety Committee of the Society for Magnetic Resonance Imaging has issued a statement on the Policies, Guidelines and Recommendations for MR Imaging Safety and Patient Management (21):

"Patients with electrically, magnetically, or mechanically activated, or electrically conducted devices should be excluded from MRI unless the particular device has been previously shown to (i.e., usually by ex-vivo testing procedures) to be unaffected by the electromagnetic fields used for clinical MRI, and there is no possibility of injuring the patient. During the screening process for MRI, patients with these objects should be identified before their examination and prior to being exposed to the electromagnetic fields used for this imaging technique. There are implants, materials, devices, or other foreign bodies, that have yet to be evaluated for MRI compatibility, which may be encountered in the clinical setting. Patients that have untested objects should not be allowed to undergo MRI"(20).

"Each MRI site should establish a policy for screening patients with suspected foreign bodies. The policy should include guidelines as to which patients require workup for

radiographic procedures, the specific procedure to be performed(i.e., number and type of views, position of the anatomy) and each case should be considered on an individual basis. These precautions should be taken with regard to patients in any type of MR scanner, regardless of the field strength, magnet type, and the presence or absence of magnetic shielding".

Patients should present to the MRI site management their history of metallic foreign bodies which include slivers, bullets, schrapnel, or other type of metallic fragments. The relative risk of scanning these patients depends upon the ferromagnetic properties, geometry and size of the object, and the strength of the static and gradient magnetic fields of the MRI scanner. Another important aspect is the strength with which the object is fixed within the tissue and whether or not it is positioned in or adjacent to a potentially hazardous site of the body, such as a vital neural, vascular, or soft tissue structure.

The U. S. Food and Drug Administration (FDA) requires that patients with internal cardiac pacemakers, implantable cardiac defibrillators, cochlear implants, neurostimulators, bone growth stimulators, implantable electronic drug infusion pumps, and other similar devices that could be adversely affectd by the electromagnetic fields used for MRI should not be examined by this imaging technique. Prior ex-vivo testing of certain of these implants and devices may indicate that they are, in fact MRI compatible.

The associated risks of scanning patients with cardiac pacemakers are related to the possibility of movement, reed switch closure or damage, programming changes, inhibition or reversion to an asynchronous mode of operation, electromagnetic interference, and induced currents in lead wires. There is the possibility of that the pacemaker,lead wires could act as an antenna in which the gradient and/or RF electromagnetic fields may induce sufficient current to cause fibrillation, burn, or some other potentially dangerous event. Cochlear implants which employ a high field strength cobalt samarium magnet

used in conjunction with an external magnet to align and retain a radiofrequency transmitter coil on the patient's head and other electronically activated cochlear implants are contraindicated for MRI because of the possibility of injuring the patient and/or damaging or altering the implant operation. Dental implants, magnetic sphincters, magnetic stoma plugs, magnetic ocular implants, and other similar devices that may require surgery to replace the damaged implant, should be removed from the patient prior to MRI otherwise MRI should not be performed on the patient. Only patients that definitely have nonferromagnetic aneurysm clips should be exposed to magnetic fields used for MRI, while any patient with one of the previously-tested hemostatic clips may safely undergo MRI.

Patients with intravascular coils, filters or stents, in which there is possibility that the device is not properly positioned or held firmly in place should not undergo MRI.

Orthopedic implants, materials and devices made from nonferromagnetic materials may be imaged safely by MRI. Patients with foreign bodies like pellets, bullets and schrapnel should be regarded on an individual basis with respect to whether the object is positioned near a vital neural, vascular, or soft tissue structure. This may be assessed by taking a careful history and using plain film radiography to determine the location of the foreign body. Patients with artificial sphincter made from nonferromagnetic material which have been tested previously can undergo MRI examination. Ferromagnetism tests on cerebral ventricular shunt tube connector and tissue expander which is magnetically activated have exhibited deflection forces that may pose a risk to patients during MRI. Contraceptive diaphragms tested for ferromagnetism have displayed significant deflection forces. However, patients with these devices undergoing MRI, have not complained of any sensation related to the movement of these objects. Therefore scanning patients with these devices is not physically hazardous to patients (20).

7. QUESTIONS/ISSUES NEEDING CLARIFICATION

MRI (magnetic resonance imaging) is one of the most rapidly advancing technologies. As new machines with innovative design and operational features are being brought into the healthcare facilities, questions/issues which need clarification, to ensure patient safety, also arise and they have to be addressed.

A few of the important questions have been addressed here (22).

1. How should we define acceptability criteria for MR exposure? What safety margins are needed?

   In order to predict the thresholds of stimulation for magnetic field exposure, it would require carefully designed experiments that take into account the stimulus waveform, its spatial distribution, and anatomical properties of the test subject. In the matter of electrical exposure, there are questions which cannot be answered with scientific objectivity. Minimum excitation thresholds applicable to MRI exposure have not been adequately established. The threshold criterion used for electrical fields need further experimental clarification. The influence of cardiac pathology on electrical thresholds and the effects of drug treatment have received little attention to date. Some evidence exists to indicate the possibility of heightened sensitivity in patients with cardiac pathology. The answer lies in more research data.

2. What properties of the patient determine acceptable "dose" of magnetic exposure?

   Static and time varying magnetic fields are known to cause mechanical stress to

the cells. The condition of patients with skin disease psoriasis might be exacerbated if they are exposed to EMFs in the MRI procedure. Pulsed electromagnetic fields are known to cause increased proliferation of normal and cancer cells (23). Should a patient known to have cancer, on medication for cancer treatment, be allowed to go through the MRI procedure? The procedure may exacerbate the cancerous condition or inhibit the drug metabolism. Similarly a patient with cardiac pathology, on medication, may have heightened sensitivity to to the electromagnetic fields being exposed to. Obviously the safety margins and electrical and magnetic stimulation thresholds for normal hearts and non-cancerous patients are not applicable. What safety margins apply in such cases? Only more research can provide the essential data to arrive at new thresholds. Heightened sensitivity should dictate lower thresholds relative to normal population. These questions cannot be answered with scientific objectivity. Frequently these are policy or judgemnt issues that are settled on the basis of historical precedent or some other basis. Policy issues may include the population percentile that should be assumed for a threshold reaction or the safety factor that should be applied to theoretical predictions. A purely scientific approach cannot provide the "absolutely correct" exposure criteria, but it would in the process of criteria selection.

8. Suggestions for Research Strategies

Figure 2 and Figure 3 show the research approaches which can provide data for arriving at the acceptability criteria for MR exposure, thresholds and safety margins for nerve and cardiac stimulation (23).

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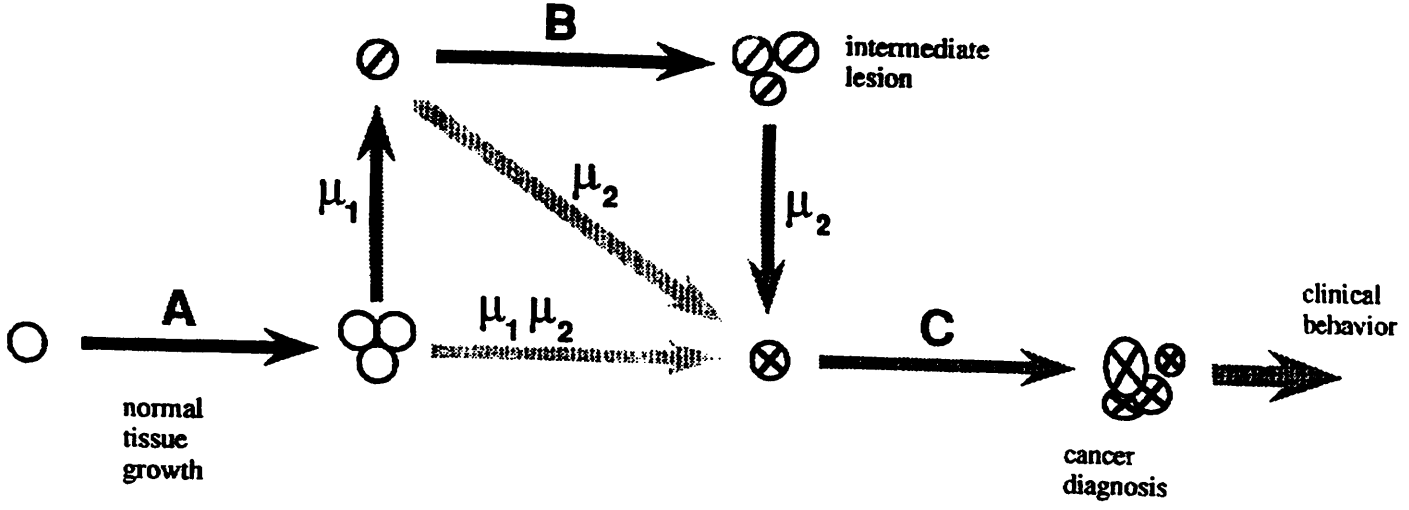
Figure 1: Two-stage model for cancer adapted from Moolgavkar and Knudson (1981). A normal cell divides as part of a normal tissue. With small probability a normal cell may divide to give one normal and one intermediate cell, which in turn can divide to become an intermediate lesion. With small probability an intermediate cell may divide to give one intermediate and one cancer cell. A "promoter" greatly increases the chance that a malignant cell will arise by increasing the pool of intermediate cells.



○ normal cell

⊘ intermediate cell

⊗ cancer cell

μ_1 = first mutation rate

μ_2 = second mutation rate

A = growth rate of normal cells

B = growth rate of intermediate cells

C = growth rate of malignant cells

Cardiac Stimulation

Issues needing clarification

Effects of patient pathology or medication (causing stimulation, stress) ischemia, infarction of heart muscle

Special hazards associated with patients having metallic implants, other non-metallic implants

Research Approaches

Experiments on isolated perfused hearts, normal heart tissue

Heart muscle cell (in-vitro) electric and magnetic stimulation, ionic environment, drug treatment

Figure 2

Peripheral Nerve & Muscle Stimulation

Questions/Issues needing clarification

Patient pathology in medication

Factors that lower threshold relative to normal population

Body location at which pheripheral nerve and muscle responses begin

Research Approaches

Study on nerve cell preparations

Magnetic stimulation study on animals

Figure 3

ACKNOWLEDGMENT

In the name of God Almighty, the Beneficent, the Merciful.

First I thank my Lord for giving me the guidance in my pursuit of academic work. A great credit goes to my deceased parents who initially guided, encouraged and supported me.

I am greatly indebted to Professor Gordon L. Brownell for accepting me in the Radiological Sciences program in the Department of Nuclear Engineering at the Massachusetts Institute of Technology and giving me the freedom to do a research project of my choice. This work would not have been accomplished without the constant encouragement, guidance and advice of Professor Frank P. Castronovo, Jr. at Harvard Medial School, who provided me an opportunity to work with him at Massachusetts General Hospital and Brigham and Women's Hospital to gain practical experience.

May God Almighty bless both Professors Brownell and Castronovo and their families.

Financial assistance from Brigham and Women's Hospital is gratefully acknowledged.

My special thanks to RoseAnne Crescenzi for her assistance in computer work.