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INTRACELLULAR HYPERTHERMIA

A BIOPHYSICAL APPROACH TO CANCER TREATMENT VIA INTRACELLULAR TEMPERATURE AND BIOPHYSICAL ALTERATIONS.

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ABSTRACT

This paper introduces a new multi-disciplinary "intracellular" biophysical treatment of cancer. The basic concept uses locally induced heat energy after tumor phagocytosis of submicron particles whose composition permits magnetic excitation. The key to this process is the utilization of the cancer cell membrane to contain the energy within the cancer cell. Any magnetic or electric dipole contained within or introduced into the cell, or that is capable of being produced by an external field, can be used. Submicron particles are colloidally suspended, injected intravenously and are phagocytized by cancer cells. Application of an external high frequency or pulsed electromagnetic field then raises the particles' temperature thus generating intracellular heat in precise increments. This results in selective thermal destruction of cancer cells with little effect on normal cells. Experimental evidence is presented showing tumor cell destruction in spontaneous mammary tumors in Sprague Dawley rats. In addition, we suggest that certain biophysical properties are altered within the cancer cells and could be used to enhance this effect. Specific radioisotopes or tumor specific antibodies bound to particles or chemotherapeutic microspheres increase cancer cell sensitivity and affinity for these particles. This "intracellular" treatment of cancer has a wide potential range of applications.

Intracellular
Hyperthermia
Biophysical
Selective
Multi-disciplinary
Cancer
Cell
Membrane
Electromagnetic

1. Hyperthermia
2. Neoplasms
3. Magnetics
4. Electromagnetics
5. Neoplasm Circulating Cells
6. Phagocytosis
7. Cell Transformation, Neoplastic
8. Particle Size

INTRODUCTION

A number of approaches have been developed seeking an effective means of treating neoplastic disease, the most successful being surgery, chemotherapy, irradiation and immunotherapy. In a number of malignancies, these treatments have had limited effectiveness. Attempts to isolate one single etiologic agent have been unsuccessful: a number of agents chemical, irradiation, chronic trauma, viruses, etc. have been related to the development of cancer.

The biophysical approach described in this paper differentiates the cancer cells from the normal cells and selectively destroys the cancer cells without demonstrably affecting the normal cells. Micro-particles capable of magnetic polarization have been experimentally injected into rats with spontaneous mammary carcinomas. These particles were ingested by the tumor cells. External electromagnetic fields were used to excite these particles, thus raising the "intracellular" temperature and destroying the cancer cells.

MATERIALS AND METHODS

The primary tumor system utilized in this study was the Sprague Dawley rat with spontaneous mammary tumors. Spontaneous tumors were chosen since they are the most difficult to destroy and because seemingly they are most closely related to human neoplasms. Implanted and induced tumors often lead to problems with rejection and spontaneous necrosis in control groups. 26 animals were obtained. Purina ground rat chow and water were available to each rat ad libitum. Ambient temperature was maintained at 72° F - 76° F.

In addition, one available Sprague Dawley rat with a DMBA induced tumor was subjected to the same treatment protocol. 3 Sprague Dawley rats were injected with particles at 5-day intervals for 3 injections in order to determine if the method of injection affected the particle uptake by the tumor cells.

The particles utilized were primarily FeO(OH) and Fe_3O_4. Fe_2O_3 and FeC were also used in some studies. Particle sizes were obtained via electron microscopy: FeO(OH) - 26 Å, and Fe_3O_4 - 60 Å. The concentration of the FeO(OH) solution was 40 mg/ml in a 70% sucrose solution. The Fe_3O_4 solution was

50 mg/ml in a 60% sucrose solution. Each animal received 2 ml. injections by tail vein, intravenously (slowly over 10 minutes), on days 0, 1, and 2.

48 hours after the last injection, the animals were exposed to the external high frequency electromagnetic field. The EMR exposure was accomplished by placing each animal into a plexiglass restraining tube ventilated with holes to allow free passage of air, body heat, and EMR-generated heat in and/or out of the tube. Various sizes of tubes and coils were used to accommodate variations in the body sizes of the animals treated. In most instances, a plexiglass tube (2.5" diameter) and a coil (3.5" diameter) were used.

The generator utilized to create the electromagnetic field was a 30 kilowatt generator set at a frequency of 450,000 HZ. This frequency is by no means ideal, but was selected for this study because it was below 10 MHZ and because the equipment available was so designed. Studies have confirmed that frequencies below 10 MHZ have minimal effects on human tissues and avoid the problems encountered in diathermy heating and microwave heating at higher frequencies.[1] Ideally, a variable frequency generator with a range from 0→10 MHZ would have been used to allow scanning of the entire range to determine which frequency has the best effect on the particles or on the dipoles present or induced in the cell; however, the cost of this equipment was prohibitive for our present studies. The entire animal was scanned while exposed to EMR for 12 minutes. The time period for exposure of the animals in the high frequency field was determined by placing a generous portion of tumor tissue, fully phagocytized with particles, within the field. Using an alcohol thermometer (not affected by EMR), the time required to raise the temperature by an increment of 8.0°C was noted.

48 hours after EMR treatment, biopsies were obtained. Biopsies were also taken prior to the EMR treatment to determine that the particles were, indeed, within the tumor cells. Great care was taken to make sure the biopsies were from two different areas so that the artifact from one biopsy would not appear on the second biopsy. At one week, the animals were sacrificed and the entire tumor submitted to pathology. Also at this time, the heart, lungs, liver, spleen, kidneys, adrenal glands, small intestines, bone marrow, spinal cord, and brain were sent for histological studies.

While living, the animals' urinary and fecal excretion of particles were studied as well as the blood for serum iron levels. The animals' weight and food and water intake were also monitored.

Sections for light microscopy were stained with Gomori's method for iron and with hematoxylin and eosin stains. Sections to be examined by electron microscopy were embedded in Epan 812, cut at 600 A on a Porter Blum Ultramicrotome, stained with

uranyl acetate - lead acetate and examined with a Siemens Elmiskop 101 electron microscope.

RESULTS

The only toxicity associated with the animal restraint and injection of the particles FeO(OH) was discoloration and swelling of the nose, ears, legs, and feet occurring 20-30 minutes post-treatment (injection) and lasting 3-4 hours.

Maximum fecal levels of FeO(OH) and Fe_3O_4 occurred 4-7 days after injection. A small secondary peak occurred 9 days following the first injection. Maximum FeO(OH) excretion in the urine occurred two days following the first injection. FeO(OH) is excreted in the urine and feces whereas Fe_3O_4 is mainly excreted in the feces. Water and food intake as well as body weight did not change considerably during the treatments. (Fig. 1,2)

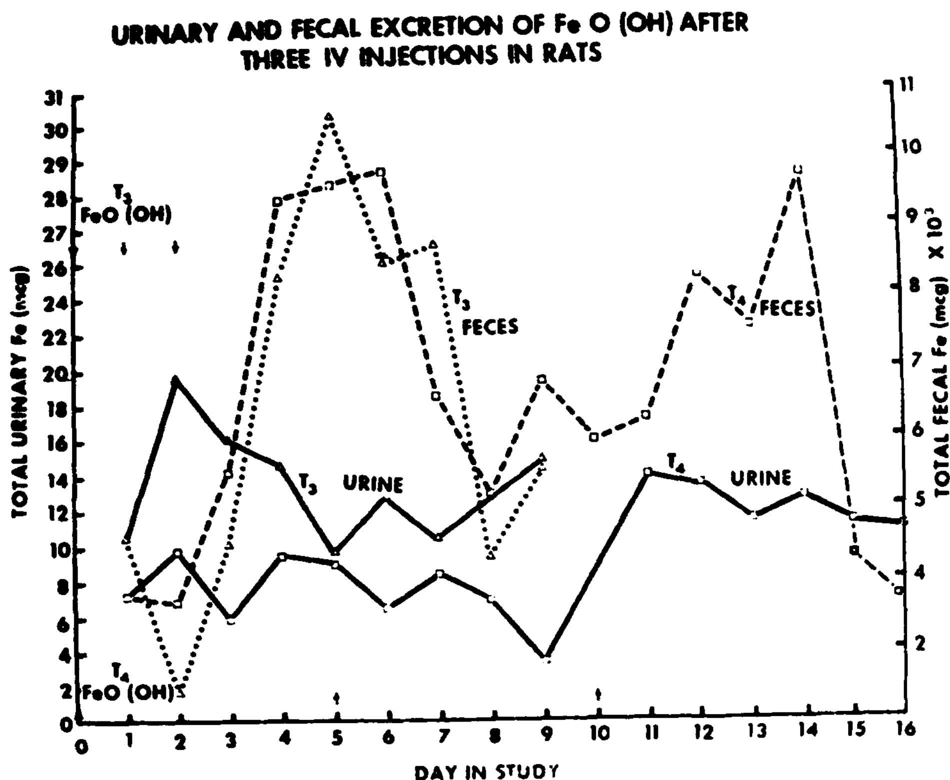

Figure 1

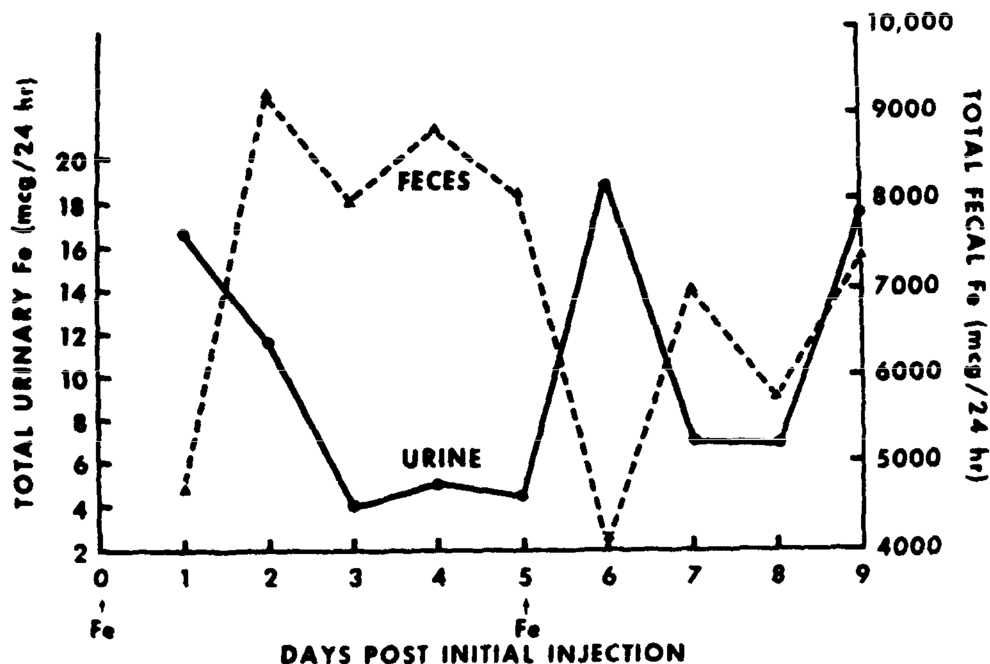

Figure 2

This study involved 26 animals. One animal of the 26 accidentally did not receive particles intravenously yet was exposed to the electromagnetic field. This animal served as a control although it is well documented in the literature that a field of this level will not affect living tissues.[1] When determining the parameters for the experiment, 21 Sprague Dawley rats with spontaneous mammary tumors served as controls and received no injection of particles but were exposed to the electromagnetic field. These control animals showed the tumors unaffected and no effect on the normal tissues. 28 control animals received particles without being exposed to the alternating electromagnetic field. The particles were localized in the tumor but as expected, the tumors were unaffected. (Fig. 3, 4)

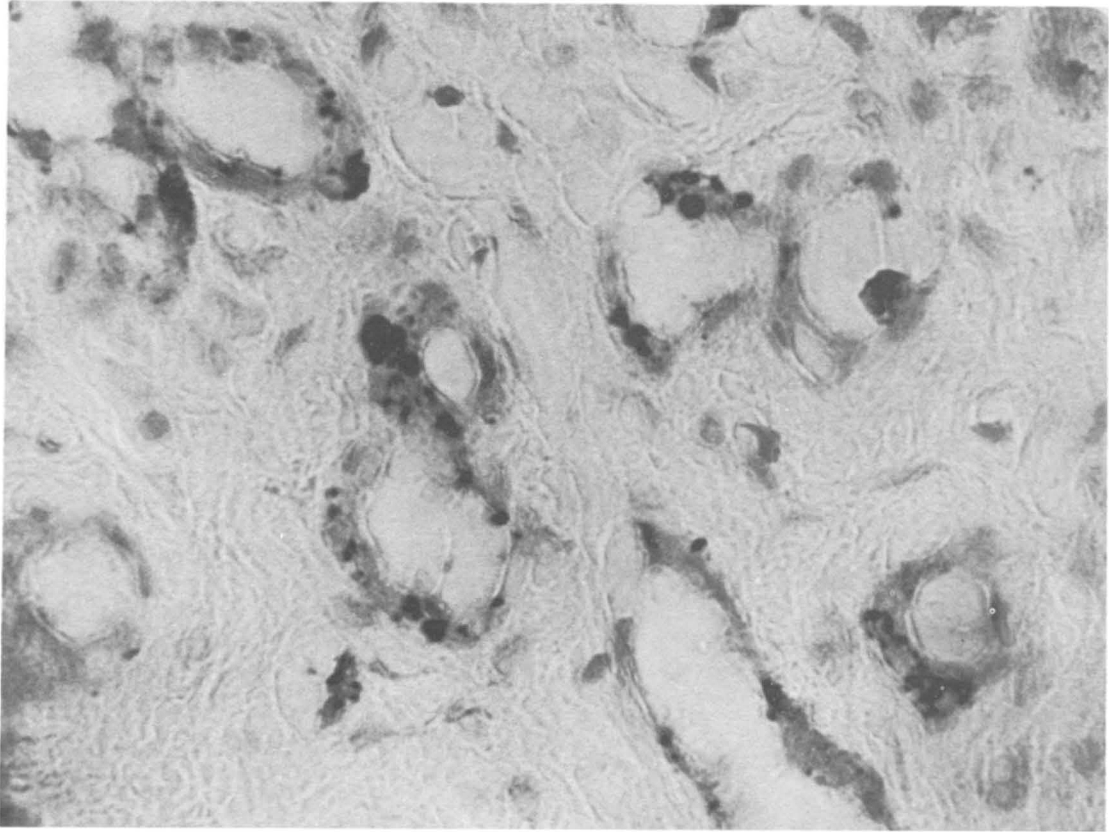

Figure 3 - Gomori iron stain illustrating the uptake of the particles by the adenocarcinoma cells. One point represents an accumulation of many particles.

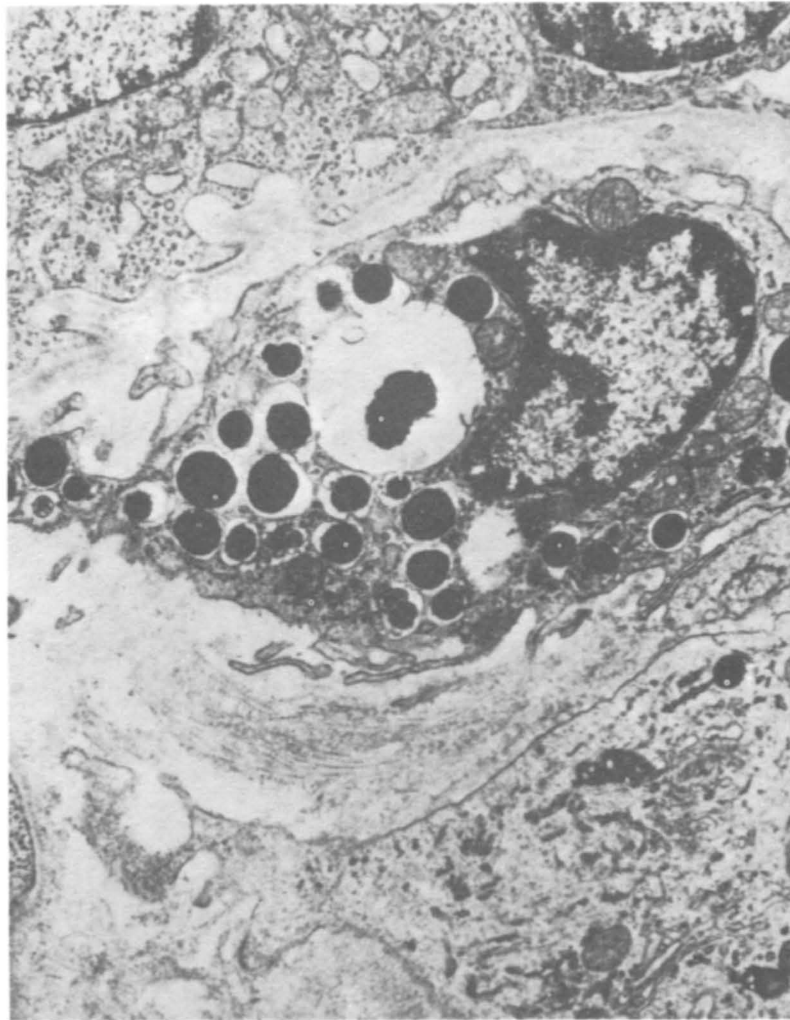

Figure 4 - An electron micrograph showing the actual particles in the tumor cell. (magnification 21,900 x)

The particles can be found to some extent in the Kupffer cells of the liver, proximal convoluted tubules of the kidney, adrenal cortical cells and macrophages of the splenic pulp. The particles were also found in histiocytes throughout the body.

In 11 of 12 animals treated in the described manner, tumor necrosis was seen. Tumor biopsies before the EMR treatment revealed the presence of particles in the tumor cells in 25 of 26 (96%) of the animals. At a metastatic tumor site discovered in one animal, the metastatic tumor cells were found to contain a large number of particles. After the EMR treatment, the changes seen were easily distinguishable from spontaneous necrosis. The cytoplasm of affected cells was shrunken and

stained more intensely. The cytoplasmic borders were more distinct than those of the unaffected cells. The nuclei of the destroyed tumor cells were decreased in size, hyperchromatic and very dense. Nuclei had often progressed from this early pyknosis to the more advanced stage of nuclear degeneration, i.e. karyorrhexis and karyolysis. Blood vessels within the affected tumors showed coagulative heat-induced necrosis generated from the EMR effect upon the iron particles. The destroyed tumor cells were no longer able to form their organized ring-like structure and underwent pyknosis. As the tumor cells died, they lost their cohesiveness and dropped off into the lumen, eventually replaced with connective tissue. (Fig. 5, 6, 7, 8)

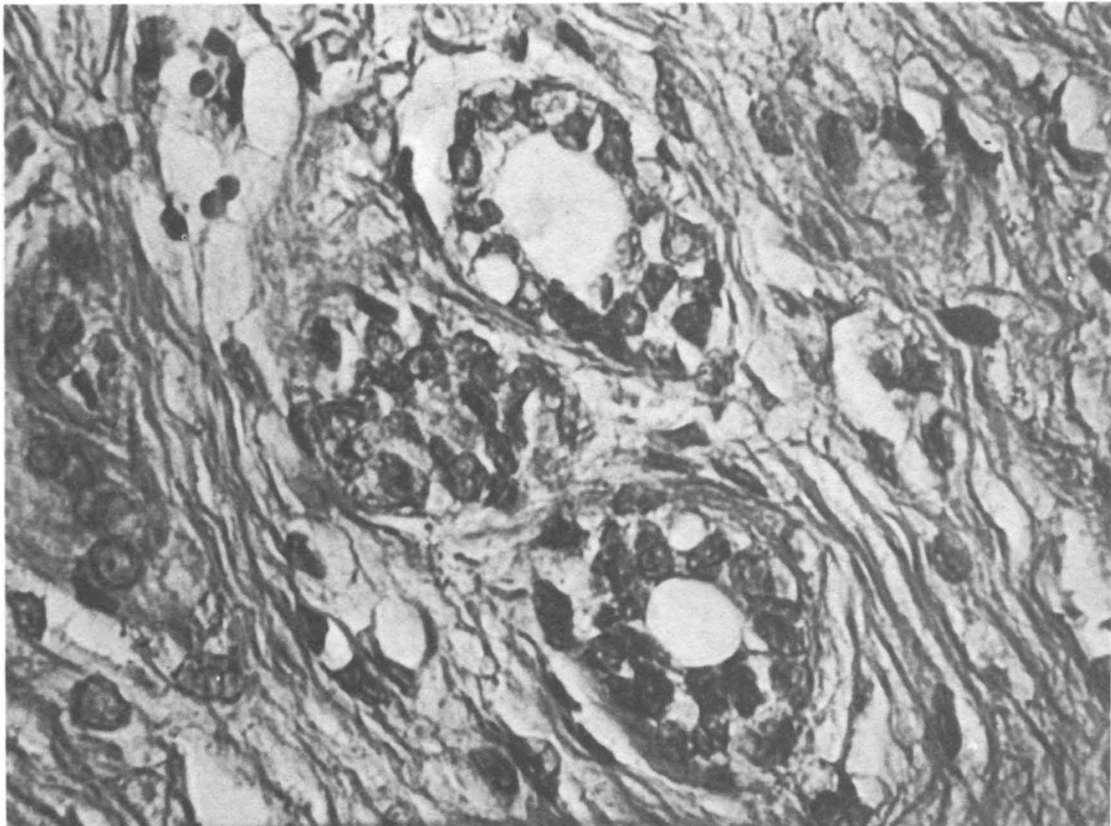

Figure 5 - **BEFORE TREATMENT** - Living tumor tissue before treatment with viable cancer cells. Cytoplasm healthy, not defined well, nuclei-vesicular, nucleoli visible, no sign of cancer cell death. **NOTE:** Tendency of groups of cells to form ring-like structures, hence term adenocarcinoma.

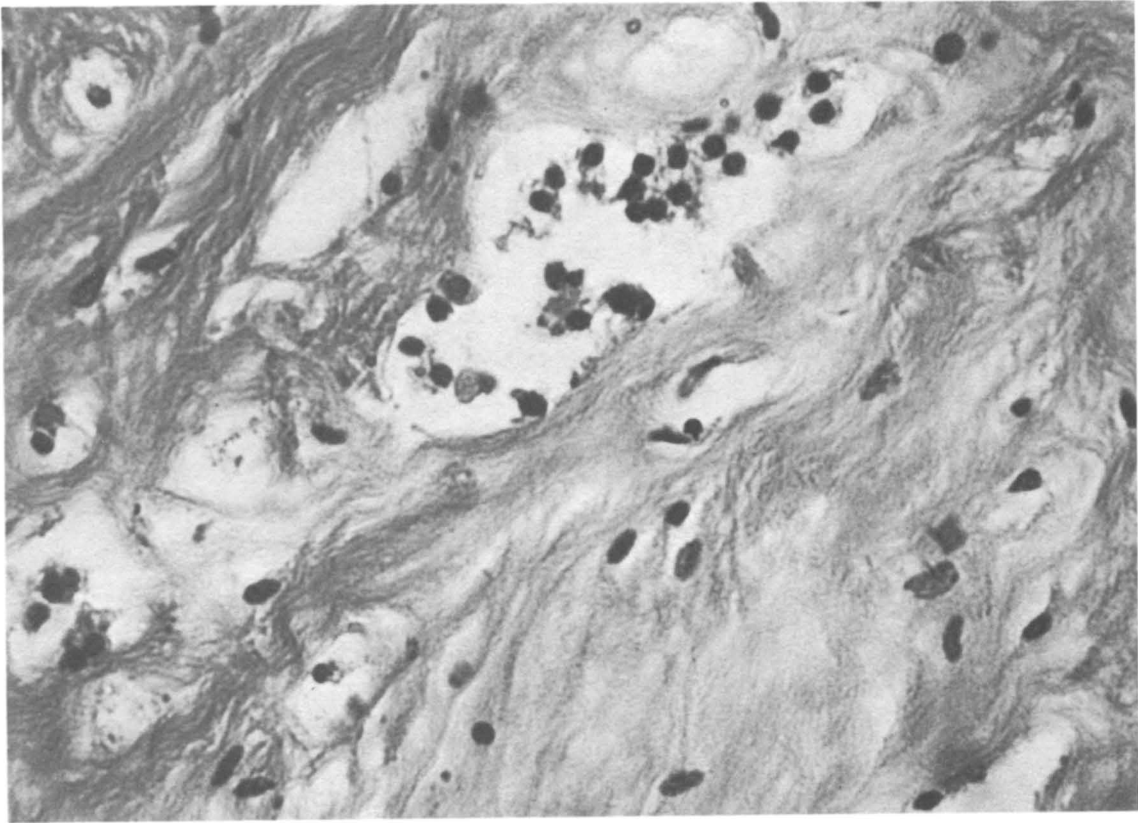

Figure 6 - AFTER TREATMENT - Tumor cells dead. Condensed cytoplasm, condensed pyknotic nuclei. Cytoplasm now stains well. Cellular and nuclear boundaries distinct, clumping of chromatin. Tumor cells have lost ability to form ring-like structures or to adhere to surrounding cells. NOTE: Dead tumor cells. Surrounding connective tissue cells, alive and unaffected.

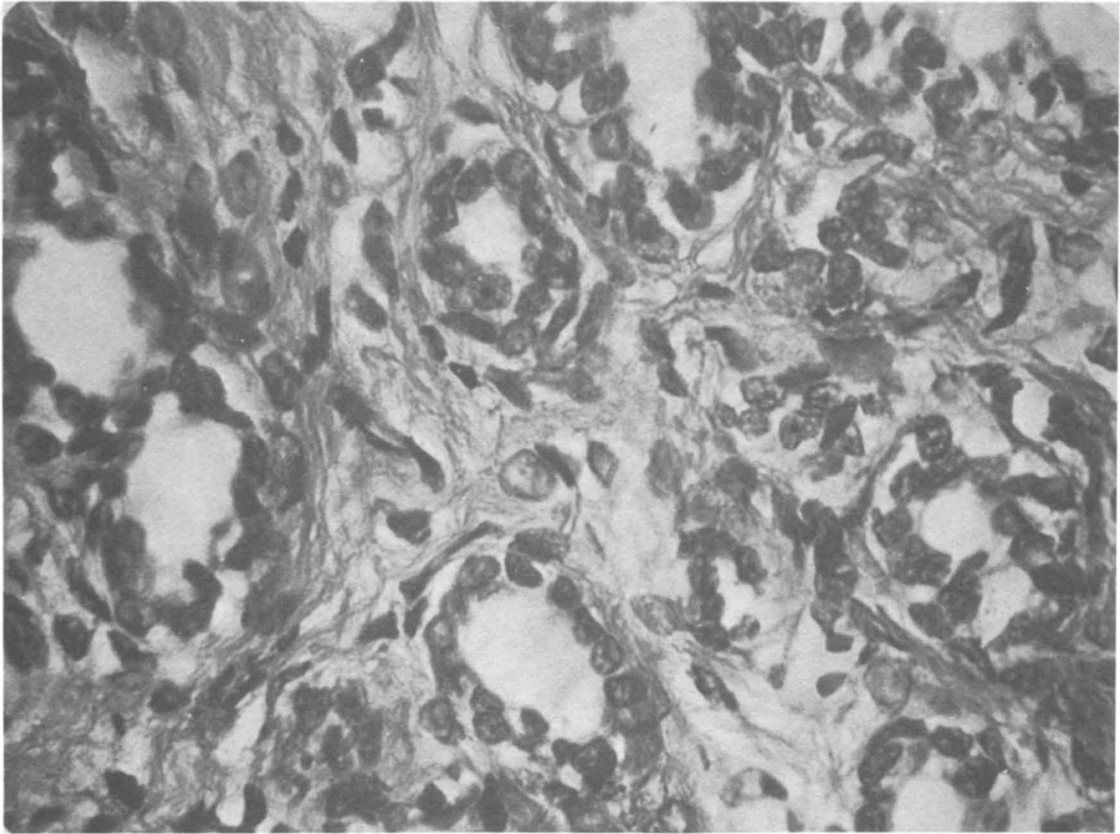

Figure 7 - BEFORE TREATMENT - Actively growing living tumor cells, mammary adenocarcinoma. Tumor cells alive and well. Cytoplasm normal, nuclei vesicular.

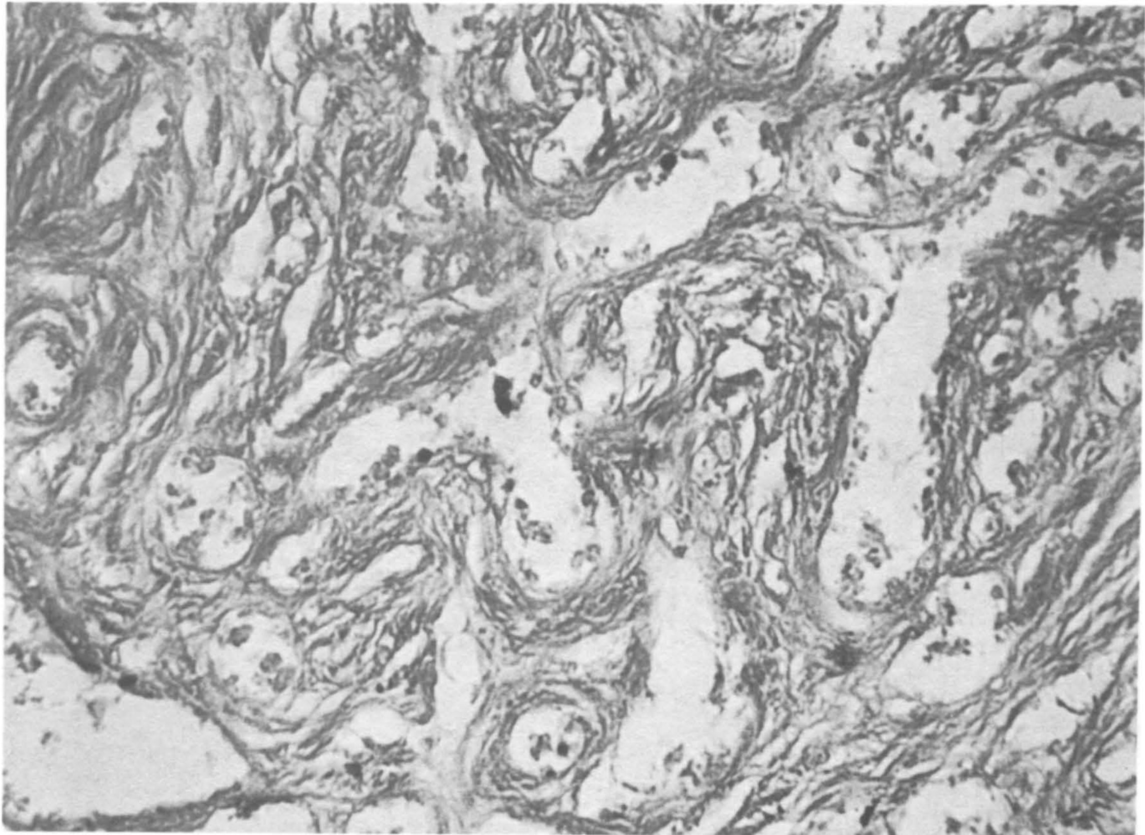

Figure 8 - **AFTER TREATMENT** - **Dead tumor cells** with clumped cytoplasm and dead pyknotic cells. In some areas, only debris of tumor cells remain (with karyorrhexis). Tunor cells have lost ability to adhere and have fallen into the lumen. Surrounding connective tissue is normal and unaffected.

The other normal tissues which were examined, including heart, lungs, liver, spleen, kidneys, adrenal glands, small intestines, bone marrow, spinal cord and brain, showed no changes, even when some of the particles were found in these organs. In the animals where the tumor cells were destroyed, the normal tissues were all histologically unchanged, even if particles were located in these tissues. Effects from either the intracellular particles or from the EMR treatment were not apparent in these normal organs. Interestingly, at the time periods studied, there was no uptake of particles and no effect seen in the bone marrow. There was no effect of the treatment on the surrounding connective tissue.[1]

Electron microscopy confirmed the light microscopy findings with regard to the destroyed cancer cells. All the cancer cells were necrotic and individualized in appearance. There were interstitial pools of iron particles, apparently released from necrotic tumor cells shortly after cell death. The tumors which showed cell death secondary to the treatments were spontaneous mammary adenocarcinomas, fibroadenomas, and one DMBA induced tumor. (Fig. 9,10)

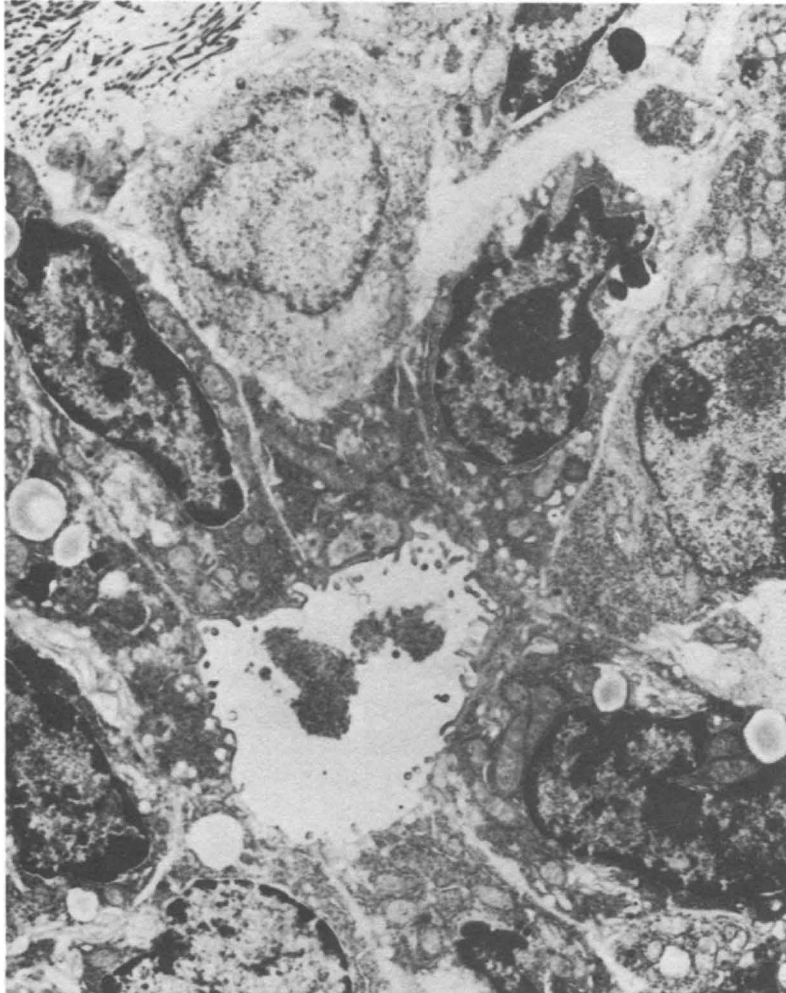

Figure 9 - BEFORE TREATMENT - An electron micrograph showing the healthy tumor cells forming a ring-like configuration with healthy nuclei, etc. (magnification 11,000 x)

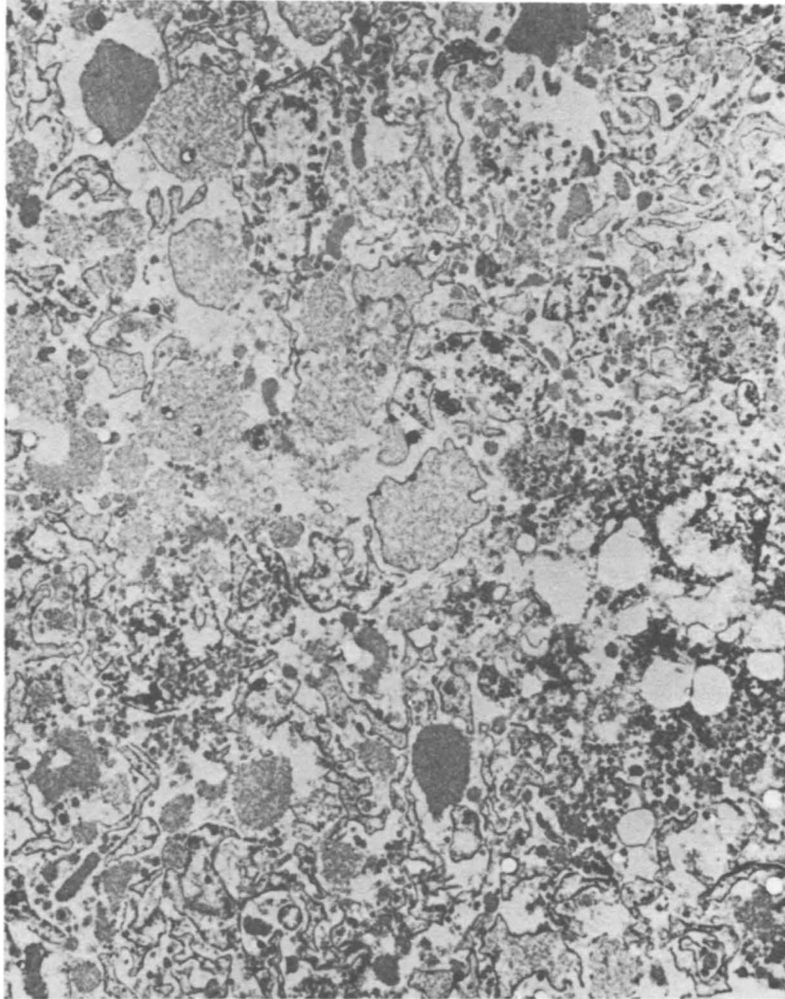

Figure 10 - **AFTER TREATMENT** - An electron micrograph showing destruction of the tumor cells. (magnification 11,000 x)

One series of 3 rats injected with particles at 5 day intervals for 3 injections showed even more of the particles in the tumor cells and less in the normal tissues and cells. It may be that with time, the particles are cleared from the normal body organs while being retained in the tumor cells.

Of the fibroadenomas 26/27 had the particles in the tumor cells. Of the rats with adenocarcinomas, 14/15 contained the particles within the tumor cells. Interestingly, in one animal, the tail injections were accidentally subcutaneous and consequently the animal did not receive any particles intravenously. This animal, exposed to the same field for the same duration of time as the other animals injected intravenously, showed no effect on the tumor cells with no tumor cell death, illustrating that the field, alone, has no visible effect on tumor cells. 21 control animals receiving no injections and therefore containing no particles whatsoever, subcutaneously or intravenously, when subjected to the electromagnetic field for the same duration of time and the same frequency used in the previously described experiments, showed no effect on the tumor cells with no tumor cell death and no effect on normal cells and tissues.[1]

Tumor destruction was documented in 11 of 26 animals. 96% of the animals contained particles within their tumor cells. The results in 14 animals were affected by malfunction in the transformer of the electromagnetic high frequency equipment which completely changed the parameters of the electromagnetic field. Precision is most important in this treatment and we did not then have the proper instrumentation to provide compensating parameters. The filament transformer of the EMR equipment and the replacement of the 7½ volt filament transformer with a 8.25 volt filament transformer (a 7½ volt filament transformer was not available to us), completely changed the flux characteristics of the EMR equipment thereby affecting the results obtained in the 14 animals.

DISCUSSION

The greater sensitivity of cancer cells to hyperthermia as compared to normal cells is well documented.[2,3,4,5] The reasons for this increased sensitivity and the effects of hyperthermia on nuclear structure and DNA, changes in the RNA, mitochondrial changes as well as membrane, lysozomal and cytoplasmic alterations continue to be discussed. Attempts at utilizing hyperthermia to treat cancer have been made using hot baths, wax encasement, induced fevers, local perfusion of extremities with heated chemotherapeutic agents, diathermy, radio-frequency and microwave heating, and the injection of substances locally with the use of energy fields.[6,7] These approaches have failed to provide a uniformly effective means of treatment because they are "extracellular" in approach. The internal temperature of the cancer cell and the internal energy changes are important in the destruction of the cancer cell. The cell membrane, comprised of lipids and proteins, is an excellent thermal barrier and a very poor thermal conductor. Cancer cells, with their phenomena of sludging have an even greater thermal barrier secondary to the accumulation of materials around their cell membrane.[2,8] With the extracellular methods previously reported, the very high external temperature required to establish a sufficient gradient

across the cell membrane to kill the cancer cell results in the destruction of the surrounding normal cells. Effective treatment is limited both by the destruction of the normal surrounding cells and tissues and by the host's tolerance for such external heat or other fields of energy.

In the technology described in this paper, the cancer cell membrane is used to advantage and enhances the process by containing the energy within the cancer cell. Hence, the key to this technology is that it is "intracellular." Submicron particles of composition permitting magnetic excitation are colloidally suspended in an appropriate solution and introduced intravenously into the animals, (magnetic or electric dipoles present or induced intracellularly may also be utilized). Later, an external high frequency or pulsed electromagnetic field is applied so as to raise the intracellular temperature. This permits the alteration of the biophysical properties by a precise increment and results in the selective thermal destruction of the cancer cells without affecting the surrounding normal cells. The inductive heating of the minute particles is achieved by using an electronic oscillator operating in the high frequency range which heats the particles by subjecting them to an intense high frequency field within a helical coil. The field energy is converted to heat through hysteresis losses and the resistive dissipation of eddy currents.

As shown experimentally, injected particles are taken up predominantly by the cancer cells which have a far greater affinity for particles and for foreign substances than do the normal cells. Electronmicrographs taken of tissue following the introduction of such particles clearly illustrate the concentration of the particles in the cancer cells due to their phagocytic characteristics. This may be partially due to the higher rate of metabolism of the cancer cells and partially due to new blood vessel formation as neo-vascularization occurs. New blood vessels have an increased permeability to foreign particles and allow the cancer cells to phagocytize these particles in large amounts. (2,9,10)

Even if equal particle uptake by cancer cells and normal cells should occur, the described technology could successfully destroy the cancer cells without affecting the normal surrounding cells and tissues as there are the established differential temperature characteristics between cancer cells and normal cells. The application of intracellular heating to the particles would produce a similar rise in temperature in all cells which, within the precise range desired, would destroy the cancer cells without harming the normal cells. Tumor cells have been noted to have a slightly higher resting temperature than do normal cells (37.5°C as compared to 37.0°C). Tumor cells are also known to undergo cell death at lower temperatures than do normal cells (45.5°C as compared to 46.5°C) and often the differential in temperature cell death is much more than 1.0 C (2,11,12,13) Therefore, the

cancer cell's temperature must be raised only 8.0°C to produce irreversible cell death whereas the normal cell's temperature must be raised 9.5°C. This ΔT of 1.5°C allows a sufficient margin to work within. Hence, by precisely raising the intracellular temperature of the cells above the temperature required for destruction of the cancer cells while remaining below the temperature at which the normal cells die, the cancer cells are destroyed without affecting the normal cells using our process. Precision is an essential element in this "intracellular" treatment of cancer.

To further enhance the selectivity of the particles for the cancer cells in our approach, several techniques could be utilized. Particles bound with antibodies induce increased phagocytosis by the cancer cells.[14,15,16] Cancer cells taken from one patient with cancer and injected into another human or animal will form antibodies in the immunocompetent. The injection of the cancer cells will, in turn, form antibodies in the substitute host specific to the cancer cell's antigens as defense against the foreign tumor cells from the original cancer patient. These antibodies, selectively isolated, can be used to treat selected specific tumors. Bound chemically or physically to the minute particles used in this technology, and re-injected into the original cancer patient to be treated, these antibodies will selectively deliver the particles to <u>only</u> the cancer cells (with their specific antigens). An external high frequency or pulsed field then applied, will selectively destroy the cancer cells.

A second method of enhancement involves labeled antibodies. Antibodies with radioactive isotopes may be produced by feeding labeled amino acids to the animals producing the antibodies. This labeled amino acid is then incorporated into the antibody. Large chemical entities can be attached to antibody molecules. Large proteins may be attached via diazotized atoxyl (p-amino-benzene arsenic acid). Antibodies may be bound while they are attached to a hapten or to an antigen. This protects the immunologically specific site of the antibody during the binding procedure. Cancer cell seeking agents such as radioisotopes of composition permitting magnetic excitation (i.e. gallium-67, indium-113m, technetium-99m, fluorine, selenium-75, etc.) can be introduced intravenously and due to their specific affinity for cancer cells may be utilized to enhance this process. Whether chemically or physically combined with other particles, or used <u>alone</u>, the effect of the external high frequency electromagnetic field would raise the temperature of the cancer cells to selectively destroy the cancer cells without affecting the normal cells. Many isotopes are capable of being excited by an alternating electromagnetic field.

Scans can be used to show the location of these radioisotopes within the cancer cells prior to treatment, and after treatment to monitor the progression of the therapy. A localized field could be used to help direct the particles to a specific area of tumor growth, although experimentally this has not been found to be necessary. The use of a selective cancer cell seeking agent such as the antibodies or the radioisotopes described above is desirous for increased efficiency in the utilization of all of the particles and in order to permit the smallest dosage possible.

By and large the chemotherapeutic agents currently being used in cancer therapy are not selectively taken up by the cancer cells. Many oral or intravenous drugs are distributed to all the cells in the body. The side effects of gastro-intestinal upset, bone marrow depression, infection, anemia, thrombocytopenia and reproductive problems are due to the effects of the drug on these rapidly dividing normal cells as well as upon the rapidly dividing cancer cells.

The technology described in this paper allows the chemotherapeutic drug to be delivered primarily to the cancer cells, and in concentrations capable of destroying the cancer cells. Microspheres of composition permitting magnetic excitation and filled with chemotherapeutic agents have been produced and injected intravenously.[17] These microspheres are phagocytized by the cancer cells and the external high frequency electromagnetic field applied. Since these microspheres can be constructed to break at a given electromagnetic frequency or at a given temperature, the chemotherapeutic agent could be released selectively into the cancer cells, <u>only</u>, without affecting the surrounding normal cells and tissues. For increased selectivity in delivering these microspheres to the cancer cells, the microspheres could be bound to one of the radioisotopes or to specific antibodies.[18]

The treatment of known tumor areas and peripheral tumors (rectal carcinomas, prostatic carcinomas, etc.) could be enhanced with the localized fields used in this process. The monitoring of this technique could be accomplished by several methods. External probes may be utilized; however problems might arise due to the interaction with the external high frequency electromagnetic field. Probes of the order of 0.5u have been utilized.[19] Thermography has been used primarily for surface determinations. Laser micro-probes analysis has been used at the experimental level. Magnetic mapping techniques are most applicable in monitoring this new biophysical technique. Scanning the patient before and after exposure to a constant field $\vec{B}_m$ and subtracting the two Scans, allows identification of the location of the particles and the cancer cells in the patient. This then permits computerized monitoring of cancer cell destruction and provides information necessary for judgment concerning a repeat treatment.

Parameters are currently being optimized for purposes of increasing the effectiveness and the efficiency of this biophysical technology for the treatment of cancer and other diseases. Research continues in designing specific particles for specific tumor systems. The uptake of different particles by different tumors and the reaction of the particles to the induced field are being studied. The utilization of sugar (sucrose + dextran) or dextran, both high and low molecular weights, attached to the particle to aid phagocytosis introduced in this study is being maximized. Innovations in essential sophisticated instrumentation and monitoring devices designed as a result of these experiments, specifically for increased "precision" when used with this technology, will further enhance the efficiency and the effectiveness of this "intracellular" biophysical approach to the treatment of cancer and other diseases.

SUMMARY

The selective uptake of the particles by the tumor cells as shown on light and electron microscopy suggests that the technology described is feasible for the effective treatment of cancer. Although magnetic or electric dipoles present or induced intracellularly may be utilized, the inductive heating of the particles is a physical process and the fact that this is a physical process implies that the approach will extrapolate to man. It has already been demonstrated that human tumors will take up foreign particles.[2,8,20]

This biophysical approach to the treatment of cancer represents new technology for effective treatment by the "intracellular" alteration of biophysical properties, resulting in the selective destruction of cancer cells while the surrounding normal cells and tissues remain unaffected. This is confirmed in the histologic sections studied in this experimentation. It is expected that this new technique may prove useful in the treatment of metastatic disease as cancer cells are destroyed at a cellular level (intracellularly) wherever they exist.[21]

This research and experimentation documented with physical examination, necroscopy examination, biopsies, electron microscopy, and light microscopy clearly shows that this new "intracellular" technology selectively destroys cancer cells without affecting normal cells and tissues. This study is not a conclusion, but an introduction; not an end, but a beginning to a new and hopefully effective biophysical treatment of cancer as well as to the possible application in other diseases.

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REFERENCES

1. California State Department of Public Health, Biological Effects of Nonionizing High-Frequency Radiation in Microwave Radiation Hazards, Technical Information Service Publications, Berkeley, 1964.

2. Rossi-Fanelli A, Cavaliere R, Mondovi B, Moricca G, Selective Heat Sensitivity of Cancer Cells, pp 1-185 in Recent Results in Cancer Research, Springer-Verlag, Berlin Heidelberg, New York, 1977.

3. Cavaliere R, Moricca G, Fanelli AR, Biochemical Mechanism of Selective Heat Sensitivity of Tumor Cells: Preliminary Results, Istituto Regina Elena Per lo studio e la cura dei Tumori, Roma, Istituto di Chimica Biologica, Universita di Roma, p. 101, 1968.

4. Simard R, Bernhard W, A Heat-Sensitive Cellular Function Located in the Nucleolus, Journal of Cell Biology 34:61, 1967.

5. Warocquier R, Scherrer K, RNA Metabolism in Mammalian Cells at Elevated Temperature, European Journal of Biochemistry, 10:362, 1969.

6. Henderson MA, Pettigrew RT, Induction of Controlled Hyperthermia in Treatment of Cancer, Lancet, p. 1275, 1971.

7. Stehlin JS, Giovanella BC, de Ipolyi PD, Muenz LR, Anderson RF, Results of Hyperthermic Perfusion for Melanoma of the Extremities, Surgery, Bynecology, and Obstetrics 140:339, 1975.

8. Feldherr CM, The Effect of the Electron-Dpaque Pore Material on Exchanges Through the Nuclear Annuli, Journal of Cell Biology 25:43, 1965.

9. Duran-Reynals F, Studies on the Localization of Dyes and Foreign Proteins in Normal and Malignant Tissues, Laboratories for Medical Research, p. 98, 1937.

10. Copeland ES, Effect of Selective Tumor Heating on the Localization of ^{131}I Fibrinogen in the Walker Carcinoma 256 (Heating by immersion in warm water), Acta Radiation Therapy, Physics and Biology 9:25, 1970.

11. Cavaliere R, Ciocatto EC, Giovanella BC, Heidelberg C, Johnson RO, Margottini M, Mondovi B, Moricca G, Rossi-Fanelli A, Selective Heat Sensitivity of Cancer Cells, Cancer 20:1351, 1967.

12. Giovanella BC, Heidelberg C, Biochemical and Biological Effects of Heat on Normal and Neoplastic Cells, Cancer Research, p. 24, 1968.

13. Giovanella BC, Lohman WA, Heidelberg C, Effects of Elevated Temperature and Drugs on the Viability of L1210 Leukemia Cells, Cancer Research 30:1623, 1970.

14. Bale WF, Spar IL, Goodland, RL, Experimental Radiation Therapy of Tumors with I^{131}-carrying Antibodies to Fibrin, Cancer Research 20:1488, 1960.

15. Bale, WF, Spar IL, Goodland RL, Wolfe DE, In Vivo and In Vitro Studies of Labeled Antibodies against Rat Kidney and Walker Carcinoma (21876), Dept. of Radiation Biology, Univ. of Rochester, P.S.E.B.M. 89:564, 1955.

16. Goldenberg DM, Preston DF, Primus FJ, Hansen HF, Photoscan Localization of GW-39 Tumors in Hamsters Using Radio-labeled Anticarcinoembryonic Antigen Immunoglobulin, G, Cancer Research 34:1, 1974.

17. Ayers JW, Pigment Particles Coated with Organo-Aluminum Compounds, U.S. Patent 3,294,686, Nov. 16, 1964.

18. Madden RE, Agostino D, Gyure L, Some Unusual Aspects of Microsphere Migration at the Microcirculatory Level, Archives of Surgery 101:425, Sept., 1970.

19. Plumb HH, Designs and Applications of Thermal Sensors, pp. 2144/5 and 2212 in Temperature: Measurement and Control in Science and Industry, Vol. 4, Part 3, Instrument Society of America, Pittsburgh, 1972.

20. Yonshiro EG, Perry JF, Shahon D, Marvin JP, Wangensteen OH, The Localization of Radioactive Iron in Malignant Neoplastic Tumor, Surgery 17:195, 1960.

21. Gordon, RT, Cancer Treatment Method, U.S. Patent 4,106,488, Aug. 15, 1978.