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Technical Feature

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Interdisciplinary research teams composed of engineers from Georgia Tech and members of the medical profession from the School of Medicine at Emory University and from the Medical College of Georgia are investigating the potential beneficial applications of electromagnetic radiation (particularly in the microwave region) in biology and medicine. This research utilizes the heating property of electromagnetic radiation as a function of the characteristics of the electromagnetic field and the medium being affected, biological tissue.

Biomedical Applications of EM Radiation

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Microwave engineering, thermodynamics, physiology, pharmacology, and surgery are just some of the disciplines necessary in assessing the utility of biological and medical applications of electromagnetic radiation. Not only must temperature and field strength be measured at various depths within biological tissue, but also any effects of heating and the presence of an electromagnetic field must be observed and measured. Thus, teams composed of both engineers and members of the medical profession are required to conduct the research.

SELECTIVE HEATING OF CANCER TUMORS TO ENHANCE CHEMOTHERAPY

The heating property of electromagnetic radiation has been used for many years in medical applications for various types of diathermy treatments. During the last five years, a Georgia Tech-Emory University team has been working on a new application of electromagnetic radiation: selective heating (rewarming) of tumors in deeply cooled animals to enhance the effectiveness of tumor chemotherapy treatment. This new type of tumor treatment (warm tumor - cold body) was first developed in Dr. Vojin P. Popovic's laboratory at Emory University and is called differential hypothermia.[1] In the differential-hypothermia technique, the body of the whole animal is profoundly cooled to a temperature of 40-50°F. After the animal becomes hypothermic, electromagnetic radiation is used to increase and to maintain the temperature of the tumor at approximately normal (98°F) through selective and uniform heating. After differential hypothermia is stabilized, anticancer drugs are administered. These drugs are extremely destructive and fully unspecific; that is, they can adversely affect every cell and every tissue in the body. However, when the drugs are administered in differential hypothermia, the cooled healthy tissues utilize very little of the drug, whereas the warm tumor, which has a high metabolic rate, is affected to a much higher degree. Thus, the objective of the differential hypothermia technique in the treatment of cancer is to increase susceptibility of tumor cells to a chemotherapeutic agent (anticancer drug) and, at the same time, to decrease the effects of the administered drug on other healthy parts of the body.

Fig. 1 Anesthetized rat with cancerous tumor being measured *in vivo.*

The amount of electromagnetic heating produced in biological tissues is dependent on the depth of penetration of the electromagnetic energy into the tissue and on the power absorbed per unit volume. Both of these quantities can be calculated from the tissue permittivity and resistivity parameters. Relative permittivity and resistivity for various organs in the frequency range of 100 MHz to 10 GHz are well known.[2] Values of these parameters in the frequency range of 1 to 100 MHz were determined at Georgia Tech utilizing a new technique of measurement which allows the data to be obtained from animals *in vivo*.[3] **Figure 1** shows a rat with a tumor with a probe implanted to measure the electrical properties of the tissue. This method is contrasted to previous techniques which utilize *in vitro* tissue samples.

The *in vivo* measurements of the electrical properties of tissue in the 1 to 105 MHz range yielded somewhat higher values for relative permittivity and loss tangent than did *in vitro* measurements. The differences in values appear to be produced by differences in temperature and in blood flow between *in vivo* and *in vitro* tissues. For example, measurements of fluid-filled and homogenous mammary tumors in mice revealed as much as a 2 to 1 difference in loss tangent depending on fluid content.

The penetration of electromagnetic radiation into biological tissues is the limiting process which controls the capability of selective heating. In biological tissues, penetration depth is of the order of a wavelength of the incident electromagnetic radiation. Therefore, the longer the wavelength of the radiation, the deeper the penetration. However, power absorption per unit volume is inversely proportional to wavelength so that the shorter the wavelength, the higher the power absorbed per unit volume. In summary,

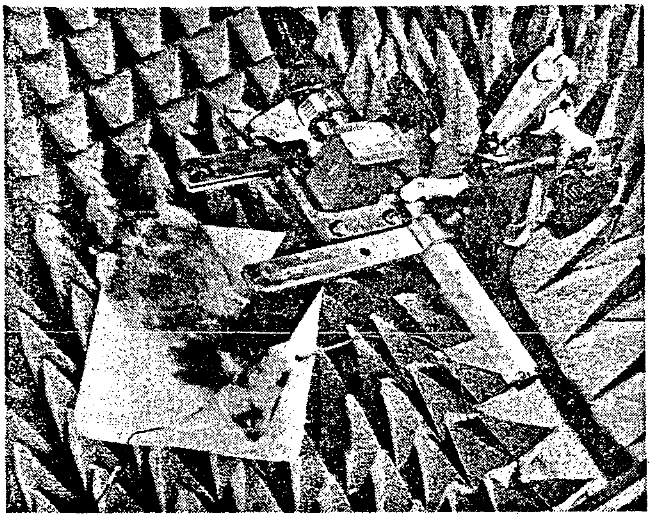

Fig. 2 Anesthetized hamster with implanted thermocouples being radiated at 2450 MHz by a dielectrically loaded waveguide illuminator.

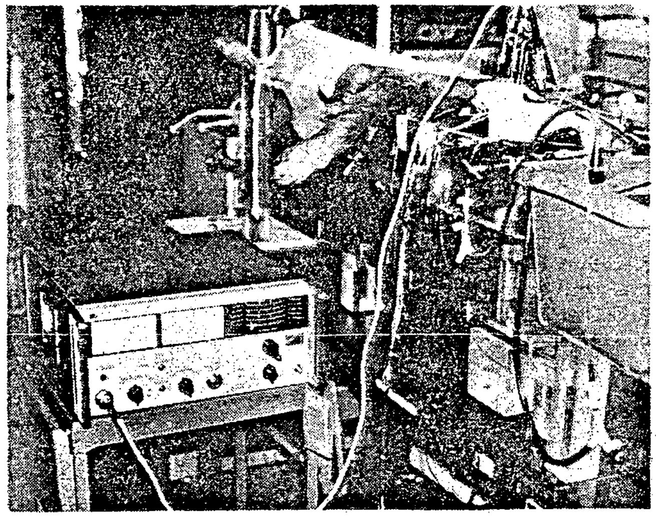

Fig. 3 Anesthetized dog cannulated for cooling of the brain with an electrical probe implanted.

short-wavelength radiation provides the best heating with tissues whose dimensions are of the order of centimeters, but it is not effective for the deep heating of central body organs or the brain.

Because living systems adaptively control their own temperature, it was necessary to determine experimentally the exact power requirements to produce heating to a specified temperature. **Figure 2** shows an animal with implanted thermocouples to measure heating as a function of microwave power and penetration depth. Thermocouples worked well at microwave frequencies if they were oriented orthogonally to the electric field so that undesired coupling to the thermocouple itself was minimized. Currently, small bead thermistors and lithium crystals are used to measure temperature at lower frequencies.

Curtis C. Johnson of the University of Utah has developed a new temperature probe which uses liquid crystals as a temperature-sensitive sensor and fiber optics to transmit light to and from the sensor.[4] Because the probe is completely non-metallic, it is well suited for making temperature measurements in tissue that is irradiated with electromagnetic energy. Measurements by Johnson indicate that the probe can measure temperature with an accuracy of 0.1°C.

Our experiments with differential hypothermia have indicated that microwave energy (2450 MHz) can be used to achieve selective heating in tumors in rats and mice.[5] Results of the differential hypothermia treatments, while administering 5-fluorouracil to mice with spontaneous tumors, verify that significant tumor regression occurs when the animal is treated for several hours. Similar results were obtained for chemically induced tumors in rats. In the rat experiments, tumor regression was observed for all cases after treatment with differential hypothermia and chemotherapy. Subsequent experiments with dogs have shown the technique can be applied to larger animals. **Figure 3** shows a dog cannulated for cooling the brain with an implanted probe for measurement of electrical properties.

A modified technique has been investigated for heating tumors deep in the brain and most other body tissues by the use of high frequency (HF) electromagnetic radiation (in the range of 3 MHz to 30 MHz) in combination with doping the tumor with high-loss particles. The penetration depth at these frequencies is much greater than at microwave frequencies and the radiation can penetrate the complete body. Of course, heating of the whole body is not desired, but by using the doping materials, which are significantly more lossy than the surrounding tissue, the heating will be concentrated in the doped area, *i.e.*, the tumor.

The high loss of some ferrites at 1 MHz provides a mechanism for selectively insuring the loss in biological tissues through injection of ferrite powder into the areas to be treated. The particle size of the ferrite doping material may be as small as ten microns without significantly changing its magnetic properties; therefore, the implanttation of such doping material can be accomplished by injection rather than surgery. Subsequent investigations of metallic powders and conductive particles as doping materials have shown that stainless-steel balls one millimeter in diameter are even more effective than ferrite for doping tumors to produce differential hypothermia.

This research has demonstrated the possibility of applying electromagnetic radiation in a new method for the treatment of cancer. Especially significant is the potential for treatment of brain tumors without the need for major surgery. Brain tumors have been emphasized because of the special problems associated with brain surgery, but the doping techniques would be useful for treatment of cancer in many of the major organs of the body without surgery. The use of differential hypothermia with selective electromagnetic heating would improve the effectiveness of known anticancer drugs while reducing harmful effects on healthy tissues. This technique would allow a more general use of chemotherapeutic drugs on cancer tissues.

THAWING OF FROZEN ORGANS

The surgical transplantation of human organs is a developing clinical technique which promises to be of great value in the treatment of disease. However, today transplantation is performed infrequently, often because of the lack of organs properly matched to the bodies of the recipients. A complete bank of possible donor organs could be maintained if long-term preservation of viable organs could be attained. Long-term preservation by freezing offers hope for development of these organ banks if freezing and thawing techniques can be developed that do not produce excessive damage to the organ.[6]

Although freezing techniques appear to be satisfactory, if the subsequent thawing process is non-uniform, serious organ damage will occur. Conventional thawing techniques that have been tried previously have led to non-

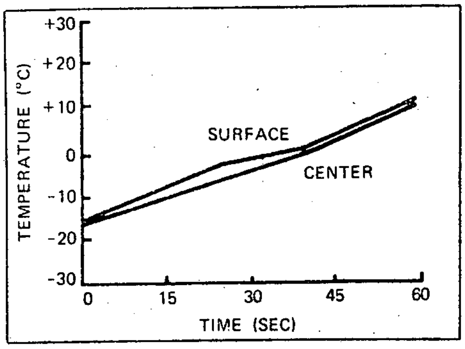

Fig. 4 Temperature of continuously rotated frozen rabbit kidney as a function of time when radiated with 1000 W CW power at 2450 MHz.

Fig. 5 Dielectrically loaded rectangular horn for thawing of frozen granulocytes.

uniform thawing and, therefore, to unsuccessful results. The use of high-power electromagnetic radiation, with multiple frequencies and field configurations specifically chosen to produce uniform and rapid heating, offers promise for a new thawing technique.

Some of the basic problems in achieving uniform thawing include the following:

- different electrical properties for frozen and thawed tissue,
- different thermal conductivity properties for frozen and thawed tissue, and, therefore,
- different power absorption and heating properties for frozen and thawed tissue.

The variation of the tissue properties with temperature and state of thawing must be considered in the selection of frequencies and of the time schedule of applied power to achieve uniform thawing.

If the frozen organ is small, such as a rabbit kidney, uniform thawing can be achieved with microwave radiation at 2450 MHz. Although the penetration depth at this frequency is greater than the thickness of the rabbit kidney, continuous rotation of the kidney is required for uniform thawing. An example of the temperature of the surface and center of the kidney as functions of time during thawing is shown in **Figure 4.**[7]

The work on thawing of frozen organs at Georgia Tech has been conducted in collaboration with a team from the Medical College of Georgia led by Dr. Armand M. Karow. Dr. Karow's group has developed the cryopreservation and freezing techniques, and it has provided Georgia Tech with the frozen organs for experiments.

Currently, experiments using electromagnetic radiation at 2450 MHz and at 7 MHz are being conducted by the Georgia Tech-Medical College of Georgia team using frozen canine kidneys. Very small stainless-steel spheres are inserted into the pelvis of the kidney to enhance the heating at 7 MHz in the center portion of the kidney. Thus, the energy from the 7-MHz radiation produces heating from the center toward the surface of the kidney, and the energy from the 2450-MHz radiation produces heating from the surface toward the center of the kidney. It appears that this combination of frequencies, with a properly selected time schedule of power for each frequency source, could provide rapid and uniform thawing for the relatively large frozen canine kidneys.

MICROWAVE THAWING OF FROZEN GRANULOCYTES

The problem of long-term storage of blood for later clinical use is one upon which a great deal of attention has recently been focused. In July 1973, the Department of Health, Education, and Welfare urged hospitals to freeze the blood which they collect to increase the shelf life of the blood. However, the currently-used freezing and thawing techniques preserve the viability of the red blood cells but kill certain types of white blood cells. The normal blood of an adult person contains 6 different types of white cells. Four of these types are members of the granulocytic series, which fight diseases such as pneumonia, appendicitis, tonsillitis, meningitis, asthma, scarlet fever, and parasitic infections. Thus, transfusion of blood that has been frozen and thawed with conventional techniques is much less durable than unfrozen blood.

Also, the recurrent usage of anticancer drugs depletes the supply of granulocytes (white blood cells), thus making the patient leukopenic. This situation is dangerous because even a common cold could easily lead to pneumonia and result in death to the patient. Granulocyte transfusions are often given to patients using anticancer drugs to enable the body to fight common infections so the viability of white cells is particularly important in these cases.

Donor granulocytes must be exactly matched with those of the recipient to prevent the occurrence of transfusion reactions. However, under normal storage conditions, these donor cells have a very short life—typically 24 hours. These problems could be eliminated if techniques were developed for long-term frozen storage and rapid, uniform thawing. Recent work by the Georgia Tech-Emory University team has resulted in freezing and microwave thawing results for granulocytes that are very encouraging.

Numerous alternatives for thawing of frozen granulocytes were considered. Efforts were concentrated on utilizing commercially available blood bags because they are known to be nontoxic and to maintain their integrity over the desired temperature range. The rectangular shape of commercially available bags made rotation of the sample during radiation undesirable because of the wide variation of SWR with sample rotation. It was decided to design a flared waveguide horn with dielectric loading and an aperture shaped to accommodate the flat side of the blood bag. The properties of the dielectric loading in the horn could then be chosen to match the impedance between the blood bag and the source. The horn aperture was made slightly larger than the commercially available 3-inch by 9-inch blood bag.

Because little information was readily available on the electrical properties of frozen and thawed blood, measurements were made of both whole blood and synthetic blood composed of 85% normal saline, 10% DMSO, and 5% dextrose. The dielectric constant and loss tangent of each of these compositions were measured over the temperature range of $-30^\circ C$ to $20^\circ C$. The resulting data were used to determine the characteristics of the dielectric loading in the waveguide horn to thaw uniformally the relatively flat blood bag across the aperture with minimum mismatch.

In the final configuration, shown in **Figure 5**, the rectangular horn was oriented vertically and a combination of titanium dioxide (TiO_2) and silicon dioxide (SiO_2) was used in powder form as the dielectric loading. The

SiO_2 powder was used as the main loading element, and TiO_2 powder was used near the edges of the horn to shape the aperture distribution to be more uniform.

Frozen bags of granulocytes and lymphocytes at a temperature of -196°C were thawed using the dielectrically loaded rectangular horn as the illuminator and a magnetron operating at 2450 MHz as the power source. The bag was thawed in 70 seconds with an average input power into the horn of 250 watts. After thawing, *in vitro* viability tests were made on the granulocytes and lymphocytes and positive results were obtained in each case.

Small bead thermistors were inserted in the blood bag prior to freezing to sample the temperature in several locations as thawing occurred. When the entire volume was thawed, the maximum range of temperature variation was only 5°C. Typically, minimum temperature in the volume was about 1°C and the maximum was 6°C. After irradiation was discontinued, the temperature within the blood bag quickly stabilized to a value between the extremes.

CONCLUDING REMARKS

Experiments at Georgia Tech have indicated at least three potential new medical and biological applications of electromagnetic radiation. Many questions are yet to be answered concerning the practicality of these applications. However, the results of these initial investigations are sufficiently encouraging to warrant further work.

The research to date on electromagnetic radiation for heating of tissue in biological and medical applications has indicated four critical areas in which further work is required:

1. The investigation of simultaneous irradiation with multiple frequencies to achieve more uniform heating in large volume;
2. The development of new illuminators or applicators to shape field distributions within samples being irradiated;
3. Further development of temperature and power absorption measurement techniques in tissue samples during electromagnetic irradiation;
4. The development of techniques for biological and physiological measurements of tissue and organ characteristics in the presence of electromagnetic radiations without introducing artifacts.

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