In 1960 he was appointed an Instructor, and in 1961, became an Associate Professor in the Department of Electronic Engineering, University of Tokyo, where he worked primarily in the field of microwave circuits, microwave measurements, and microwave electron devices. From 1963 through 1964, on leave of absence from the University of Tokyo, he joined Bell Laboratories, Inc., Murray Hill, NJ, where he was engaged in research on electron guns. In 1972 he joined the Technical University of Munich on a temporary basis as a Guest Professor. In January 1977 he became a Professor at the University of Tokyo. At present, his main fields of interest are optical fibers, optical fiber communications, three-dimensional imaging, microwave planar (two-dimensional) circuits, and holographic memories. He has written nine books, including two in English entitled *Three-Dimensional Imaging Techniques* (New York. Academic PreSs, 1976), and *Optical Fibers* (Academic Press, 1982). He has been awarded nine prizes from three Japanese academic institutions.

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Clinical RF Hyperthermia by Magnetic-Loop Induction: A New Approach to Human Cancer Therapy

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Invited Paper

Abstract—**There has been mounting laboratory evidence that temperatures of $\geq 42°C$ (108°F) are tumoricidal in tumor cell cultures and animal models. Localized heat by electromagnetic waves appears to be the most practical means for producing hyperthermia and has been shown to be potentially effective against human surface tumors. However, attempts to treat deep internal human cancers with available techniques have been either ineffective or dangerous because of injury to surface tissue.**

A fundamentally new approach, magnetrode magnetic-loop induction hyperthermia, which was cooperatively developed by electrical engineers and oncologists for the treatment of deep-seated human tumors, is the subject of this report. The concept, rationale, design, and performance of this applicator in phantoms, animals, and humans is presented, as are the early results of clinical cancer trials. The data suggest reason for enthusiasm for the future treatment of advanced human tumors.

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I. INTRODUCTION

ONE IN four Americans has or will develop cancer, but only one in three will be cured of their disease by present methods of therapy, including surgery, radiation therapy, chemotherapy, and immunotherapy. Thus, oncologists must seek additional safe and reliable methods of treatment, particularly for large internal solid tumors. Initial investigations from laboratory models, animals, and human clinical trials suggest that hyperthermia may have a significant place in the armamentarium against this disease.

At $\geq 42°C$ (108°F), there is irreversible damage to cancer cell respiration [1], [2]. Coincident alterations occur in

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nucleic acid (DNA, RNA) synthesis and protein synthesis, including reduced activity of vital enzyme systems [3], [4]. These effects, associated with an increase in cell membrane porosity [5], [6] and the liberation of intracellular digestive enzymes [7], cause autolytic cell destruction. Other substantial thermal effects upon the microvasculature, pH, oxygen tension, and sugar metabolism probably have a major role in the destruction of solid tumors as well [8].

As a second property, low-dose hyperthermia (42°–44°C) sensitizes tumor cells to the effects of ionizing radiation [9], [10]. Radioresistant hypoxic tumor cells seem to be at least as sensitive to hyperthermia as well-oxygenated tumor cells, and the heat may inhibit cell recovery from sublethal radiation damage, reasons for combined thermo-radiotherapy. Since heat appears to alter cell membrane permeability, many chemotherapeutic drugs may have enhanced transport into cancer cells [5], an implication that has formed rationale for combined chemo-thermotherapy. Moreover, the adverse effects of low-dose hyperthermia at 42°–44°C may be selective for tumor cells. Throughout the late 1960's and early 1970's, evidence showed that not only were tumor cells slightly more sensitive to heat than their normal cell counterparts, but that malignant cells might be killed at 1°C lower temperature [8], [11]. In a classic experiment, nearly all cell cultures of tumor-derived and tumor-producing cells died after 2 h at 42.5°C, whereas less than half of all cultured normal and non-tumor-producing cells died under similar conditions. When a cell subline derived from a non-tumor-producing line acquired high tumor-producing ability, it also acquired reduced thermo-tolerance [12]. These and other investigations suggested that the acquisition of malignant potential was associated with increased thermo-sensitivity.

It is well known from experiments on exposed tumors that electromagnetic energy concentrated within a solid tumor can provide enough heat for potential tumor destruction. It is a less well known fact that nonfocused microwaves and radio-frequency waves applied to the body region containing a tumor may also provide high temperature "selective tumor heating." Most solid tumors contain an immature, primitive vasculature [13], [14] that seems to be incapable of augmenting blood flow in response to thermal stress, as do normal tissues [15]. Thus, many tumors have a selective inability to dissipate heat, becoming heat reservoirs, compared to adjacent normal tissues. Thus, it may be that precisely targeted energy to an exact location may be unnecessary for effective hyperthermia.

Various methods of localized heating with acoustic and electromagnetic energy have been used effectively for treatment of exposed or superficial tumors. However, most lethal tumors reside deep within the body, but until recently the means to produce safe internal hyperthermia was elusive. In this communication, we summarize the historical methods for production of localized heat and the problems encountered with the attempts at deep heating. With this background, the development of magnetrode [1] radio-frequency magnetic-loop induction hyperthermia is presented in detail. Clinical results from several medical centers throughout the country suggest that this fundamentally new approach to thermal therapy may hold great promise for patients with cancer.

[1] Magnetrode™, Henry Medical Electronics, Los Angeles.

II. Classical Methods of Localized Hyperthermia

A. Low-Frequency Current Field (LCF)

Interstitial hyperthermia, a form of resistive heating, has been achieved by passing a LCF of 500 kHz between electrodes implanted directly into tumors [16]. The size and configuration of the field can be manipulated by the number and position of needle electrodes. This technique has been useful for the treatment of small tumors in the oropharynx, vagina, and rectum [17]. However, the tumor must be accessible for direct implantation and its full extent must be known. Few deep tumors lend themselves to this invasive treatment approach.

B. Ferro-Magnetic Coupling

Directly implanted ferro-magnetic "seeds" [18], or liquid silicone impregnated with finely powdered iron particles that vulcanizes at body temperature, can be heated by external means. Preliminary experiments in dogs using an ac magnetic field at 20 kHz and hysteresis heating of these iron particles demonstrated significantly elevated temperatures (50°–90°C) in injected organs and insignificant heating of noninjected organs [19].

C. Ultrasound (US)

Ultrasound is a well-defined and spatially manipulative source of narrow-beam acoustic energy at 0.5–2 MHz at wave lengths of 3 mm – 0.75 mm. When focused, it has the potential for noninvasive heating of a tumor at extreme depth [20]. Moreover, the temperature rise of the target tissue as the result of insonation may be controlled and reproduced [21]. However, unlike electromagnetic energy, ultrasound does not propagate efficiently through air; the applicator must be coupled to the body surface (which is frequently irregular) with degassed salt water and/or sound-transmitting gel. Because of the high acoustic impedance mismatch between air and soft tissues, ultrasound is totally deflected at these interfaces and is ineffective near air-containing spaces (viz., oral-nasal cavity, lungs, stomach, intestinal tract). Thus, its application has been limited to surface or near-surface tumors [23].

D. Microwaves (MW)

Microwaves at 433, 915, and 2450 MHz have provided effective noninvasive localized hyperthermia to large surface areas containing superficial tumors [24]. Microwaves have been quite popular for animal investigations because their application is easy; however, in-depth penetration in humans has been limited to a few centimeters because of the energy absorption that occurs in the high water content overlaying musculature [25].

Multiple applicators have been used in attempts to achieve heating at depth, but results so far have been

disappointing. One innovative method (BSD Corporation, Salt Lake City, UT) employs an annular phased array applicator operating at 55 MHz. Clinical use of this device has been limited thus far to a series of treatments for advanced recurrent cancer. Although deep central heating of tumor to 40°C has been demonstrated, treatment has been limited because of preferential heating of the surface tissues [26].

E. Radio-Frequency Waves (RF)

Low-frequency waves at 13.56 and 27.12 MHz have relatively greater depth of penetration in tissue compared to microwaves [25], [27] and have been useful in specific situations.

1) Induction Coils: The so-called "pancake" applicator is a compact coil–capacitor combination that induces circular eddy-currents in tissue by magnetic induction. This activity tends to be much less in the fatty subcutaneous tissue [25]. Muscle heating to 40°C at 4-cm depth has been achieved in the human thigh with a fat/muscle interface at 0.6 cm (Ultratherm 608™, Siemens Corporation, Erlangen, West Germany). Prototype coils (International Medical Electronics, Ltd., Kansas City, MO) have been useful for safely heating surface tumors ≥ 42°C [28].

2) Capacitive Electrodes: Capacitively coupled parallel opposed plates have provided effective localized and regional heating. The field may be shaped by varying the size, contour, and placement of the two electrodes. However, this method also has been generally reserved for the treatment of surface or near-surface tumors because of the extreme energy absorption by the overlaying subcutaneous fatty tissue.

To a limited degree, injurious heating of surface tissues has been reduced with cooled-contact electrodes, and intratumor temperatures to 57°C at 10-cm depth have occurred in selected individuals who had minimal overlaying fatty tissues [15]. Investigations in dogs, sheep, and pigs have indicated that 3–4 W/cm^2 are required to achieve effective internal hyperthermia, which is possible in these animals if surface tissues are cooled to 15°C. However, humans with similarly thick surface tissues can only tolerate $<$ W/cm^2, even with cooling to 3°C [29].

In an effort to circumvent these problems of deep heating employing RF, multiple portals of energy and "crossfire" techniques have been explored. This method employs at least three pairs of sequentially activated cooled-contact capacitance electrodes placed on opposite sides of the body and energized with serial bursts of power (Life Extension Technology, Inc., Westport, CT). Unfortunately, the only successfully treated patients have been thin with almost no fat left on their bodies [30].

Thus, several investigations indicate that cooled capacitive heating in humans is effective only if the combined thickness of the skin and subcutaneous tissues are less than 1 cm in thickness [29].

F. Conclusions

The classical methods of applying acoustic and electromagnetic energy have been valuable tools for increasing the understanding of localized hyperthermia and will continue to contribute to the treatment of superficial cancers. However, by 1977 we had concluded that these methods were virtually ineffective and even dangerous from attempts to heat deep tissues [15]. Since the majority of lethal tumors arise within internal organs, we felt that research into alternative methods of deep thermal therapy was warranted. This research led to the development of magnetic-loop induction hyperthermia.

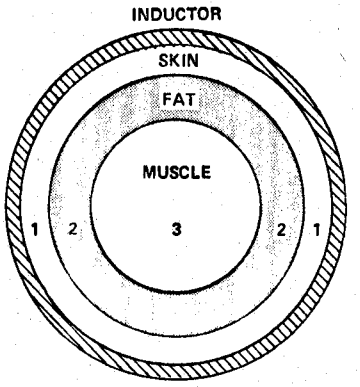

Fig. 1. Model of inductor-type electrode and specimen. (Reproduced by courtesy of *IEEE Trans. Bio-Med. Eng.* [32].)

III. Development of Magnetrode Magnetic-Loop Induction Hyperthermia

A. Rationale

The use of an inductor to provide nonradiating electromagnetic heating of a living specimen was modeled as shown in Fig. 1. The inductor (coil) occupies the shaded region and surrounds three concentric layers of nonmagnetic lossy dielectric, representing, respectively, skin, subcutaneous fat, and muscle, in an idealization of practical situations, e.g., when an inductor coil is wrapped around a portion of a human thigh.

Maxwell's equations, which must be satisfied in the region encompassed by the inductor, require that the flux lines of the E-field be concentric circles if the magnetic field is axially directed inside the coil. This was a reasonable assumption to make. It led to the conclusion that the E-field at a boundary between tissue layers is tangential to the boundary and has the same value at infinitesimal distances on each side of the boundary. Thus, for example, $E_1 = E_2$, with E_1 the value of the electric field strength in volts/meter in the skin layer at a point close to the skin/fat interface, and with E_2 the value of the electric field in the fat layer at a point close to the skin/fat interface, and with σ_1 and σ_2 the respective conductivities in mhos/meter. The heat generated at these two points, in watts/cubic meter, is in the ratio

$$\frac{P_2}{P_1} = \frac{\sigma_2 |E_2|^2}{\sigma_1 |E_1|^2} = \frac{\sigma_2}{\sigma_1}.$$

Using the known constitutive parameter values for σ at a radio frequency (27.12 MHz) [31] we obtained

$$\frac{P_2}{P_1} = \frac{0.11}{0.61} = 0.2 \text{ (low)} \quad \frac{P_2}{P_1} = \frac{0.43}{0.61} = 0.7 \text{ (high)}.$$

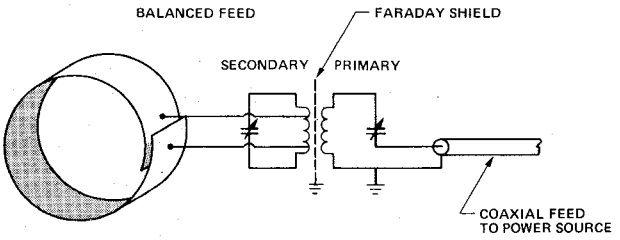

Fig. 2. (a) Magnetrode and (b) its matching network. (Reproduced by courtesy of *IEEE Trans. Bio-Med. Eng.* [32].)

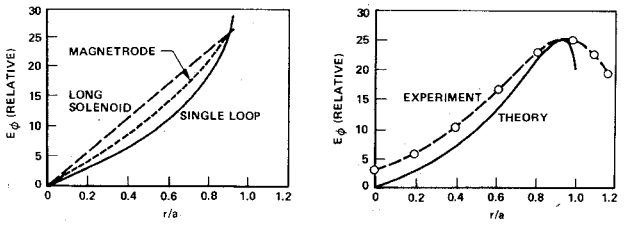

Fig. 3. E_ϕ-field distribution for a typical magnetrode contrasted to a long solenoid and a loop. (a) Central plane. (b) Noncentral plane. (Reproduced by courtesy of *IEEE Trans. Bio-Med. Eng.* [32].)

Thus, the heat generated in the subcutaneous fat layer was predicted to be only 20–70 percent of the heat generated in the skin or muscle layers, whereas when employing a capacitive-type field the heat in the subcutaneous fat layer was 1.5–5.6 times higher than that of the other tissues. While this calculation was made for points near an interface, human skin and fat layers are typically thin enough to extrapolate this conclusion to apply for all points in these two layers. The important conclusion was reached that, if the E-lines could be made to run parallel to the layer interfaces, instead of perpendicular to them, excessive unwanted heating of the superficial fat layer might be avoided, making safe deep heating possible [32].

B. Design of the Magnetrode

The coil/specimen arrangement shown in Fig. 1 initially posed some severe engineering difficulties. In order to produce the needed ampere turns in the coil efficiently, a resonant circuit had to be devised. The required capacitance would have to handle high current densities if conventional commercially available lumped capacitors were used. This was not a satisfactory solution. Ultimately, an extremely simple design was adopted and has proved to be very effective. The coil is a single turn of a rolled conducting sheet which overlaps itself in a noncontacting sense, as shown in Fig. 2(a). The area of overlap and the gap size can be adjusted to provide the proper amount of capacitance.

The problems of impedance transformation to a level appropriate to interface with the RF generator and impedance adjustment occasioned by the introduction of a limb or torso to be heated remained. A matching network of the type shown in Fig. 2(b) was designed. Placed between the magnetrode and the generator, simple adjustments its controls will reduce the reflected power to an insignificant value for a wide range of loads placed within the magnetrode.

C. Field Distribution of a Magnetrode

If the current distribution in the magnetrode is assumed to be entirely $\varnothing$-directed, then the magnetic field can be expressed in cylindrical coordinates in the form

$$\boldsymbol{H} = [\boldsymbol{l}_r H_r(r,z) + \boldsymbol{l}_z H_z(r,z)]\, e^{j\omega t}.$$

Maxwell's equations reveal that in this case the electric field has only a $\varnothing$-component; it can be represented by $E_\varnothing(r,z)e^{j\omega t}$. Thus, the electric field lines are concentric circles, a desirable feature already alluded to in the discussion concerning Fig. 1.

The field distribution in the central transverse plane of the magnetrode is intermediate between what one would deduce for an infinitely long solenoid and for a single wire turn. For the latter, it is well known [33] that

$$H_z = \frac{2I}{a}\left\{\frac{K(k)}{[1+(r/a)]} + \frac{E(k)}{[1-(r/a)]}\right\}$$

with a, the loop radius, with $0 \leqslant r \leqslant a$, and with $K(k)$, $E(k)$ elliptic integrals, wherein $k^2 = 4ar/(a+r)^2$. Since these elliptic integrals are tabulated functions [33], it is a simple matter to construct $H_z(r,0)$.

For a concentric circular contour C of radius r in the plane of the loop

$$\oint_C \boldsymbol{E}\cdot d\boldsymbol{l} = 2\pi r E_\phi(r,0) = -j\omega\mu_0 \int_S \boldsymbol{H}\cdot d\boldsymbol{S}$$

$$= -j\omega\mu_0 \int_0^r H_z(r',0)2\pi r'dr'.$$

When E_ϕ is computed from this relation, the result is as shown in Fig. 3(a). The central plane field distribution for a long solenoid is shown for comparison.

One should expect the central plane E_ϕ distribution for a magnetrode to lie between these two curves, with the intermediacy governed by the ratio L/a, with L the length of the magnetrode and a its radius. In a noncentral plane, flaring of the magnetic field causes a roll-over in the E-field plot, as suggested in Fig. 3(b). Experimental confirmation is also included in that figure.

If a nonmagnetic specimen of low conductivity is placed inside the magnetrode, one would expect only minor changes in the field distributions. This validated the assumptions made in Fig. 1 and indicated that the magnetrode could be a useful device for establishing an E-field parallel to layer boundaries, with the potential for avoiding severe skin and subcutaneous fat burning while still providing effective deep heating.

From the curves of Fig. 3(a), a "dead spot" was observed in the E-field on the axis of the magnetrode. This finding implied that no useful heat would be generated in the portion of the specimen coinciding with the axis. However, we reasoned that heat generation per se was not the total process involved in a living specimen because the complex thermodynamic system can and does redistribute generated heat through its blood flow. In fact, the final

temperature distribution in living systems might be advantageous to eventual human cancer therapy. This assumption led to continued research in static phantoms, animals, and man.

D. Thermal Distribution in Phantoms

Experiments were carried out in both homogeneous and heterogeneous tissue equivalents and in animal tissue phantoms. The phantom carrier was a thin-walled Plexiglas™ cylinder 12 cm in diameter and 30 cm in length supported by a dielectric fixture that did not intrude upon its contents. The supporting fixture allowed concentric or acentric placement of the phantom within a 21-cm diameter and 13-cm width magnetrode. Needle thermometers could be introduced to various depths through openings in the carrier to provide two-dimensional temperature sampling. Standard homogeneous muscle equivalent phantoms [34] were prepared, poured into the carrier, and allowed to gel at room temperature before testing. Homogeneous animal tissue phantoms were prepared by packing the carrier with 9 lb of lean ground beef. One type of heterogeneous animal tissue phantom was prepared by introducing a peripheral void into the ground beef phantom with a 3-cm diameter thin-walled polyethylene cylinder. Other heterogeneous animal tissue phantoms were prepared by loosely packing the carrier with intact "hot dogs" (in effect, providing multiple contacting units of homogeneous animal tissue encased in a thin tissue capsule surrounded by multiple small air voids). Large voids were achieved by removing units and/or introducing plastic cylinders. To test a dead animal extremity model, a 12×19×25-cm leg of lamb with 2-cm subcutaneous tissue at an ambient baseline temperature of 20°C was used.

The thermal patterns produced in homogeneous tissue-equivalent phantoms and animal tissue phantoms were remarkably similar (Fig. 4). In each case, as predicted by electrodynamic theory, significant preferential peripheral heating was observed with minimal central heating. When these phantoms were placed concentrically within the magnetrode, there was gradual radial reduction in temperature with increasing depth. If the phantom was placed off the central axis of the magnetrode, there was some alteration of the thermal gradients, and preferential heating occurred at the site nearest the applicator. This finding suggested that the position of the test object within the field has some bearing on thermal distribution, as we had previously predicted [32]. Perhaps of greater significance, more complex thermal gradients were observed in heterogeneous animal tissue phantoms and near voids and interfaces of varying types, as has been indicated by others [35], similar to those expected in humans.

Electrodynamic theory predicted a central null in the *E*-field on the axis of a magnetrode magnetic-loop induction applicator in the absence of a specimen. Our measurements on static phantoms and dead animals confirmed the electrodynamic theory when the thermal effect of the circulatory system and blood flow were not present [36]. *Thermodynamic* theory predicts redistribution of heat when a

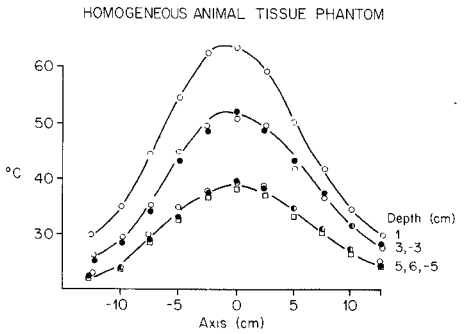

Fig. 4. Homogeneous animal tissue static phantom placed concentrically within a magnetrode. Power at 500 W for 5 min resulted in potentially injurious peripheral and axial heating under the applicator and ineffective central heating. (Reproduced by courtesy of *Int. J. Radiat. Oncol. Biol. Phys.* (36).)

live specimen with a functioning vascular system is inserted into the apparatus. However, when living specimens as complicated as a large animal or a human are inserted, present thermodynamic theory is unable to predict heat redistribution quantitatively. Phantoms have proved to be satisfactory models of energy deposition and have been particularly useful in evaluating various applicators at higher frequencies. However, phantoms cannot account for the thermoregulatory effect of a functioning vascular bed. For this reason, further investigations were undertaken on live animals.

E. Thermal Distribution in Live Animals

Heat distribution patterns were evaluated in male dogs weighing 30–33 kg. The animals were shaved, anesthetized with sodium pentobarbitol (65 mg/ml) at a dose of 10 ml for induction and 1 ml for intermittant maintenance, and intubated without mechanical ventilation support. The animals were suspended supine between dielectric supports to lie centrally within a 35-cm diameter magnetrode. A midline abdominal opening was made from the xyphoid to the pubis to allow temperature measurements with particular care for thorough hemostasis. Upon opening the abdomen, an anterior air space occurred and the intestines floated posteriorly. The dog spleen, being on a long and redundant mesentary, was easily displaced to a midline and central internal location without compromise of its blood supply. The exact size and location of each organ relative to the body wall was determined by caliper measurements. The dog was then repositioned such that the central spleen was lying at the center of the applicator. These alterations provided a living model for assessment of thermal distribution patterns within the magnetrode not only of surface tissues but for peripheral (liver, kidney) and central (spleen) internal organs as well (Fig. 5).

The initial investigations in living dogs were designed to determine the effect of heat dosage on the thermal distribution patterns. Rapid high-dose hyperthermia always produced preferentially injurious peripheral tissue heating with a central "cold spot" similar to that observed in the phantom models [36]. However, with moderate-dose hyperthermia for the same interval, there was virtually equiva-

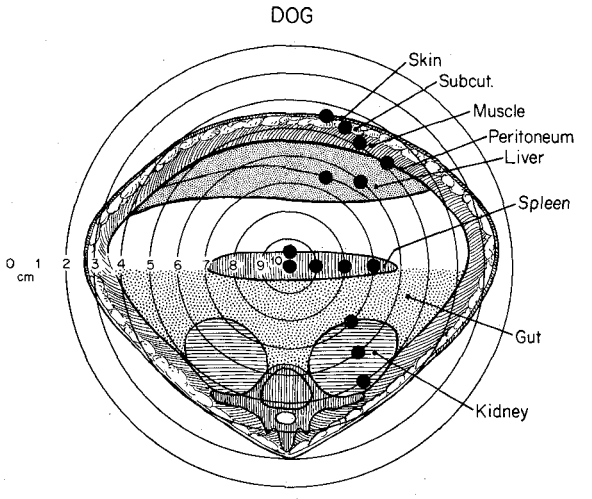

Fig. 5. Temperature measurement sites (●) in a living anesthetized dog. The spleen, being on a long and redundant vascular pedicle, was easily relocated to a central internal location without compromise of its blood supply. The exact location of organs and temperature monitoring sites were determined by caliper measurements in centimeters. (Reproduced by courtesy of *Int. J. Radiat. Oncol. Biol. Phys.* [36].)

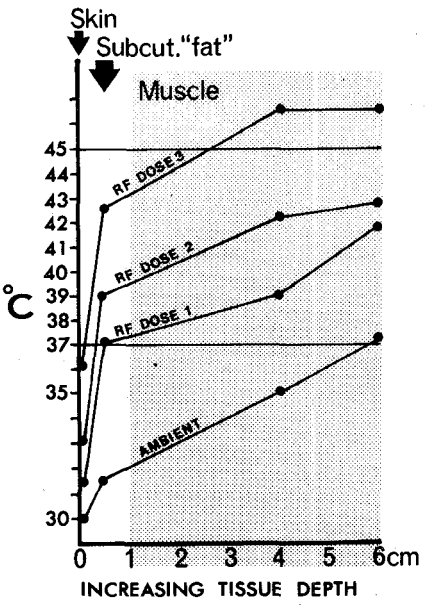

Fig. 6. Performance of the magnetrode applicator in a human thigh with 1 cm of subcutaneous tissue at three RF doses. No surface cooling was employed. Note the uniformity of deep heating with minimal heating of the surface tissues. (Reproduced by courtesy of *J. Natl. Cancer Inst.* (29).)

TABLE I
THERMAL DISTRIBUTION PATTERNS IN LIVE DOGS

TISSUE LOCATION	ORGAN	AMBIENT °C	TX. NO. 1 MEASURED °C/ (CORRECTED °C)		TX. NO. 2 MEASURED °C/ (CORRECTED °C)		TX. NO. 3 MEASURED °C/ (CORRECTED °C)	
SURFACE	SKIN	34.5	40.7	(40.7)	44.6	(44.6)	44.2	(44.2)
	SUB. CUT.	35.7	43.0	(43.2)	44.7	(44.9)	44.6	(44.8)
	MUSCLE	36.8	43.0	(43.4)	44.4	(44.7)	43.8	(44.1)
	PERITONEUM	--	41.8	--	42.8	--	42.6	--
PERIPHERAL INTERNAL	LIVER SURFACE	--	40.1	(40.3)	41.3	(41.5)	42.4	(42.6)
	LIVER CENTRAL	37.3	40.2	(40.4)	41.4	(41.6)	42.4	(42.6)
PERIPHERAL INTERNAL	KIDNEY SURFACE	--	39.6	(39.7)	40.7	(40.8)	41.4	(41.5)
	KIDNEY PERIPHERAL	--	39.9	(40.1)	41.2	(41.4)	42.2	(42.4)
	KIDNEY CENTRAL	37.0	40.0	(40.9)	41.0	(41.1)	42.3	(42.4)
CENTRAL INTERNAL	SPLEEN SURFACE	--	40.3	(40.5)	41.1	(41.3)	42.7	(42.9)
	SPLEEN CENTRAL	37.2	39.9	(40.1)	41.4	(41.7)	42.4	(42.6)
	SPLEEN 1 CM.	--	40.0	(40.2)	41.3	(41.5)	42.1	(42.3)
	SPLEEN 2 CM.	--	40.1	(40.3)	41.4	(41.6)	42.0	(42.2)
	SPLEEN 3 CM.	--	--	--	41.5	(41.7)	42.2	(42.4)

lent heating of both peripheral and central visceral organs without surface tissue injury. It appeared that the amount of heat deposition per unit of time, or the velocity of heating, had significant influence on thermal distribution patterns. We surmised that rapid high-dose hyperthermia induced a "flash burn" effect so quickly that effective heat transfer was impossible. A typical thermal distribution profile for the live dog employing moderate dose hyperthermia is shown in Table I. During three sequential hyperthermia treatments, all surface tissues remained within a physiologically tolerable temperature range and showed no signs of injury. Virtually uniform internal heating occurred. In contradistinction to the observations in phantoms, potentially tumoricidal temperatures $\geq 42°C$ occurred in both peripheral and central organs to a nearly equivalent degree. Intraparenchymal measured and corrected temperature samples of all visceral organs showed a temperature gradient of less than 1°C.

The thermal distribution profiles of a dog that was subjected to equivalent hyperthermia while alive and dead are shown in Table II. While alive, nearly uniform internal organ heating occurred, as was hoped based on thermodynamic theory.

TABLE II
THERMAL DISTRIBUTION PATTERNS OF LIVE VERSUS DEAD DOG

TISSUE LOCATION	ORGAN	ALIVE MEASURED °C/ (CORRECTED °C)		DEAD MEASURED °C/ (CORRECTED °C)	
SURFACE	SKIN	42.6	(42.9)	39.5	(39.8)
	SUB. CUT.	43.7	(44.2)	42.7	(43.2)
	MUSCLE	44.2	(44.6)	46.0	(46.6)
	PERITONEUM	44.6	--	48.4	--
PERIPHERAL INTERNAL	LIVER SURFACE	42.4	(42.8)	52.1	(52.5)
	LIVER CENTRAL	42.4	(42.8)	48.1	(48.5)
PERIPHERAL INTERNAL	KIDNEY SURFACE	41.4	(41.5)	41.2	(41.4)
	KIDNEY PERIPHERAL	41.4	(41.6)	42.3	(42.5)
	KIDNEY CENTRAL	41.5	(41.6)	43.1	(43.3)
CENTRAL INTERNAL	SPLEEN SURFACE	42.1	(42.3)	39.0	(39.2)
	SPLEEN CENTRAL	42.1	(42.3)	39.9	(40.1)
	SPLEEN 1 CM.	42.6	(42.8)	39.2	(39.2)
	SPLEEN 2 CM.	41.5	(41.7)	39.3	(39.6)

These findings were in accordance with the postulate that the final thermal distribution in the living state is not the simple result of energy deposition per se as predicted by electrodynamic theory and static phantoms, but is ultimately dependent upon the presence of thermoregulatory systems [32], [36].

These encouraging results suggested that the capability to achieve deep-heat in live animals could be applied to investigations in humans.

F. Thermal Distribution in Humans

The thermal profile of the magnetic-loop applicator in the human normal thigh is shown in Fig. 6. As can be seen, an extraordinary deep-heating capability was possible with minimal and physiologically tolerable heating of the over-

laying skin and subcutaneous tissues, even when the surface fatty tissue was of substantial thickness (viz. ≥ 1 cm) [29]. This observation was in accord with our earlier conclusion based upon theoretical calculations that indicated that if *E*-lines could be made to run parallel to layer interfaces, excessive heating of surface tissues could be avoided.

Tests were carried out in awake persons with minimal or no sedation in existing hospital environments without the necessity of special shielding or Faraday cages. Moreover, because of the highly effective impedance match, technicians were able to touch, monitor vital signs, place intravenous needles, and otherwise interact with subjects undergoing magnetic-loop hyperthermia. With these techniques, it also appeared that overall energy absorption could be monitored and predicted with >80-percent reliability, suggesting that future data from divergent sources might be compared for therapeutic outcome.

III. Human Clinical Cancer Trials

These observations suggested that safe and potentially effective localized hyperthermia tumor therapy might be possible in man. In 1977, clinical cancer trials were begun. The following is a brief summary of the knowledge and results gained to date.

A. Tumor Heating Capacity

Of 89 tumors evaluated in skin, subcutaneous tissue or muscle, intraabdominal organs, lung or bone, temperatures $\geq 42°C$ were possible in 69 (78 percent) tumors, $\geq 45°C$ (113°F) in 32 (36 percent), and $\geq 50°C$ (122°F) in 22 (25 percent), while normal tissues remained within physiologic temperatures [29]. These data were consistent with in vivo animal tumor models that showed that potentially tumoricidal hyperthermia $\geq 42°C$ could be achieved safely in living systems. Moreover, "independent" tumor heating $\geq 45°C$ observed in one-third of the patients confirmed that many tumors retained heat compared to normal tissues (Fig. 7).

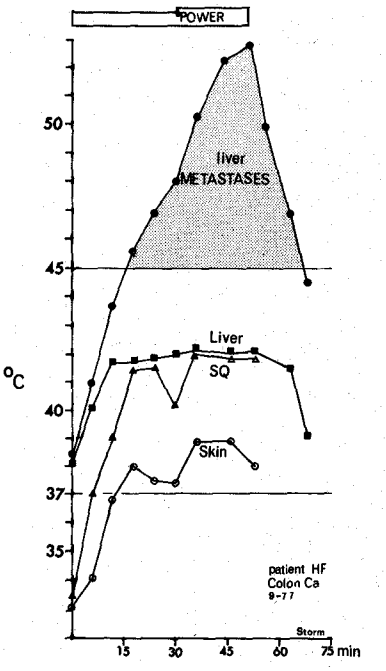

Fig. 7. Thermal profile of a secondary (metastatic) human colon cancer in liver, 10×10 cm. Note the independent heat retention in the liver tumor, with the normal liver and surface tissues at physiological temperatures. No form of surface tissue cooling was employed. (Reproduced by courtesy of *Cancer Res.*, (15).)

Tumor heating capacity was compared by the histopathological type of malignancy. We found that heating $\geq 42°C$ was possible in 21/22 (95 percent) sarcomas, 18/24 (75 percent) melanomas, 24/36 (67 percent) adenocarcinomas, 3/4 epidermoid carcinomas, and 3/3 teratocarcinomas [37]. These findings suggested that potentially tumoricidal hyperthermia was possible in most varieties of solid human cancer.

Heating capacity was also compared by the size of the tumor treated [29]. Of 53 tumors ≥ 5 cm in *least* dimension, 47 (89 percent) could be heated $\geq 42°C$, while only 22/36 (61 percent) tumors <5 cm could be effectively heated. The trend of these findings suggested that localized hyperthermia may be uniquely beneficial in larger cancers, i.e., those cancers for which little effective therapy exists at the present time.

B. Tumor Thermoregulation

It has long been postulated that because of their abnormal *neo*-vascularity, most cancers could not regulate blood flow and would, therefore, react passively to thermal stress. However, we found that in 20/89 (22 percent) tumors effective temperatures were not possible without exceeding normal tissue tolerance. These tumors displayed thermal adaptation to constant or increased incident heat similar to that previously observed in animal normal muscle [15]. This inherent ability to adapt to thermal stress was again independent of tumor type, but appeared to be related to tumor size. Spontaneous cooling with progressive heat application occurred in 14/36 (39 percent) tumors <5 cm, but in only 6/53 (11 percent) ≥ 5 cm in size. These data indicate that some tumors retain their ability for vasco-regulation and may dissipate heat in a manner similar to normal tissues.

While hyperthermia per se should be ineffective in these cases, it is interesting to speculate whether or not increased blood flow might not render such tumors more susceptible to radiation (due to enhanced oxygenation) or to chemotherapeutic agents (due to increased drug delivery).

C. Dose/Response of Thermal Therapy

In an attempt to evaluate the thermal death time of human tumors, we compared the net tumor necrosis (total absence of viable cells) to pretreatment samples from 44 patients with highly advanced cancer who were treated by magnetic-loop induction hyperthermia at various temperatures and fractionated exposure times [38]. We found that a single treatment at $\geq 50°C$ for 17–45 min resulted in 20–100-percent tumor necrosis, whereas lower temperatures had no apparent effect. Two or three weekly treatments at 45–50°C for 30–72 min total treatment time produced 70–100-percent necrosis, whereas 40–45°C pro-

duced nearly equivalent necrosis but required more than twice the time. Five weekly and 10 daily treatments for 135–600 min produced some tumor necrosis at 40–45°C. However, for similar amounts of treatment time, temperatures above 45°C were the most tumoricidal.

The results of this study in man suggested that higher temperatures, longer treatments, and multiple treatments were the most effective, in accordance with those predicted from previous animal experiments [8]. Optimal dose/time regimens and treatment fraction schedules remain to be determined. Prospective trials of magnetrode hyperthermia are currently underway at several institutions in an effort to answer these important questions.

D. Physiologic Response and Toxicity of Magnetic-Loop Induction Hyperthermia

Localized deep internal hyperthermia at 500–1000 W absorbed power resulted in profuse sweating, skin flushing, a modest rise in core temperature (0.5–1°C), respiratory rate (2–12 rpm), blood pressure (20–40 mmHg), and a moderate to marked rise in pulse rate (20–60 beats/min) [15].

In 3000 treatments, there were 10 (0.3 percent) incidences of surface tissue injury and none of systemic toxicity. Focal areas of subcutaneous scarring occurred at temperatures from 42–45°C in very obese patients, probably as a result of the extremely poor vascularity of this tissue. Partial thickness skin burns also occurred at < 45°C in patients with skin grafts and severely damaged tissues from excessive prior *x*-irradiation.

These results indicated that magnetic-loop induction hyperthermia is remarkably safe, but that damaged normal tissues with compromised blood flow are thermosensitive at otherwise physiologically tolerable temperatures.

IV. Future Potential

Hyperthermia may have its greatest role when combined with other forms of cancer therapy.

At temperatures $\geqslant 45$°C, tumor blood vessel collapse rapidly occurs, rendering tumors nearly avascular [15]. In the 25 percent or so instances where this collapse appears to be possible, localized hyperthermia might be administered preoperatively to large cancers to reduce blood loss and facilitate surgical intervention [39].

Pilot studies at our institution also have shown an apparent synergism of combination thermochemotherapy (heat plus drugs). In patients with a variety of advanced cancers whose disease was progressing on chemotherapy alone, the combined treatment induced 20-percent disease regression and 50-percent disease stabilization for brief periods of time. Historically, patients whose malignant melanoma has spread to their liver have a dismal prognosis despite standard chemotherapy, with few treatment responders and a median survival of 2.5 months. When chemotherapy infused directly into the liver was combined with localized hyperthermia in ten patients, eight responded to treatment and survived 3–18 months (8.5 months median) [40]. The quality of life in this group of patients was also enhanced significantly.

With advanced laboratory methods, clones of human tumor stem cells have been established in tissue culture, providing the means to test an individual patient's tumor for sensitivity against various anti-cancer drugs *in vitro*. We now are using this assay at both normothermic and hyperthermic temperatures, and our early results suggest that the assay has the potential ability to predict the best available therapy for individual patients [41].

Localized heat also has been combined with radiation therapy [17], [23], [24], [28]. While few controlled studies exist, preliminary reports with the magnetic-loop induction system indicate a potential for treatment of deep tumors with minimal side effects [42].

Pilot studies at our institution also suggest that refractory brain tumors may someday yield to the effects of hyperthermia. Until the development of the magnetrode, there was no known way to penetrate the skull and provide safe deep heat to the brain by external means. In rabbits and dogs, virtually uniform brain temperatures of 42–43°C have been possible without injury [43], probably because relatively little energy is absorbed by the high resistance surrounding bone, for the reasons presented earlier. We recently achieved brain temperatures of 41°C safely in humans. That may enhance the effectiveness of standard chemotherapeutic agents and radiation.

V. Conclusions

Hyperthermia has been shown to have a potential role in cancer therapy. Magnetrode magnetic-loop induction appears to provide a unique means for safe deep visceral heating of internal sites where refractory tumors most frequently reside, thus far unattainable by conventional methods. Preliminary results indicate that most solid human cancers, regardless of type, can be effectively heated, but that overall tumor heating capacity is dependent upon blood flow and size. Higher temperatures, longer treatments, and multiple treatments seem to be most effective when heat is employed as a single agent. However, the greatest potential of hyperthermia may be in combination with radiation therapy or chemotherapy, where synergism occurs.

References

[1] J. A. Dixon and M. Suzanger, *Brit. J. Cancer*, vol. 28, pp. 81–85, 1973.

[2] B Mondovi, R. Strom, G. Rotilio, A. Finazzi-Agro, R. Cavaliere, and A. Rossi-Fanelli, *Eur. J. Cancer*, vol. 5, pp. 129–136, 1969.

[3] B Mondovi, A. Finazzi-Agro, G. Rotilio, R. Strom, G. Moricca, and A. Rossi-Fanelli, *Eur. J. Cancer*, vol. 5, pp. 136–147, 1969.

[4] R. Strom, A. S. Santoro, C. Crifo, A. Bozzi, B. Mondovi, and A. Rossi-Fanelli, *Eur. J. Cancer*, vol. 9, pp. 103–112, 1973.

[5] G. M. Hahn, "Heat and drugs in vitro and in vivo," in *Proc. Int. Symp. Cancer Therapy by Hyperthermia and Radiat.* (Washington DC), Apr 28–30, Amer. Coll. Rad. Press, 1975, pp. 61–65.

[6] R. Strom, in *Atti. Soc. Ital. Cancer V Nat. Congr.*, vol. 7, (part 2), pp. 49–60, 1970.

[7] C. Turano, A. Ferraro, R. Strom, R. Cavaliere, and A. Rossi-Fanelli, *Eur. J. Cancer*, vol. 6, pp. 67–72, 1970.

[8] J. A. Dixon, "Hyperthermia and laboratory animal systems: Chairman's address," in *Proc. Int. Symp. Cancer Therapy by Hyperthermia*

and Radiat., (Washington, DC), Apr. 28–30, Amer. Coll. Rad. Press, 1975, pp. 105–106
[9] L. E. Gerweck, E. L. Gillette, and W. C. Dewey, *Eur. J. Cancer*, vol. 10, pp. 691–693, 1974.
[10] E. W. Gerner, W. G. Connor, M. L. M. Boone, D. J. Doss, E. G. Mayer, and R. C. Miller, *Radiology*, vol. 116, pp. 433–439, 1975.
[11] R. Cavaliere, E. C. Ciocatto, B. C. Giovanella, C. Heidelberger, R. O. Johnson, M. Margottini, B. Mondovi, G. Moricca, and A. Rossi-Fanelli, *Cancer*, vol. 20, pp. 1351–1381, 1967.
[12] B. C. Giovanella, A. C. Morgan, J. S. Stehlin, and L. J. Williams, *Cancer Res.*, vol. 33, pp. 2568–2578, 1973.
[13] N. Westermark, *Skand. Arch. Physiol.*, vol. 52, pp. 257–322, 1927.
[14] M. J. Mantyla, *Cancer Res.*, vol. 39, pp. 2304–2306, 1979.
[15] F. K. Storm, W. H. Harrison, R. S. Elliott, and D. L. Morton, *Cancer Res.*, vol. 39, pp. 2245–2251, 1979.
[16] J. D. Doss, and C. W. McCabe, *Med. Instrum.*, vol. 10, pp. 16–21, 1976.
[17] M. R. Manning, T. C. Cetas, R. C. Miller, J. R. Oleson, W. G. Connor and E. W. Gerner, *Cancer*, vol. 49, pp. 205–216, 1982.
[18] P. R. Stauffer, T. C. Cetas, and R. C. Jones, in *Proc. Third Int. Symp. Cancer Therapy by Hyperthermia, Drugs, Radiat.*, (Fort Collins, CO), June 22–26, Colorado State Univ. Press, abstract no. Te 35, 1980, p. 71.
[19] R. W. Rand, M. Snyder, D. Elliott, and H. Snow, *Bull. L. A. Neurol. Soc.*, vol. 41, pp. 154–159, 1976.
[20] H. P. Schwan, *Radiat. Environ. Biophys.*, vol. 17, pp. 189–203, 1980.
[21] P. P. Lele, "Hyperthermia by ultrasound," in *Proc. Int. Symp. Cancer Therapy by Hyperthermia and Radiat.*, (Washington, DC), Apr. 28–30, Amer. Coll. Rad. Press, 1975, pp. 168–178.
[22] P. P. Lele, *Radiat. Environ. Biophys.*, vol. 17, pp. 205–217, 1980.
[23] J. B. Marmor, in *Proc. Third Int. Symp. Cancer Therapy by Hyperthermia, Drugs, Radiat.*, (Fort Collins, CO), June 22–26, Colorado State Univ. Press, abstract no. P III 3, 1980, p. 106.
[24] K. H. Luk, T. L. Phillips, and R. M. Holse, *Western J. Med.*, vol. 132, pp. 179–185, 1980.
[25] A. W. Guy, "Physical aspects of electromagnetic heating of tissue volume," in *Proc. Int. Symp. Cancer Therapy by Hyperthermia and Radiat.*, (Washington, DC), Apr. 28–30, Amer. Coll. Rad. Press, 1975, pp. 179–192.
[26] F. A. Gibbs, *J. Microwave Power*, vol. 16, pp. 185–192, 1981.
[27] D. A. Christensen and C. H. Durney, *J. Microwave Power*, vol. 16, pp. 89–105, 1981.
[28] J. H. Kim and E. W. Hahn, *Cancer Res.*, vol. 39, pp. 2258–2261, 1979.
[29] F. K. Storm, D. L. Morton, L. R. Kaiser, W. H. Harrison, R. S. Elliott, T. H. Weisenburger, R. G. Parker, and C. M. Haskell, *J. Nat. Cancer Inst.*, 1982.
[30] H. H. LeVeen, N. Ahmed, V. A. Piccone, S. Shugaar, and G. Falk, *Ann. NY Acad. Sci.*, vol. 335, pp. 362–371, 1980.
[31] H. P. Schwan and G. M. Piersol, *Amer. J. Phys. Med.*, vol. 33, pp. 371–404, 1954.
[32] R. S. Elliott, W. H. Harrison, and F. K. Storm, *IEEE Trans. Bio-Med. Eng.*, vol. 29, pp. 61–64, 1981.
[33] W. R. Smythe, *Static and Dynamic Electricity*, New York: McGraw-Hill, 1939, pp. 266–268.
[34] A. W. Guy, *IEEE Trans. Microwave Theory Tech.*, vol. 19, pp. 205–210, 1971.
[35] J. R. Oleson, M. S. Stauffer, T. C. Cetas, M. W. Dewhirst, R. S. Heusinkveld, and R. C. Jones, *J. Nat. Cancer Inst.*, 1982.
[36] F. K. Storm, W. H. Harrison, R. S. Elliott, A. W. Silberman, and D. L. Morton, *Int. J. Radiat. Oncol. Biol. Phys.*, vol. 8 no. 5, 1982.
[37] F. K. Storm, W. H. Harrison, R. S. Elliott, and Morton, D. L., *Amer. J. Surgery*, vol. 138, pp. 170–174, 1979.
[38] F. K. Storm, R. S. Elliott, W. H. Harrison, and D. L. Morton, *Cancer*, vol. 46, pp. 1849–1854, 1980.
[39] F. K. Storm, R. S. Elliott, W. H. Harrison, L. R. Kaiser, and D. L. Morton, *J. Surgical Oncol.*, vol. 17, pp. 91–98, 1981.
[40] F. K. Storm, L. R. Kaiser, J. E. Goodnight, W. H. Harrison, R. S. Elliott, A. S. Gomes, and D. L. Morton, *Cancer*, vol. 49, 1982 pp. 1243–1248.
[41] B. D. Mann, F. K. Storm, D. H. Kern, A. Giuliano, and D. L. Morton, in *Proc. Amer. Soc. Clin. Oncol.*, vol. 17, pp. 432, 1981.
[42] H. W. Baker, P. A. Snedecor, J. C. Goss, W. P. Galen, J. J. Callucci, I. J. Horowitz, and K. Dugan, *Amer. J. Surg.*, vol. 143, 1982 pp. 586–590.
[43] A. W. Silberman, D. F. Morgan, F. K. Storm, R. W. Rand, J. E. Bubbers, W. J. Brown, and D. L. Morton, *J. Surgical Oncol.*, 1982.

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Heat Transfer in Surface-Cooled Objects Subject to Microwave Heating

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Abstract—**Several investigators in microwave bioeffects research have exposed biological preparations to intense microwave fields, while at the same time cooling the sample with flowing water. We examine the heat transfer characteristics of this situation, to estimate the maximum temperature increase and thermal time constants that might be encountered in such an experiment. The sample is modeled as a uniform sphere, cylinder, or slab subject to uniform heating, which is located in an unbounded coolant flow. The heat transfer is determined by the Biot and Reynolds numbers (which reflect the geometry, fluid flow, and material thermal properties of the system); the temperature rise is governed by the heat conduction equation coupled with external convection. The results are expressed in terms of nondimensional quantities, from which the thermal response of a heated object of arbitrary size can be determined. At low coolant flow rates, the maximum temperature rise can be biologically significant, even for relatively small objects (of millimeter radius) exposed to moderate levels of microwave energy (with a SAR of ca. 100 mW/g). The results are valid also where the coolant is a gas or a liquid different from water, the only restriction being on the Reynolds number of the flow.**

I. NOMENCLATURE

a	Radius of the spherical tissue, in meters.
B_n	Constant of integration in (11), (18), and (25).
Bi	Biot number.
C_p	Specific heat, in joules per kilogram degrees Celsius.
d	Half the thickness of the rectangular tissue, in meters.
h	Convective heat transfer coefficient, in watts per square meter degrees Celsius.
$J_m(x)$	Bessel function of the first kind and order m, of a real argument x.
k	Thermal conductivity, in watts per meter degrees Celsius; without subscript it refers to the tissue.
L	Characteristic length $= a$ or R or d or as appropriate.
Nu	Nusselt number $= hL/K$.
Pe	Peclet number $=$ Re Pr.
Pr	Prandtl number $= \nu/\alpha$.
Q	Volumetric heat generation, in watts per cubic meter.
r	Radial coordinate.
R	Radius of the cylindrical tissue, in meters.
Re	Reynolds number $= U_\infty L/\nu$.
t	Time.
T	Temperature, in degrees Celsius.
U_∞	Free stream velocity, in meters per hour.
x	Coordinate for rectangular slab tissue.

A. Greek Letters

α	Thermal diffusivity, in square meters per hour.
θ	Nondimensional temperature $= (T^* - T_0)/(QL^2/K)$.
λ_n	Eigenvalues defined by (13), (20), and (27).

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