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# Thermoregulatory Responses to RF Energy Absorption

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This white paper combines a tutorial on the fundamentals of thermoregulation with a review of the current literature concerned with physiological thermoregulatory responses of humans and laboratory animals in the presence of radio frequency (RF) and microwave fields. The ultimate goal of research involving whole body RF exposure of intact organisms is the prediction of effects of such exposure on human beings. Most of the published research on physiological thermoregulation has been conducted on laboratory animals, with a heavy emphasis on laboratory rodents. Because their physiological heat loss mechanisms are limited, these small animals are very poor models for human beings. Basic information about the thermoregulatory capabilities of animal models relative to human capability is essential for the appropriate evaluation and extrapolation of animal data to humans. In general, reliance on data collected on humans and nonhuman primates, however fragmentary, yields a more accurate understanding of how RF fields interact with humans. Such data are featured in this review, including data from both clinic and laboratory. Featured topics include thermal sensation, human RF overexposures, exposures attending magnetic resonance imaging (MRI), predictions based on simulation models, and laboratory studies of human volunteers. Supporting data from animal studies include the thermoregulatory profile, response thresholds, physiological responses of heat production and heat loss, intense or prolonged exposure, RF effects on early development, circadian variation, and additive drug–microwave interactions. The conclusion is inescapable that humans demonstrate far superior thermoregulatory ability over other tested organisms during RF exposure at, or even above current human exposure guidelines. Bioelectromagnetics Supplement 6:S17–S38, 2003.


**Key words: human; laboratory animal; physiology; sensation; body heat balance; drug–microwave interactions**

## INTRODUCTION

The ultimate goal of research involving whole body radio frequency (RF) exposure of intact organisms is the prediction of the effects of such exposure on human beings. Most of the published research on thermophysiological responses in the presence of RF fields has been conducted on laboratory animals, with a heavy emphasis on laboratory rodents (e.g., mice, rats, and hamsters). These small mammals are poor models for human beings because their physiological heat loss mechanisms are limited. Although rats may provide valuable information on cardiovascular responses during heat stress [Kielblock et al., 1982], there are limitations to extrapolation of these models to human beings regarding other aspects of thermoregulation. Thus, basic information about the thermoregulatory capabilities of animal models relative to human capability is essential for the appropriate evaluation and extrapolation of animal data to humans. In general, reliance on data collected on humans and nonhuman primates, however fragmentary, yields a more accurate understanding of how RF fields interact with humans. Such data are featured in this review.

## FUNDAMENTALS OF THERMOREGULATION

Thermoregulation is the term that describes the maintenance of the body temperature within a prescribed range under conditions in which the thermal load on the body may vary. In humans, thermal loads come from alterations in ambient conditions (temperature, ambient vapor pressure, air velocity, clothing, and other environmental variables that may alter the temperature of the skin) and from changes in heat production within the body. The deposition of thermalizing

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energy deep in the body by exposure to RF fields provides a unique exception to the energy flows normally encountered by humans, although metabolic activity in the muscles during exercise can also deposit large amounts of thermal energy directly into deep tissues.

The pattern of thermoregulation in vertebrates is characterized as ectothermy, in which the body temperature depends on the regulated uptake of heat from the environment, or endothermy, in which the body temperature depends on a high and regulated metabolic heat production. Most mammals and birds are endothermic and are able to generate heat in their bodies through metabolism and dissipate that heat to the environment in a regulated manner.

Most of the vital internal organs of endotherms function most efficiently when they are held at a relatively constant temperature that is characteristic of the species. For humans, this characteristic temperature is $\sim 37 \pm 0.5$ °C ($98.6 \pm 1.0$ °F). While the temperature of individual body tissues may vary slightly, significant departures are associated with vigorous exercise, disease states, or possibly lethal conditions. The usual range of body temperatures extends from 35.5 to 40 °C in humans and includes circadian variation, vigorous exercise, variations in ambient conditions (temperature, humidity, air velocity), sequelae of food intake, age factors, menstrual variation in women, emotional factors, and assorted effects of drugs and alcohol.

Body tissues are extremely vulnerable to excessive changes in temperature, particularly to overheating. Humans have an elaborate system of mechanisms for regulating internal body temperature. In endotherms, two distinct control systems are available for thermoregulation. (1) Behavioral thermoregulation involves conscious, voluntary acts that adjust the characteristics of the air–skin interface. (2) Autonomic (or physiological) thermoregulation involves the involuntary responses of the body that generate and dissipate body heat. In humans, behavioral thermoregulation, supplemented by highly sophisticated technology, allows for survival in extreme environments, whereas autonomic thermoregulation provides for the fine control of body temperature in the resting state and is the principal control during exercise. In ectotherms, only the behavioral thermoregulatory system is available [Adair, 1996].

## BODY HEAT BALANCE AND THE HEAT BALANCE EQUATION

The law of conservation of energy forms the basis for the study of autonomic thermoregulation. In the steady state, heat generated in the body is balanced by heat lost to the environment, such that storage of heat is minimal [Bligh and Johnson, 1973]. This condition is expressed by a generalized heat balance equation:

$$M \pm W = \pm R \pm C \pm E \pm S, \qquad (1)$$

where $M$, the rate at which thermal energy is produced through metabolic processes; $W$, power or the rate at which work is produced by or on the body; $R$, the rate of heat exchange with the environment via radiation; $C$, the rate of heat exchange with the environment via convection; $E$, the rate of heat exchange with the environment via evaporation; $S$, the rate of heat storage in the body.

All terms in Equation 1 are expressed in the same units, for example, Watts. Negative values of $R$, $C$, and $E$ may all cause a rise in body temperature; positive values may cause a fall. Work ($W$) is positive when done by the body (e.g., riding a bicycle), and this potential energy must be subtracted from metabolic energy ($M$) to find the net heat developed within the body. When $W$ is negative (e.g., walking downhill), this energy is added to $M$. Usually, $E$ is positive; when $E$ is negative, condensation occurs and thermal injury is possible.

## MODES OF HEAT TRANSFER

No term appears in Equation 1 for heat transfer by conduction, which is usually insignificant in humans under normal conditions. However, conduction, combined with mass transfer, forms the mode of heat transfer called convection, a significant form of heat loss in humans. Heat transfer by radiation is independent of the air temperature ($T_a$). The net radiant heat exchange between two objects, such as a nude person and a radiating surface in the environment, is related to their respective surface temperatures. Clothing and solar heating complicate the analysis, as does exposure to RF [Berglund, 1983]. Heat exchange by evaporation of water is available to humans and many mammals. When 1 g of water is evaporated from the body surface, $\sim 2.4$ kJ of thermal energy is lost. Water lost in the expired air and diffused through the skin account for $\sim 25\%$ total heat loss of the resting $M$ at thermoneutrality. The major avenue of evaporative heat loss in humans is sweating. The efficiency of evaporative cooling depends on the ambient vapor pressure and the evaporative surface. When the air is at 100% relative humidity (RH), no sweat can be evaporated from the skin surface. When the air is $<100\%$ RH, evaporation can take place.

### Heat Production Responses: Metabolic Heat Production ($M$)

The basal metabolic rate (BMR) is the heat production of a resting human being in a thermoneutral

environment (20–27 °C), at a time exceeding 12 h from the last meal. The standard BMR for humans is 250 ml/min of oxygen or 84 W or 0.8 met (where 1 met is the metabolic rate of a sedentary person, 58. 15 W/m$^2$). The BMR can be altered by changes in body mass, diet, or endocrine levels, but not by living in a hot climate [Goldman, 1983]. In sedentary human adults, most of the heat is generated in the core of the body (trunk, viscera, and brain) and $M \approx 160$ W/m$^2$ or 1.3 W/kg or 1 met. This heat is conducted by blood flow throughout the body and is eliminated through the skin. The range of $M$ for humans, considering age, activity level, physical fitness, and assorted physiological variables, is roughly 40–800 W/m$^2$. An increase in deep body temperature ($T_{co}$), either by heat storage or febrile disease, produces a compensatory change in $M$ [Shimada and Stitt, 1983]; similar changes occur if $T_{co}$ rises during RF exposure [Adair, 1995]. In the cold, an increase in muscle tone and piloerection can increase the resting $M$ by about 35% [Swift, 1932], while active shivering can increase heat production by as much as four to five times the resting level (i.e., to 160–200 W/m$^2$) [Mountcastle, 1980]. However, steady state heat production in the cold will not exceed two times the resting $M$, and must be supplemented by active exercise [Iampietro et al., 1960].

### Heat Loss Responses: Vasomotion and Sweating

Changes in vasomotor state and sudomotor activity (sweating) constitute the efficient mechanisms of body heat loss. Fine tuning of vasodilation is the most precise and responsive method to control heat loss and retention. Sweating is a further mechanism to offload greater amounts of heat. In general, vasodilation is activated in thermoneutral $T_a$, while sweating is activated in warm $T_a$ and during exercise.

In cold $T_a$, vasoconstriction of the blood vessels in the skin increases peripheral insulation and minimizes heat loss from the body core to the skin. In thermoneutral $T_a$, when the peripheral blood vessels dilate, each liter of blood at 37 °C that flows to the skin and returns 1 °C cooler allows the body to lose 1.16 W·h of heat [Hardy, 1978]. In warm $T_a$, during vigorous exercise, peripheral blood flow can increase almost tenfold, which is essential to eliminate the increased heat produced by the working muscles. The combined effect of two modes of heat transfer in the body, conduction through layers of muscle and fat, and convective heat transfer by the blood, is called tissue conductance. Conductance thus relates to the temperature difference ($\Delta T$) between body core and skin.

Evaporation of sweat is an efficient way of losing heat, even in $T_a$ warmer than the skin. Sweating compensates for both endogenous heat production and exogenous energy absorption, including absorbed RF energy. Normal secretion of the $\sim 2.5 \times 10^6$ eccrine (sweat) glands in human skin is necessary to prevent dangerous levels of hyperthermia. Sweating occurs when the $T_a$ rises above 30–31 °C and/or the $T_{co}$ rises above 37 °C; local sweat rate also depends on the local skin temperature ($T_{sk}$) [Nadel et al., 1971a]. Sweat rate is also affected by factors such as physical fitness, state of hydration, and heat acclimatization.

## THERMOREGULATORY CONTROL

The thermoregulatory system functions as a negative feedback control system with a reference or ''set'' temperature. Thermosensors, distributed around the body, provide information about the local temperature of body tissues. The thermosensors located in the skin are the most important; other sites include the medial preoptic/anterior hypothalamic (PO/AH) area of the brainstem (locus of the ''central thermostat''), midbrain, medulla, spinal cord, cortex, and deep abdominal structures. Neural signals from the sensors are integrated by a central controller, the integrated signal is compared with the internal set point, and an output command is generated to energize appropriate responses whenever a load error occurs. A negative load error (body temperature lower than set point) will increase heat production; a positive load error will increase heat loss. The particular effector response that is mobilized, as well as its strength, depends on the prevailing $T_a$.

## HUMAN HEAT TOLERANCE AND ENVIRONMENTAL FACTORS

The basic problem posed by excessive body heating from any source, including absorbed RF energy, is whether the heat loss capability of the thermoregulatory system is sufficient to prevent heat storage in the body. Thus, for a human being exposed to a RF field, Equation 1 may be rewritten as:

$$(M \pm W) + A_{RF} = R + C + E \pm S, \qquad (2)$$

where $A_{RF}$ represents the rate of energy absorption from the RF field. If we neglect the work factor ($W$), the sum of the heat production of the heat exchange by convection ($H_c$) and radiation ($H_r$), and of the absorbed RF energy will yield a useful estimate of the evaporative cooling required ($E_{req}$) as:

$$E_{req} = M \pm H_c \pm H_r + A_{RF}. \qquad (3)$$

If the maximum available evaporative cooling ($E_{max}$) is less than $E_{req}$, $S$ will be positive and the body temperature will rise.

The degree of heat stress is predicted by the simple ratio of $E_{req}/E_{max}$, which yields a measure of the percent of skin surface that is wet with sweat. Values of $E_{req}/E_{max} < 20\%$ yield a state of thermal comfort, while higher percentages indicate tolerance limits [Gagge, 1937]. This ratio is also called the heat stress index (HSI) [Belding and Hatch, 1955]. HSI values greater than 30% are uncomfortable but tolerable and may interfere with concentration and fine motor performance; values from 30 to 60% have finite tolerance times, while values from 60 to 100% represent severe, intolerable conditions.

Clothing is considered a part of the thermal environment since it presents a resistance to the flow of heat away from the skin; this resistance is a direct function of the thickness of the air layer trapped by the clothing. The standard insulation unit (clo) equals 0.155 °C $m^2$ $W^{-1}$ [Gagge et al., 1941]. It has been suggested [American Society of Heating, Refrigerating and Air Conditioning Engineers (ASHRAE), 1986] that for each 0.1 clo deviation from the usual 0.6 clo insulation baseline for sedentary office workers (1 met), the $T_a$ for comfort can be offset by 0.55 °C.

During exercise, the $T_{co}$ rises because heat generated in the working muscles is distributed throughout the body by increased blood flow. This response, combined with peripheral vasodilation, also brings excess heat to the surface for dissipation. In the steady state, the heat produced by moderate exercise is efficiently lost to the environment so that the $T_{co}$ stabilizes at an elevated level that depends primarily on $W$, irrespective of the $T_a$.

During passive exposure to RF fields, energy may be selectively deposited in specific tissue beds; the particular pattern of energy deposition varies with many physical factors of both the radiation and the target. Similarly, during exercise the source of heat lies in specific groups of muscle fibers; the particular pattern of heating varies with the activity. Some have argued that these two scenarios may generate different thermoregulatory responses because the absorption of RF energy is "unique" [Elder and Cahill, 1984]. This view limits the application of voluminous data on exercise physiology to the prediction of human thermophysiological responses to RF fields.

Nielsen and Nielsen [1965] demonstrated the equivalence of physiological responses during exercise and during passive heating by diathermy. Short wave diathermy deposited heat directly into the deep tissues of the trunk of human subjects. In other tests, the subjects exercised on a stationary bicycle at a work rate adjusted so that the heat load during cycling and diathermic heating was the same (~5 mets). In four $T_a$ (cool to warm), the steady state $T_{co}$ increased by the same amount during the two procedures. Changes in skin blood flow, and local sweat rates were also comparable. Thus, passive heating of the trunk by diathermy and the heat generated by active exercise produced the same kind of thermal disturbance in the body as a whole, although the distribution of heat in individual tissues may have been very different in the two cases.

The elevated body temperatures produced by exercise and those occurring during febrile disease are different. Strenuous exercise may elevate the $T_{co}$ to a level above the normal, regulated (or "set") level; the magnitude of the heat loss response is directly related to this deviation as the body attempts to defend the normal level. However, during fever there is an elevation in the "set" level that is defended just as is the normal "set" level during normothermia. These differences are clearly described by Shimada and Stitt [1983].

During fever, the elevated $T_{co}$ is generated differently in different $T_a$. In warm $T_a$ heat loss will be curtailed and vasoconstriction will occur; if these responses are inadequate to increase heat storage, $M$ will be increased. In cold $T_a$, greatly increased $M$, including vigorous shivering (chill), is the only way to raise $T_{co}$. When a pyrogen is introduced into the body and the set point elevated, the thermoregulatory controller mobilizes any response appropriate to increase heat storage [Stitt, 1979].

Adair et al. [1997] suggested that a febrile animal might utilize RF energy to generate a fever in response to an injection of pyrogen into the hypothalamus, thereby sparing metabolic energy stores. Squirrel monkeys were implanted with Delrin injection cannulae and reentrant tubes in the PO/AH. Following a 90 min equilibration to $T_a = 26$ °C, a 1 μl volume of 250 ng prostaglandin $E_1$ ($PGE_1$) in saline was injected to produce a 0.6 °C fever that lasted 60–90 min. A 30 min RF exposure (either 450 or 2450 MHz) was introduced either immediately, or 30 or 60 min postinjection, allowing evaluation of the potential synergy between RF energy and fever during the three phases of the fever cycle (chill, plateau, and defervescence). Two whole body SARs (1.5 and 3.0 W/kg) were studied at each frequency. Controls included (1) $PGE_1$ without RF, (2) saline injection plus RF, and (3) no injection or RF. Results showed that during the chill and plateau phases, RF energy did indeed substitute for $M$ in the generation and maintenance of the fever. However, during defervescence, RF exposure tended to exacerbate the fever because heat loss through sweating was inadequate to eliminate excess heat stored in the body.

## HUMAN DATA FROM CLINIC AND LABORATORY

Humans are better equipped than any other mammal to withstand heat generated in the body by both exogenous and endogenous sources. Thermalizing energy deposited in the body during RF exposure is no exception. Mantiply et al. [1997] detailed the range of RF field levels associated with a variety of environmental and occupational sources. An earlier study of 486 locations within 15 metropolitan areas of the United States estimated that more than 99% of the population is exposed to background RF at $<1\ \mu W/cm^2$ [Tell and Mantiply, 1980]. At the human resonant frequency, this represents a whole body SAR of 0.0004 W/kg, or about 0.03% of the normal resting *M*, a completely insignificant amount with respect to thermoregulation. Even the whole body SAR of 0.4 W/kg, adopted as the basis for controlled exposure in many exposure standards, represents only 35% of the resting *M*. This is equivalent to the heat retained by donning a light sweater and is small enough to be unnoticeable and of little or no physiological significance during most daily activity.

Thermoregulatory processes are ongoing in each of us all the time. Small metabolic perturbations or small changes in the thermal characteristics of the environment result in fine adjustments in the thermoregulatory mechanisms discussed above. The remarkably stable $T_{co}$, with its circadian rhythm, is the result. Most young, healthy humans have the capacity to cope with exercise or work that is up to 15 times the resting *M* even when taken in thermally stressful $T_a$. The exceptional rates of human sweating, and increases in blood flow maintain a minimal rise in $T_{co}$. This is consistent with recent reports of humans exposed to modest levels of RF energy in laboratory and clinic that show only expected physiological responses and no adverse health effects.

### Use of RF Energy for Rewarming

The use of RF energy to provide thermal comfort in enclosed spaces has been proposed [Pound, 1980], but not yet implemented. However, RF energy has been used in both diathermy treatments and in localized hyperthermia as an adjunct to cancer treatment [Guy and Chou, 1983]. Also being explored are techniques that use RF energy for rewarming from hypothermia, both whole body and partial body. Studies on anesthetized Rhesus monkeys [Olsen and David, 1984; Olsen et al., 1987; Olsen, 1988] explored the potential usefulness of a 13.56 MHz RF induction coil versus a surgical heating pad to provide rapid rewarming from both moderate ($T_{re} = 28–30\ ^\circ C$) and severe ($T_{re} < 20\ ^\circ C$) hypothermia in monkeys. Physiological responses were monitored continuously during treatment. RF heating at low power (60 W) was superior to the heating pad in restoring normothermia, and also more efficient than a loop device (Magnetrode) used to rewarm hypothermic dogs [White et al., 1984]. A similar 13.56 MHz trunk coil, which provided RF warming to mildly hypothermic male subjects, restored normal $T_{co}$ more rapidly than the conventional methods of warm water immersion or use of a sleeping bag [Hesslink et al., 1989]. Special RF coils developed to resonate at 27.12 MHz were used to warm cold hands and feet [Olsen, 1990; Lloyd and Olsen, 1992]. Not only were skin areas remote from the coils warmed by heated blood, but also adverse thermal effects were absent.

### Human Overexposure Data

Chiang and Shao [1989] reported that ''hundreds of male volunteers'' in China have received localized RF irradiation as a contraceptive procedure. One study, an attempt to use RF energy to induce temporary sterility in adult males, reported data related to the thermal effects of long term, partial body exposure at high intensities [Liu et al., 1991]. Thirteen volunteers underwent localized RF exposures of the testes at 915 or 2450 MHz in weekly sessions that lasted 30 min each. Power levels were 20–30 W, sufficient to raise the temperature of scrotal skin 10 °C above its normal level. Seven subjects received over 100 such sessions, the remainder somewhat fewer. Six months later, biopsies of testicular tissue were taken for microscopic examination. While considerable cellular damage was evident, no significant gross morphological abnormalities were found. Further, despite evidence of greatly reduced spermatogenesis during the treatment, sterilization was not reliably achieved, as two men fathered children during the study.

Other data on RF overexposure of human beings in the military and/or industrial environments have been collected over the years. Mitchell [1985] reported that during the preceding 10 years, 300 reported overexposure incidents were investigated. Of these, 58 were confirmed overexposures, the remainder being within the permissible exposure limit (PEL) of $10\ mW/cm^2$ in any 6 min period. Of the 58 overexposures, most were in the frequency range of 1.5–10 GHz; 45% of the individuals reported a clear sense of warming and terminated the exposure in <6 min. The power densities (PD) ranged from 15 to 160 000 $mW/cm^2$ (with most between 40 and 1000 $mW/cm^2$), and nearly all were partial body exposures. The clinical findings of the overexposure victims were inconsistent, even for intense localized exposure. Erythema and/or edema were rarely found. Observed abnormalities in the ocular lens were not

associated with visual impairment. Follow-up tests of serum enzyme levels, blood counts, blood pressures (BPs), sedimentation rates, and EKGs were all clinically unremarkable. Unfortunately, a nearly complete lack of preexposure baseline data hampered the evaluation of any abnormal findings.

### Laboratory Studies of Human Volunteers

More than 20 years ago, Tell and Harlen [1979] lamented the dearth of laboratory investigations of humans exposed to RF energy. Progress is finally being made on this front. Adair et al. [1998] reported the first study of a series in which human volunteers were exposed in the far field to RF fields at controlled PD in highly controlled thermal environments. Thermoregulatory responses of heat production and heat loss were measured in seven adults during 45 min dorsal exposures of the body to 450 MHz CW RF fields. Two PD, measured on the antenna boresight in the center of the subject's back (local peak PD = 18 and 24 mW/cm$^2$; local normalized peak SAR = 0.32 {W/kg}/{mW/cm$^2$}) were tested in each of three $T_a$ (24, 28, and 31 °C), plus $T_a$ controls (no RF). A standardized protocol (30 min baseline, 45 min RF or sham exposure, 10 min baseline) was used. No change in *M* occurred under any exposure condition. Vigorous increases in local sweat rate on the back and chest, related to both $T_a$ and PD, cooled the skin and ensured efficient regulation of the core body (esophageal) temperature ($T_{esoph}$) to within 0.1 °C of the normal level. Category judgments of thermal sensation, comfort, sweating, and thermal preference usually matched the measured changes in physiological responses and $T_{sk}$ [Adair et al., 1999a]. At the highest PD explored (24 mW/cm$^2$), the normalized peak surface SAR was 7.7 W/kg. This PD exceeds the 20 mW/cm$^2$ allowed for partial body exposure by the IEEE/ANSI C95 [1992] standard (at 450 MHz) for a controlled environment, and is six times the comparable standard for an uncontrolled environment. Nevertheless, even under ambient conditions that were often judged uncomfortable and very warm, $T_{esoph}$ was regulated with precision because appropriate autonomic heat loss responses, principally sweating, were mobilized.

A second study [Adair et al., 1999b] compared the results described above with those collected on a second group of volunteers, exposed to 2450 MHz CW energy. The basic protocol was identical, as were the three $T_a$ and response measures, with the addition of local skin blood flow (SkBF) at three sites on the body. The normalized peak SAR, measured at the subject's center back, was the same for comparable PD at both frequencies, i.e., peak surface SAR = 6.0 and 7.7 W/kg. Again, no change in *M* occurred under any exposure conditions at either frequency. The magnitude of increase in the $T_{sk}$ under direct irradiation was directly related to frequency, but local sweating rates on back and chest were related more to $T_a$ and SAR. Efficient sweating and increased local SkBF regulated $T_{esoph}$ to within 0.1 °C of the baseline level. At both frequencies, normalized peak SARs in excess of IEEE/ANSI C95 [1992] guidelines were easily counteracted by normal thermophysiological mechanisms.

A third report [Adair et al., 2001a] compared the physiological responses of human volunteers to 2450 MHz CW and pulsed (PW) fields of equal average PD. Physiological responses of heat production and heat loss were again measured under the same protocol and 3 $T_a$. At each $T_a$, average PD studied were 0, 27, and 35 mW/cm$^2$; equivalent local peak SAR were 0, 5.94, and 7.7 W/kg. Mean data for each group showed minimal changes in $T_{esoph}$ and *M* for all test conditions and no reliable differences between CW and PW exposure. Local $T_{sk}$ showed similar trends for CW and PW exposure that were PD dependent; only the $T_{sk}$ of the upper back (facing the antenna) showed a reliably greater increase ($P = .005$) during PW exposure compared with CW exposure. Local sweat rate and SkBF were both $T_a$ and PD dependent and showed greater variability than the other measures; this variability was attributable primarily to the characteristics of the two subject groups. With the one noted exception, no clear evidence for a differential response to CW and PW fields was found, confirming extensive data collected earlier on squirrel monkeys [Adair et al., 1993].

An extension of the peak PD of 35 mW/cm$^2$, studied previously at 2450 MHz by Adair et al. [1999b] has also been reported [Adair et al., 2001b]. During partial body exposures of seven subjects, two additional peak PD were tested (50 and 70 mW/cm$^2$). The higher PD, with a normalized peak local SAR of 15.4 W/kg, was well outside the IEEE/ANSI C95 [1992] guidelines for partial body exposure, as was the estimated whole body SAR $\approx$ 1.0 W/kg. The subject volunteers, identical to the original group save one, were tested at each PD in 3 $T_a$ (24, 28, and 31 °C) under the standard protocol. The thermophysiological data were combined with comparable data at PD = 0, 27, and 35 mW/cm$^2$ from the 1999 study to generate response functions across PD. No change in $T_{esoph}$ or *M* was recorded at any PD in any $T_a$. At PD = 70 mW/cm$^2$, skin temperature on the upper back (irradiated directly) increased 4.0 °C in $T_a$ = 24 °C, 2.6 °C in $T_a$ = 28 °C, and 1.8 °C in $T_a$ = 31 °C. These differences were primarily due to the increase in local sweat rate, which was greatest in $T_a$ = 31 °C. Also at PD = 70 mW/cm$^2$, local SkBF on

the back increased 65% over baseline levels in $T_a = 31$ °C, but only 40% in $T_a = 24$ °C. Although $T_a$ becomes an important variable when RF exposure exceeds the C95.1 partial body exposure limits, vigorous heat loss responses of SkBF and sweating maintain normothermia efficiently. It is also clear, from subjective responses by the subjects, that strong sensations of heat and thermal discomfort will motivate a timely retreat from a strong RF field long before these physiological responses are exhausted.

### Clinical Data of Humans Exposed to Magnetic Resonance Imaging (MRI)

The exposure of patients to the MRI environment at 64 MHz may produce tissue heating that is related to the changing fields of the RF coils. A considerable literature describes thermoregulatory responses of humans to those fields during a variety of MRI procedures in the clinic. An early study [Kido et al., 1987] measured BP, heart rate (HR), respiration rate (RR), and axillary temperature in 27 volunteers during MRI scans of both trunk and head at 1.5 T and two RF power levels. Recently, more attention has been paid to equilibration of the patients prior to MRI scans, control of $T_a$, specification of SAR, and assessment of several physiological variables. Shellock and Crues [1988a,b] measured skin, sublingual, and corneal temperatures of 35 patients during MRI with a head coil (1.5 T at 64 MHz). The estimated peak SARs ranged from 2.54 to 3.05 W/kg. An average corneal temperature rise of 0.5 °C (range = 0.0–1.8 °C) was statistically significant ($P < .001$) as were slight elevations in the $T_{sk}$ of head regions ($P < .01$) compared to prescan levels. Sublingual temperature did not change. In another study [Shellock et al., 1989a], sublingual and $T_{sk}$ were measured in six subjects before (20 min), during (30 min), and after (20 min) MRI in a 1.5 T body coil at SARs from 2.7 to 4.0 W/kg. SkBF was also measured. Although the 30 min scans did not establish a thermal steady state, the measured temperature changes were not significantly different from zero. Scrotal MRI of eight men at 1.5 T (range of whole body SAR from 0.56 to 0.84 W/kg) and an average duration of 23 min produced a maximal rise of 3.0 °C in scrotal surface temperature [Shellock et al., 1990]. The authors claimed that this temperature elevation was well below the threshold for a reduction in spermatogenesis, confirmed by Berman [1984].

That measured tissue temperature changes during MRI are attributable to RF exposure during the procedure was demonstrated by experiments in which six male subjects were exposed to 1.5 T static magnetic fields only [Shellock et al., 1989b; Shellock, 1992]. Sublingual and several $T_{sk}$ were measured during 20 min scans that followed a 20 min equilibration to a $T_a = 21$ °C. No change from the equilibrated level occurred in any measured body temperature. The general conclusion drawn from MRI data at 1.5 T, is that tissue temperature changes are small and far below hazardous levels [Shellock, 1992].

### MRI Exposure Data (Laboratory Studies of Animals)

The thermal effects of MRI were measured on 12 anesthetized, fleeced sheep [Barber et al., 1990]. Exposures occurred in a 1.5 T MRI system using quadrature, circularly polarized field (vector) excitation for whole body scans and a head coil for scans of head only. Skin, vena caval, and $T_{re}$ were monitored during body scans (SAR = 1.5–4.0 W/kg) of 20 to 104 min duration. Other temperatures measured during head scans (SAR = 4.0 W/kg) included cornea, vitreous humor, head skin, and jugular vein. Five animals exposed at 4.0 W/kg (head or whole body) were allowed to recover from the procedure and exhibited neither incipient cataracts nor ill health 10 weeks later. During whole body scans of 4.0 W/kg, $T_{re}$ rose at a rate of about 0.023 °C/min; vena caval temperature rose at a slightly higher rate. SARs less than 4.0 W/kg produced proportionately lower rates of temperature increase. Temperature elevations in eye or cornea during a 60 min head scan at 4.0 W/kg did not exceed 1.5 °C. Although the exposure conditions were generally in excess of those used routinely in the clinic, the measured elevations in $T_{co}$ were insufficient to cause adverse thermal effects.

### MRI Exposure Data (Laboratory Studies of Humans)

Schaefer [1988] reported results of 20 min whole body MRI scans (SAR = 4.0 W/kg) of 11 adult volunteers. The scan was preceded and followed by 20 min baseline periods. Measured variables included $T_{esoph}$, several $T_{sk}$, $M$, HR, RR, and BP. Although the initial baseline did not produce a steady state, no change in the group mean $T_{esoph}$ occurred until the end of the 20 min MRI scan when the increase was 0.3 °C ($P < .005$). During the scan, $T_{sk}$ near the isocenter of the scanner rose up to $3.0 \pm 0.5$ °C, but these increases were judged to be nonhazardous. BP did not change, but slight elevations were recorded in HR and RR. In general, this study and that by Shellock et al. [1989b] indicate that MRI scans at whole body SARs up to 4.0 W/kg do not produce significant changes in $T_{co}$ and that $T_{sk}$ elevations are within the normal variation produced by changes in $T_a$ or during normal activity. However, the MRI exposure environment is

atypical. The penetrating RF field is primarily magnetic, with a small contribution from the electric field [Bottomley et al., 1985]; thus, the ohmic heating that occurs is greatest at the surface and least at the center of the body.

A more recent report [Shellock et al., 1994] describes 16 min MRI exposures of six human volunteers in a body coil at 1.5 T, 64 MHz. Subjects were equilibrated to $T_a = 21.3–23.3 \pm 0.4$ °C for about 15 min prior to the exposure. Tympanic membrane temperature ($T_{tymp}$) was recorded immediately before and after the MRI exposure, and HR, oxygen saturation, SkBF, and six $T_{sk}$ were recorded at 2 min intervals during the procedure. The RF exposure was at a calculated whole body SAR of 6.0 W/kg, achieved by use of a ''prototype pulse sequence.'' The authors reported statistically significant ($P < .05$) increases in $T_{tymp}$ and five $T_{sk}$, HR, and SkBF. These changes were not considered deleterious and such a high SAR appears to be well tolerated by persons with normal thermoregulatory function. However, the report suffers from a lack of technical detail with respect to the purported whole body SAR achieved.

As a test of a modeling effort (see below), Adair and Berglund [1992] reported the results of tests on two normal male subjects who underwent a series of three 20 min MRI scans (1.5 T) of the trunk at a whole body SAR of 1.2 W/kg. Each session began with a 30 min equilibration to $T_a = 22 \pm 1$ °C and successive 20 min scans were separated by a 35 min reequilibration period. $T_{esoph}$ and several $T_{sk}$ were monitored continuously, as was sweat rate from chest and thigh. Judgments of thermal sensation and discomfort were obtained periodically throughout each test. For both subjects, $T_{sk}$ of chest and thigh increased 1.1 °C during each scan but $T_{esoph}$ was very stable throughout the 170 min of the test session. This stability occurred despite an overall rise of about 2.5 °C in $T_{sk}$ and periodic sweating. As the test session progressed, both subjects reported increased sensations of warmth that were directly related to the increased $T_{sk}$.

## Predictions Based on Simulation Models of Physiological Responses

The modeling of physiological responses becomes important when its purpose is to simulate experiments that cannot be performed or to extrapolate variables that are not attainable through experiment. The basis of thermophysiological modeling is the energy (heat) balance Equation 1. These models incorporate the physical characteristics of the body, the heat production and heat loss responses, and all relevant environmental parameters. In such models, absorbed RF energy is added to metabolic energy and must be balanced by appropriate heat loss responses in order to prevent body heat storage.

A model by Stolwijk and Hardy, first published in 1966, updated by Stolwijk and Hardy [1977], is often used as the basis for predicting the possible thermoregulatory outcomes of RF energy deposition in selected parts of the human body. The model was used, for example, to simulate the deposition of 100 W of RF energy into the core compartment of the head for 30 min in a thermoneutral $T_a$ of 30 °C [Stolwijk, 1980, 1983]. This simulated exposure caused only a small increase in brain temperature because of the high rate of brain blood flow and the mobilization of strong heat loss through sweating. Because heat loss far exceeded heat production plus RF energy input, all body temperatures were predicted to fall. Attempts by others, for example, Kritikos and Schwan [1979], to improve on this model have had varying degrees of success that have been described elsewhere [Adair, 1995].

A simpler model was adapted to predict the consequences of human exposure to RF fields in the MRI environment [Adair and Berglund, 1986]. The model has only two nodes (core and skin) but in most other respects is similar to the Stolwijk and Hardy formulation. It predicts physiological heat loss responses in real time in terms of $T_a$, air movement ($v$), and whole body SAR. Assuming a criterion elevation in deep body temperature ($\Delta T_{co}$) of 0.6 °C, $T_a = 20$ °C, and $v = 0.8$ m/s, the model predicts that a 70 kg patient could undergo a MRI scan of indefinite duration at SAR $\leq$5 W/kg. Lowering $T_a$ or increasing $v$ permits a rise in lower permissible SAR for a given $\Delta T_{co}$. Stricter $\Delta T_{co}$ criteria result in lower permissible SARs and shorter exposure durations. The limiting response is usually the rate of SkBF, although sweating can play a role in limiting $\Delta T_{co}$.

Restrictions on the rate of SkBF, ranging from 0 to 89% of normal, have also been studied with this model [Adair and Berglund, 1989]. Model predictions showed that restrictions of up to 67% of SkBF would yield a tolerable $\Delta T_{co}$ ($\leq$1 °C) during MRI scans (SAR $\leq$ 4 W/kg) of 40 min or less under normal clinical conditions. Increased $T_a$ and RF exacerbate the thermal stress imposed by absorbed RF energy, while severely impaired SkBF encourages short MRI exposures (20 min or less) at SAR $\leq$ 3 W/kg.

After generating predictions based on many values of each parameter, a nomogram was developed based on the fact that, at any given $T_a$, a person can absorb some level (SAR) of RF energy indefinitely; i.e., achieve thermal equilibrium with the prevailing conditions. When SAR is low, $T_{co}$ will rise initially and then stabilize at an elevated level. If SkBF is impaired, the maximal SAR at which thermal equilibrium is attained

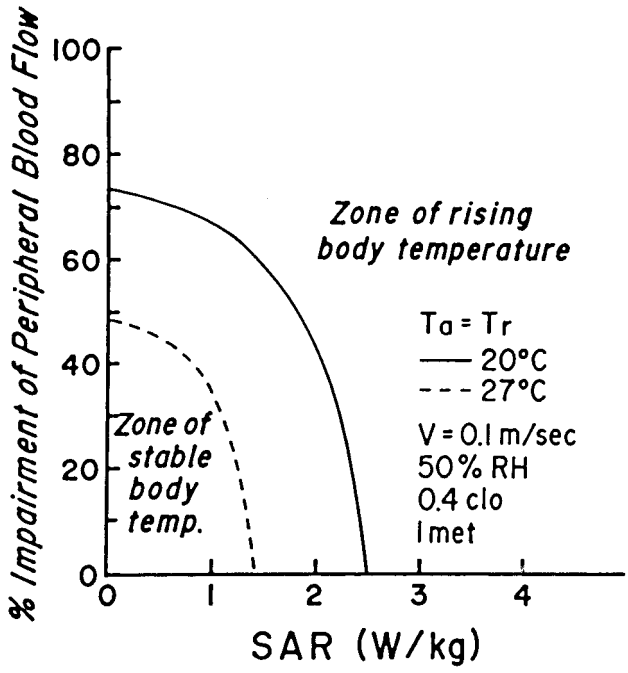


Fig. 1. Predictions of a two-node model showing zones of stable and rising body temperatures in two environments during 40 min magnetic resonance imaging (MRI) scans at different SARs when peripheral blood flow is impaired. From Adair and Berglund [1989].

will be lower. Figure 1 shows the maximal SAR for equilibrium in two $T_a$ (20 and 27 °C) as a function of the impairment in SkBF. The solid line defines the limit of the zone of stable $T_{co}$ at $T_a = 20$ °C; the dashed line defines the same limit for $T_a = 27$ °C. Thus, raising the $T_a$ by 7 °C decreases the maximal SAR for equilibrium by ~1 W/kg. If the SAR under consideration exceeds the maximal value for thermoequilibrium, a continuous rise in $T_{co}$ can be expected during RF exposure. The model predicts that the rate of $\Delta T_{co}$ depends on the impairment in SkBF, $T_a$, RH, and the clothing insulation (clo) [McCullough et al., 1989]. Adair and Berglund [1989] provided explicit corrections to the predictions of their model as a function of departure of SkBF, $T_a$, RH, and clo from those specified in Figure 1.

Schaefer [1992] used these predictions to calculate the effect of $T_a$ during a 60 min MRI scan on the average $\Delta T_{co}$ under conditions of 40% impairment of SkBF and clo = 0.2. He calculated that a scan at SAR = 4 W/kg would result in a $\Delta T_{co}$ of only 1 °C when $T_a = 19$ °C. Further, a 1 h RF exposure at SAR = 1 W/kg, even at $T_a = 27$ °C, should result in no rise in $T_{co}$. These predictions do not conflict with clinical data or with ongoing laboratory studies of human volunteers.

## HUMAN THERMAL SENSATION OF RF ENERGY

Since RF exposure generates heat in body tissues, such energy can be part of the thermal environment to which humans and animals may potentially be exposed. Although physiological responses (e.g., sweating) may be initiated automatically by thermal stimuli, the sensation of tissue warming is necessary to initiate appropriate behavioral action. The stimulation of temperature sensitive nerve endings located within the outermost 0.6 mm of mammalian skin underlies the sensations of changes in $T_{sk}$ [Hardy and Oppel, 1937]. Whether or not RF exposure produces a warmth sensation depends on many parameters of the signal, for example, frequency, intensity, duration, as well as the body locus and the exposed surface area. Many of these parameters influence the magnitude of thermal sensations derived from exposure to infrared (IR) radiation [Stevens, 1983]. Since IR energy is absorbed in the most superficial layers of skin, a similar absorption profile should be obtained for the higher microwave frequencies (≥10 GHz). However, lower RF frequencies will be absorbed in complex patterns at other depths, making prediction of thermal sensation difficult.

### Thresholds—Archival Data

Absolute thresholds for the detection of RF irradiation by human observers were determined in several archival studies [Vendrik and Vos, 1958; Hendler and Hardy, 1960; Eijkman and Vendrik, 1961; Hendler et al., 1963; Schwan et al., 1966; Hendler, 1968]. All involved brief exposures (10 s or less) and restricted areas of forehead or forearm skin. In general, the shorter the wavelength, the less energy was required to provoke a just-detectable sensation of warmth [Michaelson, 1972]. When a 37 $cm^2$ area of forehead was irradiated for 4 s, the mean absolute threshold of warmth was 33.5 $mW/cm^2$ at 3 GHz, 12.6 $mW/cm^2$ at 10 GHz, and 4.2 $mW/cm^2$ at frequencies >1000 GHz (far IR). Irradiation of small skin areas by 3 or 10 GHz PW microwaves had to last at least 5 s in order for the minimal intensity to evoke a thermal sensation and the exact intensity depended on the area stimulated. At shorter stimulus durations, the intensity had to be greatly increased to evoke comparable warmth sensations. This phenomenon is called temporal summation and the shortest duration, at which only intensity matters, is called the "critical duration" [Stevens, 1983].

Justesen et al. [1982] incorporated indirect assessment of absorbed RF energy during 10 s exposures of the human forearm to 2.45 GHz CW fields. Warmth sensations were reported when the energy density of the

RF field was ~29 mJ/cm$^2$, compared to ~1.8 mJ/cm$^2$ when the same skin area was exposed to far IR radiation. These thresholds corresponded to PD of 27 and 1.7 mW/cm$^2$ and, thus, were similar to results reported in the studies cited above.

### Recent Extensions of Classical Data

Blick et al. [1997] measured the threshold for thermal sensation across a range of five RF frequencies from 2.45 to 94 GHz plus far IR (~3000 GHz). Judgments of threshold warmth sensation, for a skin area of 327 cm$^2$ centered on the subject's back, were determined at each frequency. The stimulus duration was 10 s and the interstimulus interval was 1 min. Each of 16 adult male volunteers was tested at each frequency. Warmth thresholds were a linear function of frequency when the data were plotted in log/log coordinates. The threshold at 2.45 GHz ($63.1 \pm 6.7$ mW/cm$^2$) was more than an order of magnitude larger than that measured at 94 GHz ($4.5 \pm 0.6$ mW/cm$^2$); in turn, the latter was not significantly different from the IR threshold ($5.34 \pm 6.7$ mW/cm$^2$). Further, measured warmth thresholds reflected the skin depth at each frequency; a theoretical analysis [Riu et al., 1997] suggested that a constant temperature increase of ~0.07 °C at or near the surface of the skin was the adequate stimulus for perception. This analysis also indicated that the depth at which the thermal receptors are located is not a relevant parameter, as long as it is within 0.3 mm of the surface.

### Suprathreshold Functions Including Pain

No new data on pain sensations derived from RF exposure have been reported since the classical studies of Cook [1952a,b]. Cook investigated the potential of 9.4 and 10 cm microwaves to induce pain sensation in two exposure areas (53.2 and 9.5 cm$^2$) of human skin (forearm, thigh, and calf). The subject reported when a burning pain sensation occurred and the response latency was measured. The $T_{sk}$ at pain threshold, $46.1 \pm 1.0$ °C, was measured with a copper/constantan thermocouple held at the center of the irradiated surface. Cook concluded that the pain threshold, aroused by microwave irradiation, was directly related to $T_{sk}$. However, the PD of the radiation at threshold could depend on area exposed, exposure time, initial $T_{sk}$, anatomical site, and thermal conductivity. Cook provided a theoretical analysis based on thermal flow theory that explained the results measured with short exposures. Longer exposures had to involve vasomotor responses in the capillaries, a conclusion also reached by Riu et al. [1997] for the adequate RF stimuli for the sensation of warmth.

## SUPPORTING DATA FROM ANIMAL STUDIES/PHYSIOLOGICAL RESPONSES

### Threshold Effects

For any given species, under any given environmental conditions, an intensity of imposed RF energy can be determined that will reliably initiate or alter whatever thermoregulatory response is appropriate to those environmental conditions. For comparison, such determination requires adequate baseline or control data collected under identical conditions. Phillips et al. [1975] reported a study that achieved these requirements with remarkable precision. The thermoregulatory profile for the species in question (see below) is useful as a guide to selecting the correct response to measure. The RF intensity so determined can be designated a threshold for response mobilization. By definition, subthreshold intensities will not produce response alteration or mobilization.

### Thermoregulatory Profile

During thermoregulation, the particular response that is mobilized, as well as its strength, depends on the prevailing $T_a$. A schematic "thermoregulatory profile" of a typical endotherm (Fig. 2) illustrates how the principal autonomic responses of heat production and heat loss depend on $T_a$. The responses shown are steady state, rather than transient, and the ambient air has minimal movement and water content. Three zones are

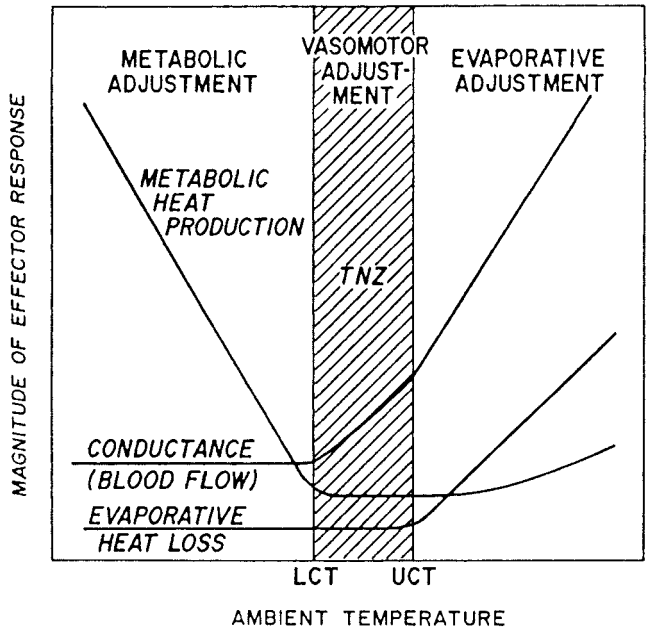


Fig. 2. Thermoregulatory profile of a typical endotherm to illustrate how the principal types of autonomic response depend on the prevailing ambient temperature. LCT, lower critical temperature; UCT, upper critical temperature; TNZ, thermoneutral zone.

defined in terms of the prevailing autonomic adjustment. Below the lower critical temperature (LCT), thermoregulation is accomplished by changes in *M*, other responses (conductance and evaporative heat loss) remaining at minimal strength. As the $T_a$ falls further and further below the LCT, there is a proportional increase in *M*.

At $T_a$ above the LCT, *M* is generally at a low, resting level that is characteristic of the species, evaporative heat loss is minimal, and thermoregulation is accomplished by changes in thermal conductance. Conductance is a measure of heat flow from the body core to the skin and reflects the vasomotor tone of the peripheral vasculature. As constricted peripheral vessels begin to dilate, warm blood from the body core is brought to the surface so that the heat may be lost to the environment by radiation, convection, and conduction. These vasomotor adjustments take place within a range of $T_a$ called the thermoneutral zone (TMZ) that is unique to each species. The TNZ for humans is extremely narrow, encompassing only a few degrees around 30 °C. The TNZ for the Rhesus monkey extends from 24.5 to 31 °C [Johnson and Elizondo, 1979], that for the squirrel monkey from 26 to 35 °C [Stitt and Hardy, 1971], and that for the mouse from 30 to 33 °C [Hart, 1971]. Comparable data for other laboratory animals are provided in the Radiofrequency Radiation Dosimetry Handbook [Durney et al., 1986].

The upper limit of the TNZ is called the upper critical temperature (UCT). At this $T_a$, the endotherm is fully vasodilated and dry heat loss is maximal. Further increases in $T_a$ stimulate the mobilization of heat loss by evaporation either from the skin (sweating) or the respiratory tract (panting) at a rate that is proportional to the deviation of $T_a$ from neutrality. In humans, whole body sweating can attain rates of 2–3 L/h and 10–15 L/day. Since human sweating is controlled by both internal and peripheral thermal signals, only an extraordinarily hostile environment (that may include a source of RF energy) can seriously threaten a healthy person's thermoregulatory system. A few reports indicate that nonhuman primates sweat efficiently during RF exposure in thermoneutral and warm environments. Human volunteers undergoing controlled RF exposures also sweat efficiently whenever skin and deep body temperatures meet established criteria for the mobilization of this response, $T_a = 30–31$ °C or $T_{esoph} \geq 37$ °C [Nadel et al., 1971b].

Many small furred laboratory animals (e.g., mouse, rat, hamster) neither sweat nor pant when exposed to $T_a$ above the UCT. Any measured increases in RR reflect the general speeding up of all bodily processes as $T_{co}$ rises. If these species are heat stressed, they must depend on behavioral maneuvers, such as spreading saliva or urine on the fur, or choosing a new environment, to achieve some degree of thermoregulation. Opportunities for behavioral thermoregulation are vital when these species undergo RF exposure, especially in $T_a$ above the UCT.

In general, RF intensities above an experimentally determined threshold will also alter the response in question, usually by an amount that depends on intensity. If field strength is great enough, the observed response will be altered maximally and the next response in the hierarchy may be mobilized. This is comparable to moving the endotherm past one of the critical temperatures (i.e., LCT or UCT in Fig. 2) in its unique thermoregulatory profile. A detailed discussion of these concepts and their implication for human thermoregulation during RF exposure is available [Adair, 1987b].

### Adjustments in Metabolic Heat Production (*M*)

During acute far field RF exposure of the whole body in cold $T_a$, the elevated *M* of nonhuman primates is reduced by an amount proportional to the PD or the SAR [Adair and Adams, 1982; Adair, 1985, 1987a; Lotz, 1985; Lotz and Saxton, 1987, 1988; Adair et al., 1992]. As a result of this *M* adjustment, $T_{co}$ is usually regulated within the normal limits for the species. Similar results had been demonstrated earlier in rodents after whole body RF exposure. In addition, chronic, low level RF exposure produces no measurable alteration in the normal *M* of infant rats [Spiers and Adair, 1987], of rats exposed throughout their lifetimes [Chou et al., 1992], or of squirrel monkeys exposed for 15 weeks [Adair et al., 1985].

A threshold SAR must be surpassed before a reliable *M* reduction occurs; this threshold is between 0.5 and 1.5 W/kg in nonhuman primates [Lotz and Saxton, 1987, 1988; Adair et al., 1992] but has not been explored systematically in other species. It should vary with $T_a$ in accordance with the unique thermoregulatory profile for each species. Many studies indicate that both the threshold and the magnitude of the *M* reduction depend, in an orderly way, on the magnitude of the cold stress when the RF field is imposed [Adair and Adams, 1982; Adair, 1985, 1987a; Lotz and Saxton, 1987, 1988; Adair et al., 1992].

For whole body exposure, the maximal absorption of RF energy occurs when the long axis of the body is parallel to the electric field vector (E polarization) and the longest dimension of the body is about 0.4 of the free space wavelength (resonant frequency) [Durney et al., 1986]. RF exposure of nonhuman primates at resonance yields somewhat less efficient thermoregulation than does exposure to subresonant or supraresonant

frequencies [Krupp, 1983; Lotz, 1985; Lotz and Saxton, 1988; Adair et al., 1992]. Although the threshold for *M* reduction may be lower at resonance, the magnitude of the response change may be less for a given SAR than at nonresonance and the $T_{co}$ may rise. However, the hyperthermia is modest and well regulated even at SARs equivalent (in W/kg) to the level of resting *M* in the TNZ. The situation is similar to that occurring in humans during exercise [Adair, 1996]. Some have expressed concern that human exposure at resonance may pose a greater hazard than exposure at other frequencies. The nonhuman primate studies are reassuring because, even though thermosensors in the skin, necessary for thermal perception and avoidance behavior, may be inefficiently stimulated, there is solid evidence that autonomic mechanisms are rapidly mobilized to dissipate heat generated deep in the body. Experiments recently completed, in which seated human adults undergo 45 min RF whole body exposures at resonance (100 MHz), demonstrate this prediction exactly; no increase in core temperature occurs even at a PD that is eight times the IEEE/ANSI C95 [1992] standard at 100 MHz [Adair et al., 2002].

If only part of the body is exposed to RF energy, the magnitude of the change in *M* reflects the total absorbed energy, as though it were integrated over the whole body [Adair, 1988]. If an endotherm is exposed to RF energy at SARs greater than those that reduce *M* to the resting level, thermoregulation will be accomplished by mobilization of the next response in the hierarchy, changes in vasomotor state or conductance [Adair, 1985; Candas et al., 1985; Lotz and Saxton, 1987].

### Vasomotor Responses

When an endotherm is exposed to RF energy at a $T_a$ just below the LCT (Fig. 2), the stage is set to initiate peripheral vasodilation as soon as *M* has been reduced to the resting level. In laboratory animals, the vessels of the tail and ears usually vasodilate before those of the extremities. Once the RF field strength is sufficient to induce vasodilation (threshold), the response occurs rapidly at field onset and the degree of vasodilation is a direct function of SAR [Adair and Adams, 1980; Lotz and Saxton, 1987] or the total heat load [Gordon, 1983]. As $T_a$ increases above the LCT, the SAR at threshold is reduced [Adair, 1985, 1987a; Lotz and Saxton, 1987]. Extinction of the RF field results in rapid vasoconstriction. In nonhuman primates, both the threshold and the degree of vasodilation depend on the imposed frequency, although in a species dependent manner. For Rhesus monkeys, the closer the exposure frequency to whole body resonance, the less energy is required to induce vasodilation at a given $T_a$ and the greater the response magnitude at a given SAR [Lotz and Saxton, 1988]. However, for squirrel monkeys exposed to RF energy in cold $T_a$, higher SARs are required to induce tail vasodilation during exposure at resonance than at a frequency above resonance [Adair et al., 1992].

Peripheral vasodilation can also occur spontaneously during the course of a prolonged RF exposure that is carried out at a $T_a$ below the LCT [Adair, 1985, 1987a; Candas et al., 1985; Lotz and Saxton, 1987]. In this case, vasodilation is mobilized because the $T_{co}$ slowly rises during the exposure, eventually surpassing a threshold for initiation of the response. These data support the conclusion that vasomotor control is exerted by a combination of central and peripheral neural signals. In addition, changes in the caliber of blood vessels deep in the body, as well as in the periphery, accompany RF exposure and the rate of local blood flow increases dramatically whenever the temperature of the heated tissue exceeds 41–42 °C [Cunningham, 1970]. This phenomenon forms one basis for the treatment of localized malignancies by microwave hyperthermia [Guy and Chou, 1983].

### Evaporative Adjustments During RF Exposure

When vasodilation of an endotherm is complete, dry heat loss from the body nears its maximum. To prevent significant heat storage and a rise in body temperature, heat loss by evaporation must be initiated. Figure 2 shows that this occurs when $T_a = UCT$; it also occurs at $T_a$ within the upper reaches of the TNZ during RF exposure at SARs sufficiently high to produce full peripheral vasodilation [Adair, 1987a]. Because cellular processes in the body speed up as tissue temperature rises, a small increase in *M*, concomitant with the initiation of evaporation, also occurs at high $T_a$. Any attempt to predict the evaporative capability of a particular endotherm during RF exposure must consider the thermoregulatory profile, the avenue of evaporative heat loss available (panting or sweating), or whether such capability may not exist (as is the case with rodents). Humans have an extraordinary capacity to lose body heat by sweating [Wenger, 1983]. Human sweating during RF exposure at high PD can be so profuse that $T_{co}$ falls significantly [Adair et al., 2001b].

In squirrel monkeys equilibrated to a $T_a$ just below the UCT, foot sweating is elicited by RF exposure at a threshold SAR equivalent to 20% of the animals' resting *M* [Adair, 1985]. Below this $T_a$, the threshold SAR is linearly related to the exposure $T_a$. Like *M*, the sweating magnitude depends on the integration of absorbed RF energy over the whole body, not energy deposited in a locus such as the PO/AH. Thermoregulatory sweating occurs when RF energy is present, even when the

PO/AH is artificially cooled to prevent a temperature rise [Adair, 1988]. During partitional calorimetric studies at cool (20 °C), neutral (26 °C), or warm (32 °C) $T_a$, steady state tolerance limits were determined for squirrel monkeys, exposed to 2450 MHz CW microwaves, in terms of both PD and SAR [Adair, 1987a]. The maximal PD tolerated (60 mW/cm$^2$) in $T_a = 20$ °C was equivalent to SAR = 9 W/kg, a value twice the animals' resting *M*. The limiting autonomic response in all cases was sweating, which is not profuse in this species [Stitt and Hardy, 1971]. Certain other nonhuman primates (e.g., patas monkey), as well as human beings, are far better equipped than squirrel monkeys to dissipate large body heat loads through sweating [Wenger, 1983].

Sweating from the calf of Rhesus monkeys, during RF exposure at the resonant frequency in $T_a = 26$ and 32 °C, occurred at somewhat higher SARs, for example, equivalent to 80% of the animals' resting *M* [Lotz and Saxton, 1988]. In $T_a = 26$ °C, peripheral vasodilation preceded the onset of sweating, as predicted (Fig. 2). However, sweating in thermoneutral $T_a$, like reduced *M* in cool $T_a$ [Lotz and Saxton, 1987], failed to prevent a substantial rise in $T_{co}$ of the Rhesus monkey during RF exposure at resonance. Most researchers agree that careful control over ambient conditions ($T_a$, RH, and *v*) is essential during such exposures to ensure that heat loss from the skin by convection, radiation, and evaporation is not impeded.

Gordon [1982, 1983] reported a much higher threshold (SAR = 29 W/kg) for initiation of evaporative heat loss in microwave exposed mice. The mice were irradiated inside a closed waveguide and the increase in RH of the air flowing through the waveguide was the measure of heat lost by the evaporation of body fluids. Mice neither pant nor sweat but are said to increase RR somewhat when heat stressed [Gordon, 1983], in addition to spreading saliva over the fur. None of these responses was observed, nor could the $T_{co}$ be recorded during irradiation, to provide evidence that the animals were thermoregulating normally. Since the $T_a$ inside the waveguide was 22 °C, well below the TNZ for the mouse, changes in *M* and conductance, not changes in evaporative heat loss, would first be anticipated during RF exposure. Evaporative heat loss should occur only after *M* was reduced to the resting level and the animal was fully vasodilated. With this perspective, the reported high evaporative threshold for mice may be more easily understood [Adair et al., 1983, 1984].

### Intense or Prolonged Exposure

Changes in thermoregulatory responses, as a result of exposure to intense RF fields, were explored by Michaelson and his colleagues [Michaelson, 1974]. A characteristic triphasic change in internal body temperature accompanied whole body exposure of dogs to 2880 MHz PW at an average PD = 1 kW/m$^2$ (SAR = 3.7 W/kg) for 6 h or 1.65 kW/m$^2$ (SAR = 6.1 W/kg) for 2–3 h. The three phases were described as (1) an initial increase in $T_{co}$, (2) a hyperthermic plateau phase, and (3) thermoregulatory collapse. The mobilization of heat loss by panting was presumed to counteract the initial effects of RF energy absorption, but only temporarily. The strain on the thermoregulatory system ultimately exhausted the dog's heat loss capabilities and death from hyperthermia would follow unless the animal was removed from the field.

The $T_a$ at which the exposure occurred was also very important [Michaelson, 1983]. Dogs could tolerate SARs of 3.7 and 6.1 W/kg at $T_a = 11$ °C and SAR of 3.7 W/kg at $T_a = 22$ °C. However, at $T_a = 40.5$ °C, dangerous hyperthermia could occur within 20 min at SAR = 6.1 W/kg. Another finding was the development of tolerance to RF exposure at SAR = 6.1 W/kg as the number of such daily exposures increased. For example, it took only 60 min on the first day, but 220 min on the 34th day, for the dog's $T_{co}$ to rise 1.5 °C. This tolerance, or adaptation, resembles human acclimatization to hot environments [Goldman, 1983].

Candas et al. [1985] measured physiological responses of squirrel monkeys exposed to strong 2450 MHz CW fields in $T_a = 20$ °C to determine if there may be a PD ceiling beyond which further changes in response (e.g., *M*) do not occur. The range of SAR explored was 1.5–6.75 W/kg for exposures of either 10 or 40 min following a 90 min equilibration to the prevailing $T_a$. During short exposures, a SAR of 5.3 W/kg was required to reduce the elevated *M* to its resting level within the 10 min. During 40 min exposures, resting *M* was achieved within 20 min at a SAR of 4.3 W/kg; at this point, tail vasodilation usually occurred. The resulting $\Delta T_{co}$ was thereby held to ~1.0 °C.

Walters et al. [2000b] examined whether fatigue during exertional heat stress occurred at a critical $T_{co}$ independent of the initial $T_{co}$ at the start of exercise. Microwaves (2.1 GHz; 100 mW/cm$^2$) were used to rapidly (3–8 min) heat rats (n = 11) to one of three levels before treadmill exercise to exhaustion. Sham exposures were conducted at the beginning and end of the study, respectively. When exercise began, hypothalamic temperature ($T_{hy}$) and $T_{re}$ ranged from 39.0 to 42.8 °C ($T_{hy}$) and 42.1 °C ($T_{re}$). The treadmill speed was 17 m/min, and $T_a = 35$ °C during exercise. Run time to exhaustion was significantly reduced after preheating. There was a significant negative correlation between run time and initial $T_{hy}$ and $T_{re}$ (r = 0.73 and 0.74,

respectively). The temperatures at exhaustion were not significantly different across treatments, with a range of 41.9–42.2 °C ($T_{hy}$) and 42.2–42.5 °C ($T_{re}$). There were no significant differences in run time in the sham tests administered at the start and end of the study. No rats died as a result of exposure to any of the treatments, and body weight the day after each treatment was unaffected. These results support the concept that a critical temperature exists that limits exercise in the heat. This temperature is very close to that determined as the threshold for a significant increase in human BF that helps prevent severe heat stress in humans [Cunningham, 1970].

Studies of the potential for high PD millimeter wave (mmw) exposure to produce lethality in the anesthetized laboratory rat have been reported [Frei et al., 1995; Ryan et al., 1996]. Such mmw exposure deposits RF energy on the animal's skin, stimulates rapid peripheral vasodilation and decreased vascular resistance in the body core, and reduces arterial BP with ultimate circulatory collapse and death. These symptoms resemble heat shock, except that the $T_{co}$ increases only a few degrees above normal. Additional studies of this phenomenon [Ryan et al., 1996, 1997a,b] found that neither age nor excess levels of nitric oxide contribute to the hypotensive state that results from mmw exposure at high PD. Jauchem and Frei [1992] reviewed the cardiovascular changes that result from excessive RF exposure versus environmental heating and that may contribute to lethality. They concluded that altered core-to-skin thermal gradients, especially during RF exposure, play an important role in the enhanced potential for cardiovascular impairment.

Exposure of endotherms, including humans, to either intense millimeter wave fields [Ryan et al., 2000] or new electromagnetic energy sources that feature very high peak power, nanosecond pulses composed of an ultra wide band (UWB) of frequencies, may pose potential health risks. Walters et al. [1995] reported the results of single 2 min exposures of 23 rats to UWB (60 Hz pulse frequency, 5–10 ns pulse width, 0.25–2.5 GHz bandwidth) on a range of physiological and behavioral variables that could indicate potential hazard. Following the acute exposure, each rat was examined on one of the following tests: (1) a functional observational battery [Moser et al., 1991], (2) a swimming performance test, (3) a complete blood chemistry panel, and (4) a determination of the c-fos protein in immunohistologically stained sections of the brain. In addition, $T_{co}$ of each rat was determined immediately before and after both sham and UWB exposure. No significant differences were found on any of the measured dependent variables between sham and UWB exposed animals.

## Effects of RF Exposure on Early Development

The young rat's ability to maintain a constant $T_{co}$ improves during the first 3 weeks after birth [Conklin and Heggeness, 1971; Takano et al., 1979; Spiers and Adair, 1986]. The immature rat might possibly be capable of responding effectively to a rapid internal deposition of RF energy. Guillet and Michaelson [1977] found that a 5 min exposure of the neonatal rat to 40 mW/cm$^2$ produced a 1.5–2.5 °C rise in $T_{co}$. Spiers et al. [1989] showed that, at 6–7 days of age, there was a 1.7 °C increase in the $T_{co}$ of neonatal rats at $T_a = 25$ °C at the end of a 60 min exposure to 2450 MHz (5 mW/cm$^2$, SAR = 3 W/kg), but no change in *M*. Exposure to 20 mW/cm$^2$ (SAR = 12 W/kg) for 60 min produced a 3.4 °C increase in $T_{co}$.

Few studies have determined if repeated RF exposure of the young mammal alters growth and physiological development. Michaelson et al. [1978] had reported that a 1 h exposure to 2450 MHz CW microwaves at 10–40 mW/cm$^2$, during days 0–2 of gestation produced offspring that might show a greater metabolic response to cold $T_a$ than did sham exposed offspring. Repeated exposure (4 h/day for 10 days) of young rats (6–17 days of age) to 5 mW/cm$^2$ (SAR = 1.8–2.7 W/kg) did not alter growth rate in cold $T_a$ or result in significant posttreatment shifts in thermoregulatory ability [Spiers and Adair, 1987]. Galvin et al. [1986] found that rats exposed prenatally (3 h/day for days 5–20 of gestation) to 2450 MHz microwaves (10 mW/cm$^2$, SAR 2–4 W/kg) weighed more than sham exposed animals at 30 days of age. Additional material concerning thermal effects on the embryo and fetus is provided in a separate white paper [Heynick and Merritt, 2003].

## Thermal Hot Spots

Thermographic studies on tissue equivalent models of humans and animals [Guy, 1971; Guy et al., 1974] indicate regions of high local SAR during exposure of the whole body to plane wave RF fields. Wrists, ankles, and neck (also the base of animal tails) are predicted to be foci of enhanced local SAR, where excessive elevations of tissue temperature may occur. Krupp [1983] studied anesthetized Rhesus monkeys, equilibrated to $T_a = 23$ °C and exposed for 1–4 h to plane-wave 210 MHz RF energy (PD = 5–27 mW/cm$^2$). Substantial increases in $T_{co}$ occurred but no evidence for localized regions of greatly elevated temperature (i.e., tissue "hot spots") in wrist, ankle, thigh, or biceps. Similar experiments at 2.06 GHz [Krupp, 1981] found different results. At PD = 15 mW/cm$^2$, 1 h of RF exposure produced no increase in $T_{co}$ or local

temperatures of neck and groin. Wrist and ankle temperatures rose slowly over the 1 h exposure but never reached the level of $T_{co}$. Krupp concluded that increased convective heat transfer by the blood, coupled with lower set point temperatures in the limbs, could protect individual tissues from overheating.

### Circadian Variations

It is essential that quantitative studies of thermoregulatory function be conducted at the same time of day, because a circadian rhythm of regulated changes in $T_{co}$ is characteristic of all endotherms. Lotz [1983] showed the influence of circadian rhythm on the elevation of $T_{co}$ in Rhesus monkeys exposed or sham exposed to 1.29 GHz pulsed energy at a whole body SAR of 4.1 W/kg. The 8 h RF exposures occurred either during the day or during the night. The change in $T_{co}$ resulting from these exposures was nearly identical ($\sim$1.6 °C), but the peak $T_{co}$ was $\sim$1.0 °C lower at night. Plasma cortisol, monitored during the experiments, was elevated only during the daytime exposures. Thus, this response may depend only on the absolute level of $T_{co}$ rather than the magnitude of $\Delta T_{co}$ during RF exposure.

### Chronic Exposure Studies

Of the several studies in which groups of animals have been exposed to RF fields for months to years, only three have evaluated any consequences for thermoregulation. Guy et al. [1980] exposed male New Zealand white rabbits to 2450 MHz CW microwaves at 10 mW/cm$^2$, 23 h/day for 180 days. Eight rabbits were studied simultaneously, four irradiated and four controls. Each animal was housed in a miniature anechoic chamber at $T_a = 24 \pm 2$ °C, with food and water available. Thermographic measurements indicated a peak SAR of 17 W/kg in the head while whole body SAR was estimated at 1.5 W/kg [Durney et al., 1986]. Periodic assessments of the animals revealed no significant differences between the groups in body mass, urinary output, $T_{co}$, hematocrit, hemoglobin, or basic blood cell counts.

Adair et al. [1985] studied changes in thermoregulatory behavior and physiological responses in pairs of squirrel monkeys, chronically exposed (or sham exposed) 40 h/week for 15 weeks to 2450 MHz CW RF energy at 2 PD (1 and 5 mW/cm$^2$) in each of 3 $T_a$ (25, 30, or 35 °C). The whole body SAR was 0.16 (W/kg)/(mW/cm$^2$). Physiological responses were measured three times (1) during a preexposure phase of 8–12 weeks; (2) during the 15 week chronic exposure period; and (3) during a postexposure phase of 4–8 weeks. Variables measured at several controlled $T_a$ were: $T_{co}$, four $T_{sk}$, $M$, and foot sweating rate. Blood samples were taken at 1, 5, 10, 15, and 20 weeks for standard indices. The results showed no significant differences in $M$, $T_{co}$, or blood indices between sham and exposed animals. The $T_a$ prevailing during the RF exposure did exert an effect on sweating rate, which was enhanced in $T_a = 35$ °C, an effect of acclimatization to heat. $T_{sk}$ was reliably influenced by both $T_a$ and RF exposure. The most robust effect was a reduced body mass in the exposed animals that was directly related to PD.

Chou et al. [1992] studied the effects of chronic exposure of 100 sham exposed rats and 100 rats exposed throughout their lifetimes to circularly polarized 2450 MHz PW (10 μs duration, 800 pps) RF energy [Guy et al., 1979]. The delivered power of 0.144 W to each waveguide resulted in a range of average SAR of 0.4 W/kg for a 200 g rat to 0.15 W/kg for an 800 g rat. The only variables among the 155 measured that relate directly to this review are $O_2$ consumption and $CO_2$ production. These were assessed in a subsample of 18 rats from each group. A significant decrease in both $O_2$ consumption and $CO_2$ production was seen in the exposed young animals, but not in the exposed mature animals.

### Pulsed (PW) Versus CW Field Effects

Few systematic investigations of the biological effects of PW versus CW fields have been undertaken and almost none have related to the thermoregulatory responses of the exposed organism. The most extensive investigations of PW effects have been a product of the circular waveguide exposure system developed by Guy et al. [1979]. Many reports by Lai [e.g., Lai et al., 1984a,b] have described complex interactions between 2450 MHz PW exposure of rats and drugs that influence the $T_{co}$. However, all conclusions are related to periodic measurements of $T_{co}$ alone; no data are provided on the specific autonomic mechanisms that may underlie changes in $T_{co}$.

Historically, it has been held that PW radiation is more likely to produce certain biological effects than CW radiation at the same average incident PD and, indeed, the results of several experiments have supported this view. A recent evaluation elaborating on this possibility may be found in Postow and Swicord [1996].

Few studies have examined the comparative effects of exposure to PW and CW fields on the autonomic responses of intact animals. In general, the effects on HR have been equivocal. Frei et al. [1988] found a significant increase in the HR of anesthetized rats in the presence of high intensity 2.8 GHz PW fields. Later reports [Frei et al., 1989a,b] found no difference between CW and PW fields at 2.8 and 9.3 GHz on HR, RR, BP, and EKG. Why the findings differ is unclear. Others [Lu et al., 1992] found no difference in HR and BP changes produced by equivalent CW and PW fields.

Several studies assessed the thermoregulatory consequences of 90 min RF exposure of squirrel monkeys under several exposure parameters [Adair et al., 1993]. Parameters investigated were frequency (450 and 2450 MHz), CW versus PW, whole body SAR (1.2–4.7 W/kg), and $T_a$ (20, 26, and 32 °C). The PW characteristics were 20 μs pulse width, $2.5 \times 10^4$ pps. Groups of four monkeys (three sessions each) were tested under each exposure condition. In general, the steady state thermoregulatory responses ($T_{co}$ and 4 $T_{sk}$, *M*, conductance, and sweating rate) to PW and CW fields were found to be the same at a given frequency, $T_a$, and whole body SAR. These studies laid the groundwork for the studies of human volunteers reported earlier [Adair et al., 1998, 1999b, 2001a,b, 2002].

## Additive Drug–Microwave Interactions, Including Anesthetics

More than 40 years ago, experimental animals treated with certain drugs were found to be especially vulnerable in the presence of RF fields. Michaelson et al. [1961] reported that dogs are more susceptible to microwave heating after administration of pentobarbital sodium, morphine sulfate, or chlorpromazine, sugesting that mechanisms of heat loss may be compromised by the drug treatment. A similar effect was reported in rats rendered hypothermic by cortisone injections; animals so treated showed greater increases in $T_{co}$ than controls during RF exposure at 40 W/kg [Putthof et al., 1977]. In rabbits and rats, increased vulnerability took the form of a delayed rise in $T_{co}$, reflecting the hypothermic action of an anesthetic [Michaelson, 1974]. On the other hand, the duration of hexobarbital anesthesia in mice [Blackwell, 1980] and pentobarbital anesthesia in rabbits [Cleary and Wangemann, 1976] was related directly to the field strength of a 2450 MHz exposure. A shortening of anesthesia apparently resulted from a higher rate of distribution of the drug through increased blood flow.

The picture is further complicated by other factors. Lai et al. [1984b] reported that both the orientation of the animal during exposure and the order of presentation of anesthetic and microwaves influence the magnitude and duration of anesthesia. When microwave exposure preceded injection of the anesthetic, recovery from hypothermia was lengthened. When anesthesia preceded irradiation, posterior exposed animals recovered from anesthesia significantly faster than anterior or sham exposed animals. Polarization was also important. When ketamine-anesthetized rats were exposed to 1.23 GHz CW microwaves at SAR = 8 W/kg, E polarization generated greater tissue heating (core, tympanic, subcutaneous, and tail surface temperatures) than H polarization [Jauchem et al., 1990]. Similar results were found for 2.45 GHz, although tissue heating was more superficial at this higher frequency [Frei et al., 1989b].

## Synergistic Effects of Psychotropic Drugs and Ethanol

Chlorpromazine has been widely investigated for possible synergistic action with RF exposure [Jauchem, 1985]. Other studies [Jauchem et al., 1984, 1985, 1988] have featured microwave irradiation of anesthetized rats injected with either saline or chlorpromazine (5 mg/kg) and held at $T_a = 24$ °C. Two RF conditions were studied: 2.8 GHz PW (2 μs pulse, 500 pps) at SAR = 14 W/kg and 5.6 GHz CW at SAR = 12 W/kg. Under both exposure conditions, chlorpromazine tended to enhance thermoregulation when $T_{co} \leq 39.5$ °C, but the drug increased susceptibility to RF when the exposure was continued until death occurred. Other psychotropic drugs of similar nature, amitriptyline HCl (10 mg/kg) and haloperidol (0.1 mg/kg), did not alter the responses of anesthetized rats to 2.8 GHz PW exposure at SAR = 14 W/kg. Unfortunately, these studies have limited generality because ranges of SAR, drug dose, and $T_a$ have yet to be explored.

The importance of conducting parametric studies becomes clearer when the potential synergy between RF exposure and other substances that tend to alter the $T_{co}$ are explored. Ethanol is a classic example. The magnitude of ethanol induced hypothermia in the rat is highly dependent on both the dose administered and the $T_a$ to which the animal is exposed. Hyperthermia is observed in ethanol treated rats if the prevailing $T_a$ is well above thermoneutrality (e.g., 36 °C), a response that Myers [1981] called the alteration of heat loss mechanisms. However, careful parametric studies [Spiers et al., 1984] have demonstrated, for $T_a$ from 17 to 32 °C, that acute administration of ethanol at a dose of 3 g/kg interferes with *M* rather than with heat loss. A more important finding was that rats, equilibrated to $T_a = 26$ °C prior to ethanol dosing and testing at $T_a = 17$ °C, showed an initial *M* depression that slowed the developing hypothermia.

Such information is essential to properly interpret measured changes in $T_{co}$ in ethanol treated (3 g/kg) rats, previously either sham exposed or irradiated for 45 min by 2.45 GHz PW, at SAR = 0.6 W/kg [Lai et al., 1984a]. The mean $T_a$ was $22 \pm 0.1$ °C, but the range was 21–24 °C. No control injections of the vehicle were given. More important, since the only response measured was $T_{co}$, it was impossible to determine whether heat production or heat loss produced the attenuation of hypothermia in the RF exposed animals relative to the shams. No change in $T_{co}$ was reported. However, abundant evidence exists for the maintenance of

normothermia (constant $T_{co}$) during RF exposure, even at moderately high SARs [Adair, 1987a; Candas et al., 1985; Lotz and Saxton, 1988]. The underlying cause is careful titration of heat production and/or heat loss. Thus, the speculation by Lai et al. [1984a] that their results might reflect stress related interference with heat loss, perhaps mediated by endogenous opioids, is open to question. A complete understanding of the subtle actions of RF exposure requires measurements of many more responses than just the changes in ''colonic temperature'' taken at arbitrary intervals.

### Rodent Data in Circular Waveguide

Lai et al. [1987] undertook an extensive research program to determine how endogenous opioids may be involved in the interaction between certain psychoactive drugs injected in rats and prior acute irradiation by circularly polarized 2.45 GHz PW microwaves at SAR = 0.6 W/kg. The early experiments usually used the same protocol: a 45 min sham or microwave exposure in a circular waveguide was followed by (1) $T_{co}$ measurement, (2) injection of a drug at a single dose, and (3) measurement of $T_{co}$ every 15 min for periods ranging from 45 min to 2 h. Most studies suffered from the limitations noted above, including a narrow range of $T_a$, a single drug dose, infrequent assessment of the effects of vehicle injection, and no tests for specific contributing thermoregulatory mechanisms. The reader is referred to Lai [1992] for an extensive description of the results of studies in this research program.

### Rodent Data in Far Field

Smialowicz [1983] used drug–microwave interactions to demonstrate subtle heating produced by low intensity ($\leq$10 mW/cm$^2$) exposure to 2.45 GHz CW microwaves in both mice and rats. Mice injected IP with 5-HT creatinine sulphate complex (20 mg/kg) and rats injected IV with *Salmonella typhimurium* LPS (100 μg/kg) became hypothermic when held at $T_a = 22$ °C. Postinjection exposure to RF energy generated an increased $T_{co}$ that was a direct function of PD. Saline injected controls, similarly exposed, did not show comparable $\Delta T_{co}$. Thus, this study showed that chemical impairment of thermoregulatory mechanisms permitted detection of significant changes in $T_{co}$ of animals exposed to low intensity RF fields that were formerly believed to be nonthermogenic.

### Primate Studies

Many other classes of drugs interact with RF exposure to alter body temperature in interesting ways. Adair [1987a] examined the potential for disruption of autonomic thermoregulatory responses by an altered metabolic state (induced by IP injections of isoproterenol) in squirrel monkeys exposed to 2450 MHz CW microwaves at $T_a = 33$ °C. Unlike shivering thermogenesis, chemically mediated nonshivering thermogenesis was unaffected by RF exposures at whole body SARs from 1.5 to 4.0 W/kg. Instead, the elevated energy production/absorption in the body, coupled with partially disabled heat loss responses, produced an exaggerated rise in $T_{co}$. These results confirm and extend a conclusion drawn by others that an endotherm whose thermoregulatory system is compromised by drugs or other agents may be at a disadvantage, in terms of its ability to regulate the $T_{co}$, during RF exposure.

## THERMOREGULATORY BEHAVIOR IN THE PRESENCE OF RF ENERGY

Any organism may adopt thermoregulatory behavior as an alternate strategy to counter the thermalizing effects of RF exposure. Changes in certain behaviors can alter the thermal characteristics of the air/skin interface and maximize the efficiency of heat transfer to the environment. Examples are the selection of a more favorable thermal environment, the resetting of a thermostat, and putting on or taking off clothing. These behaviors also minimize the involvement of autonomic mechanisms of heat production and heat loss, conserve bodily stores of energy and fluid, and generate a state of maximal thermal comfort. Because behavioral responses may be mobilized quickly and are of high gain, they must always be considered in any discussion of the thermoregulatory consequences of RF exposure. A separate white paper [D'Andrea et al., 2003] contains a summary of the behavioral responses that contribute to thermoregulation in the presence of RF fields.

## CONCLUSIONS

The study of the biological effects of RF energy is a mature scientific discipline with over a 50 years history and an extensive literature database. This review has emphasized established changes in human and animal thermophysiological responses, stimulated by tissue heating when RF/microwave energy is present. Laboratory and clinical studies of human volunteers demonstrate their superior thermoregulatory ability over other endotherms during RF exposure at, or even above current human exposure guidelines. A few problem areas for humans remain, including drug/RF interactions and exposure to millimeter waves or high peak power microwaves. The current animal data are already reassuring on the benign nature of such conditions.

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