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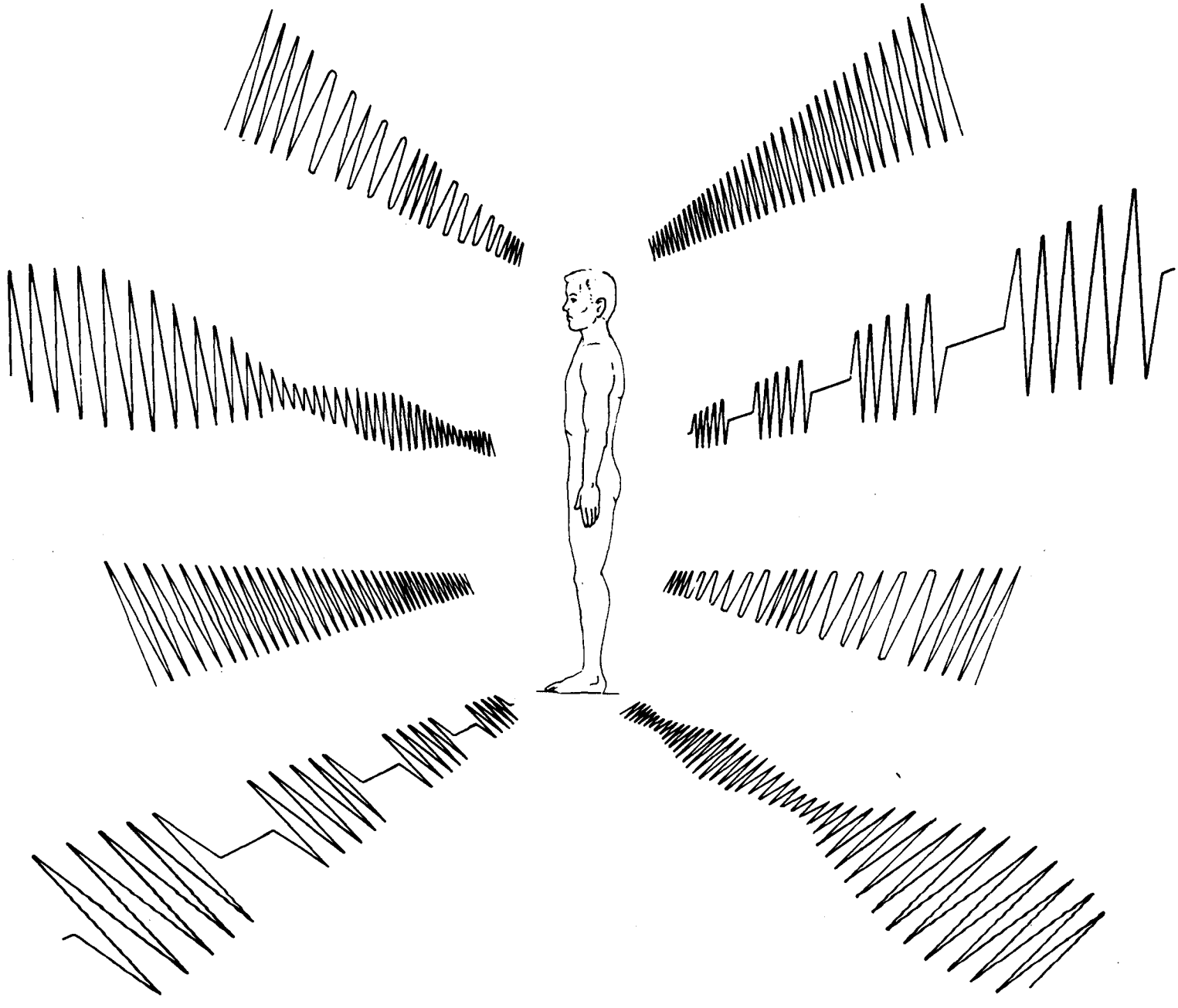

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Biological Effects of Radiofrequency Radiation

Edited by

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Foreword

The many benefits of our modern, developing industrial society are accompanied by certain hazards. Careful assessment of the risk of existing and new man-made environmental hazards is necessary to establish sound regulatory policy. Environmental regulations enhance the quality of our environment in order to promote the public health and welfare and the productive capacity of our nation's population.

The Health Effects Research Laboratory conducts a coordinated environmental health research program in toxicology and clinical studies. These studies address problems in air pollution, radiofrequency radiation, environmental carcinogenesis, and the toxicology of pesticides, as well as other chemical pollutants. The Laboratory participates in the development and revision of air quality criteria documents on pollutants for which national ambient air quality standards exist or are proposed, provides the data for registration of new pesticides or proposed suspension of those already in use, conducts research on hazardous and toxic materials, and is primarily responsible for providing the health basis for radiofrequency radiation guidelines. Direct support to the regulatory function of the Agency is provided in the form of expert testimony and preparation of affidavits as well as expert advice to the Administrator.

The intent of this document is to provide a comprehensive review of the scientific literature on the biological effects of radiofrequency radiation. The purpose of this effort is to evaluate critically the current state of knowledge for its pertinence and applicability in developing radiofrequency-radiation exposure guidelines for the general public.

F. G. Hueter, Ph.D.
Director
Health Effects Research Laboratory

Abstract

This document presents a critical review of the available literature on the biological effects of radiofrequency (RF) radiation. The objective was to summarize and evaluate the existing database for use in developing RF-radiation exposure guidance for the general public.

The frequency range of concern in this document is 0.5 MHz to 100 GHz, which includes nearly all the significant sources of population exposure to RF radiation, except 60-Hz electrical power systems. Research reports that are judged to be credible according to a set of objective criteria are examined for the relation between the RF energy absorbed and the presence or absence of biological effects. The reported consequences of the interaction between RF radiation and biological systems are examined from two perspectives: whole-body-averaged specific absorption rate (SAR) and RF-energy-induced core-temperature increases.

The existing database provides sufficient evidence about the relation between RF-radiation exposure and biological effects to permit development of exposure limits to protect the health of the general public. It has been concluded from this review that biological effects occur at an SAR of about 1 W/kg; some of them may be significant under certain environmental conditions.

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Acknowledgment

The authors thank Jan Parsons and Carole Moussalli, Northrop Services, Inc., for editorial review of this document. The authors wish to express special appreciation to Dr. Don R. Justesen for his editorial comments on an earlier draft and Dr. Charles Süsskind for his editorial assistance on the final draft.

Section 1
Introduction

Daniel F. Cahill
Joe A. Elder

The goal and purpose of this document is review and evaluation of the available scientific information on the biological effects of radiofrequency (RF) radiation. To address this broad topic most effectively and to present the information in the most useful form, several guidelines and simplifying assumptions were adopted. It is in the selection and employment of these guidelines and assumptions that differences of opinion are most likely to arise. These guidelines and assumptions are as follows:

1. The frequency range of interest is defined as 0.5 MHz to 100 GHz. This range includes nearly all the frequencies that serve as significant sources of population exposure (e.g., AM, FM, land mobile, and amateur radio; UHF and VHF TV; and air traffic control radar).
2. The general public is the population of concern. Therefore, far-field exposures are the more usual condition, rather than the near-field exposures commonly associated with the workplace. Wherever possible, the impact on all ages is considered, not only on healthy adults, who are of principal concern in occupational exposures.
3. Dose rate is defined by the specific absorption rate (SAR), which is used to normalize the rate of RF energy input into biological systems across this frequency range. The SAR is the mass-normalized rate at which the energy of an electromagnetic (EM) field is coupled into an absorbing body; the units are watts per kilogram (W/kg). Inherent in the use of a single, whole-body-averaged SAR value is a disregard of nonuniform RF energy deposition patterns and possible local SAR values in excess of the average. However, the data that describe the distribution patterns of RF energy in biological systems over a frequency band as broad as 0.5 MHz to 100 GHz are far too incomplete at this time to be directly useful.
4. In reports of pulsed RF-radiation exposure experiments the time-averaged SAR is considered, although controversy exists as to whether some biological effects are functions of the temporal pattern of energy delivery or only the result of total energy input.
5. We have accepted "no effects" data in credible reports as highly valuable in our review of the state of knowledge in this area. Both "effects" and "no effects" studies are used to determine the extent of the biological interactions of RF radiation.
6. We are assuming that data derived from the use of experimental mammalian systems have relevance for the human situation.
7. This document presents only the biological effects of RF radiation. The benefits of RF radiation are not considered, and therefore no benefit/risk analysis is undertaken.

A draft of this report (Cahill and Elder 1983) was published in June 1983 and transmitted to EPA's Science Advisory Board (SAB) for review of its scientific and technical merit (Federal Register 1983a). The initial review by the SAB Subcommittee of the Biological Effects of Radiofrequency Radiation was held on September 22-23, 1983 (Federal Register 1983b); the second review occurred on January 24-25, 1984 (Federal Register 1984). A list of the Subcommittee members is given in Appendix A.

The June 1983 draft was a critical review of the literature on the biological effects of radiofrequency radiation through 1980. The present document is a revision of the June 1983 draft and is based on the comments and suggestions of the Subcommittee, and includes a number of post-1980 references that were considered important to the conclusions of the present review of the biological effects of RF radiation by both the authors and by the Subcommittee members.

Section 2
Approach

Joe A. Elder
Daniel F. Cahill

2.1 General Approach

Although a comprehensive literature review is useful, it is even more desirable if the body of literature is consolidated, analyzed, and synthesized into a statement or statements that relate the presence or absence of biological effects to a meaningful exposure parameter such as dose rate (SAR). To this end, our general approach is essentially as follows:

1. The reports are evaluated for their scientific quality and utility. Acceptable reports contain adequate descriptions of appropriate physical and biological systems and tests.
2. The credible reports are then examined for the relation between the RF energy absorbed and the presence or absence of biological effects in the experimental systems.

2.2 Specific Approach

The literature evaluated for this document includes English-language publications, numerous English translations of Soviet research reports obtained through the U.S. Joint Publications Research Service, and selected technical reports translated from Polish, French, Italian, and Russian.

The extant literature base numbers over 5000 citations, but considerably fewer are valuable in developing exposure guidelines for the following reasons.

1. A large fraction of the literature is available only in Slavic languages.
2. The research reports are uneven in quality and usefulness because authors often failed to include sufficient experimental details to allow reviewers to estimate critical exposure parameters such as incident field intensity, dose rate, or dose.
3. In many review articles, equal currency is given to the conclusions from properly designed and executed studies and to those from less stringently conducted research. Because these uncritical reviews have contributed to the general confusion over the health risks associated with RF radiation, we have relied on original research papers rather than review articles and have chosen to be highly selective in our review.

In reviewing the literature we first evaluate descriptions of frequency, exposure parameters, RF source, experimental species, age, sex, environmental and biological controls, and the statistics employed; and whether actual data are displayed or merely referred to in the text. Many pre-1970 reports are deficient in one or more of these key areas and are either rejected outright if the flaws are judged fatal, or are segregated into the category of reports with "unresolved issues." Reports that provide adequate descriptions of these parameters are further scrutinized for the appropriateness of biological systems, tests, sample sizes, controls, and statistics employed, as well as substantiation of their conclusions. Reports that clear this second hurdle are credible reports, but are considered usable only if biological results are linked explicitly or implicitly to SAR data from the description of the exposure parameters. Reports that fail to provide these parameters are also assigned to the "unresolved issues" category.

2.3 Major Sections

Four major sections follow. They are Physical Principles of Electromagnetic Field Interactions (Sec. 3), Effect of RF-Radiation Exposure on Body Temperature (Sec. 4), Biological Effects of RF Radiation (Sec. 5), and Summary and Conclusions (Sec. 6).

The first part of Sec. 3 presents some introductory information on electromagnetic field theory. Next, RF-field interactions with both simple and complex biological objects, such as the human body, are discussed and, most important, definitions of RF dosimetric terms are given. The mechanisms of RF interactions with biological systems, particularly molecular systems, are discussed. The remaining two major subsections described experimental methods and dosimetric methods used in state-of-the-art research on the biological effects of RF radiation.

Since the absorption of RF energy by biological species can lead to an increase in the temperature of body tissues, it is important to understand how

animals, including man, regulate the additional thermal input of RF-radiation exposure, both physiologically and behaviorally. Section 4 is an introduction to the subject of thermoregulation in both animals and human beings and, in addition, discusses the specific effects of RF radiation on thermoregulatory processes. Also, a description is included of the mathematical models that are being used to predict increases in temperature and activation of thermoregulatory effectors in human beings in simulated RF fields.

Section 5 is a review of the main body of literature on the biological effects of RF radiation. The section contains ten subsections, each of which represents a biological discipline or major research area, ranging from subcellular systems to human beings. In each of the ten areas, the conclusions and generalizations that can be drawn from the review of the literature are presented.

In Sec. 6, the major conclusions and generalizations of Secs. 3, 4, and 5 are presented. Next, many of the reports are tabulated by biological variable and dose rate (SAR). In summary, the reported consequences of the interaction between RF radiation and biological systems are examined from two perspectives (whole-body-averaged SAR and RF-energy-induced core temperature increases) in order to analyze, synthesize, and consolidate the review data into statements that relate biological effects to a meaningful exposure parameter (dose rate or SAR).

Section 3
Physical Principles of Electromagnetic Field Interactions

3.1 Elements of Electromagnetic Field Theory

William T. Joines

3.1.1 Electromagnetic Spectrum

3.1.1.1 Frequency, Wavelength, and Velocity

Oscillating electric charges induce an electromagnetic (EM) field within the region surrounding the charge source. In turn, this oscillating induction field—often called the near field—of the source generates an EM wave that radiates energy from the region surrounding the charges. The radiated wave consists of coupled electric and magnetic fields that oscillate at the same frequency as the source, and the wave propagates outward from the source at the velocity of light in the medium. In free space, this velocity is $\sim 3 \times 10^8$ m/s, whereas in a medium with low EM energy dissipation the velocity is this value divided by the square root of the material's dielectric constant relative to that of free space. In a low-loss material such as fatty tissue, with a relative dielectric constant of 4, the velocity of light is 1.5×10^8 m/s. For an EM wave traveling at velocity v, the wavelength in the medium is the distance the wave travels in one time period or $T = 1/f$, where f is the oscillation frequency of the wave in cycles per second, or hertz (Hz). Therefore, the wavelength λ is expressed as

$$\lambda = v/f$$

The EM spectrum extends from zero to 10^{25} Hz (or cycles/s) and includes the ranges of visible light and ultraviolet (UV), infrared (IR), X, and gamma rays. The region from zero to 3000 GHz (lower IR range) is referred to as the RF region (Sams & Co. 1981). The region of interest here is the RF band from 0.5 MHz to 100 GHz. The wavelengths in free space for this frequency band range from 600 m to 3 mm.

3.1.1.2 Ionizing and Nonionizing Electromagnetic Radiation

EM waves of all frequencies carry energy. According to quantum mechanics, they can also be thought of as packets of energy called photons. The energy of a photon is given by

$$\text{Energy} = hf$$

where $h = 6.63 \times 10^{-34}$ joule seconds (Planck's constant)
f = frequency

The energy of a photon is thus directly proportional to the frequency of the radiation. When the frequency approaches or exceeds 3×10^{15} Hz (UV), the photon energies equal or exceed 2×10^{-18} J, or 12.4 eV, and become comparable to the binding energy of electrons to atoms. This high-frequency radiation (X rays, gamma rays, etc.) is referred to as ionizing radiation. Since even the weakest chemical bonds have energies that are several orders of magnitude greater than those of RF or microwave photons (10^{-3} eV or less), RF waves are referred to as nonionizing radiation.

3.1.1.3 Designation of Microwave and Radiofrequency Bands

Bands of radiofrequencies have been assigned designations according to frequency or wavelength as shown in Table 3-1 (Sams & Co. 1981). Typical uses of the frequencies within a band are also indicated. Certain radiofrequencies—notably the industrial, scientific, and medical (ISM) frequencies—have been assigned by the Federal Communications Commission for specific applications (Sams & Co. 1981). The ISM frequencies are

13.56 MHz ± 6.78 kHz
27.12 MHz ± 160 kHz
40.68 MHz ± 20 kHz
915 MHz ± 25 MHz
2450 MHz ± 50 MHz
5800 MHz ± 75 MHz
22,125 MHz ± 125 MHz

3.1.2 Wave Propagation

Power Density, Electric Field, and Magnetic Field

In free space, EM waves spread uniformly in all directions from a theoretical point source. The wavefront, or the surface joining all points of identical phase, is spherical in this case. As the distance from the point source increases, the area of the wavefront surface increases as a square of the distance, so that the source power is spread over a larger area. If power density is defined as the ratio of the total radiated power to the spherical surface area enclosing the source, the power density W is inversely proportional to the square of the distance from the source, and can be expressed as

Table 3-1. Radiofrequency Bands*

Frequency	Wavelength	Band Designation	Typical Uses
300-3000 GHz	1-0.1 mm	Supra EHF (extremely high frequency)	Not allocated
30-300 GHz	10-1 mm	Extremely high frequency (EHF)	Satellite communications, radar, microwave relay, radionavigation, amateur radio
3-30 GHz	10-1 cm	Super high frequency (SHF)	Satellite communications, radar, amateur, taxi, police, fire, airborne weather radar, ISM
0.3-3 GHz	100-10 cm	Ultra high frequency (UHF)	Microwave point to point, amateur, taxi, police, fire radar, citizens band, radio-navigation, UHF-TV, microwave ovens, medical diathermy, ISM
30-300 MHz	10-1 m	Very high frequency (VHF)	Police, fire, amateur, FM, VHF-TV, industrial RF equipment diathermy, emergency medical radio, air traffic control
3-30 MHz	100-10 m	High frequency (HF)	Citizen band, amateur, medical diathermy, Voice of America, broadcast, international communications, industrial RF equipment
0.3-3 MHz	10^3-10^2 m	Medium frequency (MF)	Communications, radio-navigation, marine radiophone, amateur, industrial RF equipment, AM broadcast
30-300 kHz	10-1 km	Low frequency (LF)	Radionavigation, marine communications, long-range communications
3-30 kHz	100-10 km	Very low frequency (VLF)	Very long range communications, audiofrequencies, navigation
0.3-3 kHz	10^3-10^2 km	Voice frequency (VF)	Voice, audiofrequencies
30-300 Hz	10^4-10^3 km	Extremely low frequency (ELF)	Power lines, audiofrequencies, submarine communications
0-30 Hz	∞-10^4 km	Sub-ELF	Direct-current power lines

*Sams & Co. 1981.

$$W = P/4\pi r^2 \qquad (3\text{-}1)$$

where P = transmitted power
r = distance from the source

An isotropic source radiates uniformly in all directions in space. In practice, there is no source that has this property, although there are close approximations. The inverse-square law (Equation 3-1) applies also when the source is anisotropic (directional), as long as the medium is homogeneous and isotropic (e.g., free space or a medium in which the velocity of wave propagation does not change with direction or distance).

An EM wave is also characterized by its electric-field (E) intensity and its magnetic-field (H) intensity. In an unbounded medium, the product of E and H is the power density W, or

$$W = EH \qquad (3\text{-}2)$$

where E is in volts per meter, H is in amperes per meter, and W is in watts per square meter. If the peak instantaneous values of E and H are used in Equation 3-2, then W is the peak power density; if effective or root-mean-square (RMS) values of E and H are used, then W is the effective or time-averaged power density. The ratio of E to H is the intrinsic impedance of the medium η (in ohms), or

$$\eta = E/H \qquad (3\text{-}3)$$

where η is 120π ohms in free space. From Equations 3-1 through 3-3, one can express E in free space at a distance r from an isotropic source radiating total power P as

$$E = \sqrt{30 \cdot P}/r \qquad (3\text{-}4)$$

The radiated waves that propagate outward from an RF or microwave source can be confined to travel along a two-conductor transmission line (coaxial,

stripline, microstrip, twin lead), or inside a hollow metal pipe (waveguide). The waves can also be propagated outward into the space that surrounds a transmitting antenna, as in communications broadcasting. In this case, the RF or microwave source forces electrons to oscillate on the surface of a metal transmitting antenna and thereby produces EM waves. This is a reciprocal process, for when these waves strike a receiving antenna, they force electrons to oscillate, which typically produces current in the receiver. This reciprocity phenomenon forms the basis of EM communication systems. Information can be placed on an EM carrier in several ways, including amplitude and frequency modulation of the carrier wave.

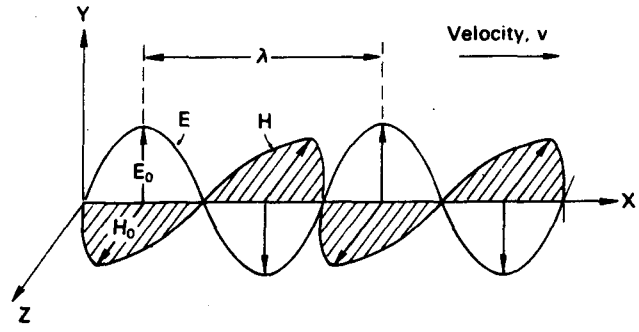
3.1.2.1 Sources of Radiofrequency Radiation

There is widespread interest in possible new applications of RF energy, especially at microwave frequencies. The growing number of commercial applications has led to an increased awareness of potential hazards due to the energy sources used. Typical sources of RF or microwave energy are klystrons, magnetrons, planar triodes, backward-wave oscillators, and semiconductor devices. In all these sources, energy is imparted to charged particles or electrons from a convenient supply, usually a direct voltage and current. A portion of the energy is then given up by the charged particles in the form of oscillations in a tuned circuit. Such sources may operate to produce (1) continuous (CW) radiation, as in the case of some communications systems; (2) intermittent radiation, as in microwave ovens, induction heating equipment, and diathermy equipment; or (3) radiation in the pulsed (PW) mode in radar systems.

3.1.2.2 Plane-Wave, Far-Field, and Near-Field Concepts

Usually the region that is more than a few wavelengths from the transmitting antenna is called the far field. In this region, the spatial relationship between the electric and magnetic fields in the EM wave is that shown in Figure 3-1. In this diagram, an EM wave is propagating in a direction perpendicular to the motion of the electrons in the transmitting antenna. The electric field E is always perpendicular to the direction of propagation and lies in the plane formed by the line of propagation and the motion of electrons in the antenna. The direction of the electric vector periodically changes along the direction of propagation, and its magnitude forms a sine-wave function. The magnetic field H, which is always perpendicular to both the electric field E and the direction of propagation, traces out a sine-wave function in the same manner as the electric field E. Figure 3-1 depicts the situation at a particular instant in time. The entire wave can be pictured as moving in the direction of propagation at $\sim 3 \times 10^8$ m/s.

Figure 3-1. Far-field electromagnetic wave at a particular instant in time.



At some distance from the transmitting antenna (within the far field), the radius of curvature of the generally spherical wavefronts is large compared with the diameter of any receiving or detecting object within the field. At this distance from the antenna the wavefronts may be treated (for all practical purposes) as plane surfaces over which the intensity of E and H is constant. In such regions, E and H form plane waves. The terms "plane-wave field" and "far field" are often used interchangeably, although the distinction between the two terms depends on the size of the receiving object, as stated above.

At distances less than a few wavelengths from a transmitting antenna, in the near field, the situation is somewhat complicated because the maxima and minima of E and H do not occur at the same points along the direction of propagation as they do in the far-field case (Figure 3-1). Near-field exposures become particularly important when one is considering radiation from microwave ovens, microwave diathermy equipment, RF sealers, broadcast antennas, and microwave oscillators under test. For investigations into the biological effects of RF-radiation exposure, studies of exposures in the far field are usually preferable; field strengths in the near field are more difficult to specify because both E and H must be measured and because the field patterns are more complicated.

Incident power density at a given distance from an antenna may be calculated from the measured power transmitted by the antenna, the known antenna gain G, and effective area A of the antenna. Antenna gain is defined as the power density at a point in front of the antenna divided by the power density at the same point if the antenna were radiating the same total power as an isotropic source. For any impedance-matched antenna (i.e., one where all the energy fed to it is transmitted), the ratio of G to A is

$$G/A = 4\pi/\lambda^2 \qquad (3\text{-}5)$$

The far-field power density is calculated from the Friis free-space transmission formula (Mumford 1961) as

$$W = GP/4\pi r^2 = AP/\lambda^2 r^2 \qquad (3\text{-}6)$$

where λ = wavelength
P = power output of the antenna
W = power density on a surface at distance r from the antenna

It is convenient to express the far-field free-space power density in terms of the power density at the antenna aperture, i.e., $W_0 = P/A$, and hence $P = W_0A$. Substituting this expression for P in Equation 3-6 and dividing both sides by W_0 yields

$$W/W_0 = (A/\lambda r)^2 \qquad (3\text{-}7)$$

Equation 3-7 may be rewritten as

$$W/W_0 = 4(A/2\lambda r)^2 \qquad (3\text{-}8)$$

This expression applies in the far-field region, and the following simple modification makes it applicable to the near-field region as well:

$$W/W_0 = 4\sin^2 (A/2\lambda r) \qquad (3\text{-}9)$$

This formula applies to uniform irradiation of square, round, or rectangular apertures or to irradiation that is tapered in amplitude for round apertures. For other shapes and tapers, a more complicated analysis is necessary (Mumford 1961).

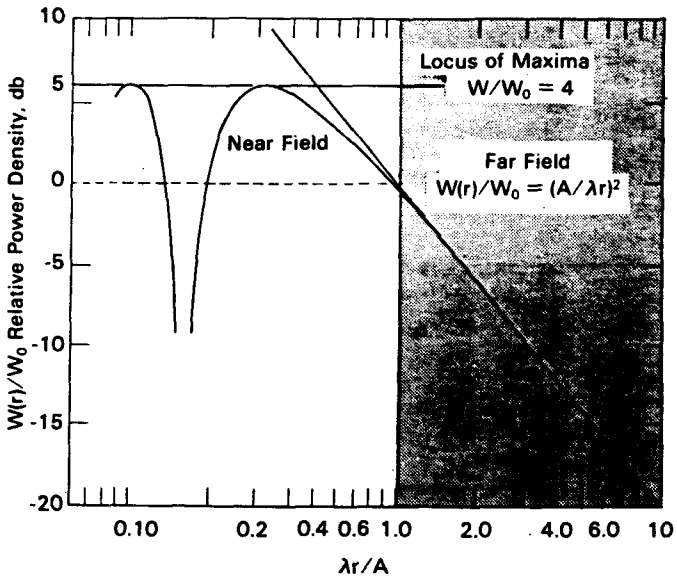
Since the power density at the antenna aperture ($W_0 = P/A$) is greater than the output power P divided by the cross-sectional area of the aperture, the effective area A is less than the actual area. For the waveguide horn and dish antennas commonly used at microwave frequencies, the effective area ranges from about 50 to 80 percent of the actual area of the cross section. For a given P, with A determined for the particular antenna used, $W_0 = P/A$ is used in Equation 3-9 to compute W at any distance r from the antenna (Mumford 1961).

Equation 3-9 is plotted in Figure 3-2 along with lines representing the maximum values in the near-field and the far-field approximations as given by Equation 3-7. In this graph, the relative power density is plotted in decibels [$dB = 10\log_{10}(W/W_0)$] on the ordinate, and $\lambda r/A$ is plotted logarithmically on the abscissa. Note the alternate maxima and minima in the near field. The maxima all are 6 dB above (4 times) the power density at the aperture. For a conservative estimate in possible near-field human exposure situations, the power density can be approximated as the maximum value or

$$W = 4W_0 = 4P/a \qquad (3\text{-}10)$$

Figure 3-2 and Equation 3-9 also show that for $\lambda r/A = 1$, $W \cong W_0$, the power density at the antenna aperture. Hence, a convenient point of demarcation

Figure 3-2. Power density vs. distance along axis from antenna aperture.



between the near field and far field is the distance from the antenna where

$$r = A/\lambda \qquad (3\text{-}11)$$

The gain of an antenna as used in Equations 3-5 and 3-6 is usually taken to be the gain in the direction of maximum radiated power. In general, the antenna will have a radiation pattern that is at a maximum in front of the antenna on an axial line perpendicular to the aperture surface. On a surface of radius r from the antenna, the power density typically decreases as the off-axis angle increases. The relative power density is expressed as $W(\Theta)/W_{max}$, where W_{max} is the power density at a given distance along the axis of maximum radiation, and $W(\Theta)$ is the power density at the same distance from the center of the aperture but at an off-axis angle Θ. Equations 3-6 through 3-9 apply to angles off-axis if their right-hand sides are multiplied by the radiation pattern $W(\Theta)/W_{max}$. While the radiation pattern may be known or determined, it does depend upon the type of antenna that is used.

3.1.3 Wave Modulation

3.1.3.1 Amplitude and Frequency Modulation

With an EM wave of a particular frequency serving as a carrier, information signals at lower frequencies are superposed onto the carrier through the process of modulation. Modulation of the carrier can be accomplished either by continuous variation of one of the parameters of the carrier (amplitude, frequency, or phase) or by interruption of the carrier by a process in which it is chopped into segments (pulse wave or PW modulation). If the impression of the information

signal on the carrier causes its amplitude to vary, the process is called amplitude modulation (AM). If the information signal causes a frequency variation of the carrier at constant amplitude, the process is called frequency modulation (FM). If the information signal causes a time-phase variation of the carrier, the process is called phase modulation (PM). Phase modulation and frequency modulation are closely related; both cause a change in the time phase angle of the carrier (Froehlich 1969).

Since the purpose of modulation is to improve the overall efficiency of transmission, the carrier frequency is chosen for its suitability to the medium in which it is to be transmitted. Transmitting unmodified audio signals is theoretically possible; however, the antenna required to transmit and receive such signals would be too large to be practical. More important, unmodulated signals are not transmitted because no other method exists to separate several information signals on the same transmission path to provide multichannel capability. This flexibility is obtained if carriers of higher frequencies are chosen and then spaced in frequency so as to prevent overlap. High-frequency carriers are also more suitable for radio propagation. One must then shift the information signal to a high-frequency range through the process of modulation. Introducing frequency translation to information signals provides a way of separating information channels and thereby improving the transmission efficiency.

3.1.3.2 Pulse Modulation

One of the more familiar applications of PW modulation is in radar. Radar is possible because EM waves at some frequencies are reflected by certain materials, including metal surfaces and water vapor in clouds. A radar antenna can transmit and receive, and it is directional; that is, it transmits and receives signals in a narrow beam. For most purposes, the radar antenna sends out short pulses of EM waves and later receives the reflected pulses. The interval between the outgoing and incoming pulse is correlated with the beam direction to pinpoint the position of the reflecting objects, such as airplanes or cloud formations. The incoming reflected pulse is smaller than the outgoing pulse by a factor of millions and sometimes billions. To detect an incoming pulse in the presence of atmospheric noise, the power of the outgoing pulse is made as large as possible.

The duty factor (DF) of a transmitter is the ratio of the width of the transmitted pulse to the time between the leading edges of consecutive pulses. Hence, average power (P_{av}) is determined from peak power (P_{peak}) by

$$P_{av} = (DF)P_{peak}$$

In general, long-range radars have a larger transmitted pulse power and a longer waiting time between pulses (lower DF) than short-range radars. Long-range and short-range radars may thus be of comparable average transmitted power.

3.2 RF-Field Interactions with Biological Systems

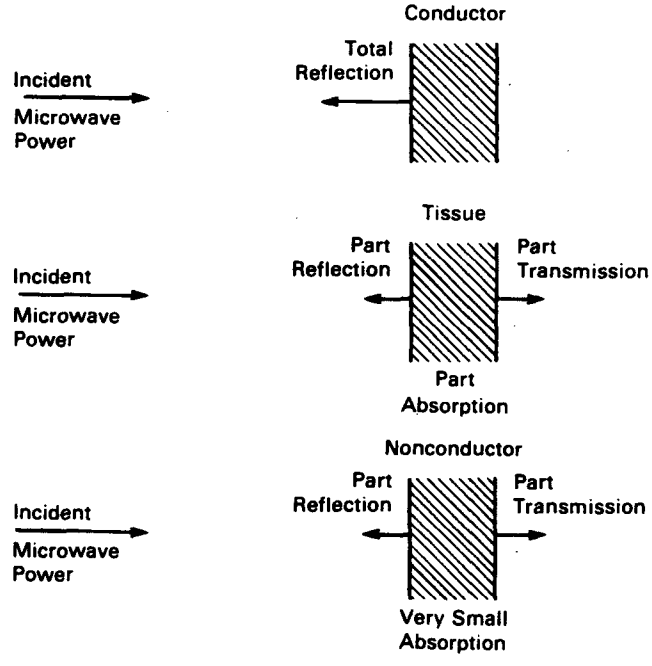
Claude M. Weil
James R. Rabinowitz

Consideration of the coupling of RF radiation into various biological objects (human, animal, etc.) is important to any study of the biological effects of RF-radiation exposure. From measurements and predictions of RF-energy absorption based on experimentation with laboratory animals, one can extrapolate data for estimating effects of RF radiation on humans. Furthermore, an adequate understanding of the interaction of RF radiation with humans has been crucial in determining exposure limits recommended in the American National Standards Institute (ANSI) C95.1 standard (ANSI 1982). Relating a health effect to a maximum permissible incident power density requires an in-depth understanding of the interaction of RF energy with humans.

3.2.1 Scattering and Absorption of Electromagnetic Waves

The interaction of EM waves with any irradiated object is a complex event that forms a large part of the study of electromagnetism. When an EM wave propagating in air impinges normal to the surface of any material with dielectric properties different from those of air, a reflected wave created at the air dielectric interface propagates in a direction opposite to that of the incident wave. This interaction is illustrated in Figure 3-3 for three materials of differing electrical properties. At the top of the figure, an EM wave is shown incident on a metallic conductor. In this case, virtually all the incident energy is reflected back to its source by the conductive plate. At the bottom of the figure, the energy is shown incident on a slab of low-loss, nonconductive material (dielectric insulator) where almost no energy is dissipated within the material. In that case part of the incident energy is transmitted through the slab, part is reflected back at the first air-dielectric interface, and a part is absorbed—a small amount, since this material exhibits almost no dielectric losses. An intermediate case, shown in the middle of Figure 3-3, is the interaction with a "complex" dielectric. Biological tissue falls between the conductor and the nonconductor in Figure 3-3; i.e., it exhibits values of relative permittivity (a measure of how strongly the material reflects energy) and conductivity (how well the material conducts electrically) that fall between the very high values for a metallic conductor and the near-zero values for a dielectric insulator. If the tissue slab is of sufficient thickness, all incident energy is reflected or absorbed and no energy is transmitted through the slab. The mechanism by which RF energy is absorbed or dissipated within the tissue slab is discussed in more detail below.

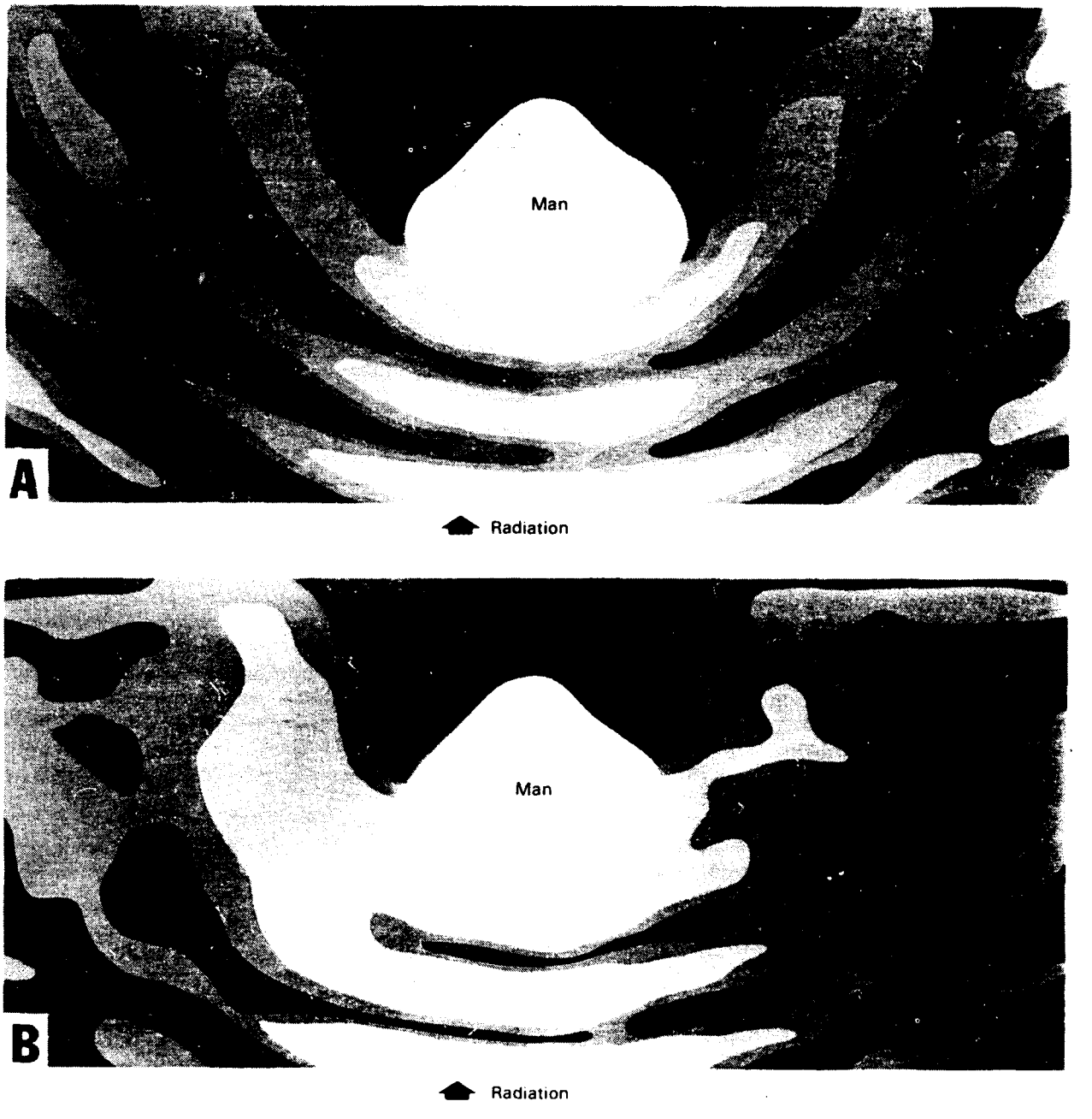
Figure 3-3. Interaction of RF radiation with electrical conductors, biological tissue, and electrical insulators (modified from Sher 1970).



In general, the reflected and transmitted waves that surround a dielectric nonplanar object irradiated by an incident RF wave together comprise what is termed the scattered field. Scattering by a dielectric object and any absorption within the object represent the two basic components of the EM interaction phenomenon. The degree to which any object interacts with an EM field when irradiated by a uniform plane wave is defined in terms of scattering and absorption cross sections. These cross sections represent the cross-sectional area in square meters of an equivalent flat plate placed normal to the direction of propagation that totally reflects (in the case of the scattering cross section) or totally absorbs (in the case of the absorption cross section) the radiant energy incident on the plate.

In general, the EM cross section is smaller than the geometric (optical) cross section that the object creates when illuminated by a distant light source. However, under certain conditions—termed resonance—when the wavelength of the incident radiation is comparable to the physical dimensions of the object, the scattering and absorption effects are enhanced, so that both respective cross sections exceed the geometric cross section. Resonance is a significant phenomenon that will be discussed in more detail in the following sections; it can be explained by the apparent ability of the resonant

Figure 3-4. Energy distribution in proximity to man at 1 GHz at the chest plane contour presentation; A) vertical, B) horizontal (Reno 1974).



object to intercept or "pull in" considerably more of the energy incident upon it relative to the optical case.

The terms "scattering coefficient" and "absorption coefficient," referring to measures of the efficiency with which an object scatters and absorbs energy, are defined as the ratio of the scattering to optical cross sections and the absorption to optical cross sections, respectively. Of the two basic measures of interaction, the absorption coefficient is considerably more prominent in the interaction of EM waves with biological bodies. Potentially adverse biological effects are related to the energy that the body is absorbing, not to what is scattered. Because absorption rate is related to internal field strength, it is conceivable that a biological effect could be related to the field strength within the tissue. For this reason, most of the remaining material in this section deals only with the absorptive aspect of the interaction phenomenon.

Some measurements have been made of the scattered fields that surround both human subjects and life-size phantom models exposed to incident microwave fields (Reno 1974). Although this work illustrates well the complex scattered fields surrounding the irradiated subject (see Figure 3-4), no attempts have yet been made to relate the field patterns to what the subject is absorbing. Although it is theoretically possible to determine the energy being absorbed and the internal distribution from measurements of the distribution of externally scattered fields, in practice this determination remains a difficult task and has not yet been attempted. Interest in this area is growing, as evidenced by a recent symposium (IEEE 1980) that addressed methods of obtaining high-resolution images of the internal dielectric structure of a biological target. The methods are based on techniques of probing the scattered fields created when the target is irradiated by an RF field. The scope for future work in this area appears large, particularly in diagnostic applications.

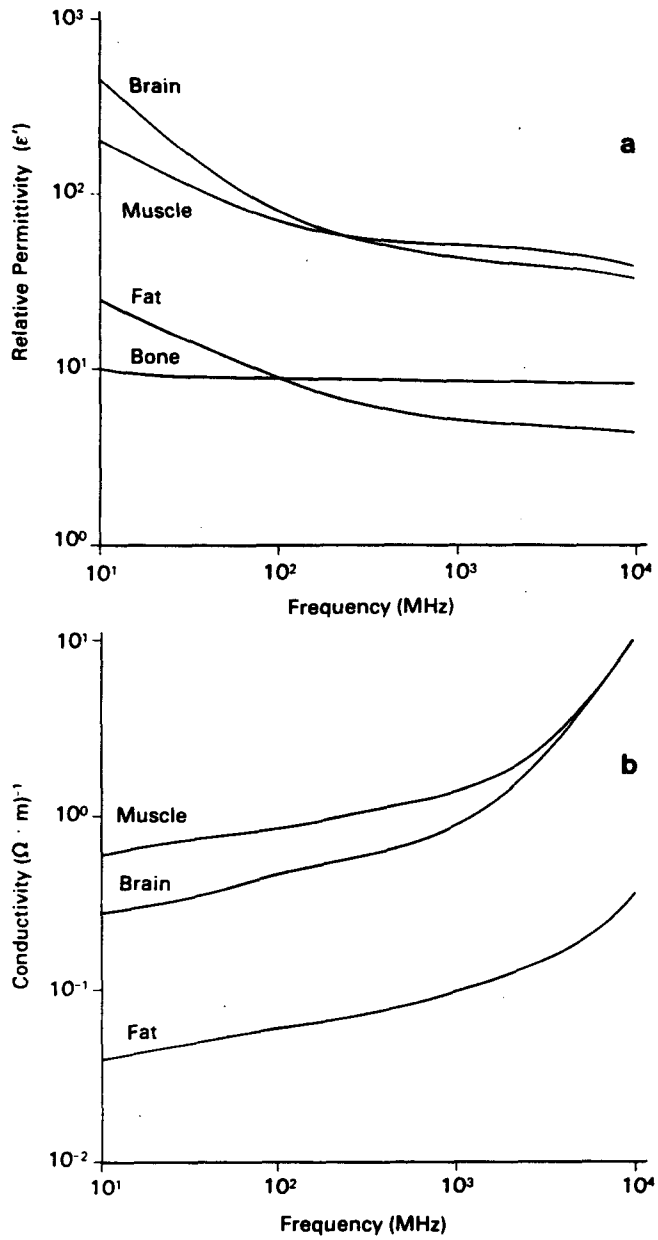
3.2.1.1 Factors Affecting the Absorption of RF Energy by an Irradiated Subject

The greater the efficiency of EM energy coupling into a biological subject, the greater the overall whole-body absorption. The factors that influence the degree of absorptive coupling are listed below and will be discussed in turn:

a. Dielectric composition of subject
b. Object size relative to wavelength of incident field
c. Shape or geometry of subject and its orientation with respect to polarization of incident field
d. Complexity of incident radiation

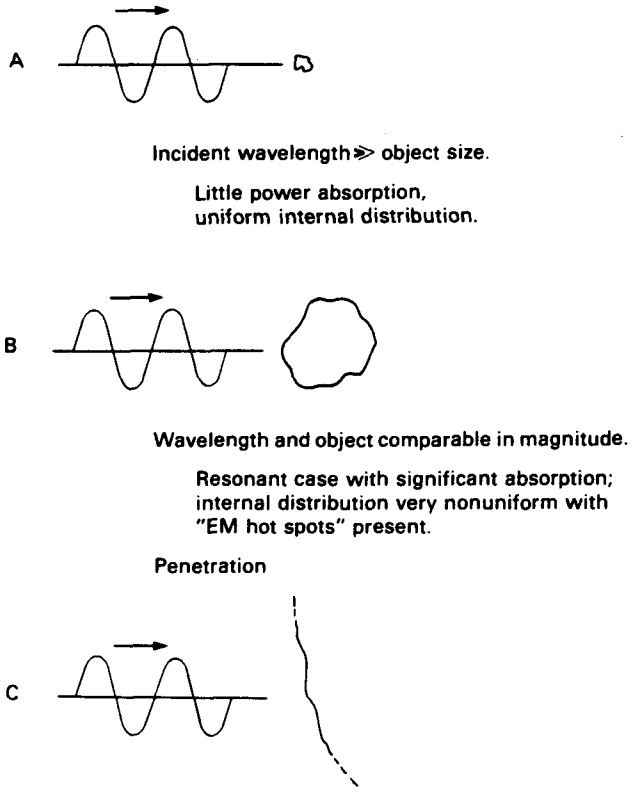
a. *Dielectric composition of subject*—As mentioned previously, absorptive coupling to the irradiated

Figure 3-5. Dielectric data for tissues in RF range 0.01 to 10 GHz. a: permittivity, b: conductivity.



subject can take place only if the subject is composed of dissipative dielectrics of finite conductivity value. The dielectric properties of all biological tissues fall into this category, primarily because their major constituent is water (average of 70 to 80 percent by mass), which contains electrically polarizable or dipolar molecules as well as free ions. The basic mechanism of dissipation of incident RF energy within these tissues is that 1) the free rotations induced in the dipolar water molecules by the externally

Figure 3-6. Illustration of object size vs. wavelength dependence. (Object is composed of tissue-like dispersive dielectric.)

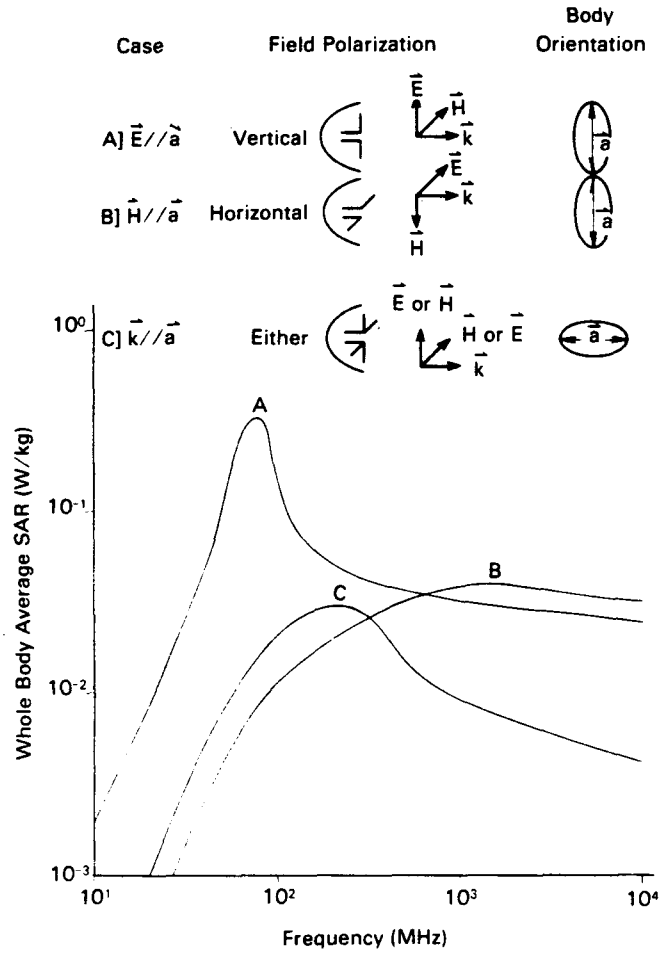


impressed electric field are damped out by collisions with surrounding molecules, and 2) conduction currents are induced within the tissue medium because of the presence of free ions. These phenomena are discussed extensively in Sec. 3.2.4, Mechanisms of RF Interaction with Biological Systems.

Over the past 40 years, many measurements have been made of the dielectric properties of biological tissues. These data have been collected in the *Radiofrequency Radiation Dosimetry Handbook* (Durney *et al.* 1978, Tables 9 and 10), as well as in a more recent paper by Stuchly and Stuchly (1980). The dielectric properties of biological tissues depend to a considerable extent on the water content of the tissue; i.e., tissues of high water content (blood, skin, muscle, brain, etc.) exhibit much higher permittivity (cf. Sec. 3.2.4.1) and conductivity values than do tissues of low water content (fat, bone, etc.). As a result, most incident RF energy tends to pass through the fatty surface tissues of the body and be deposited in the deeper tissues such as muscle and brain. Figure 3-5 illustrates some dielectric data for various types of tissues in the RF range 0.01 to 10 GHz. Note that the dielectric properties of tissue are not constant, but change with frequency. This is an example of what is termed a *dispersive dielectric*. For the case of biological tissues, the dispersive characteristic above 1 GHz is created by the Debye relaxation phenomenon in water molecules (discussed further in Sec. 3.2.4, Mechanisms of RF Interaction with Biological Systems). In part (b) of Figure 3-5, it is apparent that conductivity increases by almost an order of magnitude for all tissues in the frequency range from 1 to 10 GHz. Because of this fundamental dielectric property of tissue, microwaves in the frequency range above about 5 GHz become strongly attenuated in the increasingly lossy tissue medium. Consequently, microwave energy of such frequencies cannot penetrate deeply into body tissues and is deposited near the body surface. As a result of their poor penetration capability, microwaves in the centimetric wavelength region ($\leq$ 6 cm approximately) are less capable of inflicting potential damage on internal tissue than are those of longer wavelength ($\geq$ 10 cm).

b. *Object size relative to wavelength of incident field*—The second major factor on which energy absorption depends is the size of the irradiated object relative to the wavelength of the incident radiation. Figure 3-6 illustrates that when the wavelength is much greater than the object size (see case A at top of figure), the absorptive coupling is inefficient and little energy is deposited in the object. For this case, called the "subresonant" condition, values of the absorption coefficient lie in the range 0 to 0.5. Case B illustrates the resonant case, which occurs when the wavelength and object dimensions are comparable. For this case, the absorptive efficiency is markedly improved so that significantly more RF energy is coupled into the object and creates much greater deposition. Absorption coefficient values in the range 1.5 to 4 are obtained under resonant conditions. Furthermore, the incident energy penetrates into the object and is deposited internally in a characteristically nonuniform manner, with localized regions of enhanced energy deposition ("EM hot spots") at or near the object's center. These effects are discussed further in later sections of this document. In case C shown at the bottom of Figure 3-6, the wavelength is much shorter than the object size. This represents the quasi-optical case, where the absorptive efficiency is similar to that at optical wavelengths. The absorption coefficient

Figure 3-7. Calculated whole-body average SAR vs. frequency for three polarizations in a prolate spheroidal model of a human; incident power density = 1 mW/cm².



approaches 0.5 under these conditions, which gives intermediate absorption values that fall between those achieved with the conditions of cases A and B. Case C is also characterized by the inability of the incident energy to penetrate much beyond the surface of the object (note the dielectric factors discussed earlier); consequently, the energy coupled into the object under these conditions is confined to the object surface.

c. *Geometry and orientation of subject*—The third factor on which energy absorption depends is the shape of the object and its orientation with respect to the electric-field vector of the incident field. Most biological subjects used in studying the biological effects of RF radiation have a characteristic shape that is significantly elongated along one axis (similarly to humans). Although this observation may appear to be simplistic, it is of considerable significance in the discussion of the interaction of RF waves with such objects. When the electric-field vector of the incident radiation is oriented parallel to the major or long axis of the irradiated subject (e.g., a vertically polarized field that is incident on a standing human subject), then the subject absorbs as much as 10 times more energy at resonance than if the electric-field vector is oriented parallel to either of the two minor axes. Figure 3-7 shows absorption characteristics of a prolate spheroid model of an average human. The ordinate represents the whole-body-averaged specific absorption rate (SAR; see Sec. 3.2.2, RF Dosimetry Definitions, for discussion of units), and the abscissa represents frequency. From Figure 3-7, it is evident that when the electric-field vector is oriented parallel to the long axis of the prolate spheriod (electric-field polarization case), the absorption curve has a sharp peak at the resonant frequency of ~ 80 MHz. For the other orientations (H- and k-polarization cases), it is apparent that the absorption peak is much broader and occurs at somewhat higher frequencies. Furthermore, the resonant absorption values for the H and k cases are considerably lower than that for the E polarization case. These basic differences in absorption values hold true in both the subresonant and resonant regions, but not in the above-resonant (or quasi-optical) region, where absorption in the E- and H- polarization cases is approximately the same.

d. *Complexity of incident radiation*—The fourth and final factor on which RF-energy absorption depends involves the complexity of the incident radiation. Up to this point, most of the discussions of RF coupling in biological targets have assumed the simplest form of free-field exposure, which involves a unipath plane wave emanating from a distant source and incident on a subject suspended in space. (See Sec. 3.1 for definition of plane wave.) Virtually all the RF-radiation protection guides and standards in use throughout the world are based on this rather idealized assumption. Furthermore, most of the biological experimentation involving free-field exposures in anechoic chambers attempts to simulate this idealized concept. However, real-world, actual exposure conditions are far more complex.

One complicating circumstance arises in the near field. It is readily apparent that the most intense target exposure with the resulting greatest potential for injury would occur close to the RF-radiation source. However, in this near field, the plane-wave assumptions that are true for the far field of the source's radiating antenna no longer hold. As discussed in Sec. 3.1, the near field is characterized by complex EM field properties: the E and H fields are no longer in space quadrature (E and H vectors separated by 90°), and the value of the E/H ratio (termed the wave impedance) differs greatly from the constant value 377 Ω that characterizes the far field.

In the near field, the power density concept is meaningless in its usual sense. For an object placed in the near field of an antenna the interaction is exceedingly complex because every type of antenna possesses near-field characteristics that are unique to that type of radiator. Consequently, every phenomenon involving near-field exposures must be individually analyzed and characterized. Although it is possible to predict the spatial field distribution in the near field of an antenna, this distribution cannot be used as a basis for predicting the absorptive properties of an object placed in this field because the object will substantially alter that field distribution, as well as alter the radiating charateristics of the antenna itself. When an object is placed in the near field, it interferes with the basic purpose for which most antennas are designed: the efficient transfer of RF energy from source to far field. An object in the near field tends to load the antenna capacitively, which creates an impedance mismatch if the antenna was originally well matched to free space. As a result, the antenna reflects some of the transmitter energy output back to the source. In general, for an antenna that radiates well in free space, the closer the object is to the antenna, the greater is the mismatch condition, and the poorer is the transfer of radiated energy to the far field. Consequently, it is reasonable to conclude that whole-body-averaged SAR values in the near field do not greatly exceed those existing at the beginning of the far field, although there may be regions within the object of high energy deposition. The limited data available from EM models involving near-field exposure (see Sec. 3.2.3) seem to confirm this conclusion.

A secondary aspect of near-field exposures involves the unwanted exposure to leakage fields emanating from RF devices, such as microwave ovens, RF heat sealers, and diathermy units, which are not intended to radiate energy beyond their immediate surroundings. Such leakage fields are complex, and exposure invariably takes place in the near zone of the leakage source. Nevertheless, the limited data available from near-field exposures of EM models to leakage fields seem to show that whole-body-averaged SAR values are lower than might otherwise be expected because of the leakage-source and near-field interaction effects.

Another aspect of real-world exposures is the so-called multipath problem. People usually stand on the ground and are not suspended in space as in the idealized exposure concept; furthermore, they frequently stand close to buildings or to other reflective surfaces. This situation creates the multipath problem, in which a subject is exposed to scattered as well as to direct energy. Some of the effects are illustrated in Figure 3-8, which shows that there is a considerable enhancement in energy absorption occurring for various multipath conditions. These effects have been illustrated by means of the prolate-spheroid representation of a 70-kg man. To compute the SAR of man for the nonresonant condition, the optical cross-sectional area of the prolate spheroid is first multiplied by the power density (10 mW/cm^2), and then the resultant 38 W is divided by 70 kg to give an SAR of 0.54 W/kg. Note that when the model is in contact with a conducting ground plane, there is a doubling of the resonant whole-body energy absorption compared to that of free-space (Case II vs. Case I). Furthermore, if the model is standing at a distance in front of the reflecting plane that corresponds to an eighth of the incident wavelength (Case V, 0.125λ), there is a tenfold increase in absorption relative to that of free space. Even greater increases are recorded when the model is placed at a critical point inside a 90° corner reflector (Cases IV and VI). The enhanced absorption is a result of the reflector producing an enhanced field strength at the position of the object and not due to interaction between object and reflector.

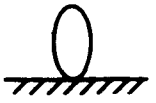
In addition to these multipath effects, enhancement of energy absorption can occur because of proximity effects that are created when two or more subjects are simultaneously irradiated. Gandhi *et al.* (1979) have found that when subjects are spaced by a critical separation of 0.65λ, a 50-percent enhancement in absorption can occur. Coupling of RF energy into biological systems is discussed further in the *Radiofrequency Radiation Dosimetry Handbook* (Durney *et al.* 1978, pp. 27-40).

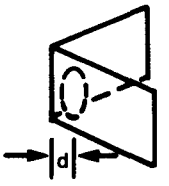
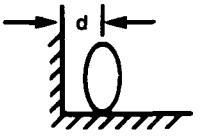
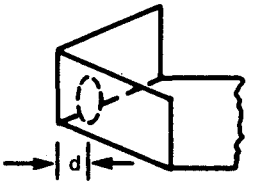
3.2.2 RF Dosimetry Definitions

Dosimetry is the measurement or estimation of RF energy or power deposition in an irradiated subject, including the internal distribution of that deposited energy. In recent years, the terminology describing dosimetric assessment has been evolving. Prior to the mid-seventies most investigators used terminology that appears to have been conveniently borrowed from the ionizing-radiation field and that employed the same cumulative dosage concept (Youmans and Ho 1975; Justesen 1975). Many investigators felt that this terminology was inappropriate for use with nonionizing or RF radiation because energy absorption in this case is not considered a cumulative phenomenon in a way that has been accepted for ionizing radiation (Susskind 1975; Guy 1975). Consequently, a new terminology was proposed that did not use the word "dose." The now widely accepted term "specific absorption rate" (SAR) was first reported in the literature by Johnson (1975); however, the term evolved from joint discussion by members of Scientific Committee 39 of the National Council on Radiation Protection and Measurement (NCRP). (This meeting, chaired by George Wilkening, took place at the Battelle Research Center in Seattle, Washington, on June 23, 1975, with members Frank Barnes, Curtis Johnson, Arthur Guy, Charles

Figure 3-8. Absorption dependence on various ground and multipath factors (Gandhi *et al.* 1977). Note that these data are based on experimental measurements.

Rate of Whole-Body Absorption (WBA) in Watts for a
Prolate Spheroid Model of Man (weight = 70 kg, height = 1.75 m) at 10 mW/cm^3

	WBA	SAR
Nonresonant conditions		
	38 W (no reflectance)	0.54 W/kg
	19 W (50% reflectance)	0.27 W/kg
Case I. At resonance for free space.		
		
	151 W	2.16 W/kg f = 62-68 MHz
Case II. At resonance for conditions of electrical contact with the ground plane.		
		
	2 x 151 = 302 W	4.31 W/kg f = 31-34 MHz
Case III. At resonance for placement in front of a flat reflector.		
		
	d = 0.125 λ	
	4.7 x 151 = 710 W	10.14 W/kg f = 62-68 MHz

	WBA	SAR
Case IV. At resonances for placement in a 90° corner reflector.		
		
	d = 1.5λ	
	27 x 151 = 4077 W	58.24 W/kg f = 62-68 MHz
Case V. At resonance in electrical contact with ground plane, in front of a flat reflector.		
		
	d = 0.125 λ	
	2 x 710 = 1420 W	20.28 W/kg f = 31-34 MHz
Case VI. At resonance in electrical contact with ground plane in a 90° corner reflector.		
		
	d = 1.5 λ	
	2 x 4077 = 8154 W	116.48 W/kg f = 31-34 MHz

Susskind, Saul Rosenthal, Karl Illinger, and Ronald Bowman attending. The committee members agreed to publicize the new term as much as possible in their publications to promote wide acceptance. Members Johnson, Susskind, and Guy published comments concerning SAR in 1975.) NCRP (1981) has formally recommended adoption of the term SAR in RF dosimetry. NCRP has also endorsed use of the term "specific absorption" (SA) for the absorbed energy per unit mass (referred to earlier as "dose").

Table 3-2 lists the various RF dosimetric quantities in general use, together with their definitions and units. Although the terms (particularly SA and SAR) for some of these quantities have now gained widespread acceptance, other terms, particularly dealing with the volume-normalized power or energy absorption, have only recently been proposed and have not yet gained wide acceptance.

The mass-normalized and volume-normalized absorption rates are directly related through the localized or whole-body-averaged tissue mass density ρ, that is, absorption-rate density, ARD = ρ(SAR), where ρ is in kilograms per cubic meter. Most biological tissues are composed largely of water, so that it is reasonable to assume a unity tissue density value. In this case, the two quantities are numerically equivalent. This approach has been adopted by many investigators engaged in predictive EM modeling (see Sec. 3.2.3, Analytical and Numerical RF-Electromagnetic Interaction Models), where the model is composed of some homogeneous tissue with average physical and dielectric characteristics that are representative of the various tissues of the body being modeled. For example, all the SAR data given in the familiar *Radiofrequency Radiation Dosimetry Handbook* were derived this way; the assumption of a unity average tissue density is specifically stated (Durney *et al.* 1978).

A subset of two additional values exists for both the mass-normalized and volume-normalized quantities listed in Table 3-2: (a) the whole-body-averaged value, which represents the overall absorption or absorption rate divided by the total mass or volume of the subject; and (b) the localized value, which describes the absorption or absorption rate in an incrementally small mass or volume at some given point within the subject. The localized ARD is mathematically defined by the expression σE^2, where σ is the local tissue conductivity and E represents the root-mean-square value of local internal E-field strength.

So far, there has been no discussion of radiant exposure rate assessment, i.e., measurements of the incident field strength or power density. Some workers unfortunately continue to include such assessment under the general heading of "dosimetry"—incorrectly, because the exposure rate is not an assessment of dose even though the two may be related. The correct terminology for incident power-density assessment is "densitometry," which should not be confounded with dosimetry. Experimental methods used in densitometry are discussed in Sec. 3.3.3, Densitometric Instrumentation. The various experimental techniques that have been developed for whole-body, as well as localized or regional dosimetry, are discussed in detail in Sec. 3.4, Experimental Methods.

3.2.3 Analytical and Numerical RF-Electromagnetic Interaction Models

Much of the discussion concerning the qualitative nature of EM interaction with biological targets contained in Sec. 3.2.1 is based on data derived from mathematical EM models in conjunction with limited experimental confirmation. Predictive physical modeling, used extensively in this research area by many workers during the past 25 years, has contributed significantly toward an improved understanding of the nature of EM field interactions with biological subjects and their absorption characteristics. In these models an object of simplified geometry, composed of dissipative dielectric materials that closely simulate the spatially averaged electrical properties of biological tissues, is irradiated by some form of noncomplex incident field such as a unipath plane wave. Solutions to the problem setup in the model can then be derived by several well-established analytical and numerical techniques. Actual computations are performed on high-speed digital computers, and the outputs represent whole-body-averaged and localized ARD, absorption cross sections, and absorption coefficients.

Besides the improved understanding of the EM interaction process already mentioned, modeling has proved to be important for two further basic reasons. First, mathematical modeling and experimental measurements on scaled-down doll and figurine phantoms have so far provided us with the only practical method of gaining qualitative and quantitative insight into the absorption characteristics of the human body under various conditions of irradiation. Any attempt to make absorption measurements on actual human subjects has so far proven impractical because of technical difficulties, high costs, and ethical considerations. Reasonably accurate quantitative data on human-absorption characteristics are necessary to determine the objective exposure limits for RF radiation. The reasons are discussed below.

The 1974 ANSI-recommended protection guide (ANSI 1974) is based on an allowable exogenous heat load due to RF-energy absorption and conversion that cannot exceed the basic metabolic rate (BMR) in an adult man ($\sim$ 70 to 100 W). For a 50th percentile standard-size man weighing 70 kg, this load

Table 3-2. Proposed System of RF Dosimetric Quantities, Definitions, and Units*

Quantity and Definitions	SI Unit Name	SI Unit Symbol	Other Units Used
Whole-Body Absorption (formerly integral dose) The total EM energy absorbed by the irradiated subject	joule	J	millijoules (mJ) (1 mJ = 10^{-3} J) calories (1 cal = 4.187 J)
Whole-Body Absorption Rate (formerly integral dose rate) The time rate of total EM energy or total power absorption by the irradiated subject	watts	W	Milliwatts (mW) (1 mW = 10^{-3} W) cal/min
Specific Absorption (formerly dose) The mass-normalized EM energy absorbed by the irradiated subject	joules per kilogram	J/kg	mJ/g cal/g
Specific Absorption Rate (formerly dose rate) The mass-normalized rate of energy or mass-normalized power absorbed by the irradiated subject	watts per kilogram	W/kg	mW/g cal/g-min
Absorption Density (also absorbed energy density or energy density, dissipated) The volume-normalized EM energy absorbed by the irradiated subject	joules per cubic meter	J/m^3	mJ/cm^3
Absorption Rate Density (also absorbed power density, density of absorbed power, heating potential, etc.) The volume-normalized rate of EM energy or volume-normalized power absorbed by the irradiated subject	watts per cubic meter	W/m^3	mW/cm^3 (1 mW/cm^3 = 10^3 W/m^3)

*Throughout this table, "absorption" refers to RF-energy absorption.

corresponds to a whole-body-averaged SAR of ~ 1 to 1.4 W/kg. To determine the power density level of incident radiation that will create this exogenous heat load in man, a detailed knowledge of human RF-absorption characteristics is required. At the time the first RF-radiation protection guide was proposed in the early 1950s, virtually no data existed on the RF-absorption characteristics of humans; the assumption had to be made that the EM absorption cross section for humans was equivalent to man's geometric cross section, which is ~ 1 m^2 (i.e., a unity absorption coefficient was assumed). From this calculation came the well-known exposure limit of 10 mW/cm^2. During the past 10 years or so, a considerable accumulation of data based largely on human interaction modeling has been developed (discussed later in this section). These data showed that under resonant conditions, the RF-absorption cross section of humans can be 4 to 8 times greater than the geometric cross section. Thus, at resonance, the RF-absorption rate for humans can potentially exceed the BMR by this factor when exposure is to incident radiation levels of 10 mW/cm^2. Such a situation clearly constitutes an excessive thermal burden for exposures of indefinite duration. Thus, EM modeling has played a significant role in demonstrating that, under certain conditions, the originally recommended exposure limit is potentially unsafe, and in providing an objective basis for the revision of that guideline.

The second reason for the importance of EM modeling is that it provides us with a method of extrapolating absorption data from animal experiments for application to humans. From the prolate spheroid representation for humans and animals, a considerable amount of data has been compiled on whole-body-averaged SAR vs. frequency characteristics for several species. These data are given in the *Radiofrequency Radiation Dosimetry Handbook* (Durney *et al.* 1978); highlights of this material are presented in Table 3-3, which shows the resonant frequency range (long axis oriented parallel to E field) and the whole-body-averaged SAR at resonance, normalized to an incident field level of 1 mW/cm^2 for five different species, including humans. The data given in Table 3-3 enable a researcher readily to determine for a particular animal species the resonance frequency range to be used during experimentation. For example, to simulate human resonance in adult rats, exposure would have to be in the frequency range of 600 to 700 MHz. This is an example of "frequency scaling," or adjusting the frequency at which an experimental animal is

exposed in order to approximate certain given conditions of human exposure. In addition, differences in the whole-body-averaged SAR between the two species must be considered; from the last column of Table 3-3, it is evident that, at resonance, the whole-body SAR for the rat is 3 times that of a human. Thus, if a certain SAR value is obtained in a rat when exposed at a 10-mW/cm^2 level, roughly 3 times that level, or 30 mW/cm^2, is needed to obtain the same SAR value in humans (resonant condition for both).

The data shown in Table 3-3 can be likewise used to determine whether a given exposure frequency falls in, above, or below the resonance range for humans. As was discussed earlier, these three categories lead to fundamental differences in absorption as well as patterns of internal energy deposition. Most likely a corresponding difference in biological effects will be seen in several frequency ranges, with the resonant range representing the potentially most hazardous condition because of the high absorption efficiency and highly nonuniform internal deposition of energy. As already emphasized, proper simulation of a given human exposure scenario by means of experimental animals requires the use of (1) frequency scaling to ensure that the type of interaction taking place is roughly comparable (i.e., subresonant, resonant, or supraresonant); and (2) appropriate adjustment of the incident exposure level to obtain a specified whole-body-averaged SAR or, where possible, a given localized SAR in some specified target organ. To check for the possibility of any effects that might be specific to a particular frequency to which humans are being exposed, animals must necessarily be exposed to that same frequency. Given such an experiment, the use of frequency scaling is obviously inappropriate.

3.2.3.1 Model Details

Gandhi (1980) and Durney (1980) published excellent reviews on EM modeling, summarizing most of the major research contributions to 1980 and detailing the status of the EM modeling field at that time. The material that follows does not duplicate these reviews, but instead traces the historical development of EM models with emphasis on the increasing complexity of such models and their application. Only a few relevant publications in the field are cited; the reader is referred to Gandhi's and Durney's reviews for more complete details, as well as to the *Radiofrequency Radiation Dosimetry Handbook* (Durney *et al.* 1980, pp. 42-44), which contains a comprehensive literature survey of all theoretical and experimental modeling work performed to 1979. The reader is also referred to the original publications for further details of the mathematical techniques used to solve the various problems that are discussed below.

Table 3-3. Range of Resonant Frequencies of Man and Animals Irradiated by Plane Waves in Free Space at 1 mW/cm^2 with Long Axis Parallel to the Electric Field*

Species	Average Weight (kg)	Average Length (m)	Resonant Frequency (MHz)	RMR (W/kg)	Average SAR (W/kg)
Man (av)	70	1.75	70-80	1.26	0.25
Woman (av)	61	1.61	80-90	1.15	0.25
Child (10 years old)	32.2	1.38	90-100	2.00	0.35
Rhesus monkey (seated)	3.5	0.04	300-350	2.36	0.30
Dog (beagle)	13.5	0.06	200-250	1.72	0.16
Guinea pig	0.58	0.02	550-600	3.83	0.55
Rat (medium)	0.32	0.02	600-700	4.8	0.75
Mouse	0.02	0.007	2400-2600	6.5	0.72

*Data derived from Durney *et al.* (1978).

Planar and spherical models—The earliest model considered involved the one-dimensional solution to the planar tissue slab irradiated by a plane wave (Schwan and Li 1956). The slab is infinitely wide and can contain several layers of various tissues. Although the solution to this problem is straightforward, the model is restricted in its application because it does not account for the obvious closed-form shape of all human and infrahuman bodies. This particular model is valid only when the wavelength is small compared to the system size, as depicted earlier in Figure 3-6, case C; for human irradiation, such wavelengths correspond to frequencies above approximately 3 GHz. The concept of "penetration depth" has been developed on the basis of this one-dimensional model. The penetration depth is the depth within the tissue slab at which the RF power has been attenuated to a value of $1/e^2$ and is shown as a function of frequency in Figure 3-9. Strictly speaking, this concept applies only to this particular planar model; however, if prudently applied the concept has an approximate qualitative meaning for other configurations. It is unfortunate that the concept has been extensively borrowed and is often inappropriately used in discussions of RF absorption in nonplanar models where the wavelength is either longer than or comparable to the object size. The penetration depth concept can be accurately applied only when the wavelength is small compared to the object size.

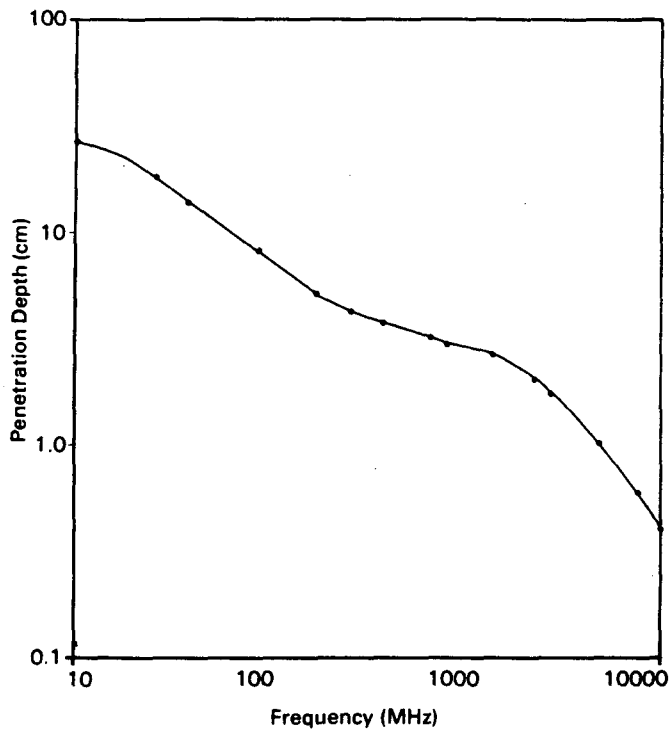
The next level of complexity involves two-dimensional solutions of the infinitely long cylinder with circular, elliptical, and arbitrary cross sections; some of these models are of homogeneous tissue and others are multilayered (Ho 1975). These models are primarily intended to simulate RF heating in human limbs under conditions of plane-wave irradiation from a rectangular applicator in contact with the cylindrical model, which is of particular interest to diathermy practitioners. Ruppin (1979) examined a lossy-dielectric cylinder model placed in front of a perfectly conducting plane (i.e., a multipath configuration). His data show both enhancement and reduction of

average SAR relative to the isolated cylinder, depending on the conditions of irradiation. Cylindrical models were also used extensively for SAR calculations in the second edition of the *Radiofrequency Radiation Dosimetry Handbook* (Durney *et al.* 1978).

The first attempts at three-dimensional solutions involved homogeneous spheres of tissue-equivalent dielectrics. Although it is only a poor approximation to the actual shape and heterogeneous dielectric composition of humans and experimental animals, the sphere model has been used extensively because of the ready availability of solutions based on the classical Mei theory involving spherical wave functions (Stratton 1941). These methods can be readily programmed on high-speed machines that yield data on the EM absorption cross section and on the distribution of localized ARD for homogeneous spheres (Kritikos and Schwan 1975). (Some approximations made by Kritikos and Schwan [1975] can be used in the subresonance or Rayleigh region and the supra-resonance or quasi-optical region, which greatly simplifies these computations.) This work demonstrated that a highly nonuniform absorption distribution is obtained under resonant conditions, including the formation of relatively intense "EM hot spots" near the sphere's center (Figure 3-10). Other workers (Weil 1975) have used a multilayered spherical model that consists of several concentric layers of different tissues representing an idealized model of an adult, child, or monkey head exposed to plane-wave radiation. However, this concept has obvious limitations because the spherical model is spatially isolated rather than attached by the neck to the body's trunk. Results for the multilayered sphere were similar to those obtained for the homogeneous sphere with the exception that, in the supraresonance region, enhanced absorption was noted in the multilayered model. This enhancement is caused by the presence of the surrounding layers of skin and fat, which appear to provide an impedance transformation mechanism by which energy transfer into the sphere is increased. A recent paper by Barber *et al.* (1979) has shown that a planar model can accurately predict this enhancement effect for any three-dimensional nonplanar shape, and that the layering enhancement factor can be applied to any nonlayered object, such as a human model, to predict the absorption characteristics of the layered object.

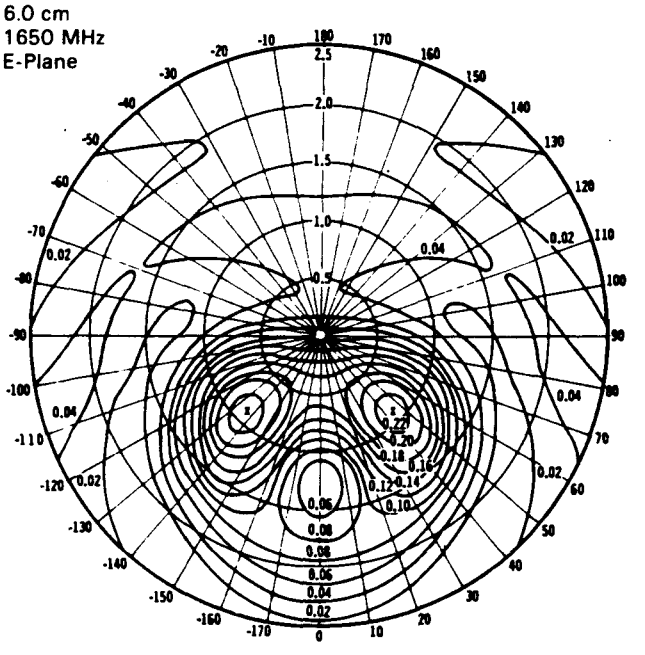
The effects of altering irradiation from plane wave to near field on the absorption characteristics of multilayered sphere models were investigated by Hizal and Baykal (1978). They found that EM hot spots continue to occur when the model is excited near resonance in the near field of a loop antenna, but not when similarly excited by a dipole antenna.

Figure 3-9. Penetration depth as a function of frequency (data from Table 3, Durney *et al.* 1978).



Prolate spheroidal and ellipsoidal models—Since prolate spheroids and ellipsoids are much better approximations to actual human and animal shapes, use of these models was a logical next step to solving this problem. Although one can in principle obtain solutions to the prolate spheroid and ellipsoid problem in spheroidal and ellipsoidal wave functions in the manner already accomplished for the sphere, in practice this approach has not been possible because of many mathematical difficulties. Consequently, workers have resorted to using several different approximation techniques, further details of which may be found in Durney's review (1980). Such methods have provided accurate data on absorption in the subresonant and near-resonant region, as well as in the supraresonant or quasi-optical region. These data have been compiled in the *Radiofrequency Radiation Dosimetry Handbook* (Durney *et al.* 1978, pp. 75-106) in whole-body-averaged SAR vs. frequency plots for many animal species. However, under some conditions, there is a gap at the resonant and immediate post-resonant regions, where these approximations no longer hold. Using approximate data derived from antenna theory and experimental observations, investigators have bridged this gap with the aid of curve-fitting techniques. This approach is illustrated in Figure 3-11, which shows SAR data for a prolate spheroidal model of man for the three basic orientations of the model's long axis relative to the E,

Figure 3-10. ARD distribution in core of 6-cm radius multilayered sphere at 1650 MHz (Weil 1975).



H, and k vectors. Note the strong orientation effect discussed earlier. Durney *et al.* (1978, 1979) have also developed a useful empirical formulation that describes the E-field polarization curve shown in Figure 3-11. It can be programmed on a hand calculator and yields reasonably accurate SAR data for a prolate spheroidal model of any size of eccentricity.

As discussed earlier, an isolated model, regardless of shape, suspended in space is an inappropriate representation of the real-life conditions under which humans are exposed. A prolate spheroidal model in contact with or in close proximity to a conductive ground plane is an obvious improvement over the isolated model. Iskander *et al.* (1979) have analyzed such a model by both antenna and circuit theory. In this model, the finite separation between feet and ground created by the usual presence of footwear can be accounted for by a lossy capacitor in the equivalent electrical circuit of the prolate spheroid. From Iskander's data (Figure 3-12), it is apparent that the primary effect of the ground plane is to shift the SAR curve for the isolated model to the left with only a slight evident increase in peak SAR. The resonant frequency of the prolate spheroidal model of man is shifted from ~ 75 MHz to 45 MHz when the model is in perfect contact with a conducting ground plane; the intermediate case shown, in which resonance occurs at 55 MHz, represents imperfect contact between model and ground plane due to a 3-cm lossy gap. The latter case is probably the most realistic of the three considered. Iskander *et al.* also concluded that when the model is separated from the ground plane by a gap of 7.5 cm or more, the whole-body SAR values are essentially the same as those for the isolated model.

It is evident from oral presentations at recent (1978-1980) scientific meetings that much effort is being devoted to analyses of the absorption of prolate spheroid and other models in the near field of an antenna. Iskander *et al.* (1980) have studied such a problem for a prolate spheroid model of man in the near field of a short electric dipole at 27 MHz. They found that average SAR values in the near field tend to oscillate about the constant value predicted for plane-wave irradiation. There are also significant alterations in the internal distribution of deposited energy in the near field.

As discussed previously, the data developed on prolate spheroidal and ellipsoidal models have played an important role in extrapolating RF absorption data from lower animals to man. Yet these data have limitations: the solutions are not exact but are approximations, and yield data that are accurate enough (± 10 percent) for most practical applications. Furthermore, with the exception of the subresonant region (long-wavelength analysis, Figure 3-11), existing solutions provide data on only the whole-body absorption characteristics of this model. No data are yet available on the three-dimensional ARD distribution and EM "hot spot" formation potential in the resonant and immediate supraresonant region. Such data would be of potential value to those engaged in experimentation with rodents because of the close similarity between the rodent shape and the prolate spheroid.

Human block models—Although prolate spheroidal and ellipsoidal models are reasonably accurate representations of many laboratory animals, particularly rodents, that is not true of the primates, including man, because the appendages (head, arms, and legs) are much larger and more significant. The importance of these appendages is underscored by experimentation on saline-filled dolls and scaled-down human phantoms (Guy *et al.* 1977), which showed relatively intense localized absorption in the ankles, legs, and neck. Since it was impossible to confirm the localized effects with the prolate spheroidal model, attempts were made to develop a more realistic human model in which numerous cubical cells form a so-called block model of man (Figure 3-13). The EM solution to this type of sophisticated problem is realized through the solution of a large system of simultaneous equations and matrix inversion or iterative techniques. Further mathematical details are given in Durney's review (1980). Such solutions can be obtained only by use of dedicated large-scale computing facilities with expensive memory capability. Furthermore, because of finite limits in the average memory capacity of all but the largest computers, the number of cubical cells

Figure 3-11. **Curve fitting of SAR data for a prolate spheroidal model of man for the three basic orientations of the model's long axis relative to the E, H, and k vectors of an incident plane wave (1 mW/cm² power density). Taken from Durney *et al.* (1978).**

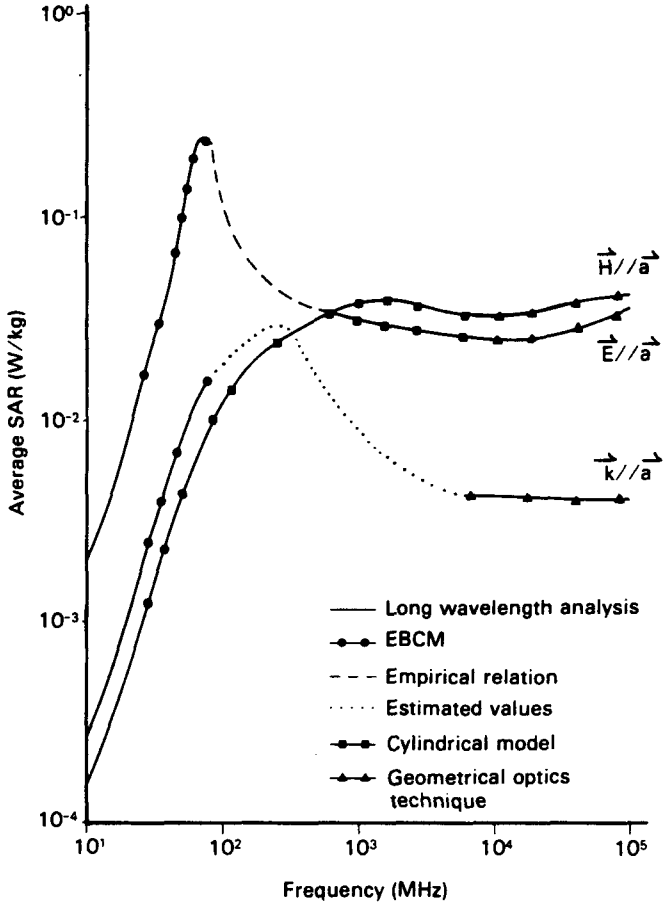
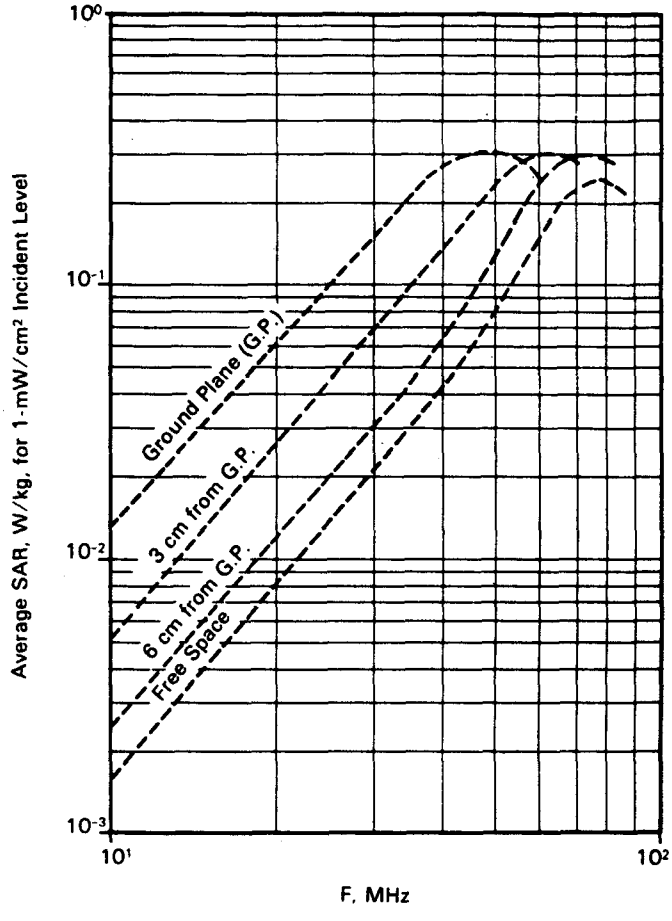


Figure 3-12. **Effect of a capacitive gap on average SAR between the man model and the ground plane (Iskander *et al.* 1979).**



that can be used to make up the model is limited. The accuracy and resolution of the solutions depend on cell size. In the work of Chen and Guru (1977), a maximum of 108 cells was used, whereas Hagmann *et al.* (1979a) used 180 cells. These limits inevitably reduce the spatial resolution with which the localized absorption distribution can be determined in the model, and they place an upper limit on the frequency range over which solutions are valid. (This range does include the resonant and immediate supraresonant region.) Since this technique readily allows for differences in the dielectric properties of individual cells in the models, it is possible to approximate the inhomogeneous tissue properties of the human body, but there is a limit to how finely such inhomogeneities can be modeled.

Figure 3-14 shows some data obtained for the human block model (Figure 3-13) when it stands on a ground plane and is irradiated by a vertically polarized plane wave. The curve labeled "whole body" gives the whole-body-averaged SAR throughout the model, which agrees closely with that obtained for the equivalent prolate spheroidal model in contact with a ground plane; whole-body resonance also occurs at ~45 MHz. Two significant conclusions may be drawn from these data: (a) At whole-body resonance, the localized SAR in the legs is about five times that of the whole-body average, which indicates the potential for relatively intense absorption in the legs; and (b) part-body resonances exist for the arms and for the head at frequencies of ~ 150 and 375 MHz, respectively. Subresonance data reported by Guy *et al.* (1976) show local SARs 26 times that of the whole-body average. Localized SAR values for the neck are seen to be relatively high throughout the frequency range 100 to 400 MHz. The significance of the head-resonance effect has been emphasized by Hagmann *et al.* (1979b), who modeled the head and neck with much improved resolution. In this study, the detailed head is attached to the same torso model used earlier (Figure 3-13), so that the head is not isolated as in previous studies involving inhomogeneous spherical models (Weil 1975) and block models of isolated

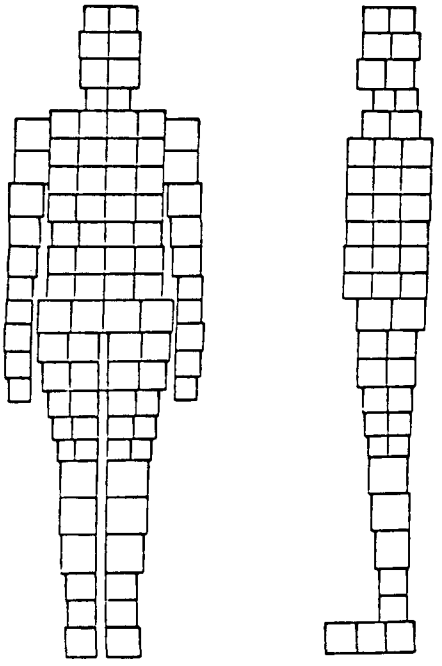
human and infrahuman heads (Rukspollmuang and Chen 1979). The Hagmann *et al.* data show strong localized absorption at the front and back of the neck and in the center-based region of the skull; localized SAR values are two and four times the whole-body average.

RF absorption in block models when irradiated under near-field conditions is being studied by some workers. Chatterjee *et al.* (1980) reported a study involving the near-field interaction of the human block model (Figure 3-13) with the measured leakage-field distribution of an industrial RF heat sealer operating at 27 MHz. Their data show that averaged and localized SAR values are much lower for near-field exposure than is the case for plane-wave exposure at equivalent power density levels.

3.2.3.2 Accuracy

As discussed already, this document and the 1982 ANSI guideline (ANSI 1982) recommend frequency-dependent exposure limits that have been derived mostly from the EM modeling data just described. The validity of this approach therefore depends strongly on the accuracy of these data. One may conclude that the accuracy of the whole-body-averaged absorption data is good (certainly within ± 10 percent). The good agreement obtained between data for the human prolate spheroidal and block models appears to support this contention. However, the accuracy of the localized absorption data is probably inferior. This is particularly true of the block models where accuracy is probably no better than ± 50 percent, because of the limitations on numbers of blocks available. On the other hand, localized absorption data for the spherical model, as well as those available for the prolate spheroid, are more accurate, since they were derived by more rigorous techniques.

Figure 3-13. A realistic block model of man (Hagmann *et al.* 1979a).



3.2.3.3 Unresolved Issues

The need for additional modeling has been discussed by Durney (1980). Improvements and refinements in existing block models are needed, especially in spatial resolution and accuracy; the same is also true in modeling tissue inhomogeneities. In coming years, a new generation of "superpower" computers with greatly enhanced computational speeds—an order-of-magnitude increase over existing machines—will undoubtedly become available for scientific studies. Such computers will almost certainly be used to refine existing EM absorption models, particularly in spatial resolution problems and in solving more complex problems that hitherto have not been attempted because of computer limitations.

As Durney (1980) emphasized, there is still a need for more solutions to near-field interaction problems, since the near field more frequently represents the real-life situation to which people are exposed. Though models involving near-field irradiation are considerably more complex than are those for the far field (plane wave), it should be possible to attempt the solutions of these based on our existing knowledge of plane-wave solutions.

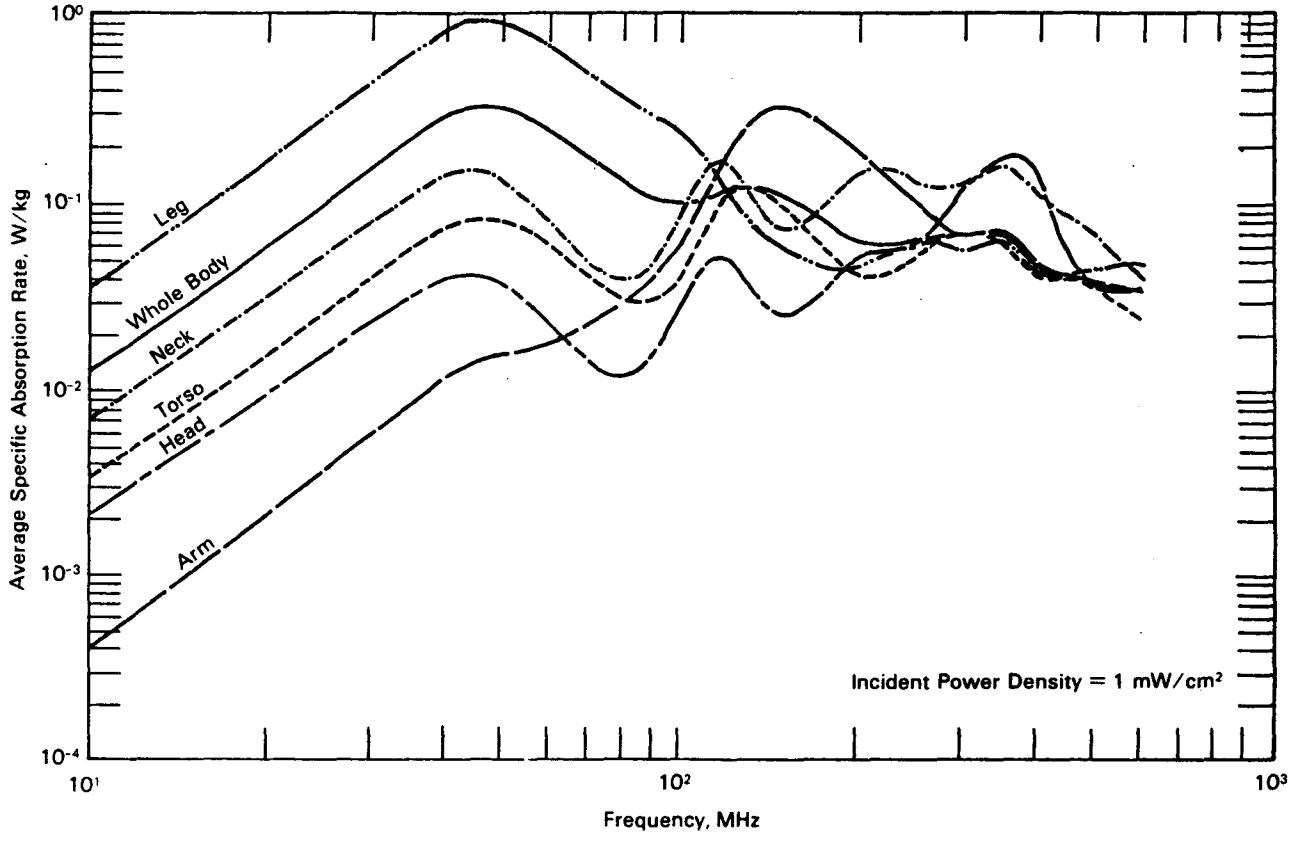
3.2.4 Mechanisms of RF Interaction with Biological Systems

Biophysical models that relate molecular structure to the interaction of RF radiation with biological systems provide a base for understanding the potential hazards of this type of RF radiation and for designing relevant experiments. The purpose of this section is to review these interactions and, where possible, to discuss the changes in structure and biological function that may result.

3.2.4.1 Complex Relative Permittivity

The molecular-level interactions may be averaged over a macroscopic biological sample and characterized by an average interaction parameter called the complex relative permittivity (ε^*) of the sample. This interaction parameter facilitates discussion of the effects of a biological sample on thermodynamic properties. It is a measure of the capacity of the charge distribution within the sample to adjust to a change in an applied electric field. This measure is composed of two parts, the real component of the complex permittivity (ε') and the imaginary component of the complex permittivity ($\varepsilon'' = \sigma/\omega\varepsilon_o$). The real component is a measure of the energy stored in the charge distribution of the sample by the interaction with the field. The imaginary component is related to

Figure 3-14. Absorption for man block model standing on ground plane (Gandhi *et al.* 1979).



the energy dissipated by the field in the sample. Initially, the dissipated energy may be restricted to just a few molecular modes within the sample. Eventually, the dissipated energy will be thermalized, but temperature gradients may persist within the sample if the rate of energy dissipation is a function of position, due to the geometry of the sample or to field gradients or differences in ε'' within the system. Finally, after the RF-radiation exposure has ceased, the dissipated energy will be equally distributed throughout the various modes of the sample and will result in either a change in sample temperature or a transfer of thermal energy from the sample as well as possible chemical and structural changes.

The ε^* of many biological tissues has been measured by several investigators. Some excellent reviews are available (Schwan 1957; Johnson and Guy 1972; Durney *et al.* 1978, 1980; Stuchly and Stuchly 1980; and Schwan and Foster 1980). Complex relative permittivity is a function of frequency over our region of interest.

Table 3-4 shows the values of ε' and ε'' (abstracted from Durney *et al.* 1978, Schwan and Foster 1980; Stuchly and Stuchly 1980). The dielectric properties of muscle tissue have been used to characterize the dielectric properties of all biological tissues with a high water content (Schwan 1957; Schwan and Foster 1980). This characterization also serves as an illustration of some of the underlying phenomena responsible for ε^*. Figure 3-15 shows the ε' of muscle as a function of frequency.

It can be seen in Table 3-4 that in the region between 0.5 MHz (the lower end of the range of interest) and ~ 50 MHz, the complex permittivity of muscle decreases by two orders of magnitude. However, between 100 MHz and 10 GHz it decreases by < 50 percent; and again, at frequencies above ~ 10 GHz, but still within the range of interest, the real component of complex permittivity decreases rapidly.

The imaginary component of the complex permittivity (ε'') has two components—one due to the movement of free charges, and the other to the orientation of either permanent dipoles or dipoles resulting from the interaction of the field with polarizable microscopic structures. The former component is proportional to the inverse of the applied RF-radiation frequency; energy absorbed this way acts directly to heat the sample. The modes of absorption of the latter component relate to the specific structure of biological molecules and molecular complexes, and this component has a maximum where the real

component of the complex permittivity ε' is changing most rapidly with respect to frequency.

Frequency regions with rapidly changing dielectric parameters indicate that a particular component of the system, or a particular type of response to the field, is reaching the limit of its capacity to respond (i.e., at higher frequencies the field is changing too rapidly for a particular component to respond). It has been suggested that the rapid change in the region below 50 MHz results from polarization effects in which cellular membranes are charged by the surrounding electrolytes (Schwan and Foster 1980). Another response that is limited to this low-frequency range is the rotation of large dipolar macromolecules or molecular complexes orienting with the changing field (Takashïma and Minikata 1975). The dielectric response below 50 MHz may result from more than one mechanism. The response above ~ 5 GHz results from the rotation of water molecules in the biological systems, and it is similar to the response seen in pure water. It has been postulated that a small decrease in ε' observed near 1 GHz results from rotation of water molecules constrained by their interaction with large molecules and molecular complexes (Schwan 1965; Grant *et al.* 1968) and, therefore, these water molecules cannot respond to the field at higher frequencies.

The general features of ε^* of biological tissues can be explained in terms of the major molecular and structural components of the tissues. However, biological systems are inhomogeneous and inherently complex at the molecular level, and interaction with a minor molecular component may have negligible influence on the dielectric parameters of tissue (an average property of a macroscopic volume) but may interfere with the capacity of that minor component to perform its biological function. Therefore, it is useful to discuss the specific mechanisms for the absorption of RF radiation at the molecular level. Furthermore, since the mechanisms are similar for the major components, this discussion also provides a more detailed explanation of the interactions responsible for the complex relative permittivity ε^*.

3.2.4.2 Mechanisms for RF-Radiation Absorption at the Molecular Level

Table 3-5 presents information on the energy of an RF beam relevant to molecular level interactions. The binding energy of a single electron in a molecule is typically of the order of tens of electron volts, whereas excitations of electrons within molecules are of the order of electron volts, and the energy of a hydrogen bond is > 0.1 eV. Accordingly, direct linear mechanisms for the absorption of a photon or a few photons by biological molecules from an RF field cannot involve changes in electronic or covalent molecular structure, nor can they involve the breaking of hydrogen bonds. That does not imply that single photons cannot cause changes in the structure of biological molecules or molecular complexes. They

Figure 3-15. The real component of the complex permittivity of muscle (ε') as a function of frequency (f) from the values for muscle (Schwan 1957).

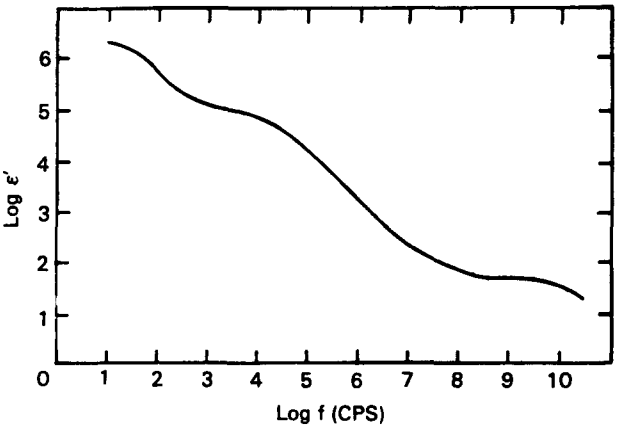


Table 3-4. Dielectric Permittivities for Various Tissues*

Tissue Type	Dielectric Value	Frequency (MHz) 0.1	1	10	50	100	10^3	10^4	1.7×10^4
Muscle	ε'	3×10^4	2×10^3	220	90	75	54	40	34
	ε''	10^5	10^4	1.2×10^3	400	80	27	21	21
Brain	ε'			240	110	80	40	35	
	ε''		2.6×10^3	500	180	95	16.5	15	
Liver	ε'	10^4	1.5×10^3	240	90	78	46	36	
	ε''	5×10^4	5×10^3	800	195	110	18	11	
Bone	ε'	8.0			7.2		5.8	4.9	
	ε''	0.5			10.8		1.3	0.7	
Fat	ε'				12	10	6.0	4.0	
	ε''				17	12	2.0	0.7	

*These values are abstracted from reviews by Schwan and Foster (1980) and Stuchly and Stuchly (1980). The original sources are quoted therein. The values have been chosen in the middle of the range for experimental values. Reported values may differ from one another by as much as a factor of 2.

contain sufficient energy to change the three-dimensional structure of biological molecules in a manner that leaves the covalent and hydrogen-bonded structure intact. The following paragraphs describe some of the excitations of biological molecules that can be induced by an RF field and the changes in three-dimensional molecular structure that may result.

A change in the rotational energy of dipolar molecules or molecular segments is a ubiquitous mode for energy absorption from an RF field by molecules in a biological system. The absorbing molecular structure increases its angular momentum by quantized units. The size of these units and the characteristic frequencies for absorption depend on the distribution of mass within that structure. In general, the more massive the rotating structure, the lower the characteristic frequencies.

The rotational mode of interaction is relevant through the entire range of the frequencies of interest for the purpose of this document. Free rotation of proteins and other bipolymers are modes for absorption in the frequency range from 10 kHz to 100 MHz and beyond. In addition, smaller molecules and molecular segments absorb at higher frequencies by this mode. The absorption of energy into free rotational modes does not lead to structural changes in the absorbing molecule or segment because it rotates rigidly. Through collisions with other molecules in the biological system, this initial increase in rotational kinetic energy is dispersed throughout the various molecular motions of the system (i.e., the energy is thermalized). With this mode of absorption, functional changes, if any, result only from these local increases in temperature. In a biological system at normal body temperatures, an individual molecular species absorbs over a broad frequency range by this mode because of its concurrent interaction with other molecules.

Since water, which has a characteristic frequency for free rotation near 20 GHz, is the major component of biological systems, a change in the rotational energy of water molecules is the principal mechanism for absorption of microwave radiation at frequencies >2 GHz. (The frequency range for which this interaction is likely to be important is broadened by the interaction of absorbing molecules with surrounding molecules.) At the lowest frequencies of interest, changes in molecular rotational motion may also make a significant contribution to the overall dielectric properties through the interaction of microwaves with large molecules.

For many biological molecules, segments as large as many amino acids or as small as a methyl group have some rotational freedom, but are constrained both by covalent bond(s) to the main structure of the molecule and by electrostatic interactions with other nearby

Table 3-5. Energy Units for RF Radiation

λ (m)	f (MHz)	Energy/photon (eV)
10^{-2}	3×10^{4}	1.2×10^{-4}
1.24×10^{-1}	2.45×10^{3}	1×10^{-5}
3×10^{-1}	10^{3}	4.1×10^{-6}
10	3×10	1.2×10^{-7}
3×10^{2}	1	4.1×10^{-9}

molecules. This rotational freedom provides a mode for the absorption of energy from an RF field. Although this mechanism is similar to the preceding one, it has been suggested (Illinger 1970; Rabinowitz 1973) that it can result in changing the equilibrium position of the rotating segment relative to the main structure of the molecule and surrounding molecules. This structural change is probably reversible but could have consequences for biomolecular function. The importance of this mechanism for a biological effect of RF radiation has not been substantiated experimentally.

More complicated intramolecular motional modes involve rotation and vibration, bond stretching, and twisting. These modes also absorb energy from an RF field and have potentially similar effects on molecular structure and function. In general, these more complicated modes are at frequencies above the range of interest, but there is some suggestion that they are important near 10 GHz. Prohofsky *et al.* (1979) have calculated the stretching modes for an artificial double-stranded DNA polymer containing one strand of adenine that is hydrogen bonded to a strand containing only thymine. They suggest that absorption of energy into these modes may affect DNA helix melting and replication. The characteristic frequencies of these calculated modes are, however, >40 GHz.

The amount of energy required to excite either rotational or the more complex motional modes is small with respect to the amount of energy exchanged in molecular collision at biological temperatures. This implies that, unless there are special circumstances (Illinger 1970; Rabinowitz 1973; Prohofsky *et al.* 1979; Ginzburg 1968), the molecular configuration that results from the absorption of energy from the RF field is not unusual. However, the relative distribution of normally occurring configurations may be affected by the absorption of energy. The effect produced may be only a relative change in a normally occurring process, and may be reversible on the molecular level. However, reversibility for the molecular-level absorber does not imply that the resulting—if any—macroscopic biological effect is reversible. If the unusual distribution of states does not return to the normal distribution as quickly as one would expect from strictly thermal considerations, then these effects will be much more important (Fermi *et al.* 1965).

Another general mechanism for the interaction of RF radiation with biological molecules results from the field-induced migration of ions associated with biopolymers. The migration may be of positively charged ions—like protons or other cations—from one negatively charged site to another within the same biopolymer (Kirkwood and Schumaker 1952) or from the polarization of the ionic cloud that surrounds the biopolymers (Schwarz 1972). The distinction between these two mechanisms has been made because in the case of the former, the migration of the ion(s) may directly affect the function of the biopolymer if the migrating ion(s) or one of the sites is directly involved in molecular function. In both cases, there are effects on the long-range interaction between biopolymers. The minimum field strength needed for the first case can be roughly estimated from the size and shape of biopolymers, and even for rod-like structures, a field of at least 10^5 V/m would be needed. For the second case, the field strength necessary is smaller and depends on the size of the surrounding ionic cloud. The frequencies at which these processes are important depend on the size and shape of the molecule (Pollak 1965). For sonically fragmented DNA segments that have a rod-like structure, broad absorption regions have been found near 10 kHz and 10 MHz (Takashima 1963; Pollak 1965).

A mechanism has been described for the direct influence of an RF-electric field on the configuration of biopolymers (Schwarz 1967). If the interaction of the field with one configuration of a biomolecular system is much greater than the interaction with other configurations, then—in the presence of that field—a shift in the relative populations of the various configurations results. The difference in interaction energy may be due to differences in the dipole moments or in the polarizabilities between configurations. This mechanism has been demonstrated in the model protein poly (γ-benzyl-L-glutamate), or PBLG (Schwarz and Seelig 1968). In its random-coil conformation, PBLG has essentially no dipole moment, whereas in its helical conformation it has a large dipole moment ($\sim 10^3$ Debye). The presence of a field of sufficient strength can induce a transition from the coil to the helical conformation. In PBLG this mechanism is responsible for absorption of energy near 1 MHz; for the distribution of conformations to be affected significantly, the field must be greater than 10^5 V/m. (If there were systems in which the change in dipole moment was larger, then the field needed would be proportionally smaller.) This change in conformation is not unusual (although the relative amounts of the two conformations are altered) or irreversible, but, as previously stated, reversibility on the molecular level does not necessarily imply that any resulting, macroscopic, biological effect is reversible. For instance, the conformations may have differing biological activities, and the products of these activities may remain even after the distribution of the conformations has returned to equilibrium.

3.2.4.3 Unresolved Issues

The mechanisms for the absorption of energy from an RF field previously discussed have been demonstrated in solutions of biological molecules, and the response of macroscopic biological systems to these fields is consistent with these molecular mechanisms. The question that remains is: Are any of these mechanisms likely to impose a potential hazard to human health? Certainly, if enough RF energy is absorbed and converted to thermal energy, corresponding biological effects ensue. Other mechanisms have been proposed for effects at the molecular level. They require changes in molecular structure and function as the result of absorption. It is extremely likely that some changes in biomolecular structure result when RF energy is absorbed. But are these changes functionally significant? Some mechanisms for biological effects in these circumstances have been proposed. They are plausible but often not quantitative, and have not been demonstrated in biological experiments. Further research to quantitate and consider these mechanisms experimentally is urgently needed. Since exposure to RF radiation often leads to increased temperature, careful studies are needed to separate effects that are not due to heating from other concomitant changes in temperature.

Two other general mechanisms at the supramolecular level need further discussion. A theoretical mechanism has been proposed for coherent action over long distances in biological macromolecular systems that are far from thermal equilibrium (Fröhlich 1968). This mechanism has been developed to explain the extraordinarily high catalytic power of enzymes; one of its consequences is an extremely long-range interaction between macromolecules. The requirements of this model are that the macromolecules possess a metastable excited state that has a large dipole moment ($> 10^3$ Debye) and that its polar modes couple with elastic modes. This highly dipolar metastable state will be stabilized by the migration of ions and by the structure of the water near the macromolecular surface. One of the implications of this model for enzyme action is that interaction with an EM field that is capable of supplying energy above a critical rate results in all of the energy going into a single homogeneous electric vibration of this system (Frölich 1975). This means that all the other modes of the system are at or near thermal equilibrium, and that single mode is far removed. Although it is unlikely that this redistribution of energy will increase the rate at which the energy is absorbed by the system, the biological consequences of putting all the energy into a single mode that is related to the functional properties of the system could be extraordinary. If that single mode relates to enzyme function or recognition, it could greatly increase

enzyme function until saturation is reached. The possibility also exists of re-emission of large amounts of energy and action at sites remote from the initial absorber. The specific biological consequences of this model relative to RF-field effects on biological systems cannot be well understood until detailed characteristics of particular biological systems are included. Some data can be explained by this model (Grundler *et al.* 1977); the resultant *in vivo* vibrational spectral properties of biological systems also have been discussed (Illinger 1982).

One of the interesting and relevant consequences of Fröhlich's (1968) model is that the particular biological result of RF-field interaction with a biological system may be frequency dependent. It has been suggested that the range of frequencies where this process is most likely to be significant is probably > 30 GHz (Fröhlich 1968, 1975). The actual range of applicability is uncertain. The effect also may be important at lower frequencies.

Fröhlich's mechanism is general. Its applicability in real or model biological systems has not been demonstrated. For potential biological effects from RF fields, it is a possible mechanism for grouping individual photons or phonons with energies $<<$ kT (the average thermal energy). This process results in the application of energy in a significant amount ($>$ kT) at a single locus. Effects resulting from this process could not be duplicated by addition of the same amount of energy to the system by a different process.

Another set of mechanisms at the supramolecular level has been proposed recently. These mechanisms are theoretical means for the direct interaction of RF fields with microscopic biological processes that depend on naturally occurring electric potentials. In general, these mechanisms depend on a nonlinear response to an applied field by the cell membrane.

Barnes and Hu (1977) have proposed that the ion gradient across a cell membrane can be altered significantly if PW radiation at 10^5 V/m peak field strength or more is applied. This theoretical view derives from consideration of the balance between field-driven and thermal currents. Changes in the time-averaged concentration gradient occur that depend on the square of the field applied across the membrane, but not on the frequency of the applied field. There are larger terms that are frequency dependent but when averaged over a complete cycle are zero. This mechanism has not been demonstrated in a biological system.

Pickard and Rosenbaum (1978) considered a similar problem and came to the same conclusion for the time-averaged concentration gradient across the membrane. In their model, they included unidirectional ion channels through the membrane, and they postulated that the new concentration gradient is achieved by the field-induced movement of ions through these channels. They calculated that, for this particular method of achieving the concentration gradient, the frequency of the field must be < 200 MHz if the ions are protons, and < 10 MHz for less mobile ions. Pickard and Barsoum (1981) have demonstrated activity across the membrane of a plant cell that begins at the onset of an RF field greater than 667 V/m with a frequency below 10 MHz. The immediate response to the field indicates that the activity is not thermally induced. The activity demonstrated is consistent with an RF-induced DC potential across the membrane. This potential could result from any nonlinear response of the membrane to the RF field, and it is not clear that any particular mechanism for that response has been demonstrated. More data are needed to demonstrate a realistic microscopic model for this process. It is difficult to proceed from these mathematical models and this single experimental demonstration to an assessment of the importance of this mechanism. The induction of DC or extra-low-frequency potentials in biological systems by an RF field could provide significant mechanisms for the biological effects of RF radiation.

3.3 Experimental Methods

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3.3.1 Exposure Methods Used in Biological Experimentation

In this section the most commonly used exposure methods employed in RF biological effects research are reviewed, and the inherent advantages and disadvantages of each are discussed. Researchers have used a diversity of exposure methods; the chosen method depends on the specialized application involved, the existing facilities available for experimentation, and the cost of setting up new facilities. This diversity may have created difficulties in reproducing biological effects studies, which have, in turn, fueled controversies on several reported effects. Whereas an effect may have been noted by one group who employed a particular form of exposure system, a second group that carefully reproduced the experiment in every detail but for the exposure method might not see the reported effects. It is possible that basic differences in the exposure environment may, in some cases, explain this lack of reproducibility.

In much of the literature, effects have been traditionally reported as a function of incident power density, the independent variable. As pointed out by several prominent workers (King *et al.* 1970; Johnson 1975), power density is an inadequate and inappropriate independent variable for two reasons:

1) Biological effects are logically related to the internal electric and magnetic fields which are in turn nonlinear and complex functions of frequency vs. body size, body shape, and orientation to field vectors, etc. (See Sec. 3.2, RF Field Interactions with Biological Systems.)
2) Although meaningful for certain plane-wave-exposure situations, such as free-field or transverse electromagnetic (TEM)-mode cells, the power density concept is no longer applicable in most other commonly used exposure systems with complex irradiation fields. Consequently, meaningful comparisons of the incident field levels in different types of exposure systems cannot be made on this basis.

For these reasons, it must be concluded that the various exposure methods are unique; experimental results obtained in different exposure environments cannot be compared except perhaps on a whole-body-averaged SAR basis, and reproducibility of experimental data is not guaranteed unless exactly the same exposure methodology has been used. Even if equivalency of whole-body-averaged SAR is achieved, there may still be differences in biological outcomes for exposures performed in multipath fields (e.g., a cavity) when compared to plane-wave fields, which have the same carrier frequency and modulation parameters.

Although many of the specialized requirements of a particular experiment are unique, some requirements are common to almost all experiments. For example, there is a critical need in virtually all work for temperature and humidity regulation of the environment in which animals, biological specimens, etc., are located. Such control ensures that the ambient air temperature and humidity are properly controlled, so that the possibility of unwanted variability in the experimental protocol is minimized. Also, airflow is an important variable, particularly in animal studies that should be regulated and reported. Two other important requirements are common to the majority of experiments involving whole-body or unrestricted irradiation of animals: (1) an animal population large enough to allow for statistically reliable conclusions to be drawn, and (2) an equally large population of control animals that must be housed during exposure periods under conditions that are, in every way, virtually identical to those of irradiated animals except for the presence of RF energy. For certain critical experiments, there may also be a need for a population of passive or reference control animals that are maintained under normal conditions in their vivarium during the tenure of a study. Much of the early experimental work on RF biological effects frequently contained no provision for controls, involved inadequate numbers of experimental subjects, and lacked adequate provision for environmental control, and thus yielded data of questionable validity. It is only within the past decade or so that researchers have succeeded in correcting most of these experimental deficiencies in exposure protocol.

Existing exposure methods have been reviewed by Weil (1977) and Ho *et al.* (1976); the latter paper discusses exposure techniques that have been used at the FDA's Bureau of Radiological Health. The commonly used methods are categorized into two groups and considered separately: (1) free-field, and (2) enclosed. In the former category, the exposure fields are generated within a reflection-free environment by a radiating antenna or applicator, whereas in the latter category, the exposure fields are those excited within a struture of reflective or conducting walls.

3.3.1.1 Free Field

Free-field exposure methods were historically the first to be used in such experimentation and remain the most commonly used techniques. These methods involve placing the experimental subject(s) in the near-field or far-field region of a radiating antenna,

such as a horn, parabolic dish, or diathermy applicator. For exposures in the far-field region, all unwanted scattering of RF energy from the surrounding room structure, etc., must be eliminated. Otherwise, the power density levels at the subject's location are not well established. A microwave-absorbing material that wholly or partially surrounds the experimental subjects must be used to create what is termed an anechoic chamber. (The term "anechoic," meaning "without echoes," has been borrowed from acoustics research.) The design of anechoic chambers is a specialized art normally performed by commercial manufacturers of absorbing material (e.g., Emerson and Cuming, Canton, Mass.). The anechoic properties of such chambers, which are defined by the characteristics of the "quiet zone" where the experimental subjects are placed, is a function of the reflective properties of the absorbing material with which the chamber is lined. (Such properties refer to the degree with which RF energy is reflected by the material, rather than absorbed.) Reflectivity is proportional to the incident wavelength, so that the performance of an anechoic chamber deteriorates as the frequency of operation is lowered. A minimum reflectivity of 20 dB (1 percent) is usually considered essential; the frequency at which this value is reached then defines the lower frequency limit of operation for the chamber. Anechoic chambers perform well at frequencies in the microwave region of the spectrum (above 500 MHz). However, satisfactory performance at lower frequencies or longer wavelengths requires using large blocks of absorbing material formed into long pyramids or cones. Consequently, a large structure is needed to house such a chamber, so that the cost of such a facility rapidly escalates to the point of nonfeasibility. For all intents and purposes, it is impractical to contemplate building anechoic facilities that operate at frequencies below ~ 250 MHz.

Some of the most extensive anechoic chamber facilities devoted to RF biological effects work are to be found at the Department of Microwave Research of the Walter Reed Army Institute of Research, Silver Spring, Md. Similar conventional anechoic facilities are found elsewhere; e.g., at the Bureau of Radiological Health in Rockville, Md. at the U.S. Environmental Protection Agency in Research Triangle Park, N.C. (Figures 3-16 and 3-17), at the U.S. Air Force School of Aerospace Medicine in San Antonio, Tex., and at the Universities of Pennsylvania, Utah, and Washington.

The principal advantages—applicable to exposures in only the far-field zone of an antenna—of the free-field exposure method are:

- The incident power density to which the subject is exposed can be well defined to an accuracy of ±1 dB (±20 percent) or less. This makes replication of experiments performed under free-field conditions fairly straightforward.

- Depending on the directionality of the radiating antenna, the exposure area where the irradiated subjects are placed is large, and the irradiation is nearly uniform (±10 percent or less).

The principal disadvantages of free-field exposure methods are:

- The facilities are costly and often require extensive floor space.

- Very-high-power RF sources are needed to obtain the necessary power density levels. Consequently, many free-field facilities employed in bioeffects research operate on either of two ISM frequency

Figure 3-16. **EPA 2450-MHz anechoic chamber facility, or 2.45-GHz far-field exposure facility. Horn antenna (top), temperature control chamber (center), and one air duct (bottom left) are visible in the shielded anechoic room (Blackman *et al.* 1975, Elder and Ali 1975).**

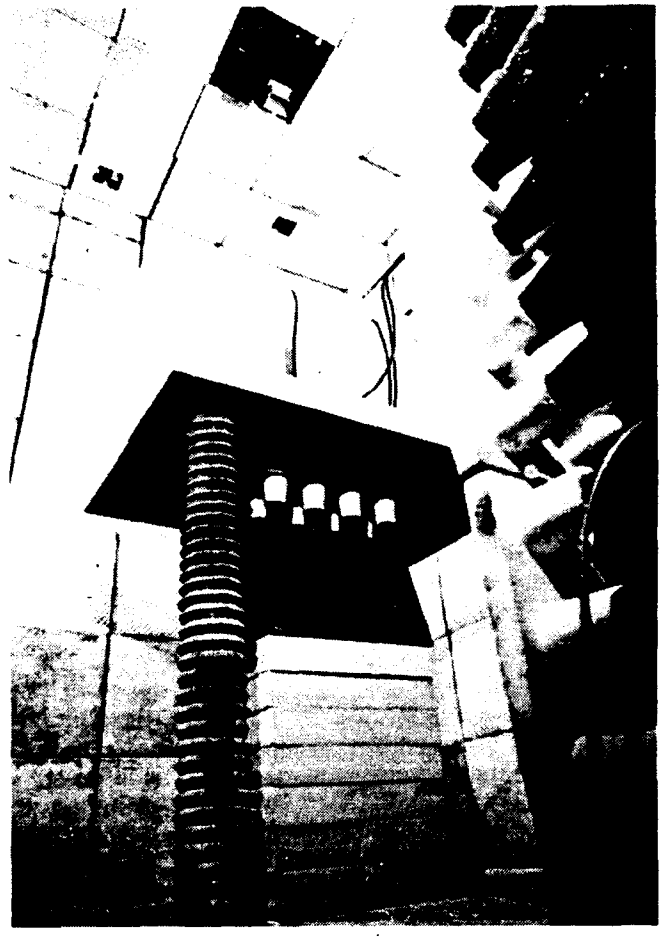
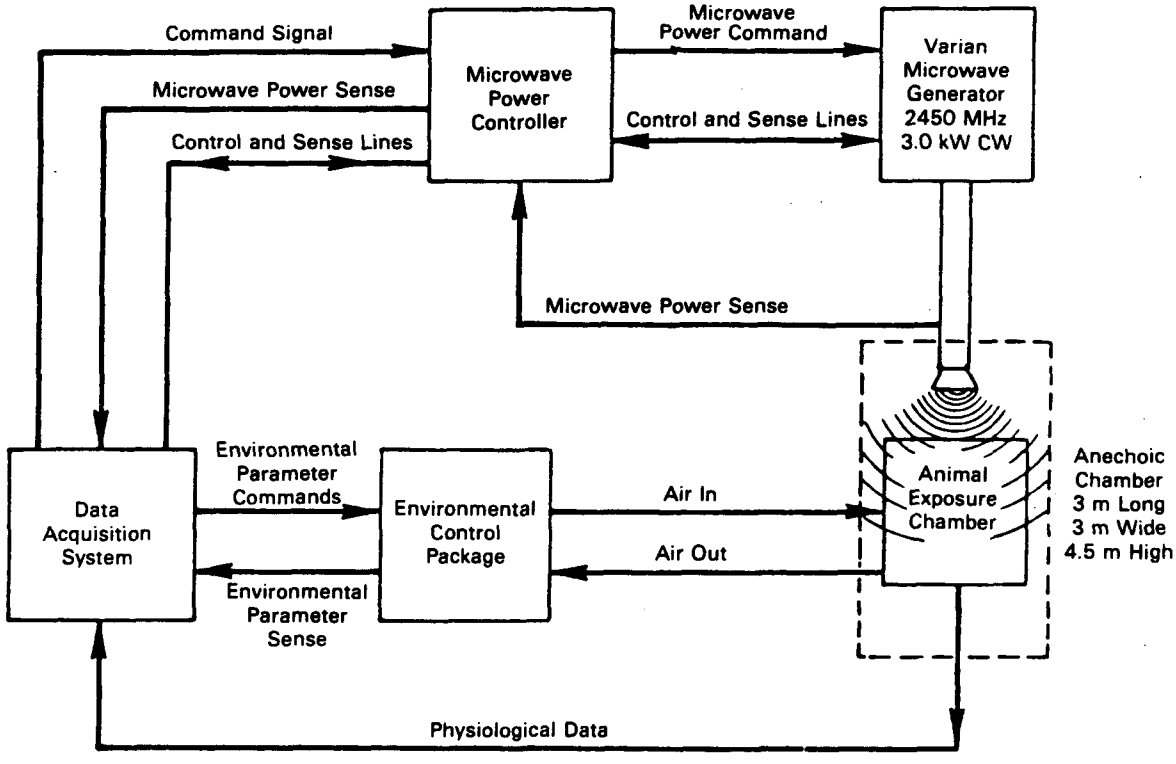


Figure 3-17. EPA 2450-MHz anechoic chamber facility: Diagram of the microwave exposure facility (Blackman *et al.* 1975; Elder and Ali 1975)



assignments used for microwave heating, 2450 MHz or 915 MHz, where high-power sources are commercially available at relatively low cost. It is for this reason, as well as the explosive growth in the use of microwave sources at ISM frequencies (e.g., microwave ovens and hyperthermia treatment devices) and the resulting potential for exposure of significant portions of the population, that 2450 MHz has become an important frequency for bioeffects research.

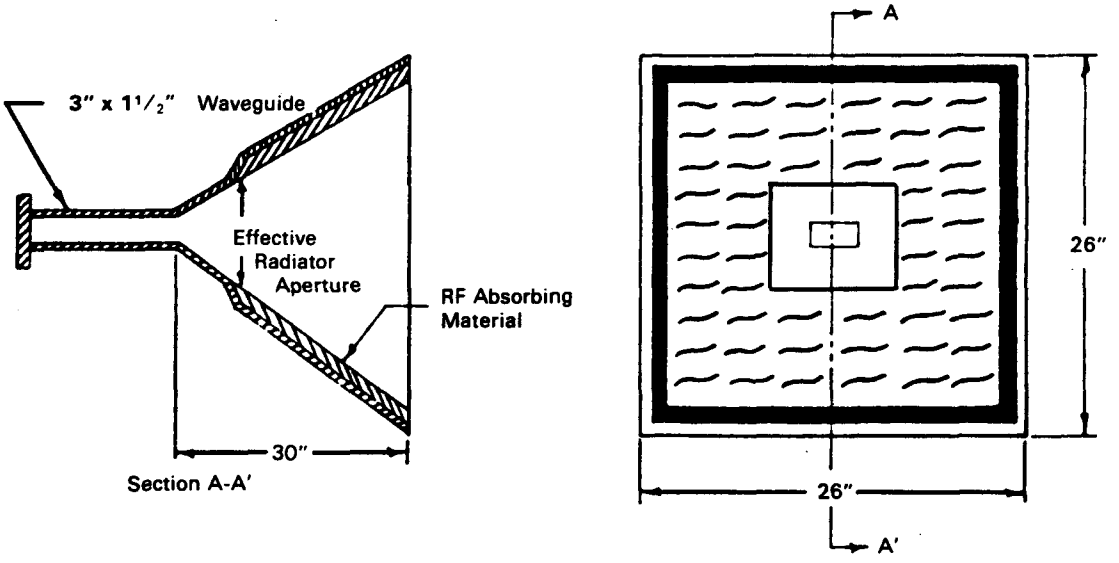
- Free-field systems are an excellent simulation of the idealized exposure concept visualized in many protection standards, but these systems do not represent the real-life exposure situation encountered by humans.

- The whole-body-averaged SAR cannot be measured directly in a free-field situation. Reasonably accurate estimates of the SAR can be made by calorimetric measurements on animal carcasses. (See Sec. 3.4, Dosimetric Methods.)

Various attempts have been made to modify conventional free-field exposure methods to ameliorate the cost and space problems associated with them. A study (Bassett *et al.* 1971) performed at the Georgia Institute of Technology developed several such techniques. One employs the absorber-lined horn antenna, which enables a subject to be placed much closer to the horn aperture than is the case with a conventional horn and yet to remain within the far-field zone of the radiator, so that a source of lower power can be used to create the same power density at the irradiated subject. One of these absorber-lined horns has been used for several years at the National Institute of Environmental Health Sciences in Research Triangle Park, N.C. (Figure 3-18). Another technique involves the compact range (Figure 3-19), which uses a feed horn to irradiate a large parabolic reflector. The test subject is exposed in the collimated beam region of the reflector. The advantage of this system is that it creates a much larger test volume of nearly uniform field intensity with associated decrease in the anechoic facility size, as well as reduced requirements for absorbing materials. The compact-range technique is used at the Naval Aerospace Medical Research facility in Pensacola, Fla.

As discussed earlier, a critical need in whole-body exposure of animals is to expose large numbers of animals. Consequently, in many experiments, unrestrained animals have frequently been placed

Figure 3-18. Diagram of absorber-lined horn (Bassett *et al.* 1971).



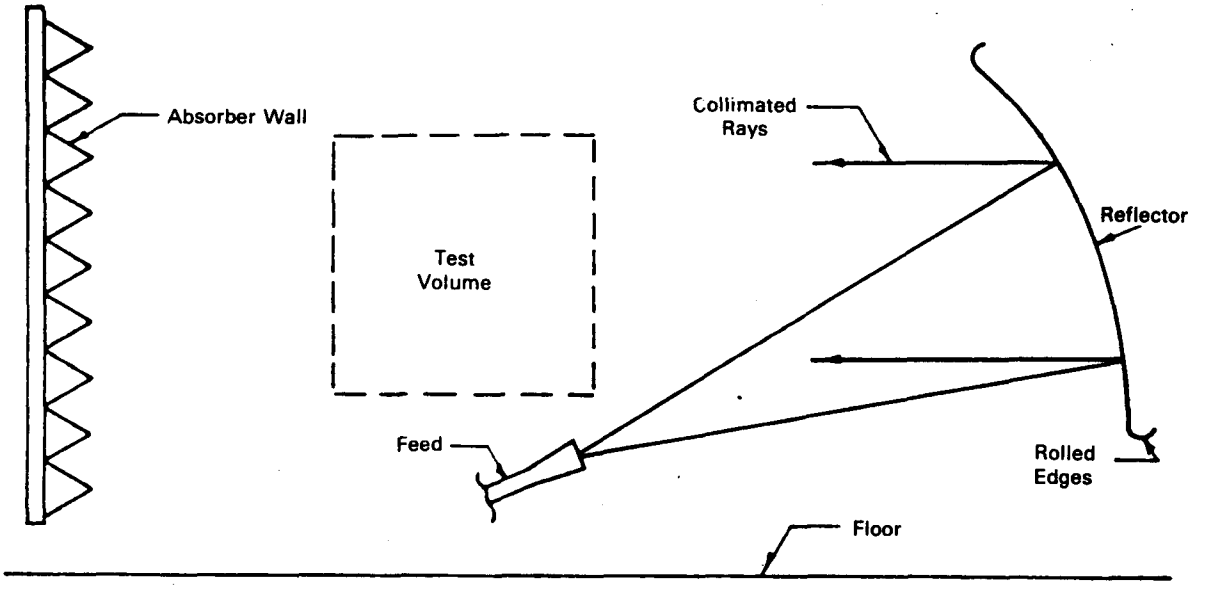
inside an anechoic chamber in a closely spaced matrix for simultaneous exposure. This practice tends to obviate the principal advantage of free-field exposure methods, because the power density to which the animal is exposed can no longer be accurately defined due to RF-energy scatter from one animal to another. The degree of scatter depends on much the same factors as absorption (see Sec. 3.2.1) and varies randomly as the animals constantly alter their relative posture and orientation. Interanimal scatter is most serious when the frequency of exposure lies in the resonant and supraresonant region. Several solutions to this problem have been devised:

(a) sequential exposures of single animals in the same free-field facility

(b) miniature anechoic chambers for exposing animals individually

(c) separating the restrained animals so that they are spaced one or more wavelengths apart

Figure 3-19. Diagram of a point-source compact range (Bassett *et al.* 1971).



The first solution is obviously costly and time-consuming, and may not be acceptable in certain critical biological experiments requiring all animals to be exposed at exactly the same age or the same time of day, etc. The second solution has been advanced by Guy (1979) at the University of Washington in Seattle. He has described a system of 16 miniature anechoic chambers designed for chronic low-level ($<$ 10 mW/cm^2) exposure of rabbits and rodents at 2450 MHz; eight of these chambers are energized, and the other eight serve as control chambers (Figure 3-20). A similar chamber has been constructed at EPA (Figure 3-21). Such a system has, of course, the advantage of ensuring total RF isolation between animals and, although costly, it may be more economical in cost and power requirements than is the conventional anechoic chamber.

The third solution has been tried by a few workers and appears to be a reasonable compromise between the conflicting requirements of adequate isolation and low cost. Oliva and Catravas (1977) have described a method for simultaneously exposing 10 animals in a conventional anechoic chamber with minimal field interaction between animals (Figure 3-22). The animal cages are located on the antenna beam's three-dimensional contour of constant power density, with cages separated by $\sim$ 2.5 wavelengths at 2450 MHz. The authors claim that the average variation of power density from one cage location to another does not exceed $\pm$5 percent. The major disadvantage of this technique is that its implementation may require a large exposure volume, which, in turn, creates costly problems of ensuring satisfactory environmental control. D'Andrea *et al.* (1979, 1980) at the University of Utah have developed an alternate method involving a monopole radiator on a vertical ground plane. The animals are located next to the ground plane on a circular locus that is centered at the monopole (Figure 3-23). Each circular array contains 10 animals that are separated by $\sim$ 5.5 wavelengths at 2450 MHz, and by 2.1 wavelengths at 915 MHz. This system offers the advantage of reducing both space and RF-power requirements. Furthermore, the presence of a ground plane makes this system more representative of the real-life exposure situation for humans. On the other hand, the exposure characteristics of this system may not be comparable to a conventional anechoic chamber facility, so that caution is needed when data are compared.

For situations involving the exposures of only one subject at greatly increased power density values, D'Andrea *et al.* (1977) and Hagmann and Gandhi (1979) have discussed a modification of this system in which a corner reflector is placed behind the monopole. By placing the subject 1.5 wavelengths from the corner point, one can get an SAR enhancement of more than 20 times that obtained without the reflector.

3.3.1.2 Enclosed Systems

Enclosed exposure systems are those in which the EM fields are contained within a conducting structure. They fall into two basic subcategories, which are considered separately: (a) transmission-line systems, and (b) cavity systems. The principal advantages of enclosed systems are as follows:

- By suitable monitoring of the incident, reflected, and transmitted power in the exposure system, more accurate SAR estimates can be made for the exposed subject than is possible in free-field facilities. The accuracy in estimating SAR depends in part on how much base-line power loss there is for the unloaded system and to what extent it is affected by the presence of the exposed subject.

- The cost and space requirements of such a system are usually lower than those for free-field methods, depending on the number of identical systems needed. Also, much smaller and less expensive power sources will suffice to establish the same field intensities.

- Better control of RF absorption in the irradiated subject is possible.

The principal disadvantages are as follows:

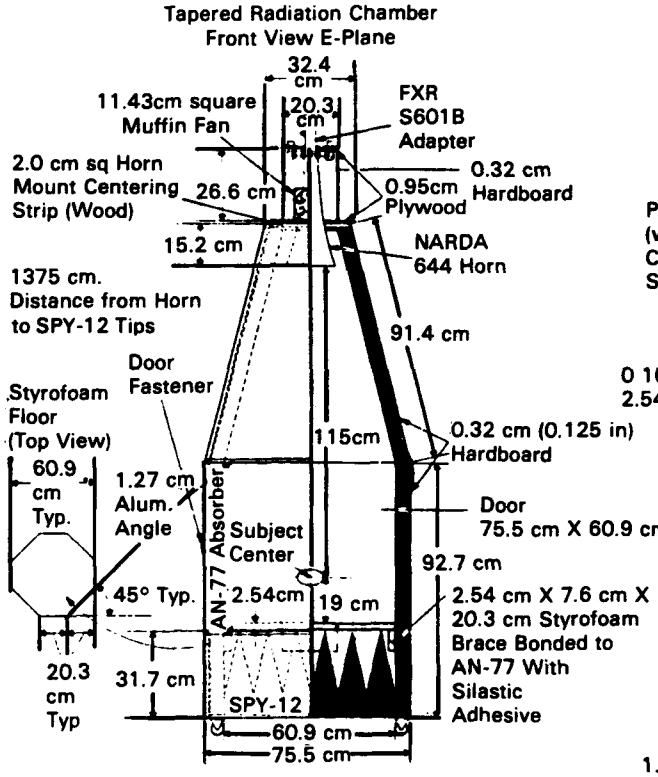
- With the exception of TEM-mode transmission lines (to be explained), the fields are complex and not plane-wave equivalent, so that comparison with free-field data is more difficult.

- With the exception of multimodal systems (also to be explained), the exposure space available inside such systems is limited. Although the available space may be adquate for small animals such as rodents, it may not be possible to fit a rabbit or monkey in it. Thus, the variety of species that can be employed in an existing facility of the enclosed type is restricted.

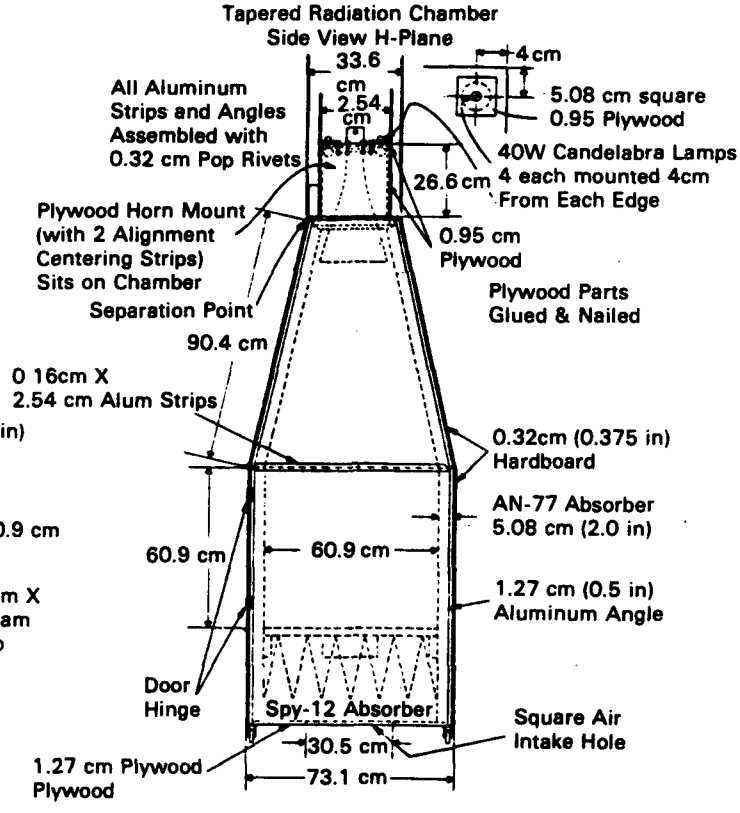
- The field distribution within the exposure system is rarely as uniform as that found in a free-field facility. The field distribution is well defined for single or dominant mode operation, but undefined for multiple-mode operation.

Enclosed systems have been the preferred exposure method for samples, specimens, *in vitro* preparations,

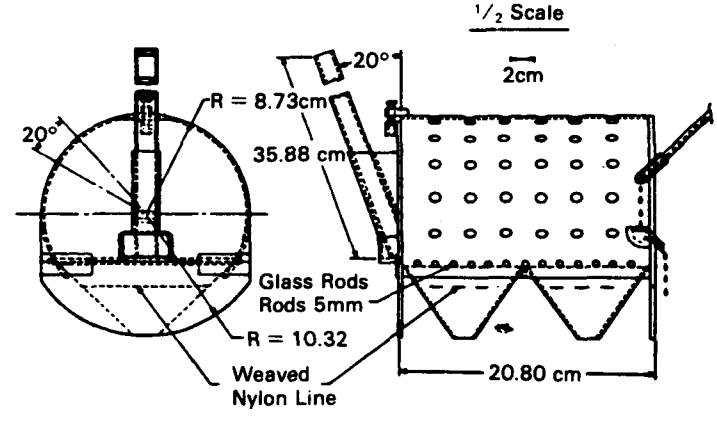
Figure 3-20. Miniature anechoic chamber facility (Guy 1979).



a) Construction details of tapered exposure chamber.



b) Construction details of tapered exposure chamber.



c) Construction details of cage for housing rat in tapered exposure chamber.

Figure 3-21. Photograph of tapered exposure chamber at EPA facility.

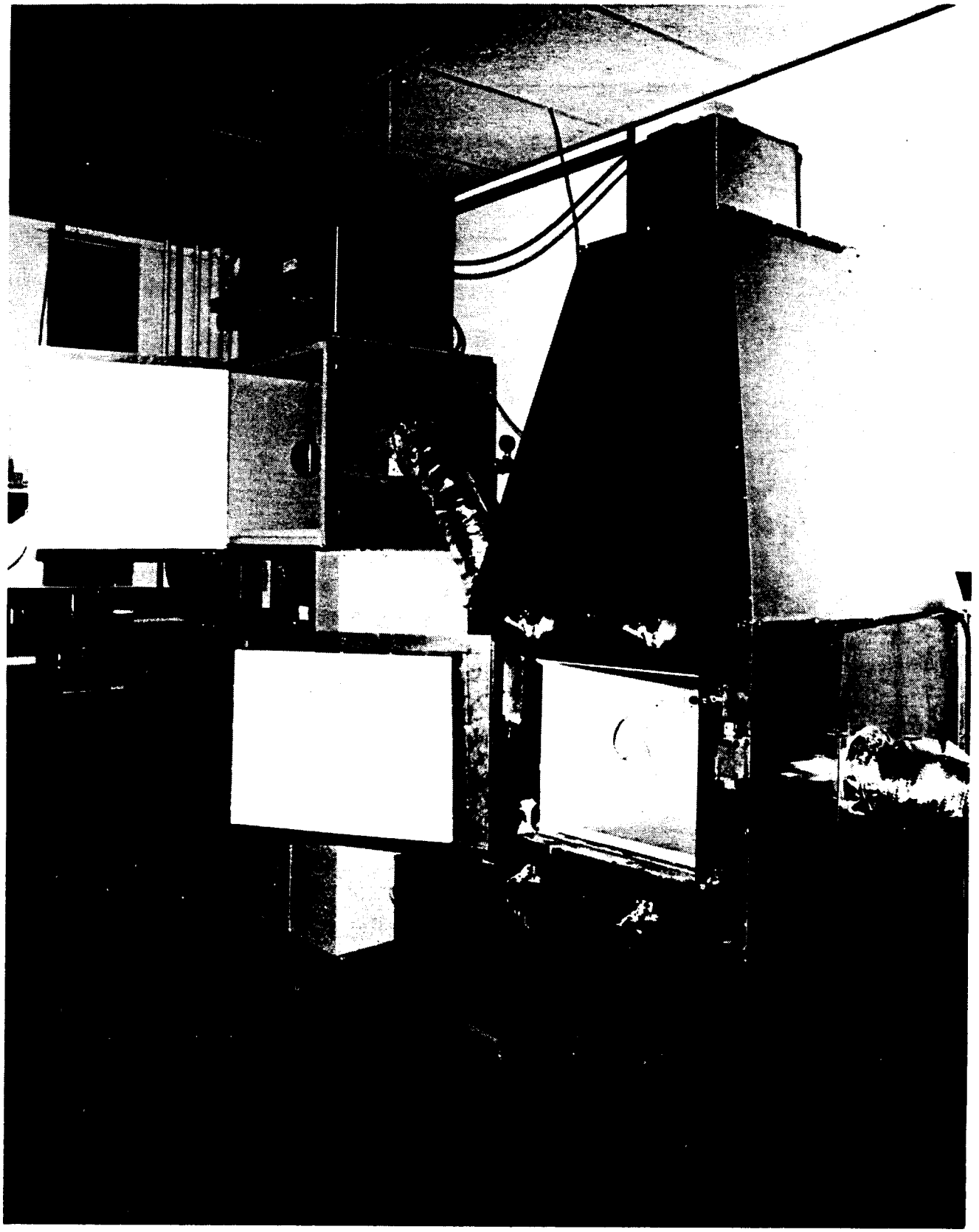
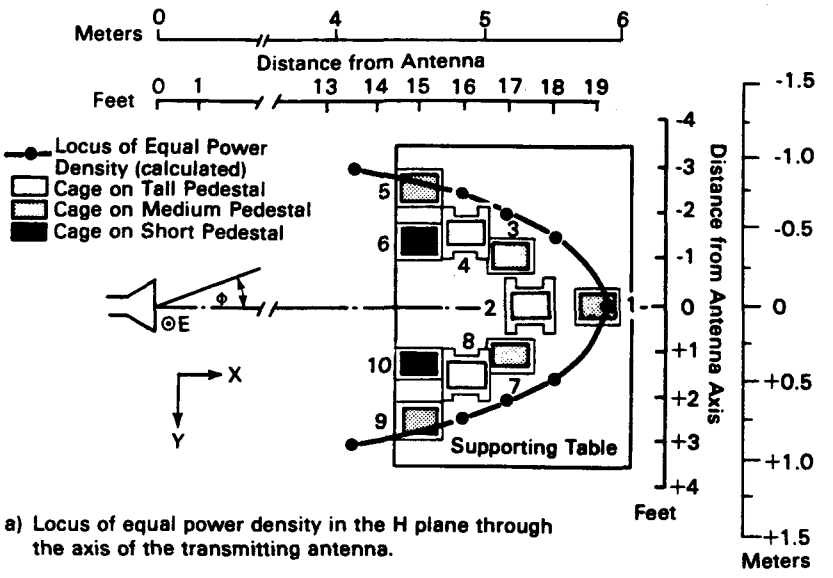
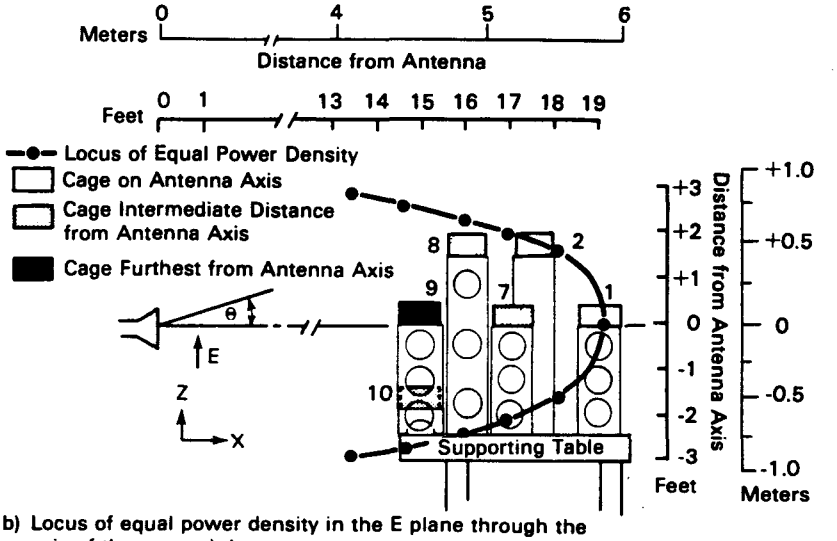


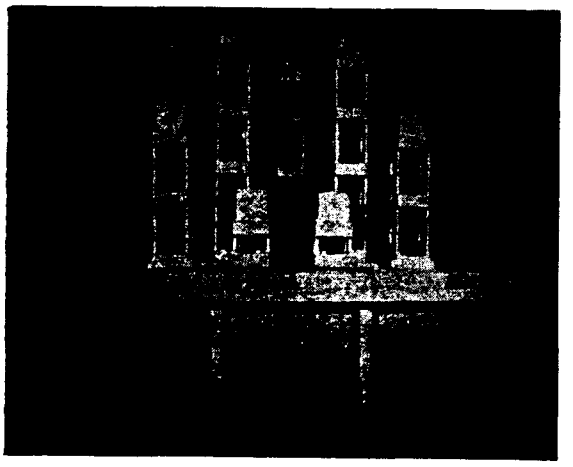
Figure 3-22. Facility for simultaneous exposure of 10 animals with minimal inter-animal interaction (Oliva and Catravas 1977).



a) Locus of equal power density in the H plane through the axis of the transmitting antenna.

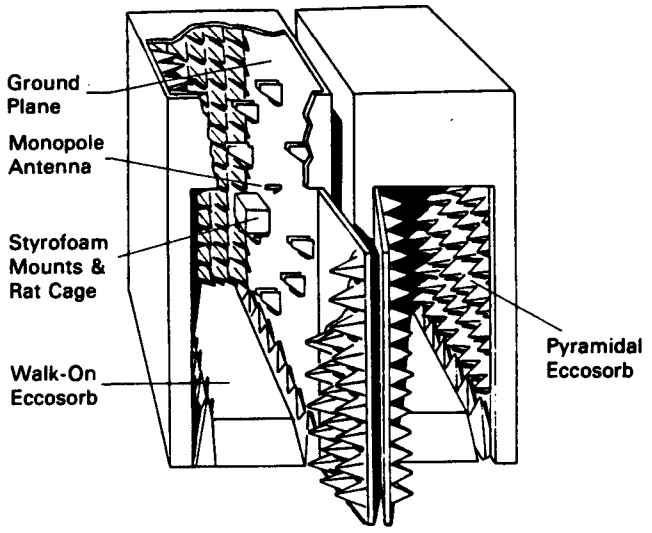


b) Locus of equal power density in the E plane through the axis of the transmitting antenna.

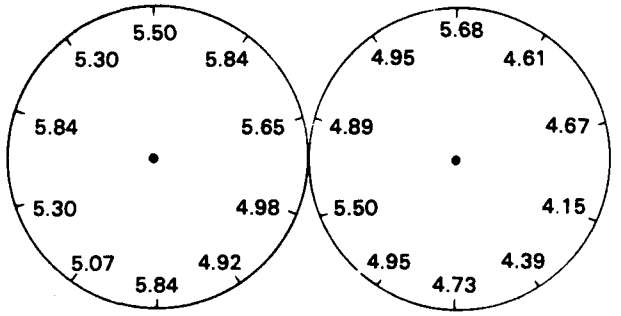


c) Multiple-animal array for equal power density microwave irradiation.

Figure 3-23. Monopole-over-ground plane irradiation facility (D'Andrea *et al.* 1979, 1980).



a) Representation of the microwave-exposure chamber.



b) Distribution of power densities measured at each rat's location within the Plexiglas holding cages for both sides of the microwave exposure chamber in the absence of the rats (2450 MHz).

etc., since these materials are small enough to fit easily inside such systems. Many experiments have been described, too numerous to survey here, in which various types of waveguide, TEM-mode lines, and cavities have been used to irradiate such preparations. In recent years, some enclosed-type systems have been specifically designed for whole-body irradiation of animals. They are discussed here in more detail. Because of the need to define accurately the field level to which the animal is exposed, dominant-mode operation of these devices has been preferred over multimode operation. However, dominant-mode operation puts an upper limit on the frequency of operation, depending on the size of the system needed to expose an experimental animal. For example, most of the dominant-mode enclosed systems that have been used to expose rats operate at frequencies below 1000 MHz; for mice, which require a smaller exposure volume, single-mode operation to ~ 3000 MHz is possible. Since free-field methods of exposure are largely impractical at these lower frequencies, as discussed earlier, enclosed systems do provide experimenters with virtually the only practical and economical method of exposing animals in the HF, VHF, and lower UHF segments of the RF spectrum. A few large-scale systems have been built to operate in the dominant mode at HF and lower VHF frequencies; they are large enough to accommodate a group of animals within the exposure area, and the animal-to-animal interaction problem is minimized because exposures are conducted in the subresonant region where interanimal scatter is minimal. However, at higher frequencies such methods become impractical, and it becomes necessary to provide an identical exposure system for each animal to be irradiated. Each exposure device is fed from a single high-power source by a power dividing network. One of the basic electrical problems associated with any enclosed exposure system is that, when loaded, there is considerable reflection of RF energy from the load, which propagates via feed lines back to the RF power source. This characteristic creates particular problems for multiple systems fed by a single power source because, without sufficient isolation between each exposure device, energy is continuously reflected from one system into the others and causes unwanted fluctuations in the RF energy incident to each system. These problems can be solved by installation of isolators in each feed line to prevent the reflected energy from reaching the dividing network and the RF power source. The two categories of enclosed system are discussed separately.

Transmission lines—In these systems, an EM wave propagates down the line from source to termination. When the line is terminated in its characteristic impedance, only the outwardly propagating wave exists with no reflected wave present. (The characteristic impedance is a basic electrical parameter that is defined by the line's configuration and dimensions.) However, if the line is terminated in a short circuit or an open circuit, all the energy is then reflected at the line's termination. The two systems of traveling waves together create a standing wave that possesses successive maxima of electric and magnetic fields (E and H, respectively) spaced a quarter of a wavelength apart. (This property is a useful feature that has been used by some workers to

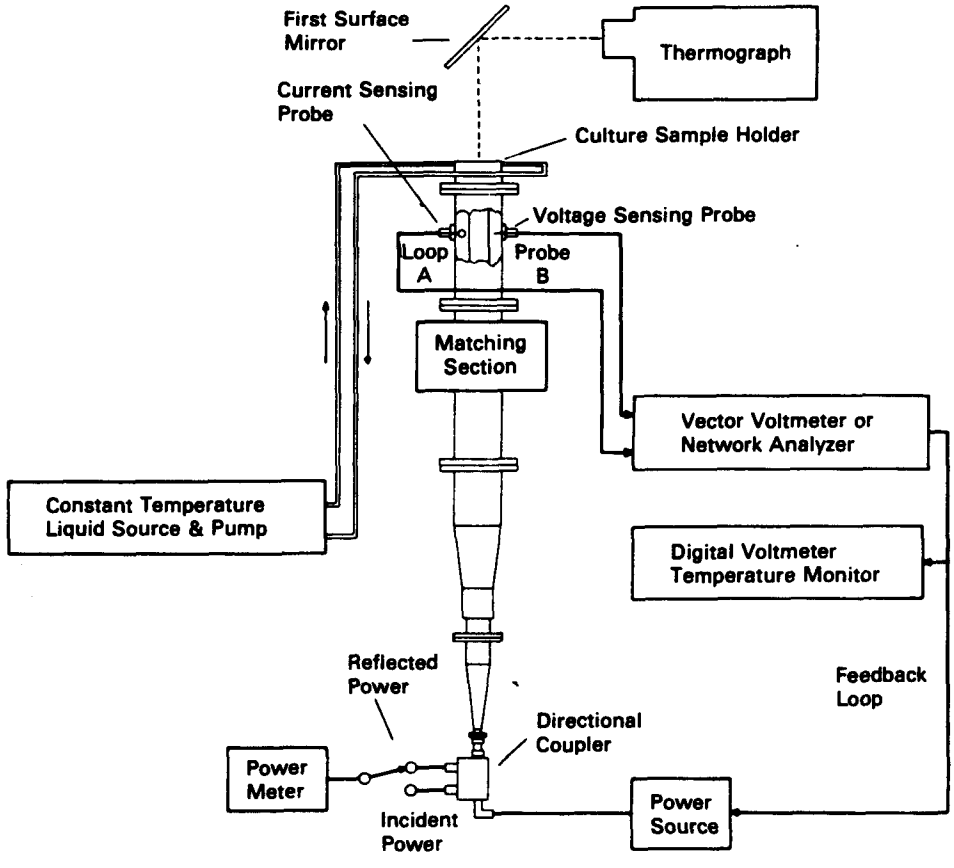
expose specimens or samples to isolated E or H fields, depending on the location along the line.) The characteristics of a shorted or open transmission line are similar to those of the resonant cavity, and are discussed below.

Transmission-line devices can be subcategorized into TEM-mode or waveguide. In TEM-mode lines—coaxial air lines, parallel-plate (strip) lines, etc.—the dominant mode of operation is a propagating TEM mode, provided the line is properly terminated in its characteristic impedance. In TEM-mode operation the E- and H-field vectors are mutually orthogonal, and they lie only in the plane transverse to the direction of wave propagation. The resulting fields are virtually identical to those of a plane wave, so that it is possible to simulate free-space conditions inside such lines, provided that the exposed subject does not occupy more than about a third of the line's cross-sectional area. (If the one-third restriction is exceeded, ground-plane effects are observed.) Because of its circular cross section, the coaxial air line has been used only with fluid or precut solid samples; the primary application has usually been in making dielectric measurements. A sophisticated coaxial air-line system, designed to expose cell cultures to high field strengths, has been described by Guy (1977) (Figure 3-24). Parallel-plate systems consisting of a conductor located over a ground plane or between two ground planes are better suited to animal exposures since they provide a rectangular volume where animals can be exposed. D'Andrea *et al.* (1976) have described a simple parallel-plate system used in the range 200 to 500 MHz (Figure 3-25). This system is equivalent to a large-scale version of a microstrip line with air dielectric. Capacitive-plate devices, which are equivalent to a short length of parallel plate that is terminated in an open circuit, have been used for exposing *in vitro* preparations to isolated electric fields. This type of simple device has been incorporated in a unique HF-band (10- to 40-MHz) exposure system developed by the National Bureau of Standards (Figure 3-26). Termed a near-field synthesizer, it is capable of separate E- and H-field excitation, the latter generated by special loop inductors (Greene 1976). By altering the spatial position of the loop with respect to the E vector and by changing the phase relationship between the signals exciting the plates and the loop, one can simulate the complex field environment existing in the near field of an HF source. Two of these systems are being used at present: one is at the U.S. Air Force School of Aerospace Medicine, Tex., and the other at the National Institute of Occupational Safety and Health laboratory in Cincinnati, Ohio.

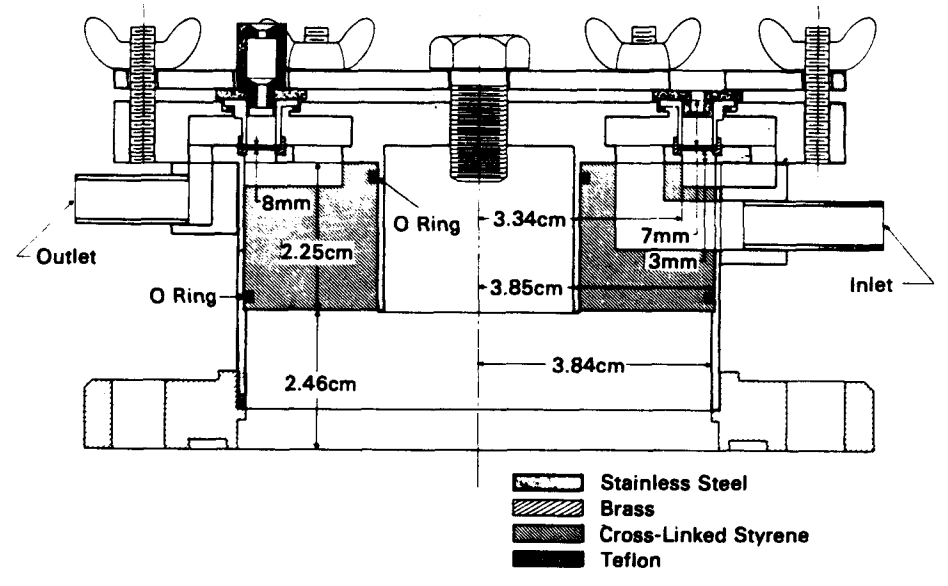
Triple-plate lines, in which a conductor is mounted between two ground planes, have been used by a few workers. These lines have the advantage of allowing for simultaneous irradiation of two animals while maintaining good isolation between them. In a more popular version of this system, the open sides of the structure are closed off with two side plates so that the center plate is entirely surrounded by a rectangular ground structure. Such lines are commercially available in different sizes (from Instruments for Industry, Inc., Farmingdale, N.Y.) and have been termed "Crawford cells" by the manufacturer, after M.L. Crawford (1974) of the National Bureau of Standards, Boulder, Colo., (also available from Narda Microwave Corp., Plainview, N.Y.). This author prefers the term "rectangular strip line." In addition, a few large-scale facilities of this type have been built for various specialized exposure applications at relatively long ($\geqq 3$ m) wavelengths. The largest is at the Defence Research Establishment in Ottawa, Canada, and is being used to measure human RF absorption in the HF band. A smaller facility has been used at the U.S. Air Force School of Aerospace Medicine for exposing infrahuman primates and phantoms to 10- to 50-MHz radiation (Allen *et al.* 1976). The U.S. Environmental Protection Agency has also built a Crawford-type structure (Figure 3-27) for exposing 20 rats to 100-MHz radiation.

The second category of transmission-line devices, waveguides, cannot support the propagation of a TEM mode so that the incident radiation is inevitably more complex than that in a TEM-mode line. However, the lack of a center conductor means that more exposure space is available in waveguides than in the corresponding TEM line. Multiple systems that use commercial waveguide systems have not been applied much for animal whole-body irradiation because of high cost. Ho *et al.* (1973) have described a single, environmentally controlled system employing a standard S-band rectangular waveguide that has been used in studies of mice at 2450 MHz. Ho *et al.* (1976) have also described a system of six waveguides fed from a common 2450-MHz source that provides simultaneous irradiation of six mice. Besides cost, another problem associated with using standard waveguides for whole-body irradiation is the high mismatch condition created by the presence of an animal in the waveguide. As discussed earlier, this necessitates the use of costly isolation circuitry. This problem has, to a certain extent, been eliminated in a specialized waveguide system developed by Guy and Chou (1976) at the University of Washington in Seattle. Guy's system is specifically tailored for chronic whole-body irradiation of rats for extended periods of time with known and reproducible dosimetry. It consists of a number of 20-cm (8-in) diameter circular waveguides (Figure 3-28), economically constructed from galvanized wire mesh and short lengths of brass tubing, in which a circularly polarized TE_{11} dominate mode is excited at 915 MHz. Figure 3-29 is a photograph of this type of facility. The use of circular polarization (see Sec. 3.1,

Figure 3-24. Coaxial air-line system for high power exposures of cell cultures (Guy 1977).



a) Complete system for exposing cell cultures to EM fields.



b) Cross-sectional view of assembled transmission-line cell-culture sample holder and heat exchanger. (A section of the outer conductor is machined to 7.70-cm ID so a 7.71-cm diameter dielectric support can be firmly locked into place after being pressed in while the conductor is heated.)

Figure 3-25. **Parallel-plate (microstrip) exposure system (D'Andrea *et al.* 1976).**

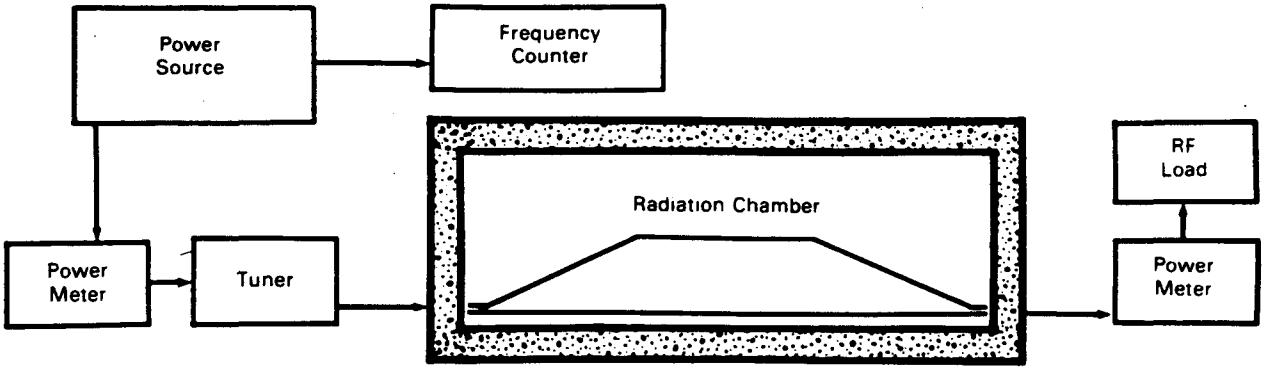


Figure 3-26. **Block diagram of the complete RF near-field synthesizer showing all principal components including RF power sources.**

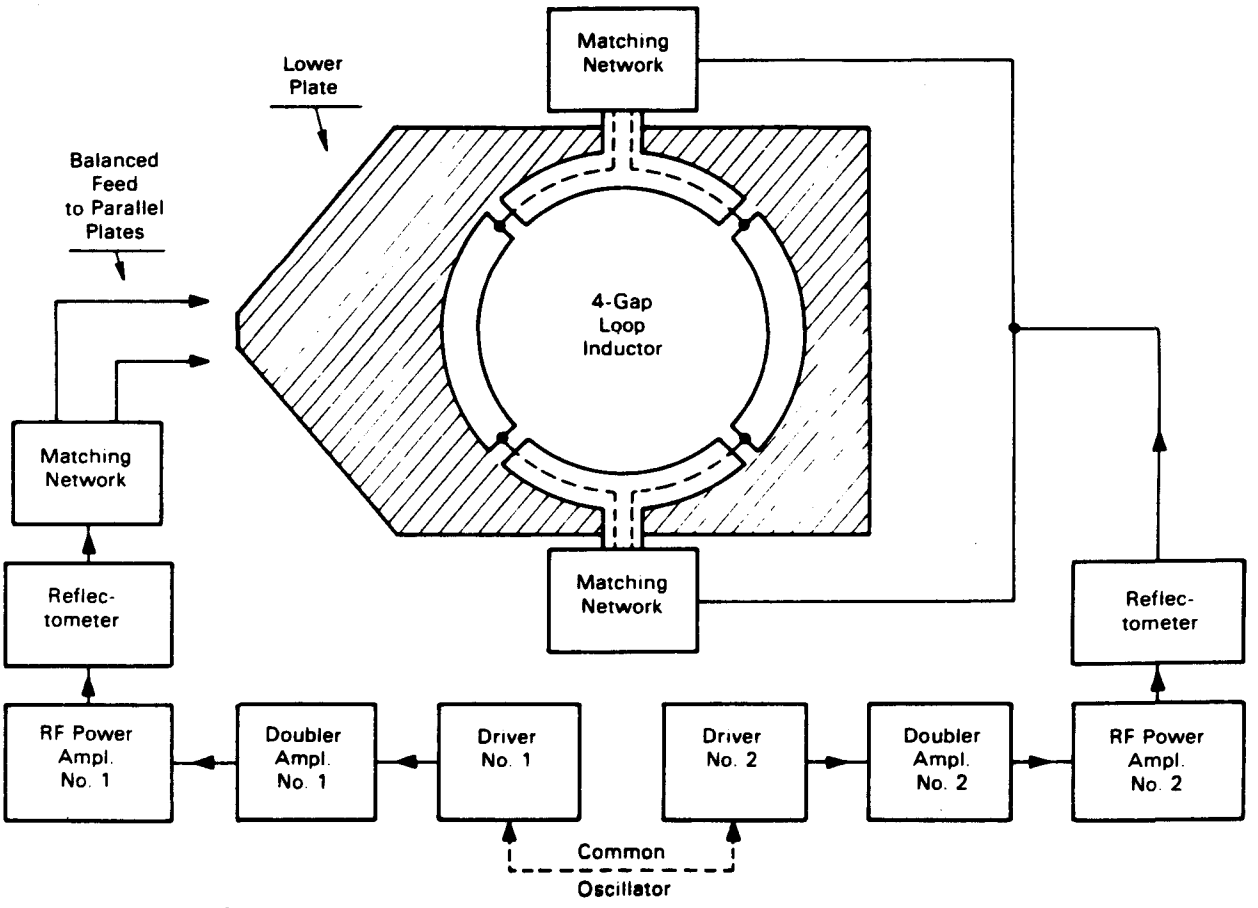
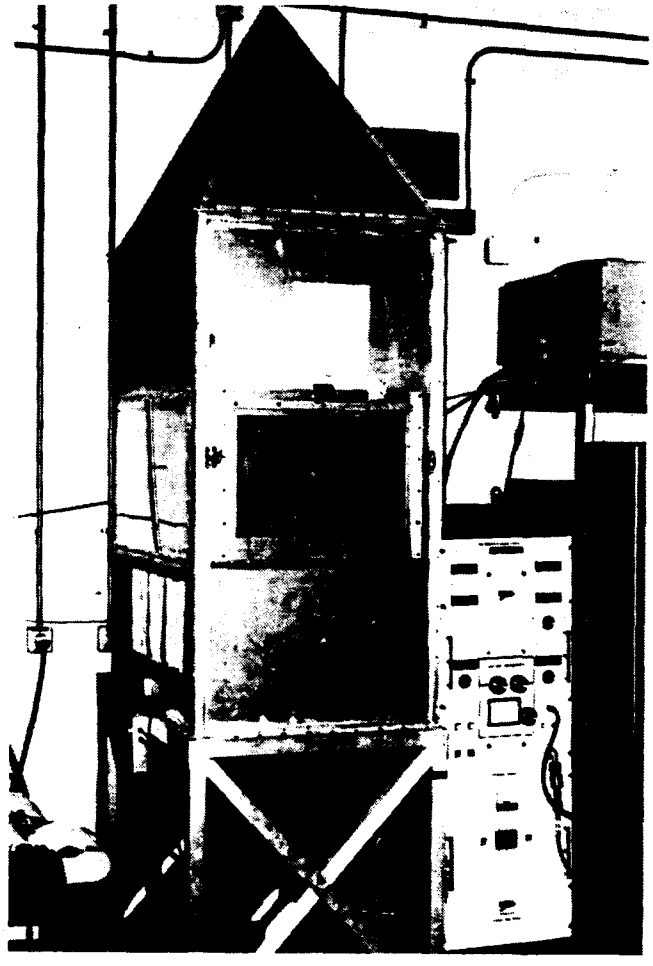


Figure 3-27. EPA 100-MHz rectangular strip line or Crawford cell.



Electromagnetic Field Theory) has two major advantages:

1) The wide variations in absorption due to constant changes in the animal's orientation are partially reduced so that the energy coupled to the animal load remains relatively constant. Note that, whereas in a linearly polarized free-field of perfect field uniformity, the average SAR can vary by ±5-8 dB (±50 percent) at or near resonance, in this system, the average variation of SAR does not exceed ±0.4 dB (±8 percent), even though the incident field uniformity is far from constant.

2) The hybrid coupler used to establish the circular polarization in the waveguide provides a way to isolate reflected from incident energy. One achieves the isolation by dumping most of the unwanted reflected energy into a load connected to the hybrid, rather than allowing it to return through the power dividing network to the source. This technique effectively reduces the mismatch normally encountered with loaded waveguides (mean voltage standing wave ratio of less than 1.5:1) and permits parallel operation of multiple units with less isolation circuitry.

Guy *et al.* (1979) have described a modifiction of this waveguide system such that it operates in a multimode field configuration at 2450 MHz. Though it is difficult to define quantitatively the incident energy levels in these units because of the complexity of the fields, the absorption characteristics have been well defined for rats of varying weights. An extensive system of 100 of these units has been installed at Guy's laboratory (Guy *et al.* 1980a) for conducting a chronic radiation study in which rats will be continuously irradiated over a 3-year life span. This

Figure 3-28. Physical details of the exposure chamber of the circularly polarized 915-MHz waveguide facility (Guy and Chou 1976).

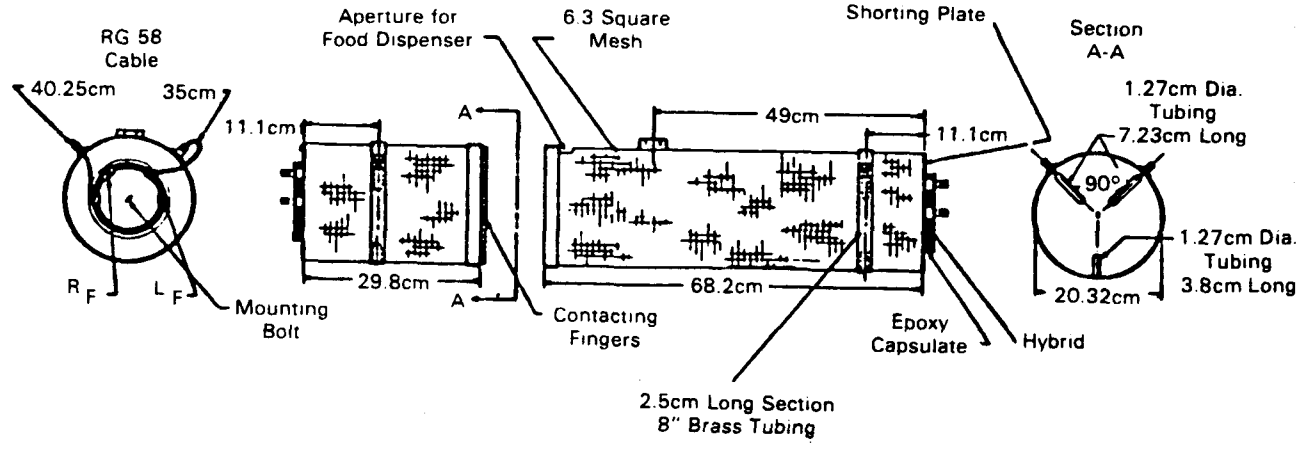
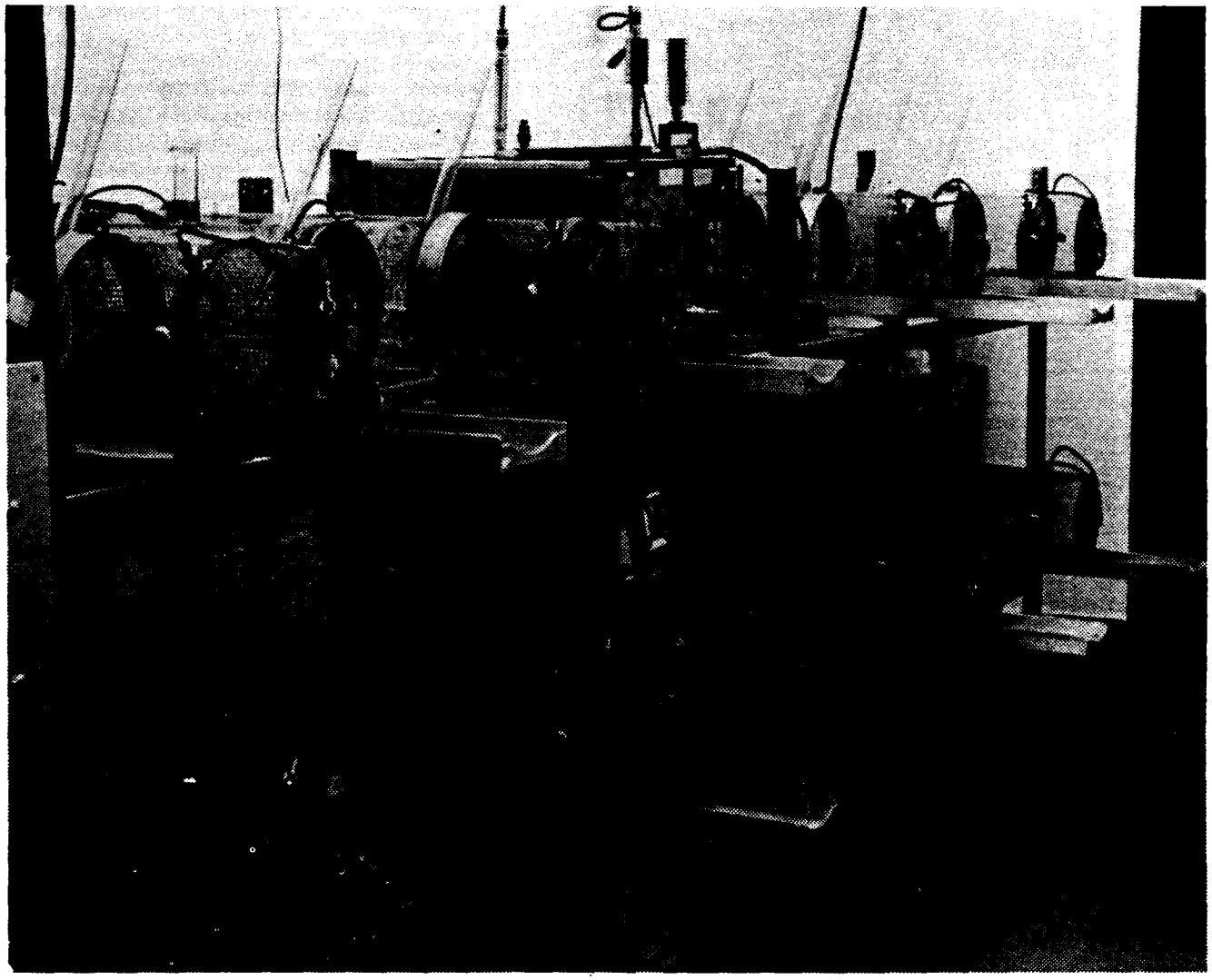


Figure 3-29. Exposure chamber with associated instrumentation for the 970-MHz circularly polarized waveguide facility at EPA.



study underlines a major advantage of Guy's waveguide systems: animal subjects are able to live continuously in their exposure system with minimal disturbance to their normal living patterns and without artifactual perturbation. Consequently, the system is ideal for the kind of chronic, long-term studies that are now being emphasized.

Cavities—The resonant cavity, which is the microwave analog of the lumped-element tuned circuit, consists of a cylindrical, rectangular, or square box with conductive walls. By suitable means, a system of standing waves may be excited within the cavity. By adjusting the cavity dimensions, the system can be made to resonate at the frequency of excitation, such that intense field levels are created within the cavity. The use of the resonant cavity as an exposure device has both a major advantage and disadvantage. A cavity system represents the most efficient way to couple RF energy into a subject per watt of input power; this coupling constitutes its principal advantage. The primary disadvantage is that the field structure within a resonant cavity is probably the most complex to be found in any exposure device. Although some researchers have argued that the field structure within a resonant cavity, particularly when operated multimodally, is a good simulation of the complex multipath environment in which humans are often exposed, it is unlikely that the human exposure environment ever approaches this level of complexity. For the reasons already discussed, the field complexity existing within a cavity makes it difficult to compare experimental data obtained in a particular cavity with those obtained in free-field exposures or even another cavity. Indeed, there are some basic differences between a free-field exposure system and a resonant cavity. For a resonant cavity

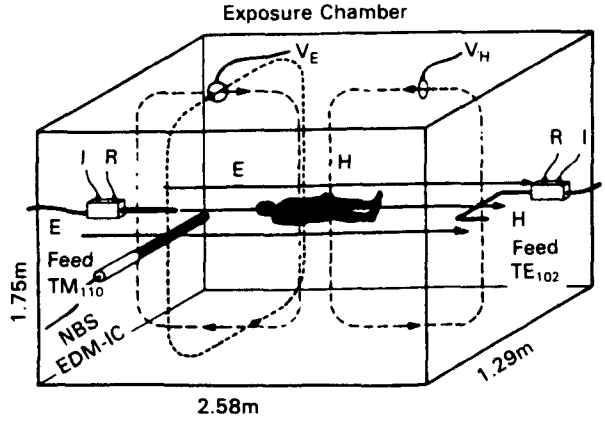
that is empty (unloaded), or that contains a biological load small in comparison to the cavity's volume (minimal loading), the fields in the cavity are in a standing-wave condition and do not propagate; the energy within is only stored. When the loading is greater (i.e., when the exposed subject occupies an appreciable fraction of the cavity's volume) the fields are hybrid, containing both stored and propagating energy. Because the fields are in a standing-wave pattern, minimally loaded cavities are useful for simulating a quasi-static interaction in which object size is small relative to wavelength (i.e., a long-wavelength type exposure). This characteristic has been used by Guy *et al.* (1976), who designed a large rectangular cavity that could be excited either separately or jointly in the TM_{110} or TE_{102} modes at frequencies of ~ 147 MHz (Figure 3-30). This system has been used to study absorption distributions in scaled-down phantom models of man independently exposed to electric or magnetic fields, depending on the mode of excitation. Single-mode circular cavities have also been used by Edwards and Ho (1975) for exposing the head of a monkey at 385 MHz. Guy and Korbel (1972) have discussed the dosimetric aspects of a rectangular cavity used to multiply expose rats at 500 MHz and have sought to emphasize some of the problems associated with cavity exposure systems. Recently, Spiegel *et al.* (1980b) described an interesting variable-volume cavity that contains movable walls such that the cavity can be tuned across a wide frequency range. The system is capable of simultaneously exciting two independent cavity modes and can be used to synthesize complex EM fields.

Multimodal cavities, such as microwave ovens, have been used frequently for experimental purposes because of ready availability and modest cost (Justesen *et al.* 1971). Where ovens have been used, they have been extensively modified to achieve the experimenter's objectives. Multimodal cavities have often been preferred over single-mode types because of the larger exposure volume available and the more uniform field distribution. The latter is achieved by a mode stirrer that helps average out the field variations within the cavity. The degree of field uniformity achieved in these devices seems to depend greatly on its design. Heynick *et al.* (1977) have described a multimodal cubical cavity suitable for irradiating nonhuman primates at 2.45 GHz (Figure 3-31). Each unit possesses its own regulated power source. Twelve of these units have been used at SRI International, Menlo Park, Calif., for chronic irradiation of a group of squirrel monkeys as part of an EPA-sponsored project. Each cavity housed two animals plus offspring.

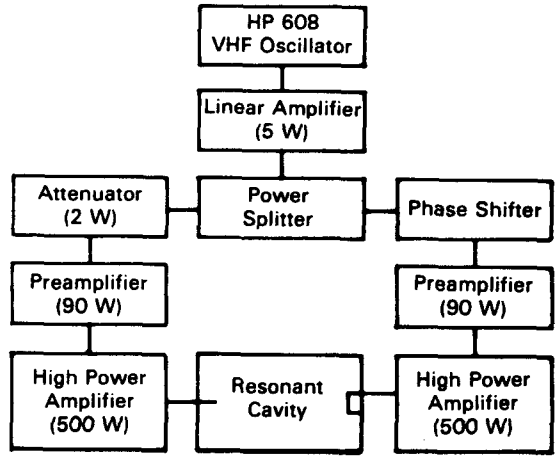
3.3.1.3 Conclusions and Unresolved Issues

Diverse exposure methods are used in biological effects experimentation, most of which differ considerably in their field characteristics. Since each has its own particular advantages and disadvantages, the choice of which system to use has depended on the application. For experiments involving whole-body irradiation of animals, some kind of standardized method of exposure on which most researchers can agree is needed. Although such ideas have been proposed and discussed in the past, they are difficult

Figure 3-30. VHF resonant cavity facility (Guy *et al.* 1976)

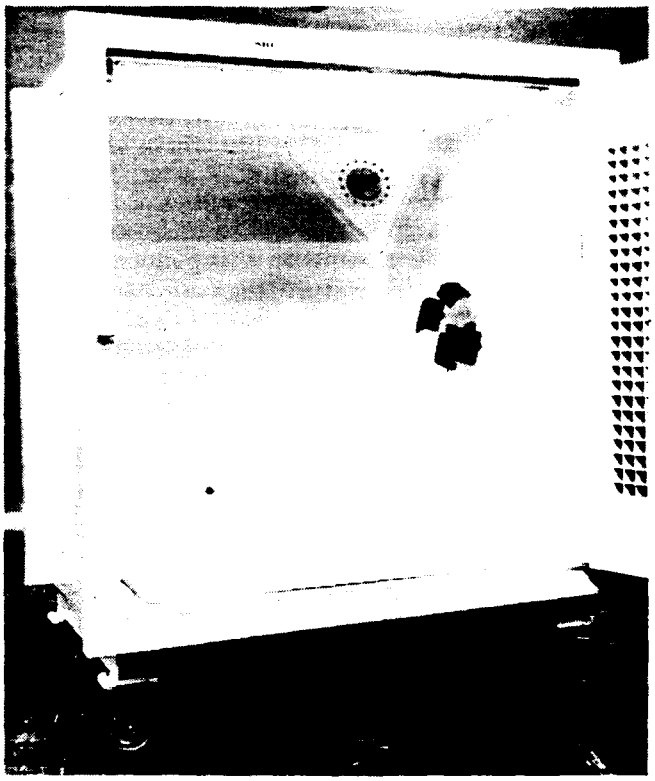


a) Exposure of phantom scale model of man in a resonant cavity.

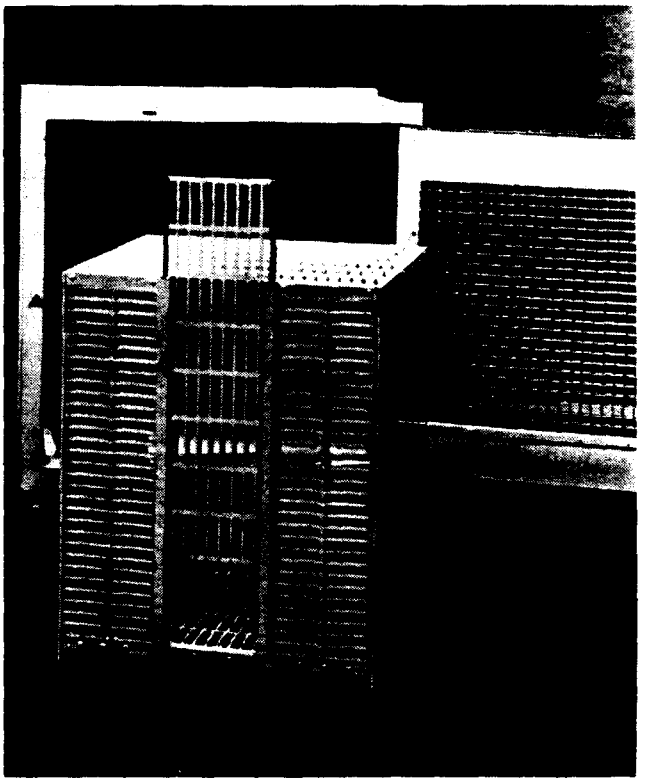


b) Block diagram of resonant cavity driving system.

Figure 3-31. SRI multimodal cavity facility for primate irradiation (Heynick *et al.* 1977).



a) Microwave cavity with door open, showing mode stirrer, iris, radiopaque windows, and waste-collection tray.



b) Dielectric cage.

to implement because many exposure requirements are conflicting, and, therefore, no one exposure system can satisfy all of the various requirements. However, some agreement on standardization should make experiments more readily replicable and effects more readily confirmed. Further efforts are needed to this end.

During the past decade, there has been significant improvement in the exposure facilities available for biological experimentation. Many of these facilities have succeeded in overcoming the deficiencies inherent in many of the older exposure devices. Exposure systems specifically designed for chronic irradiation studies must also be developed further, particularly to reduce their cost without significant sacrifice in performance.

Also seriously needed are further studies that compare absorption and biological end points for different forms of exposure. This problem can be summarized as follows: For the same experiment performed in different exposure systems involving plane-wave, complex, or multi-path fields, are there differences in biological outcomes even where the same whole-body-averaged SAR is maintained throughout?

3.3.2 Animal Holders

Any experimental irradiation of nonanesthetized animals requires use of some form of holder or restrainer to keep the animal in a location of known field strength or power density. For multiple animal exposures, it is also necessary to keep the animals separated from each other. From a dosimetric point of view, the optimal exposure condition is one in which the animal is constrained in one orientation and posture. This way, both whole body and regional dosimetry could be determined with satisfactory precision. However, complete restraint of an animal is considered by most biologists an excessive stress and, therefore, unacceptable. Consequently, the commonly accepted exposure environment represents a reasonable compromise between these conflicting demands: the holder is designed to restrain the animal, allow it to change posture and orientation, and also allow for a small degree of lateral and vertical movement.

3.3.2.1 Perturbation by Restrainers

One of the important criteria in designing animal holders is that they be constructed of materials that

cause the least perturbation of incident fields possible. What that means is that cages can be built only from nonmetallic materials. Various types of low-loss dielectric materials are available in rigid and semirigid form, and have been the material of choice. The most popular has been acrylic plastic (polymethyl methacrylate), because of its optical transparency, superior mechanical strength, and ease of machining. Some experimental and analytical studies have been performed to determine the degree to which these materials perturb the incident field (Weil 1974; Lin *et al.* 1977). These studies showed that, under certain conditions, these materials can indeed cause serious field perturbations, so that the real power density of the field to which the animal is exposed is not known precisely. Use of foamed polystyrene instead of acrylic is a possible solution. Foamed polystyrene has a relative permittivity value close to unity and creates only minimal field perturbation. However, two disadvantages are associated with polystyrene materials: They are optically opaque, so that animals cannot be observed in their cages; and they are not strong and can be readily gnawed by rodents. Coating the material with a substance to which the rodents are averse, such as quinine, has been tried by a few workers (Catravas 1976) to reduce gnawing. However, this practice adds an unwanted additional insult to the experimental subjects. Nonetheless, foamed polystyrene is useful in studies involving short-term exposures.

A more recent paper by Ho (1978) questioned the significance of the incident-field perturbations created by holders made of acrylic materials. In an analytical study involving a two-dimensional model that contained a cylinder of muscle-equivalent material mounted concentrically inside an acrylic cylinder, Ho showed that despite a significant perturbation of the incident field in the empty holder, there was relatively little perturbation in the whole-body-averaged SAR and the SAR distribution inside the muscle-equivalent cylinder when compared with that which existed when no holder was present. Ho concluded that large perturbations of the field created by animal holders do not automatically create a correspondingly large perturbation in the animal's absorption rate because the presence of a mass of lossy dielectric (i.e., the animal) tends greatly to damp out the standing-wave patterns created by the acrylic holder. Further experimental observations are needed to confirm this conclusion.

As part of a behavioral investigation, Gage *et al.* (1979) investigated the influence of two different holders on the whole-body SAR of rats and mice at 2450 MHz. One holder was a cuboidal container made of foamed polystyrene; the other was an acrylic cylinder. They concluded that there was a significant alteration of SAR values for both rats and mice due to the presence of the acrylic cylinder when the animals were oriented parallel to the E field. This effect was considerably more pronounced in the mouse, probably because 2450 MHz is a frequency close to resonant absorption for the E-parallel orientation of the mouse.

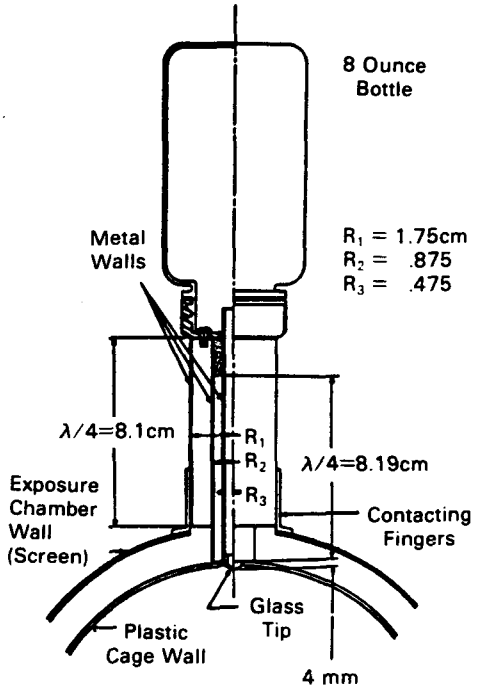
3.3.2.2 Feeding and Watering During Exposure

Experiments involving chronic, long-term RF irradiation of animals usually require that some arrangements for food and water be made during irradiation. Provision of food does not present difficulties if the standard form of dry food pellets fed to laboratory animals is used, since these pellets absorb little RF energy. However, providing drinking water or liquid nutriment does present some problems because water is a comparatively good conductor and, therefore, absorbs energy. Two methods of supplying water have been used; each has problems.

In the first, the water reservoir is placed in the exposure system with the animal. The major disadvantage here is that, since the water supply is located in a high-field-strength environment, it absorbs RF energy and perturbs surrounding fields. These factors create uncertainty in both dosimetric and densitometric measurements. Furthermore, it is conceivable that, if the field levels are intense enough, the water temperture could rise until the animal would refuse to drink. Consequently, this approach is not recommended.

The second method involves placing the reservoir outside the exposure system in a region of little or no field strength, and supplying water to the animal via a supply tube or pipe.This method is superior, but it too has associated pitfalls which, without special precautions, can introduce serious experimental artifacts. As Guy and Chou (1976) have pointed out, the water tube or pipe provides a conductive pathway for microwave currents. When the animal attempts to drink, a circuit is closed between the animal, which is at high potential, and the water reservoir, which is at zero or ground potential. RF currents then pass from the animal to the watering system; because the contact point area is small and involves sensitive tissue, a high current density may exist in the animal's tongue. Since the animal will find this condition aversive, it will probably refuse to drink. Therefore, the RF current flow through the water supply system must be interrupted. Three methods of interruption have been devised: (a) When the animal interrupts a beam of light using a tongue-licking operant, a small bolus of fluid is injected into the animal's mouth (King *et al.* 1970); (b) the animal holder is equipped with a small water trough which is continuously supplied through a water drip system; and (c) an RF-choke assembly is placed between the animal and the water reservoir to effectively decouple the animal from the water supply when drinking (Figure 3-32). In the choke assembly design (applying

Figure 3-32. Water-supply system for exposure chamber (Guy and Chou 1976).



only to enclosed systems), water is supplied through copper tubing that forms the center conductor of a shorted quarter-wave section of a triaxial air line. To prevent the animal from coming into contact with the copper tubing, a short section of glass or acrylic tubing is mounted at its tip. The choke assembly effectively provides a high impedance at the point of animal contact and thus reduces the RF current in the watering system to near zero.

3.3.3 Densitometric Instrumentation

Densitometry is the measurement of RF-field strength and is usually expressed in units of equivalent plane-wave power denisty. Dosimetry is the measurement of absorbed energy, or the rate of energy absorption by some object in an RF field. In this section, the relationships between the strength or intensity of an RF field and a suitable and measurable field variable are given. The question of what constitutes a suitable variable has been addressed (Bowman 1970). For a linearly polarized plane-wave EM field in free space—and, for practical purposes, in air—the following relationships exist between the electric field, the magnetic field, the power density, the electric energy density, and the magnetic energy density:

$$\frac{E}{H} = \eta_o \qquad (3\text{-}12)$$

$$\eta_o = (\mu_o/\varepsilon_o)^{1/2} \qquad (3\text{-}13)$$

$$W = \frac{E^2}{\eta_o} = \eta_o H^2 \qquad (3\text{-}14)$$

$$U = \tfrac{1}{2}(\varepsilon_o E^2 + \mu_o H^2) = U_E + U_H \qquad (3\text{-}15)$$

$$U_E = U_H \qquad (3\text{-}16)$$

where E = electric field, V/m
H = magnetic field, A/m
η_o = characteristic or intrinsic impedance of free space, 377 Ω
μ_o = permeability of free space, H/m
ε_o = permittivity of free space, F/m
W = power density, W/m²
U = total energy density, J/m³
U_E = electric energy density, J/m³
U_H = magnetic energy density, J/m³

The quantities μ_o and ε_o are properties of the medium and are scalar constants for free space. Equation 3-12 therefore states that in free space the magnitudes of E and H are related by a constant factor η_o. Equation 3-14 relates the power density W to individual field components E and H for the basic plane wave. Equation 3-15 is a general relationship for the total energy density U of an RF field and defines the individual electric- and magnetic-field energy densities U_E and U_H.

The relationships between field variables for a plane wave are simple, so that the measurement of any one field parameter allows calculation of the others. Although power density is a variable of interest in biological effects studies, it is particularly difficult, if not impossible, to measure directly because it is a time-averaged vector cross product that, in general, is not expressed as simply as Equation 3-14. However, it may be indirectly evaluated for plane waves by measurement of the E or H field, as indicated by Equation 3-14. This measurement, when coverted to units of power density (W/m²) by Equation 3-14, is referred to as the "equivalent plane-wave power density." Above 1 GHz, it is usually not necessary to measure both the E and the H fields (Bowman 1970), whereas below ~ 300 MHz, the H field becomes increasingly important, and an independent measurement of H is necessary (Aslan 1979; Lin *et al.* 1973).

However, power density is inappropriate in the evaluation of near fields of antennas or fields near reflecting surfaces because intense fields can exist in these regions when the power density is low or even zero. A plane wave normally incident on a conducting surface can create standing waves with large E and H values but very low power density. Since power density is a measure of the power flow across a unit area, the net power flow of a plane wave normally incident on a conducting surface and reflecting back

is zero (or small in practical cases), and hence the power density is zero. The E and H fields in that case would be in a standing-wave pattern with amplitudes twice those of the fields of the incident wave.

In the near field of sources or for complex RF fields, the E and H fields are not related by Equation 3-12; however, Equation 3-15, which related the individual E and H fields to their respective energy densities, is always true. Therefore, measurements of both the E and H fields are required to evaluate the total energy density where Equation 3-12 does not apply.

Bowman (1970), Swicord (1971), and others have described the desirable characteristics of an instrument for quantifying hazardous EM fields. The instrument and probe should (1) measure in terms of energy density and respond only to the variable being measured, (2) be small to permit a high degree of spatial resolution and thus be useful in small volumes, and (3) have an isotropic response and be insensitive to field polarization. The probe should also cause little scattering of the field and operate over a broad frequency range. The instrument and probe should be battery powered, lightweight, and rugged, and should read either peak or average values and have a dynamic range of at least 20 dB (one hundredfold) without the need to change probes. The readout instrument should be direct reading and free from susceptibility to RF interference.

Many approaches have been used to develop field probes that meet these criteria. The most successful and enduring designs have centered around the thin-film thermocouple or bolometer sensor/antenna and the crystal detector/antenna. The first type of sensor is a square-law-responding device that senses a temperature change due to the absorption of energy. The second type uses a semiconductor diode that produces a voltage or current related to the strength of a field variable. The diode can respond as either a square-law detector or a linear detector, depending on the region in which it is operating. Some commercially available electric-field probes are shown in Figure 3-33.

3.3.3.1 Electric-Field Probes

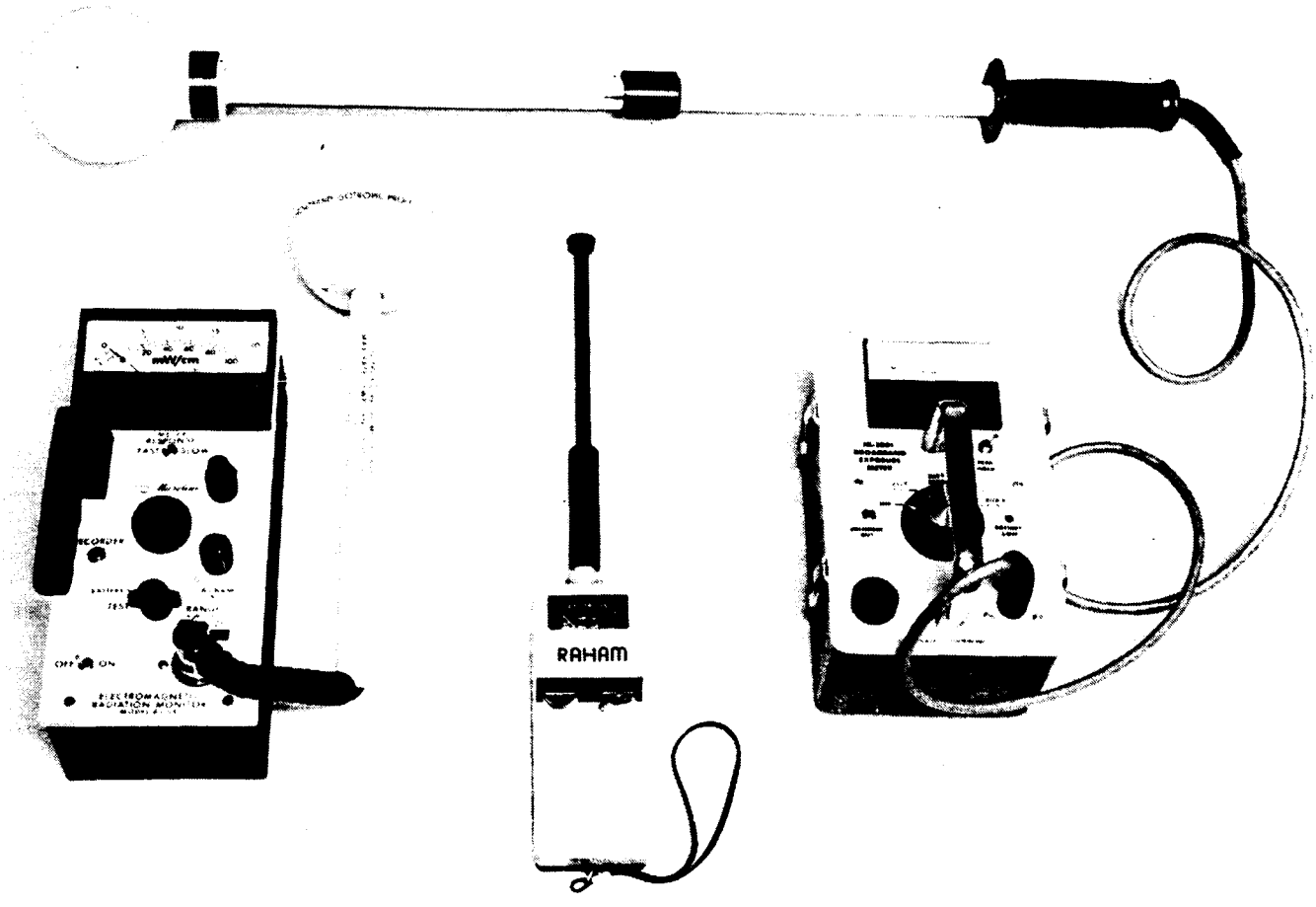
The NBS EDM-2 electric energy density meter (Belsher 1975) was developed for accurate measurement of occupational exposure to EM fields from 10 to 500 MHz. This probe uses three short orthogonal dipoles terminated by crystal rectifiers to detect the RF field, and produces an isotropic response within ±1 dB. The DC signal appearing on the diodes is conducted to the meter's circuits through RF-transparent high-resistance lines. The meter displays electric energy density in units of microjoules per cubic meter. Energy density was chosen as the field variable to be displayed because of the ambiguity of power density in the near field of radiating elements. The meter has a dynamic range of 50 dB in nine ranges from 0.003 to 30 $\mu J/m^3$. Although the probe's detector diodes are used in both the square-law and linear regions, a square-law response is achieved over most of the range by a varistor network. The meter is calibrated at specific frequencies within the FCC ISM bands at 13.56, 27.12, and 40.68 MHz. The frequency response is flat within ±1.0 dB over the 10- to 500-MHz operating range. One of the improvements in the EDM-2 device over previous designs is reduced temperature-induced drift. The reduced drift is achieved by loading of the dipole-detector diodes with equivalent load diodes. This technique has reduced the temperature response to $< \pm 0.7$ percent/°C in the 15 to 35°C range. The field probe design provides a rapid response time to permit observation of the modulation of the field and the measurement of peak values. The rise and fall times (10 to 90 percent of the signal and 90 to 10 percent of the signal, respectively) are both < 0.6 ms on the most sensitive range.

A commercial version of the NBS electric-field probe is marketed by Holaday Industries (Edina, Minn.). This field-strength meter (Model HI-3001) operates over the frequency range 0.5 to 1000 MHz and is accurate within ±1.0 dB over this range. The meter has an isotropic response within ±1.0 dB and has peak-hold and read circuitry to capture the highest reading observed. The response time is 1.5 s. Measuring range of the meter is 1 to 3160 V/m in six ranges on an analog meter. An audible tone, with a pitch proportional to the meter reading, is provided to prevent operator overexposure in survey applications.

In 1980 the General Microwave Corporation (Farmingdale, N.Y.) introduced the RAHAM Model 4A radiation-hazard meter. This instrument is a broadband crystal-detector design with a frequency coverage of 200 kHz to 26 GHz, and a display calibrated in units of equivalent plane-wave power density that ranges from 0.001 to 20 mW/cm^2. This meter has an isotropic response, is battery powered, and has a response time of 1.5 s.

For use in the near field, Rudge (1970) constructed an electric-field probe using two short crossed-dipole antennas. This meter was designed to operate from 915 to 2450 MHz in proximity to RF emitters. The probe detected the electric field in two perpendicular planes, and was calibrated in power density terms. Rudge carefully analyzed sources of error in the design of near-field probes. His study included the effects of field curvature and antenna backscatter, particularly with regard to multiple coupling and impedance variation, both of which affect the calibration of the field probe. The major source of scattering was the probe's antenna, particularly when the lengths of the dipole wings were of the order of one-fourth wavelength. The prototypal probe achieved a dynamic range of 47 dB with a square-law

Figure 3-33. **Samples of commercially available survey meters for measuring RF electric-field strength. From left to right the units shown are: The Narda Microwave Corporation Model 8315A meter with a Model 8321 isotropic probe; the General Microwave Corporation Model 481A meter with a Model 81 probe; and the Holaday Industries, Inc., Model HI-3001 meter and probe.**



response, by addition of fixed values of load resistances at increasing power levels to keep the detector diode operation in the square-law region. Sensitivity was reported at 300 nW/cm² with a probe antenna of 8-mm overall dipole length.

Bassen *et al.* (1975) developed a miniature broadband electric-field probe. Although the probe was designed for free-space operation, the ultimate goal was to develop an implantable isotropic probe for biological effects research (Bassen *et al.* 1977a). With 3-mm dipole elements, the free-space probe achieved a relatively flat frequency response over the range of 915 MHz to 10 GHz. After some refinements were incorporated (Bassen 1977; Bassen *et al.* 1977b), the probe was tested over a frequency range of 200 MHz to 12 GHz. The improved version had a 30-dB dynamic range with a 20-μW/cm² sensitivity, isotropic response to $\pm$2 dB, a detection bandwidth of 2 kHz, and a spatial resolution of ~ 3mm.

The requirement of small size was imposed on the implantable-probe design to ensure minimal alteration of the field when the probe is used relatively close to sources and dielectric boundaries. At the same time, the constraint of small dipole size has the further advantage of extending the frequency response of the probe into higher frequencies. With 3-mm dipoles, theoretically, resonance should occur at 50 GHz. The probe uses dipole elements terminated with three zero-bias Schottky diodes for a maximal square-law response, arranged in an "I"-beam configuration. High-impedance leads are connected to the diodes and routed along the probe's body to an optical telemeter. A fiber-optics cable then routes the digitally encoded field-strength signal to a digital receiver that is calibrated to display the equivalent plane-wave power density. A commercial version of the miniature field probe is marketed by Electronic Instrumentation and Technology (Sterling, Va.).

An electric-field sensor (EFS) and readout system capable of operating over the frequency range 10 kHz to 200 MHz has been developed by Instruments for Industry, Inc. (Farmingdale, N.Y.) and was described by Ruggera (1976). The EFS-1, -2, and -3 are linearly

polarized square-law electric field detectors with an analog readout calibrated in volts per meter. The EFS-1 is intended for CW fields, the EFS-2 for pulsed fields, and the EFS-3 for both types of fields with the addition of a peak-reading provision. The dynamic range is 1 to 300 V/m with antennas of different lengths. An optical transmitter is used when remote readout is required, which eliminates field perturbations introduced by metallic cable. An isotropic monitor has also been designed (RHM series) that essentially encloses three EFS-series sensors in one box. Readings from each sensor can be summed (by the square root of the sum of the squares of the field strengths) to measure the total electric field, or a particular sensor can be read directly when field polarization is a variable of interest.

Another design of an electric-field probe uses thin-film thermocouple arrays acting as both the dipole antenna and the detection element. The dipole elements are lossy; therefore, their temperature increases proportionally with the square of the tangential electric field. The dipole elements can be thought of as the series connection of a large number of tiny thermocouple dipoles. This detection method provides true square-law response and produces signals proportional to the average energy density of the electric field in the measured volume.

The Narda Microwave Corporation (Plainview, N.Y.) produces a wide selection of RF-radiation monitoring instruments, such as the Model 8606 broadband isotropic radiation monitor. This instrument uses three orthogonal, thin-film thermocouple sensors that respond to the square of the electric field. Two probes are available that have the combined dynamic range of 0.02 to 100 mW/cm^2 over the frequency range 0.3 to 26 GHz. The probes have isotropic response within $\pm$0.5 dB except when the electric field is aligned with the handle axis. The General Microwave RAHAM Model 3, another electric-field-sensitive meter with thin-film thermocouple sensors, performs comparably to the Narda 8606 system. The Narda 8100 series meters were designed earlier (Aslan 1970) for measuring the leakage of microwave ovens, dryers, and medical equipment, which operate at 915 and 2450 MHz. The probe used with the 8100 series meters is not isotropic but must be oriented with the probe handle perpendicular to the wavefront. Three probes are used to measure across a dynamic range of 0.02 to 200 mW/cm^2. The probes contain two orthogonal, thin-film vacuum-evaporated thermocouple elements that function both as antennas and detectors. When the probes are used at 915 MHz, an adapter is attached to the end of the probes, so that the effective length of the dipoles is increased. This increase in length compensates for the reduced efficiency of the antenna at 915 MHz.

3.3.3.2 Magnetic-Field Probes

As discussed previously, measurement of only the electric field for frequencies below ~ 300 MHz does not fully characterize the hazard or heating potential of an RF field, because the electric and magnetic fields are not related by the free-space intrinsic impedance at frequently encountered distances from radiation sources. In the mid-1970's, NIOSH supported an NBS effort to develop a magnetic-field probe that would operate in the 10- to 300-MHz band. Two probes were developed (Greene 1975a,b) that consist of small single-turn, balanced loop antennas 10 and 3.16 cm in diameter. The dynamic ranges of the two probes are 0.5 to 5.0 A/m and 5.0 to 50 A/m, respectively. The probes are capable of measuring the magnetic field within a few centimeters of an RF-radiation source, in the near field. The loop antennas are constructed with two short gaps; one gap is terminated with a silicon diode that detects the induced RF voltage; the other gap is terminated with a capacitor to bypass RF currents without short-circuiting the DC output. The DC signal is then transmitted over NBS-developed conducting plastic lines to an electrometer voltmeter. One of the inherent problems of loop antennas is that the response is proportional to frequency, which makes these antennas particularly sensitive to errors if harmonics (integral multiples of the fundamental frequency) are present in the field under study. Greene also shows that both the electric-dipole response of the loop and the partial-resonance effect increase with frequency. An experimental method is provided to minimize the error due to electric-field sensitivity, and plots are provided for the two probes to indicate worst-case measurement error vs. frequency due to the electric-dipole response. The self-resonant frequencies of the two loops were computed to be 280 and 760 MHz for the 10- and 3.16-cm loops, respectively, and a correction curve was provided to estimate the increase in response due to this effect.

Aslan (1976) reported the development of a magnetic-field-radiation monitor that has a frequency response within $\pm$1.0 dB over the frequency range of 10 to 200 MHz. Two probes, the Narda Corporation Models 8631 and 8633, are used to provide a full-scale measurement range of 0.2 to 100 mW/cm^2. (Sensitivity extends to 20 μW/cm^2 on the Model 8631 probe.) These probes have an isotropic response ($\pm$0.5 dB) and accept all polarizations. Each probe has three orthogonal coils; each coil has two turns. The coils are terminated with thin-film thermocouple elements. High-resistance lines are used to route the DC signal to a preamplifier in the handle of the shielded probe, and the preamplifier output is connected via shielded cable to an indicating meter. To achieve a partial solution to the problems of frequency dependence of loop antennas, the coils

were designed to be series resonant slightly below the low-frequency end of the operating band. The response of the coils increases at frequencies above 200 MHz, as the electric-dipole effect begins to govern the response.

Magnetic-field probes of various designs were reviewed by Ruggera (1976); many were commercially available and others were experimental. Ruggera described electric-field-shielded loops constructed with semirigid coaxial transmission line from 2 to 6 cm in diameter. Ruggera also described an isotropic, electric-field-shielded, three-loop, orthogonal, magnetic-field probe that has a cross-polarization rejectivity of ~ 20 dB from 40 kHz to 50 MHz. Signals from the probe are recovered with terminated, coaxial cables. In addition, the author described a three-axis, magnetic-field-measuring instrument developed by Southwest Research Institute. The original design was plagued by cable-pickup problems, which limited the usable frequency to 50 MHz. Refinements by the FDA Bureau of Radiological Health (BRH) that incorporated the optical telemetry systems (see Sec. 3.3.3.1) used on the BRH miniature electric-field probe led to a flatter frequency response over the extended frequency range of 150 kHz to 150 MHz.

In 1981 Holaday Industries introduced a new magnetic-field probe for their 3000 series of field-strength meters. The Model STH-01 probe has a frequency response of 5 to 300 MHz within ±2 dB. The uniformity of response improves to ±1 dB over the range of 10 to 200 MHz. When used with the HI-3001 meter (Sec. 3.3.3.1), full-scale sensitivity of the probe is 0.1 A^2/m^2 in the low range and 1.0 A^2/m^2 in the high range. The sensor consists of three orthogonal loops terminated with detector diodes that rectify the RF voltages induced in the loops. The sensors can withstand an 800-percent overload above the full-scale field strength without damage.

3.4 Dosimetric Methods

James B. Kinn

Dosimetric methods are used to determine where and how much energy is absorbed by a biological target. Two areas are considered: (1) whole-body dosimetry, dealing with the integrated or spatially averaged SAR for the entire animal; and (2) regional dosimetry, dealing with the SARs or internal field strengths in a specific site of the biological target.

3.4.1 Whole-Body Dosimetry

Whole-body dosimetry is based on either a power difference or a calorimetric method. The power-difference method is limited to closed exposure systems such as waveguides, TEM-mode transmission cells, and coaxial air lines. In this method, power meters are attached to the exposure systems by directional couplers to measure the incident, reflected, and transmitted power through a section of the closed system containing the biological target. The power absorbed by the biological target is then measured by subtracting the values of the reflected and transmitted power from the incident power. In the case of exposure systems using live animals, the values of those three measurements vary as the animals move, because absorption is a function of the animal's orientation relative to field polarization. What is needed is a data-collection system that can integrate the measured power difference and then determine an average over a period of time, usually the exposure duration (Christman *et al.* 1974; Ho and Edwards 1977b). The advantage of this method is that it provides on-line instantaneous measurements of absorbed power. A disadvantage is that its optimum application is in single-animal exposure; simultaneous exposures of multiple animals in the same closed system would result in average dose rate values for the group, rather than for an individual animal. A second disadvantage is that, under exposure conditions where the RF energy absorption rate is very low, it may be impossible to measure the power absorption, because the measurement error in the power meter exceeds the computed power difference.

Calorimetric methods use the thermalization of the absorbed power as a measure of SAR. Under the tacit assumption that all the RF energy absorbed by a biological target is converted to heat, the calorimetric method measures the heat added to the target. The approach is to irradiate an animal carcass with a short exposure at high power to reduce heat loss errors due to conduction and convection during the exposure. The thermalized energy added to the carcass is measured with the calorimeter. Calories per unit time per unit mass are then converted to W/kg, the SAR for the high incident power density. The SAR for any other power density is then scaled from this measured value in direct proportion to the ratio of power densities. Three calorimetric methods that have been used in whole body dosimetry are gradient-layer calorimetry (Gandhi *et al.* 1979), Dewar-flask calorimetry (Blackman and Black 1977), and twin-well calorimetry (Hunt and Phillips 1972; Kinn 1977). All three methods use a freshly killed animal carcass that has been briefly exposed to high-power RF fields and thus raised to a higher temperature. It has been assumed that the dielectric properties of the carcass do not differ significantly from those of a living animal.

The gradient-layer calorimeter measures the rate at which heat passes from the heated animal through the walls of the calorimeter to the room air. It is accurate, but it takes several hours to make the measurement.

The Dewar-flask calorimeter method uses the difference between the average temperature of the animal carcass before and after rapid heating with RF radiation to determine the heating rate and thus the dose rate. To determine the average temperature of the animal carcass, it is placed (with a coupling fluid, usually water) into a Dewar flask, and the equilibrium temperature of the mixture is measured. From the theory of mixtures and a knowledge of the average specific heat capacity of the animal, the average carcass temperature is determined. The average temperature of the heated carcass is determined similarly, and the SAR is computed. Although the method is simple by design, a disadvantage is that a long time is required to measure equilibrium temperature. Furthermore, the average specific heat capacity of the carcass must be known, and, because the body's composition is complex, this capacity cannot be precisely determined.

The twin-well calorimeter method uses pairs of carcasses of equal mass. One carcass of a pair is heated with RF radiation; the heated and unheated carcasses are each placed in a well of the calorimeter, and the calorimeter is allowed to return to equilibrium. The twin-well calorimeter measures the increment of heat introduced by the exposure. The SAR is then calculated from the measured caloric increase, carcass mass, and exposure time. This method does not require the specific heat capacity of the carcass but requires 4 to 16 h to make a measurement. A recent improvement of the method (Kinn *et al.* 1984) has reduced the measurement time to 15 to 30 min and increased measurement accuracy by control of the calorimeter with a microprocessor system. This arrangement is the same as the standard setup except that the unexposed carcass is in contact with a heating element (Figure 3-34). The microprocessor program controls the rate at which heat is applied to the unexposed carcass. Using the twin-well calorimeter as a "thermal" balance, the program controls the

heating rate so that equilibrium is established in as short a time as possible. All of the power applied to the heating element, and thus to the animal carcass, is integrated and divided by the mass of the carcass to determine the SAR. A 2-percent error due to heat lost to the calorimeter walls has been measured using electrically heated water bottles as animal substitutes.

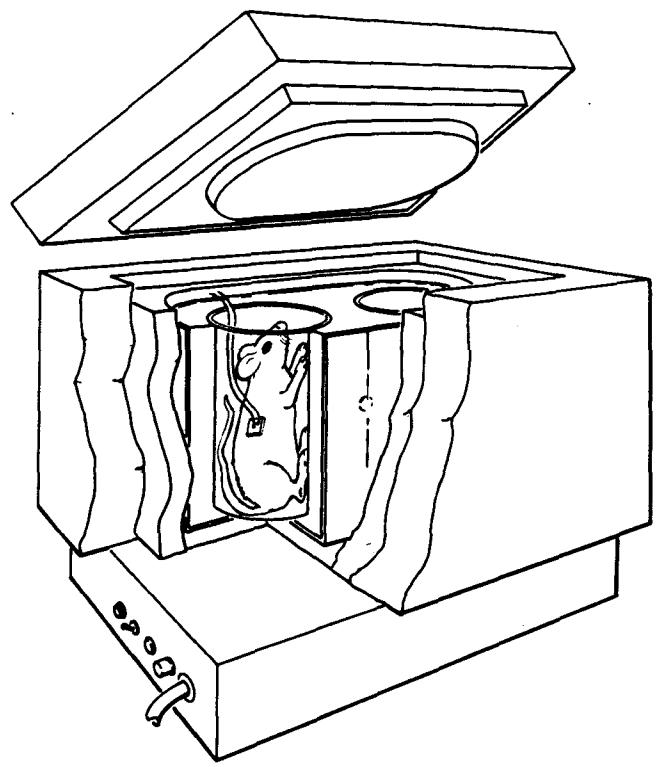
3.4.2 Regional Dosimetry

Regional dosimetry is performed to determine either the energy absorption rate or the field strength at a specific location within an animal or tissue preparation. The average field strength within the animal can be measured directly or inferred from the SAR. Direct measurement of field strength is made with an implantable probe containing one or more miniature diodes mounted on a dielectric substrate and attached with high-resistance leads to a voltage-reading device (Bassen *et al.* 1977b). The voltage across the diode is a measure of the field strength at the diode, provided the animal tissue material in which the probe is implanted does not differ significantly in dieletric properties from the material used in the calibration procedure (Bassen 1977). The useful frequency range over which such field strength measurements can be made is 100 to 12,000 MHz. The reduced sensitivity at lower frequencies and the greatly reduced field strength in biological targets at the higher frequencies delineate the useful frequency range. Indirect measurement of internal field strength is derived from the SAR value. The heating rate is proportional to the square of the electric-field strength.

Measurement of regional SAR can also be accomplished by temperature probes or by thermographic imaging. Temperature probes are small (1-mm diameter) and are designed to be implanted in the site of interest without altering the EM field in that area (Rozzell *et al.* 1974; Bowman 1976; Christensen 1977; Wickersheim and Alves 1982). An animal or preparation is briefly exposed to RF fields of high intensity, and the temperature rise is measured. The rate of temperature rise, together with the amount of heat loss, is then used to compute the SAR at a specific site in an absorber, such as a rat brain.

The technique described above is a special case of heating and cooling curve analysis, i.e., estimating the initial rate when the rate of heating is much higher than the rate of cooling. The analysis of the complete heating and/or cooling curve is especially useful in cases where the RF energy absorption is of the same order of magnitude as the cooling rate of the animal or preparation. In this procedure, the temperature is recorded continuously during exposure and/or after exposure until a steady state or equilibrium temperature is reached. Analysis of either curve yields the cooling rate, which is directly related to the SAR. The heating curve also contains

Figure 3-34. Microprocessor-controlled twin-well calorimeter.



the cooling rate that can be determined by the appropriate analysis; therefore, the SAR can be determined from either a heating or a cooling curve (Allis *et al.* 1977).

Thermographic imaging also requires very high power exposures. This method uses a thermographic camera containing a mirror scanning system, a liquid-nitrogen-cooled detector, and a data-collection system usually interfaced to a minicomputer (Guy 1971; Guy *et al.* 1968, 1977; Kantor and Cetas 1977). The investigator prepares specimens by cutting a frozen carcass into halves and supporting each half in an RF-transparent medium such as urethane foam. The surface of the cut plane is covered with either a plastic film polyester "silk" screen material to hold each half of the specimen in its foam support. The "silk" screen material allows electrical contact between the two halves when they are readjoined during exposure. Unlike plastic film, which prevents induced current from flowing across its surface, the "silk" screen material allows current flow, and the model may be placed in a complex field of unknown polarization. The assembled specimen is allowed to equilibrate to room temperature (25°C). Thermographic pictures are taken of the animal specimens at

the plane of the cut before and after exposure, and the SAR is computed from the point-to-point temperature change during exposure. The SAR values are then used to produce a contour plot of iso-SAR lines or averaged values over a specific area.

Scaled-down or full size physical models made with materials having dielectric properties similar to those of biological tissues are also used to determine the SAR distribution in a biological specimen, such as man and small animals. Animal models have been used for the investigator's convenience. Scaled models of man (Guy *et al.* 1976; Gandhi *et al.* 1977) have been used to simulate human exposures under varying conditions. This procedure involves frequency scaling, in which a combination of higher-frequency radiation with a smaller-than-life-size model is used to simulate the absorption characteristics of man when exposed to lower-frequency radiation. The technique also requires suitable scaling for the dielectric parameters of the tissue-equivalent materials used in the model. The validity of the models used to date is open to some question, because the physical "equivalent" model is filled with a homogeneous material whose complex dielectric constant is the estimated average for the whole body; a more realistic model would attempt to simulate the inhomogeneous tissue structure of the body. The dielectric material normally used in human modeling is gelled water whose conductivity has been adjusted with sodium or potassium chloride. The model is made in two halves, and the thermographic method described above for animal specimens is used.

3.4.3 Unresolved Issues

Refinements are lacking for models of the inhomogeneous tissue structure of man and animals, and the equivalency of these models to the actual biological target has not been validated. In simultaneous exposure of multiple animals, to what extent do animal movements create uncertainty in the SAR estimates? How much target separation is required before this uncertainty falls within acceptable limits? As research into RF-induced biological effects grows more sophisticated and as the sites for many of the reported effects—particularly those associated with the nervous system—become better isolated and defined, there will be an ever increasing need for localized dosimetry of greatly improved spatial resolution. Finally, although it is well understood that RF energy is converted to heat in a biological target, the question remains: Are there transient "field-specific" effects not explicable by a temperature change?

Section 4
Effect of RF-Radiation Exposure on Body Temperature

4.1 Thermal Physiology

Christopher J. Gordon

4.1.1 Temperature Regulation

Almost all animal species, including vertebrates and invertebrates, are capable of sensing and responding to changes in environmental temperature. The ability to maintain a constant body temperature independent of ambient temperature, termed homeothermy, is restricted to humans and other mammals, as well as most birds. Reptiles, amphibians, fish, and invertebrates generally have a body temperature similar to ambient temperature, and are thus termed poikilotherms (i.e., having changeable temperature). Many poikilotherms use behavioral mechanisms (e.g., seek shade or sunlight) to regulate their body temperature against fluctuations in ambient temperature.

Homeotherms employ an array of physiological mechanisms to control body temperature. Thermal stimulation of the skin or sites within the body, especially the central nervous system (CNS), leads to the activation of heat-dissipating or heat-producing/conserving effectors such as evaporation, vasomotor tone, metabolism, and behavior.

Since the absorption of RF radiation can lead to an increase in tissue temperature, the bioeffects from RF-radiation exposure at these thermal levels may be a principal manifestation of a homeothermic response to rising tissue temperature rather than a direct RF-radiation effect (i.e., athermal effect) in a biological system. Thus, it is important to have a detailed assessment of the characteristics of thermoregulation in animals and man. This section is divided into two major parts. First, the structure and physiology of the thermoregulatory system of humans and commonly used experimental mammals are discussed in enough detail to allow the reader to interpret the second division of the section, the specific effects of RF radiation on the activity of the thermoregulatory system. The major conclusions of this section are:

- Thermoregulatory effectors such as vasomotor tone, metabolism, evaporative water loss, and behavior are activated during exposure to RF radiation.
- Many effectors are activated in the absence of any measurable change in deep-body temperature during RF-radiation exposure.
- The SAR required to increase activity of a thermoregulatory effector or raise body temperature generally decreases with increasing body mass of the exposed species.
- Thermoregulatory effectors employed by homeotherms during RF-radiation exposure at levels that produce heat stress are similar to the response during exposure to high ambient temperature.

4.1.1.1 Effect of Temperature on Biological Systems

Below the point of protein denaturation at about 42 to 45°C, temperature has a direct effect on the rate of biochemical reactions and thus affects the rate of physiologic processes. The effect of temperature on biological reactions is described by the Q_{10} parameter, a dimensionless number equal to the change in the reaction rate for a 10°C change in temperature:

$$Q_{10} = \frac{R_2}{R_1}^{10/(T_2 - T_1)}$$

or $\log Q_{10} = (10/T_2 - T_1)(\log R_2 - \log R_1)$

where R_1 = reaction rate at T_1
R_2 = reaction rate at T_2
T = temperature, °C

Thus, a Q_{10} of 2 means that the reaction rate doubles with a 10°C increase in temperature, a Q_{10} of 3 means a tripling of the rate, and so forth. For biological reactions, the Q_{10} generally ranges between 2 and 3. In many biological systems the Q_{10} is temperature dependent; thus, T_1 and T_2 must be specified in the calculation of Q_{10}.

The activity of poikilotherms is dictated by the prevailing environmental temperature. At low temperatures enzymatic activity is decreased, causing reduced muscle activity, active transport, etc. Hence, poikilotherms generally have a narrow range of ambient temperature (~ 20 to 40°C) where normal life functions can take place. On the other hand, many homeotherms, by maintaining a relatively constant body temperature, can function normally at ambient

temperatures far below 20°C and occasionally above 40°C. Of course, to maintain a constant body temperature at extremely high and low ambient temperatures requires additional metabolic energy. These metabolic demands can be attenuated through activation of behavioral mechanisms (e.g., for humans, by the addition or removal of clothing at low and high temperatures, respectively).

4.1.1.2 Heat Balance

For body temperature to remain constant, heat loss must equal heat gain. If heat gain exceeds heat loss, body temperature increases, and if heat loss exceeds heat gain, body temperature decreases.

Heat exchange between the body and the environment takes place by the principal mechanisms of conduction (including convection), radiation, and evaporation. Normally, each of these represents heat loss from the body. However, if air temperature exceeds the surface temperature of the body, there is a net exchange of heat into the body by conduction. Infrared radiation from external sources may also result in a net transfer of heat from the environment to the body.

The variables for heat loss can be incorporated into a simple equation, patterned after the first law of thermodynamics, which relates metabolic heat production to whole-body heat loss (Bligh and Johnson 1973):

$$M = \pm K \pm C \pm R \pm E \pm S$$

where M = metabolic heat production (always positive)
K = conductive heat transfer (+ for loss)
C = convective heat transfer (+ for loss)
R = radiative heat transfer (+ for loss)
E = evaporative heat transfer (+ for loss; generally always positive)
S = heat storage by body (+ for increase)

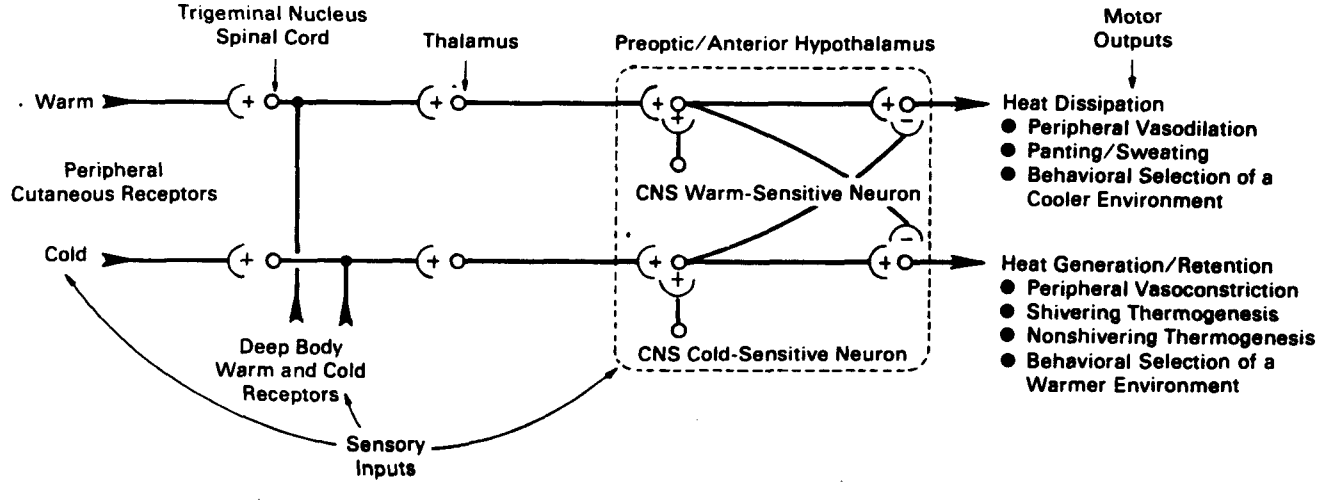
M may include heat produced in the body during work, as well as heat produced by absorption of RF radiation. Dimensions of each term in the heat balance equation are usually normalized with respect to heat transfer per unit surface area per unit time or heat transfer per unit body mass per unit time (e.g., W/m^2 or W/kg, respectively).

The three avenues of heat exchange depend on a number of external factors, the most important of which is temperature. As ambient temperature (T_a) increases, heat loss by radiation, convection, and conduction decreases, leaving evaporative heat loss as the primary avenue for heat loss. When body temperature is constant, S = 0, and M = K + C + R + E.

4.1.1.3 Autonomic and Behavioral Mechanisms of Temperature Regulation

The neural regulation of body temperature is depicted in a simple scheme in Figure 4-1. Thermal receptors located on the periphery and deep in the body transduce temperature into nerve impulses which are relayed to the anterior hypothalamus and preoptic area (POAH), the primary site in the CNS for the integration of temperature information. A relatively high percentage of the POAH neurons are sensitive to changes in temperature (e.g., POAH and/or skin temperature). Activity from the peripheral and deep-

Figure 4-1. Simple neural model of thermoregulation in a mammal for predicting the motor responses to short-term (i.e., hourly) changes in ambient and/or body temperature. Activation of the warm-sensitive pathway leads to an increase in heat dissipatory mechanisms, whereas activation of the cold-sensitive pathway leads to an increase in heat-generating/retaining mechanisms. This information is taken from several models proposed by Hammel (1968) and Hensel (1973).



body thermal receptors is integrated within the POAH and other CNS sites. Electrophysiological studies have shown that neurons in the POAH are approximately 10 times more sensitive to changes in POAH temperature than to changes in T_a (Reaves 1977). Specific areas in the CNS generate appropriate signals to drive thermoregulatory effectors that either raise or lower heat loss or increase heat production to maintain core and skin temperatures at their regulated (i.e., set point) levels.

There is a complex interaction of systems in the body that are, in some part, responsible for the regulation of body temperature. Werner (1980) developed a schematic of the major components of the thermoregulatory system that is useful in explaining, in general terms, the physiological and behavioral mechanisms of temperature regulation (Figure 4-2A). The complex systems portrayed in Figure 4-2A can be grouped into four principal parts: sensory system, control system, effector system, and passive system (Figure 4-2B). Simply stated, heat exchange between the environment and the passive system causes changes in temperature that are detected by the sensory system and are then integrated in the controller system for generating appropriate motor signals to the effector system, which then counteracts the influence of environmental heat exchange. However, each system is relatively complex; Figure 4-2A shows that the temperature regulatory system operates through the utilization of a variety of physiological systems to achieve a regulated body temperature.

The sensory and control systems are very important but are only briefly described here (see above), because few studies on the bioeffects of RF radiation have been directed toward these components of thermoregulation. For review of sensory studies in humans, see Sec. 5.6.5. The main thrust of work has leaned toward effects on the effector and passive systems; thus, the basic characteristics of effector control and regulation of the passive system, body and skin temperatures, will receive primary attention.

4.1.1.4 Metabolism

The effects of changing T_a on tissue blood flow, cardiac output, and evaporation impart additional metabolic demands on a homeothermic species, thereby increasing its basal metabolic rate (BMR). Because measurement of BMR in experimental animals is generally not feasible, resting metabolic rate is a parameter commonly used to assess thermoregulatory function of homeotherms.

The resting metabolic rate of a homeotherm normally exhibits three major phases as a function of T_a (cf. Figures 4-6, 4-7, and 4-10). There is typically a range of T_a's where metabolism is at a minimal, stable level (close or equal to the BMR). This range of T_a's is identified as the thermoneutral zone (TNZ). In the TNZ the body temperature of a homeotherm at rest can be kept constant by controlling the amount of passive heat loss through adjustments in thermal conductance. When T_a increases above the TNZ, the rates of metabolic heat production and evaporative heat loss increase because excess body heat must be dissipated actively rather than passively (e.g., sweating, increase in ventilatory rate). Metabolism also increases because of the "Q_{10} effect" of rising temperature on metabolism (Sec. 4.1.1.1). The T_a where metabolism begins to increase with rising T_a is defined as the upper critical temperature (UCT). As T_a decreases below the TNZ, metabolism increases as a result of activation of thermogenic physiological processes to maintain a constant body temperature (e.g., shivering). The T_a at the low end of the TNZ where metabolism increases is defined as the lower critical temperature (LCT).

Ideally, at all T_a's equal to and below the LCT, a homeotherm has reduced heat loss to the minimum through vasoconstriction of blood vessels in the skin. Therefore, whole-body thermal conductance, which relates to the ease at which heat is lost from the body, is as low as physically possible. As T_a increases above the LCT, more blood is shunted to the peripheral vessels, and whole-body thermal conductance increases.

Minimal whole-body thermal conductance is rather simple to calculate and has been reported for a multitude of avian and mammalian species with a body mass less than 10 kg (Aschoff 1981). In an idealistic situation, decreasing T_a below the LCT is associated with a linear increase in metabolic rate. Under these conditions, metabolic rate can be calculated with a linear equation derived from the principles of Newton's law of cooling which relates the heat loss of a warm object placed in a cold environment (Kleiber 1972):

$$MR = C(T_b - T_a)$$

where MR = metabolic rate, W/kg
C = whole-body thermal conductance, W/kg/°C
T_b = body temperature, °C
T_a = ambient temperature, °C

Solving for C when T_a is below the homeotherm's LCT,

$$C = \frac{MR}{T_b - T_a}$$

This equation is commonly used in thermal physiological studies of relatively small homeotherms. Above the LCT, thermal conductance begins to increase as the animal's metabolic rate stabilizes and T_a approaches body temperature. Above the UCT, thermal conductance takes a sharp increase because of the combined increase in metabolism, along with a

Figure 4-2A. Current view of the principal systems employed in the regulation of body temperature (from Werner 1980).

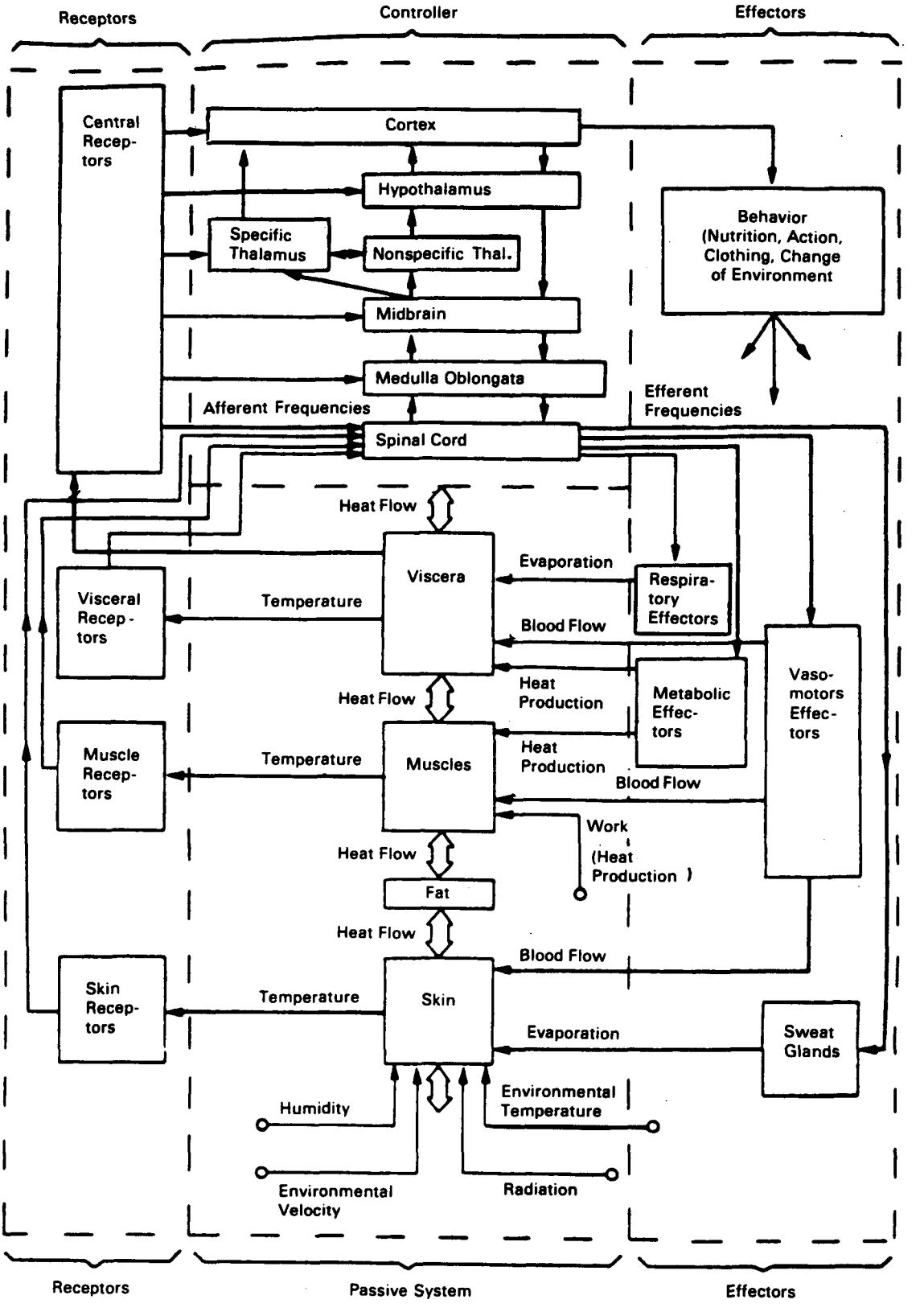
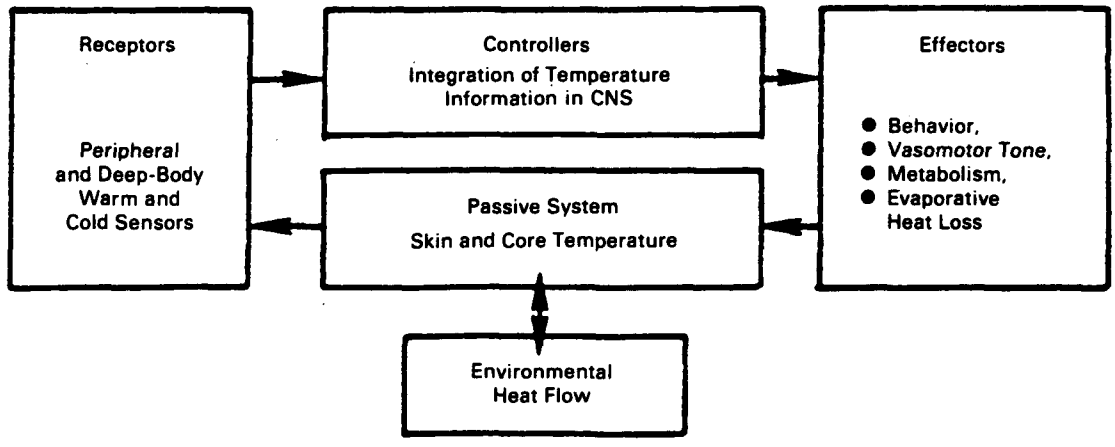


Figure 4-2B. Overall relationship of the sensory, controller, effector, and passive system components of the thermoregulatory system. Note that the overall structure of Figure 4-2A is retained (modified from Werner 1980).



further reduction of the ambient-body-temperature gradient.

There is an inverse correlation between minimal thermal conductance and body mass (Figure 4-3). In general, the thermal conductance of a 10,000-g homeotherm is 10 times less than that of a 100-g species (Scholander *et al.* 1950). Simply stated, for a given decrease in T_a, to maintain a normal body temperature a small homeotherm must elevate heat production (W/kg) much higher compared to a larger homeotherm. The relationship also implies that at a given T_a the rate of passive heat loss (W/kg) increases with decreasing body mass.

In studies on the thermal physiology of humans and other primates, thermal conductance is often calculated as follows:

$$K = \frac{MR - E}{T_{re} - \overline{T}_{sk}}$$

where K = tissue thermal conductance, $W/m^2/°C$
MR = metabolic rate, W/m^2
E = respiratory evaporative heat loss, W/m^2
T_r = rectal temperature, °C
$\overline{T}_{sk}$ = mean skin temperature, °C

This value of conductance is commonly called tissue thermal conductance. The numerator includes all heat produced from metabolism minus the heat lost through respiration. The lower the gradient between rectal and mean skin temperature, the greater the peripheral blood flow and the higher the value of tissue thermal conductance. For example, total skin blood flow in humans ranges from 150 to 200 ml/min in a cool environment, to as high as 2000 ml/min in a hot environment (Bullard 1971).

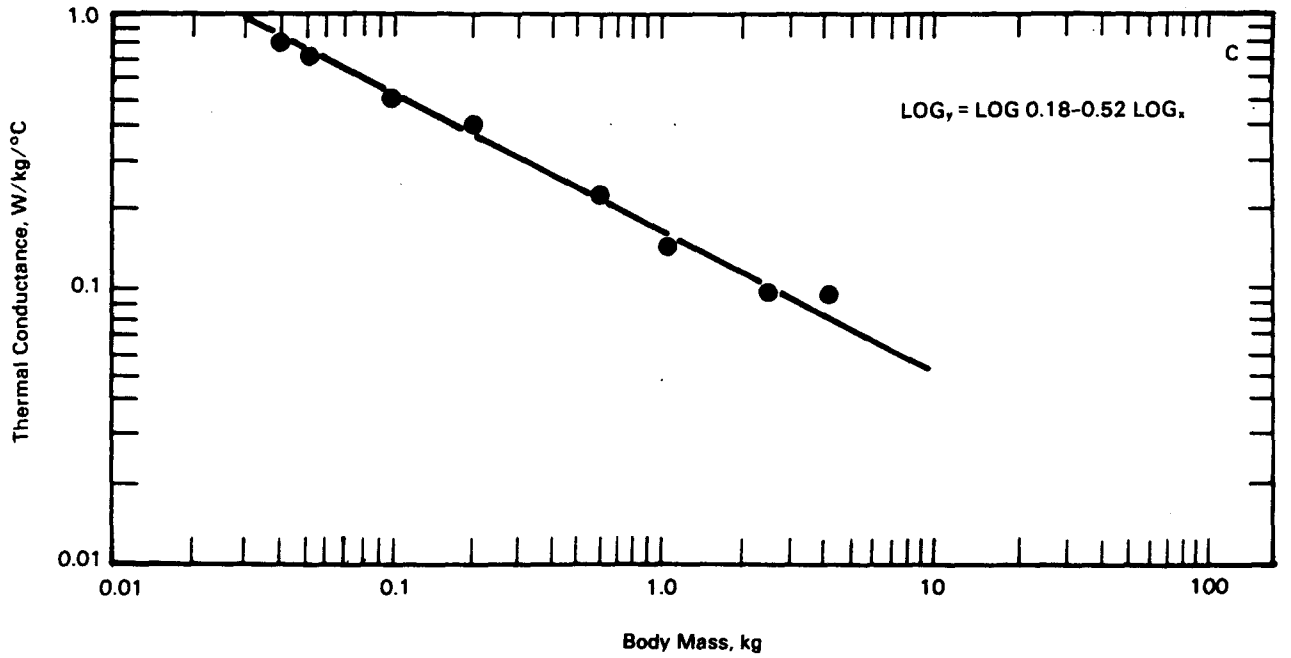
4.1.1.5 Cardiovascular and Vasomotor Responses

The thermoregulatory system is a unique control system in that it has no specific organ or tissue devoted solely to thermoregulation. (Sweat glands may be an exception.) The cardiovascular system is a primary example of a thermoregulatory effector which is perhaps more critical to other bodily functions (e.g., tissue perfusion). Heat transfer from the deep body to the skin and thence to the environment would be nil if it were not for the enhanced convective transfer of heat via blood flow by the cardiovascular system.

Blood flow to the skin is a crucial mechanism of thermoregulation. In humans the rate of blood flow to the fingers ranges from 0.5 to 1.0 ml/min/100 ml of tissue during maximal vasoconstriction, to 80 to 90 ml/min/100 ml of tissue during maximal vasodilation (Burton 1939). This tremendous adjustment in peripheral blood flow allows for a five- or sixfold change in tissue thermal conductance (Hardy *et al.* 1941). Blood flow from the deep body to the skin allows for dissipation of internal heat loads accrued during exercise. In hot environments, raising the skin blood flow increases skin temperature, which reduces the temperature gradient between the air and skin and so lessens overall heat gain from the environment. In extremely cold conditions, blood flow to the skin prevents cold-induced tissue damage (such as frostbite).

Decreasing T_a below the thermoneutral zone (see Sec. 4.1.1.6) also results in an elevation in heart rate and cardiac output, which is a response to the need for more oxygen in skeletal muscle and other tissues that are metabolically more active at lower T_a's. When

Figure 4-3. Effect of body mass on whole-body thermal conductance of various mammals (data modified from Aschoff 1981).



T_a increases above the thermoneutral zone the increase in metabolism, along with the shunting of more blood to the skin, increases the requirement for a greater cardiac output.

The rat is often used in a variety of thermophysiological studies. The tail of the rat is the principal site for the control of nonevaporative heat exchange. At T_a's between 27 to 30°C there is an abrupt increase in tail blood flow (Figure 4-4A). Below these T_a's blood flow to the tail is minimal. For comparison, the blood flow versus skin temperature in the hand, foot, and forearm of a human is shown in Figure 4-4B. The overall response pattern is similar for the two species, but the flow rates differ substantially, with the rat having a much higher rate of blood flow at given temperatures above 27°C.

4.1.1.6 Evaporation

Evaporation of water from the skin and respiratory tract is a major avenue of heat loss in homeotherms at high T_a's. Approximately 2426 joules (580 calories) of heat are lost from the body in the evaporation of 1 g of water. Insensible water loss, the water lost by diffusion through the skin and expired during ventilation but excluding sweating, occurs at all times, provided the relative humidity is below 100 percent. In the rat, a nonpanting and nonsweating homeotherm, up to 50 percent of evaporative water loss occurs through insensible water loss through the skin (Tennent 1946).

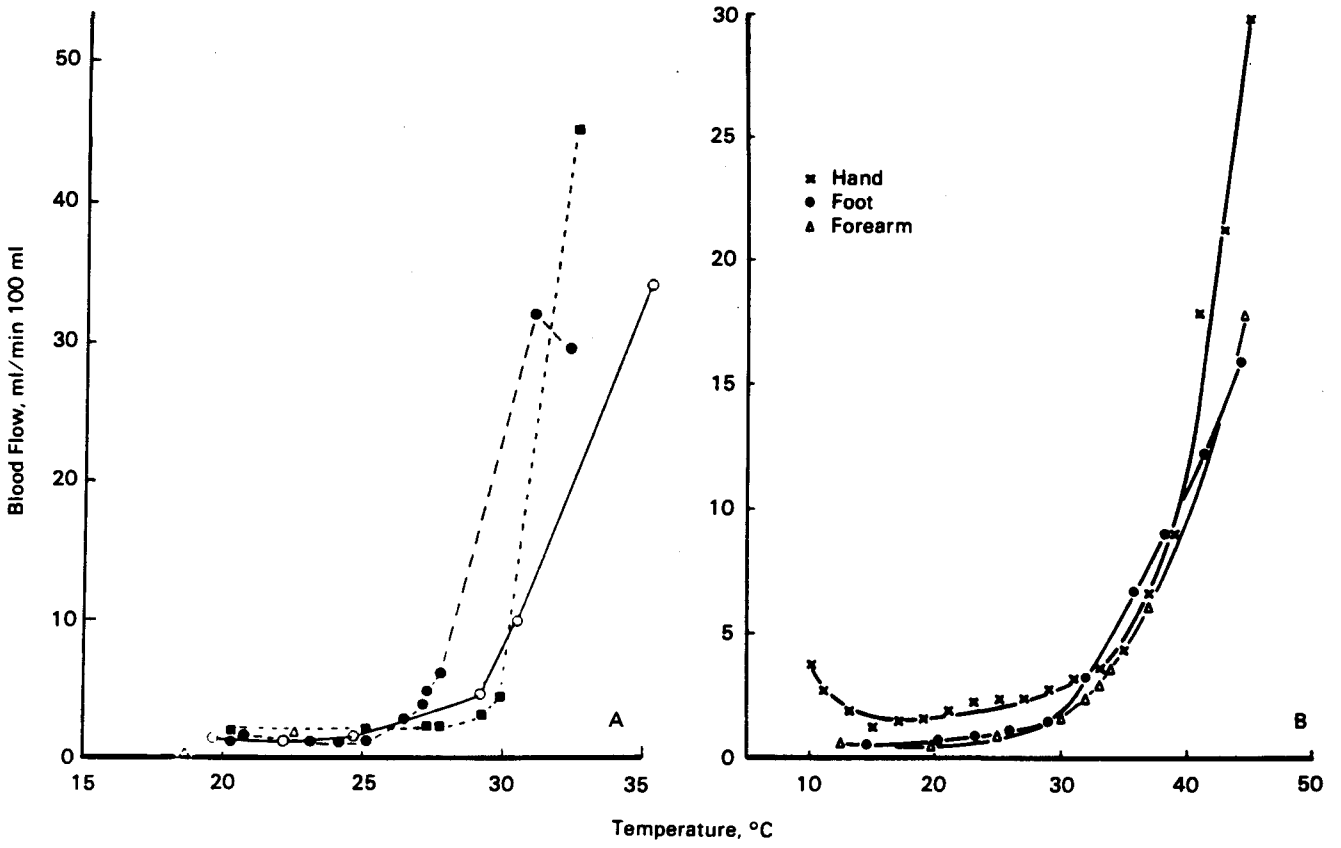
Typically, as T_a increases above the upper critical temperature (approximately 30 to 32°C for many species), homeotherms undergo an active increase in evaporative heat loss (EHL). Below this T_a EHL is relatively stable and amounts to roughly 25 percent of the total heat loss. As T_a increases the temperature gradient between the skin and air decreases, which reduces the rate of the heat loss by conductance, convection, and radiation. Thus, EHL is a crucial avenue of heat dissipation in homeotherms at relatively high T_a's above the thermoneutral zone.

The major avenues of active evaporative water loss are sweating and panting. Humans and many other primates sweat to dissipate heat by evaporation (Sec. 4.1.1.9). The dog, cat, and rabbit have few sweat glands and dissipate heat evaporatively by panting. Rodents neither pant nor sweat when heat stressed but increase their ventilatory rate, and subsequently, increase pulmocutaneous water loss. Rodents also apply saliva to their fur to enhance evaporative heat loss. Denervating saliva glands in rats reduces their tolerance to heat exposure (Stricker and Hainsworth 1971).

4.1.1.7 Thermoregulatory Behavior

Heretofore, the principal autonomic thermoregulatory responses, metabolism (heat generation), blood flow, and evaporation, have been discussed. Thermoregulatory behavior is another important effector which animals and humans use to regulate the body

Figure 4-4. Blood flow vs. skin temperature. (A) Tail blood flow vs. tail skin temperature in three different rats. Notice the abrupt rise in blood flow at temperatures of 27 to 30°C (data from Rand *et al.* 1965). (B) Blood flow in a human hand, foot, and forearm vs. temperature of the water in which the limb is immersed (skin temperature equals water temperature) (data from Thauer 1963).



temperature in response to changes in T_a. Changes in behavior require less metabolic energy compared to changes in activity of autonomic effectors; thus, behavioral responses normally take precedence over autonomic responses (Adair 1976; Gordon 1983a). For example, when placed in a temperature gradient (Ogilvie and Stinson 1966) adult mice will select a temperature of approximately 31°C (Figure 4-5). This is a thermoneutral T_a where the animals maintain normal body temperature without increasing metabolic rate or evaporative heat loss. Very young mice select notably warmer temperatures in a gradient because their metabolic capacity is not fully developed compared to the adult. A wide variety of species can be trained to bar-press for heat or cold reinforcements and thereby select a comfortable T_a (Satinoff and Hendersen 1977).

All organisms display subtle thermoregulatory behaviors in the absence of complex experimental apparatus. For example, in the cold, groups of rodents huddle together to minimize heat loss. Mice build dense, thick nests in the cold and thin-walled nests in the heat. Solitary animals adjust their posture to control heat loss. For example, in a very hot environment the rabbit extends its limbs in a sprawled position to maximize the surface-area-to-volume ratio, whereas in a cold environment it withdraws its limbs under the body and assumes a ball shape to minimize the rate of passive heat loss. Humans vary clothing in accordance with T_a.

4.1.1.8 Autonomic Thermoregulatory Responses vs. Ambient Temperature

Because the absorption of RF radiation may activate thermoregulatory mechanisms similar to those that occur during an increase in T_a, it is of importance to show in this section the effect of T_a on the activity of autonomic effectors. In Figures 4-6 and 4-7 the rectal temperature, evaporative heat loss, tissue thermal conductance, and metabolic rate are plotted as functions of T_a for the dog and rhesus monkey. (For data on humans, see Sec. 4.1.1.9). These thermoregulatory profiles were selected from the literature because they demonstrate not only basic thermo-

Figure 4-5. Effect of age on the preferred ambient temperature of mice (data from Ogilvie and Stinson 1966).

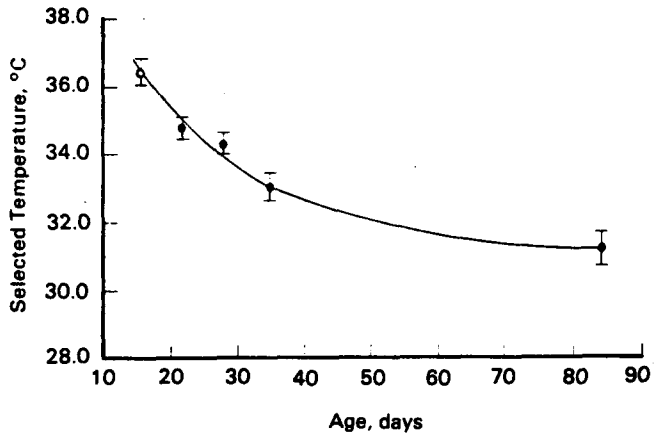


Figure 4-6. Effect of T_a on evaporation (E_{tot}), conductance (K) rate (M), and rectal temperature (T_{re}) of dogs acclimatized to summer and winter (data from Sugano 1981.

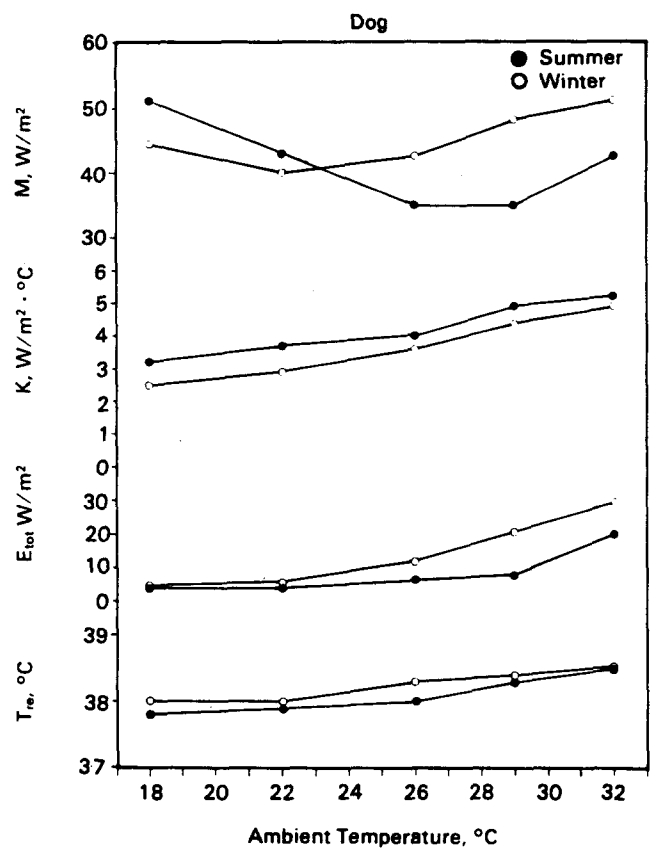
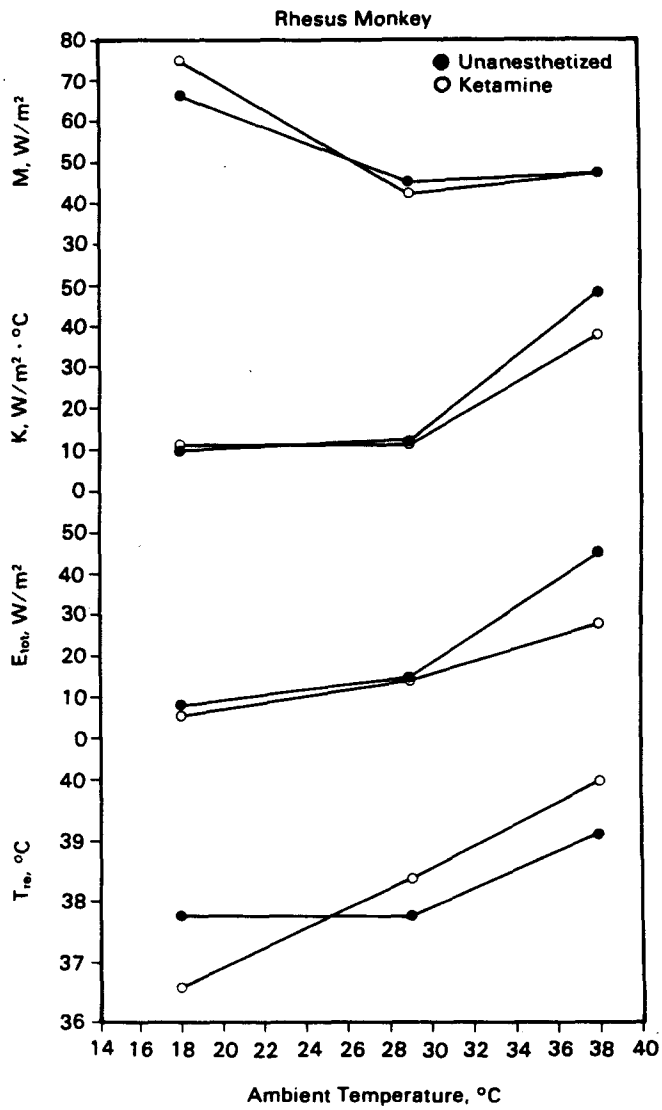


Figure 4-7. Effect of T_a on evaporation (E_{tot}), conductance (K) metabolic rate (M), and rectal temperature (T_{re}) of the rhesus monkey under unanesthetized and ketamine-anesthetized conditions (data from Hunter *et al.* 1981).



regulatory effector activity as a function of T_a, but also the effect of anesthesia and seasonal acclimatization on thermal responsiveness.

In the dog (Figure 4-6), seasonal acclimatization has a tremendous effect on the thermoregulatory profile (Sugano 1981). For example, summer-acclimatized dogs (mean T_a = 25.3°C) have a UCT of 29°C, whereas winter-acclimatized dogs (mean T_a = 3.1°C) have a UCT of 22°C. At warm T_a's the winter-acclimatized dogs have a higher rate of metabolism and evaporation. These differences in thermoregulatory profiles in the dog may prove to be helpful in understanding the metabolic and evaporative response of other mammals to RF-radiation exposure.

The effect of ketamine anesthesia on the thermoregulatory response in rhesus monkeys is shown in Figure 4-7. These data are presented because many RF-bioeffects studies are done with anesthetized animals. The anesthetized monkeys have a reduced thermal conductance and depression in heat loss at the high T_a (38°C), which contributes to an elevated rectal temperature compared with unanesthetized animals. Note the linear relation between T_a and T_{re} in the anesthetized monkey. This and other studies on the effects of anesthesia on thermoregulation indicate a general depression in the ability of the animal to defend its body temperature against heat stress or cold stress. Anesthetized animals exposed to RF radiation are likely to also be more susceptible to RF heating depending on the prevailing T_a (Sec. 4.1.3).

4.1.1.9 Thermal Physiology of Humans

In view of the paucity of studies on human physiology during RF-radiation exposure, this section deals primarily with the responses of laboratory mammals. One must be cautious in relating measured biological effects in experimental mammals to man because the thermal physiology of humans and other mammals differs substantially in certain aspects.

The human body has an inner core with a temperature of approximately 37°C and an outer shell with a variable temperature (Figure 4-8). The normal strategy of the human thermoregulatory system is to have a well-controlled inner-core temperature at the expense of a fluctuating shell temperature. Circadian rhythms cause core temperature to oscillate daily with an overall amplitude of approximately ± 1°C (Hardy and Bard 1974).

Generally, about two-thirds of the body mass is assumed to be at the core temperature and one-third is at the skin temperature. This assumption may be in error because of shifts in the relative size of the core and peripheral shell. The average body temperature ($\bar{T}_b$) can be calculated as:

$$\bar{T}_b = 0.33\bar{T}_{sk} + 0.67\,T_{re}$$

where T_{sk} is the average skin temperature collected over a variety of sites on the surface of the body, and T_{re} is rectal temperature.

The average body temperature is a useful variable because it allows one to calculate the rate of heat storage (S) in watts:

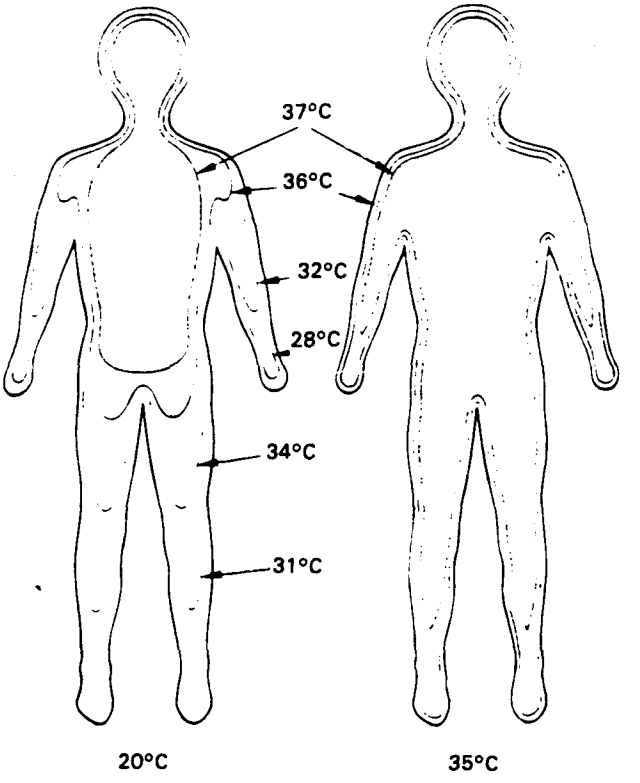
$$S = \frac{c\,(\bar{T}_{b1} - \bar{T}_{b2})\,m}{t}$$

where $\bar{T}_{b1}$ and $\bar{T}_{b2}$ = initial and final average-body temperatures, respectively, during the specified time (t, seconds)

c = specific heat of the body tissues (~3.48 kJ/kg/°C)

m = mass (kg)

Figure 4-8. Temperature distributions in the human body at T_a's of 20 and 35°C (data from Aschoff and Wever 1958).



The calculation of rate of heat storage from average body temperature is useful because the dimensions for the rate of heat storage are the same as that used in RF-radiation dosimetry (W or W/kg). For example, humans placed in a very hot environment (T_a = 55°C, vapor pressure = 15 torr) for 2 h undergo a more than 1°C rise in rectal temperature and an increase in heat storage from 2.1 to 6.5 kJ/kg, or a heat storage rate of 0.6 W/kg. At a slightly cooler but more humid environment (T_a = 48°C, vapor pressure = 34 torr) the change in heat storage over 80 min was 2.0 to 6.5 kJ/kg, or a heat storage rate of 0.94 W/kg. These heat storage rates were associated with large increases in plasma cortisol and the feeling of discomfort (Follenius *et al.* 1982).

A major difference between humans and most experimental mammals is the ability to secrete sweat on the skin. Under resting, thermoneutral conditions there is a certain amount of insensible EWL through the skin, which accounts for about 8 W of heat. Approximately 25 percent of the total metabolic heat at rest is lost through evaporation. Raising T_a causes a tremendous increase in the amount of heat lost by

evaporation. The partitioning of heat loss at various T_a's in humans is listed in Table 4-1.

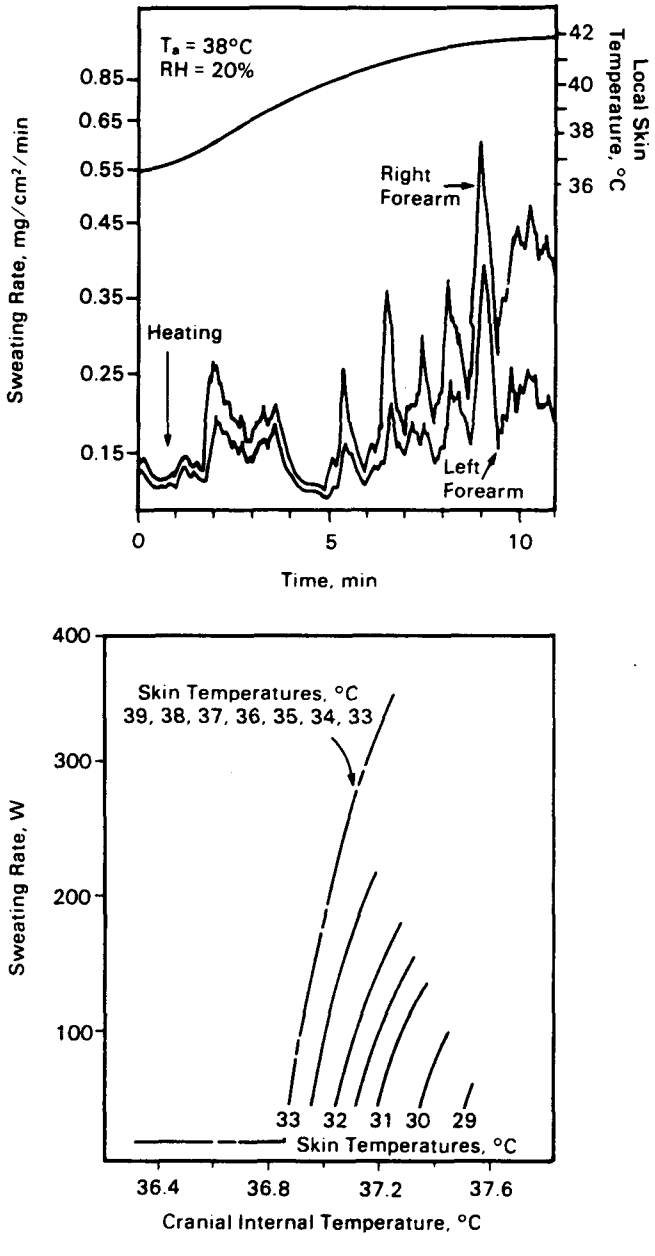
Sweating in man and certain other homeotherms may be evoked by heating the skin or thermally sensitive sites in the nervous system (Figures 4-9A,B). It is interesting to compare the relatively high threshold of sweating at low vs. high skin temperatures (Figure 4-9B). This comparison may be relevant to some deep penetrating frequencies of RF radiation that heat predominantly the inner tissues and organs without first substantially warming the skin. Such responses may affect the organism's ability to respond to RF heating.

Table 4-1. Partitioning of Heat Loss in Humans as a Function of Ambient Temperature under Still Air Conditions

Ambient Temperature (°C)	Radiation, IR (%)	Convection (%)	Evaporation (%)
25	67	10	23
30	41	33	26
35	4	6	90

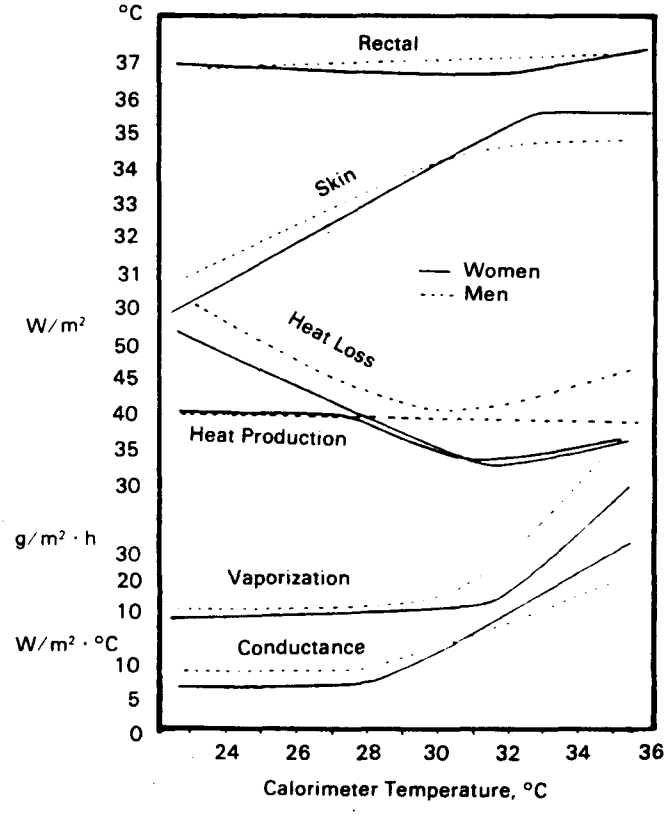
Data derived from Hardy *et al.* (1941) and compiled by Folk (1974).

Figure 4-9. Effect of skin temperature on sweating: (A) Effect of increasing skin temperature on sweating from the forearms of a human (data from Elizondo 1973); (B) effect of skin temperature on the threshold internal cranial temperature for activation of sweating in humans (data from Benzinger 1969).



The effect of T_a on the steady-state rate of heat production, heat loss, evaporative water loss, thermal conductance, and rectal and skin temperature of nude adult men and women is shown in Figure 4-10. Sweating is activated at T_a's of 30 to 32°C. For both sexes, thermal conductance increases at a T_a of 28°C, which is indicative of an increase in skin blood flow. The thermoneutral zone is quite narrow: the upper and lower critical temperatures are approximately 32 and 30°C, respectively. At warm T_a's women have a

Figure 4-10. Effect of calorimeter temperature (x-axis) on rectal and skin temperature, heat loss, heat production, evaporation, and thermal conductance in men and women (data from Hardy *et al.* 1941).



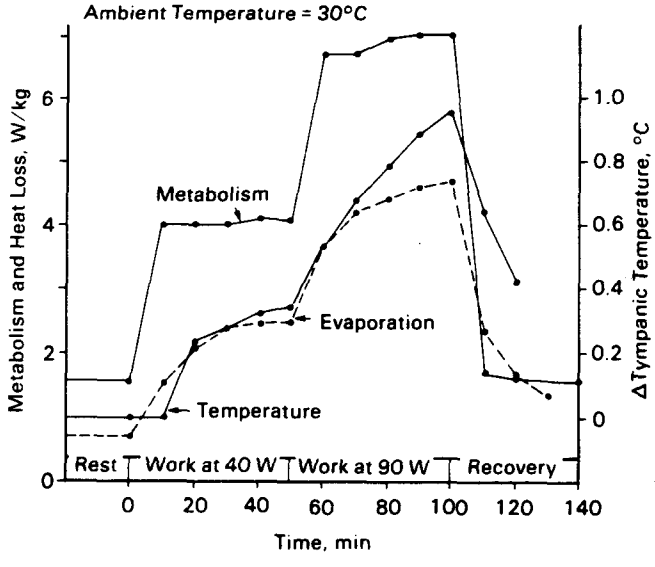
steeper thermal conductance response, which perhaps indicates increased ability to shunt blood to the skin compared to males.

It is important to understand the thermoregulatory responses of humans during exercise and fever, since these represent two cases where internal temperature can increase without rising ambient or skin temperature and, in this respect, may appear similar to that of RF heating at certain frequencies. However, as will be demonstrated, thermoregulation during exercise and fever may differ substantially from thermoregulation during RF exposure.

Humans are well adapted to dissipate excess heat loads accrued from exercise. Examples of thermoregulatory responses during two levels of exercise on a bicycle ergometer are shown in Figure 4-11. A work load of 40 W causes an increase in metabolism from 1.5 to 4.2 W/kg and a concomitant 0.34°C rise in tympanic temperature. The temperature of the tympanic membrane in the ear is considered to be a good indicator of the internal temperature of the head. A 90-W work load increased metabolism to 7.0 W/kg and raised tympanic temperature by 0.96°C.

The rise in metabolism from pedaling the ergometer and the heat load normalized to time and mass from RF-radiation exposure have the same dimension (W/kg), albeit the two forms of heat loading may not always evoke the same physiologic effects. However, measuring the rise in body temperature, evaporation, and other physiological parameters during an exercise-induced heat load may aid our understanding of the human response to RF radiation. It is clear from the data in Figure 4-11 that healthy humans can tolerate exercise-induced metabolic heat loads of 7.0 W/kg without significantly stressing the thermoregulatory system. However, it remains to be shown whether humans can tolerate RF-induced heat loads of the same magnitude under similar ambient conditions.

Figure 4-11. Effect of exercise on heat loss, metabolic rate, and tympanic temperature of humans (data from Chappuis *et al.* 1976).



Fever can be distinguished from forced hyperthermia in that the former represents a regulated increase in body temperature whereas forced hyperthermia can be defined as an increased thermal load on the organism (Stitt 1979; Gordon 1983d). The process of pyrogenesis can be described in three major steps, as shown in Figure 4-12: (i) a hypothermic state where the reference or set-point temperature (in the POAH) has been raised above body temperature as a result of the introduction of a pyrogenic agent, so that the animal generates and conserves heat to raise body temperature to the new reference temperature; (ii) a febrile state where body temperature is regulated at the new reference temperature; and (iii) a hyperthermic state where the influence of the pyrogen is removed, so that body temperature is now higher than the reference temperature and heat-dissipating mechanisms are employed to reduce body temperature to the original normothermic level (Bligh 1973).

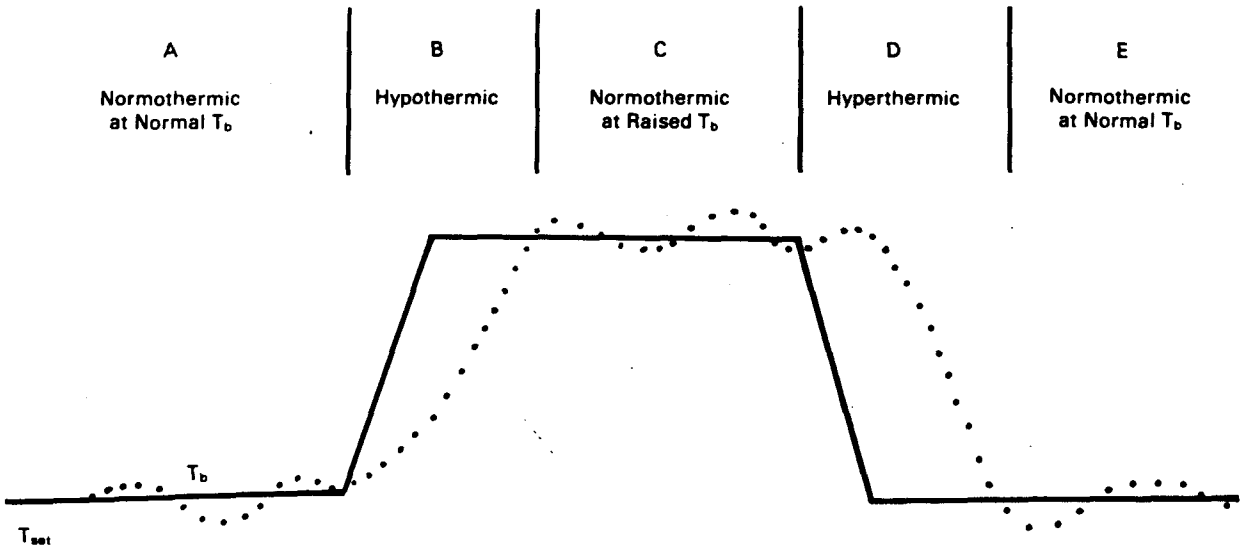
The thermoregulatory state of a homeotherm exposed to RF radiation is similar to the hyperthermic stage of fever only when body temperature is above the normal set-point temperature of 37°C. Otherwise, the thermoregulatory responses of fever and RF-radiation exposure are radically different. Fever entails a regulated change in body temperature, whereas during RF-radiation exposure the organism activates heat-dissipating effectors in an attempt to maintain normal body temperature.

4.1.1.10 Mechanisms of Heat Gain During RF-Radiation Exposure

The coupling of RF energy into irradiated biological subjects exposed to RF radiation was discussed in detail in Sec. 3.2, RF-Field Interactions with Biological Systems. To introduce the following material, some of the important features of that discussion are reiterated and summarized here.

The penetration of RF energy into biological tissues is dependent on the wavelength of the incident energy. Longer wavelengths can penetrate deeply into living tissues, but the shorter wavelengths found in the microwave region of the spectrum cannot penetrate deeply. For example, at 2450 MHz (wavelength of 12.5 cm) the RF energy is largely absorbed within approximately the first 2 to 3 cm of muscle tissue, assuming that the RF radiation is incident on an object that is large in comparison to this wavelength (such as a human). Similarly, RF energy of still higher frequencies (i.e., in the millimeter wave region of the

Figure 4-12. **Relationship between body temperature (T_b) and set point (T_{set}) during pyrogenesis; (A) before the onset of fever; (B) during the rising phase of the fever; (C) during a maintained fever (heat loss and heat gain are balanced); (D) during the subsiding phase, and (E) after the return to normal body temperature (data from Bligh 1973).**

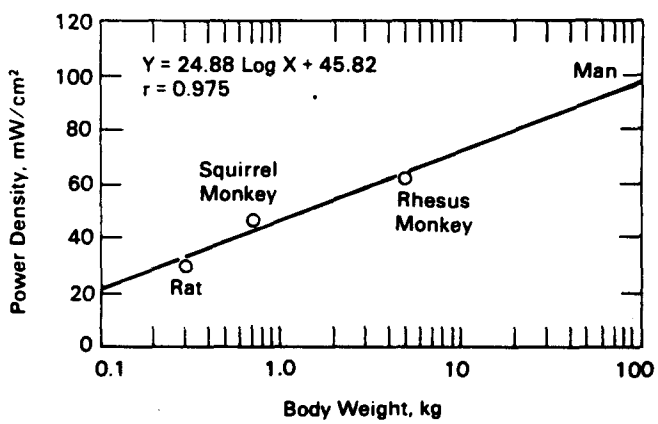


RF spectrum) does not penetrate more than 1 to 2 mm and will be absorbed primarily in the skin.

This difference in penetration poses a major problem for comparing the effects of RF radiation of various wavelengths on thermoregulatory function in various species. For example, when a 20-g mouse or a 70-kg man is exposed to RF radiation of millimeter-size wavelengths or to infrared (IR) radiation, the energy is deposited in the first 1 to 2 mm of the skin in a basically similar fashion. However, at 2450 MHz a mouse is comparable in size to the wavelength so that a resonant absorption condition exists and results in efficient energy coupling with deep penetration and nonuniform internal energy deposition. On the other hand, when a human is exposed to the same 2450-MHz radiation, the energy will be deposited peripherally within a few centimeters of the body's surface in the area facing the radiation source.

Notwithstanding these problems, some attempts have been made to compare thermoregulation in different species when subjected to RF radiation of the same frequency. For example, de Lorge (1979) compared the power density at 2450 MHz that induced a 1°C elevation in the rectal temperature of rats, squirrel monkeys, and rhesus monkeys. Using a semi-log plot of power density vs. body mass (Figure 4-13), de Lorge extrapolated the data on rats and sub-human primates to a 70-kg man. He predicted that a value of 92 mW/cm² is needed to raise the rectal temperature of man by 1°C at 2450 MHz. This comparison is probably acceptable because, for the four species considered, a supraresonant kind of RF interaction takes place at this frequency (Sec. 3.2). The coupling of RF energy into the animal is less than optimal (i.e., the coupling is of intermediate efficiency), and most of the energy is peripherally deposited, although less so for the rat than for the man. If the same interspecies comparison were to be performed under conditions in which the RF-radiation coupling is optimal (i.e., the resonant absorption case), then the results would probably be very different (i.e., the power density values needed for a 1°C elevation in rectal temperature may well be significantly reduced). Tell and Harlen (1979) have

Figure 4-13. **Power densities at 2450 MHz necessary to raise the rectal temperature by 1°C in 60 min for the rat, squirrel monkey, and rhesus monkey (de Lorge 1979). T_a ranged from 22.5 to 24°C.**



indicated that if a human were exposed to 2450 MHz at a power density of approximately 90 mW/cm^2, irreversible local peripheral tissue damage may occur without an appreciable rise in body temperature.

When there are supraresonant-type interactions, the absorption coefficient is roughly constant and is ~0.5. Under these conditions, the RF-energy absorption depends only on the geometric cross-sectional area of the exposed animal. Assuming a spherical shape of radius r for the animal, it can be shown that the cross-sectional area-to-volume ratio is proportional to $r^{2\,3}$ (Sec. 4.1.4.1). This means that the area-to-volume ratio, as well as the area-to-mass ratio, decreases as animal size increases. Consequently, at a given power density, the absorbed energy per unit of body mass (i.e., whole-body-averaged specific absorption rate, SAR) decreases with increasing size. This general rule of thumb is valid only for interaction conditions of the supraresonant type and for resonant- and subresonant-type conditions.

4.1.2. Effect of RF-Radiation on Thermophysiological Effectors

4.1.2.1 Vasomotor Control

Interest during the early 1940's in using short-wave diathermy (13 to 43 MHz) as a therapeutic agent prompted research into the effect of RF radiation in producing localized changes in peripheral blood flow. Near-field diathermic application with capacitance plates (SAR not determined) was shown to produce a more than twofold increase in blood flow of an exposed limb of a dog (Wakim *et al.* 1948) and of a human (Abramson *et al.* 1957). Using the ^{133}Xe clearance technique, McNiven and Wyner (1976) found that localized exposure to 2450 MHz caused nearly a fourfold increase in blood flow of the *vastus lateralis* muscle (femoral) in humans. Using local diathermy application to the human thigh (915 MHz) Lehmann *et al.* (1978) found that at a muscle temperature of 43 to 45°C, blood flow to the muscle increased, which caused a reduction in muscle temperature. Although it was not possible to determine the SAR, these studies are important because they contain some of the few data concerning RF effects on blood flow in humans.

RF-radiation-induced increases in peripheral blood flow can be attributed to a direct effect of heat on the caliber of arterioles, or to an indirect, neurally induced vasodilation via the activation of peripheral and deep-body thermal receptors (Sec. 4.1.1.5). The increase in femoral blood flow during RF-radiation exposure (2450 MHz and 27.3 MHz) is similar in dogs with intact and denervated limbs (Siems *et al.* 1948). Hence, RF radiation can directly affect peripheral vascular resistance; however, the fact that this response occurs in the denervated limbs does not preclude a neural response to RF radiation under normal circumstances.

Gordon (1983b) recorded the tail skin temperature of mice exposed to 2450 MHz in a waveguide. As in rats, the tail of the mouse is a principal site of nonevaporative heat exchange (Sec. 4.1.1.5). Heat loss from the tail is proportional to the difference between tail skin temperature and T_a. At a T_a of 25°C an SAR of 11.5 W/kg was sufficient to promote vasodilation in the tail. It was shown that the vasodilation response was sensitive to the rate of heating (i.e., SAR). The integrated vasomotor response (°C · s) was normalized to the absorbed heat load (J/g) to yield a skin temperature index (°C · s · g/J). A doubling of the SAR leads to more than a twofold increase in the skin temperature index (Figure 4-14). These data indicate that the mouse responds not only to the total amount of energy (heat) absorbed from RF radiation but also the rate at which the energy is absorbed.

Phillips *et al.* (1975b) measured tail skin temperature in the restrained rat immediately after exposure for 30 min to 2450 MHz at SARs of 0, 4.5, 6.5, and 11.1 W/kg. At a T_a of 24°C an SAR of 4.5 W/kg resulted in a 1.5°C increase in tail skin temperature. This was associated with a 0.5°C increase in colonic temperature. Higher SARs caused larger increases in colonic temperature with minor additional increments in skin temperature.

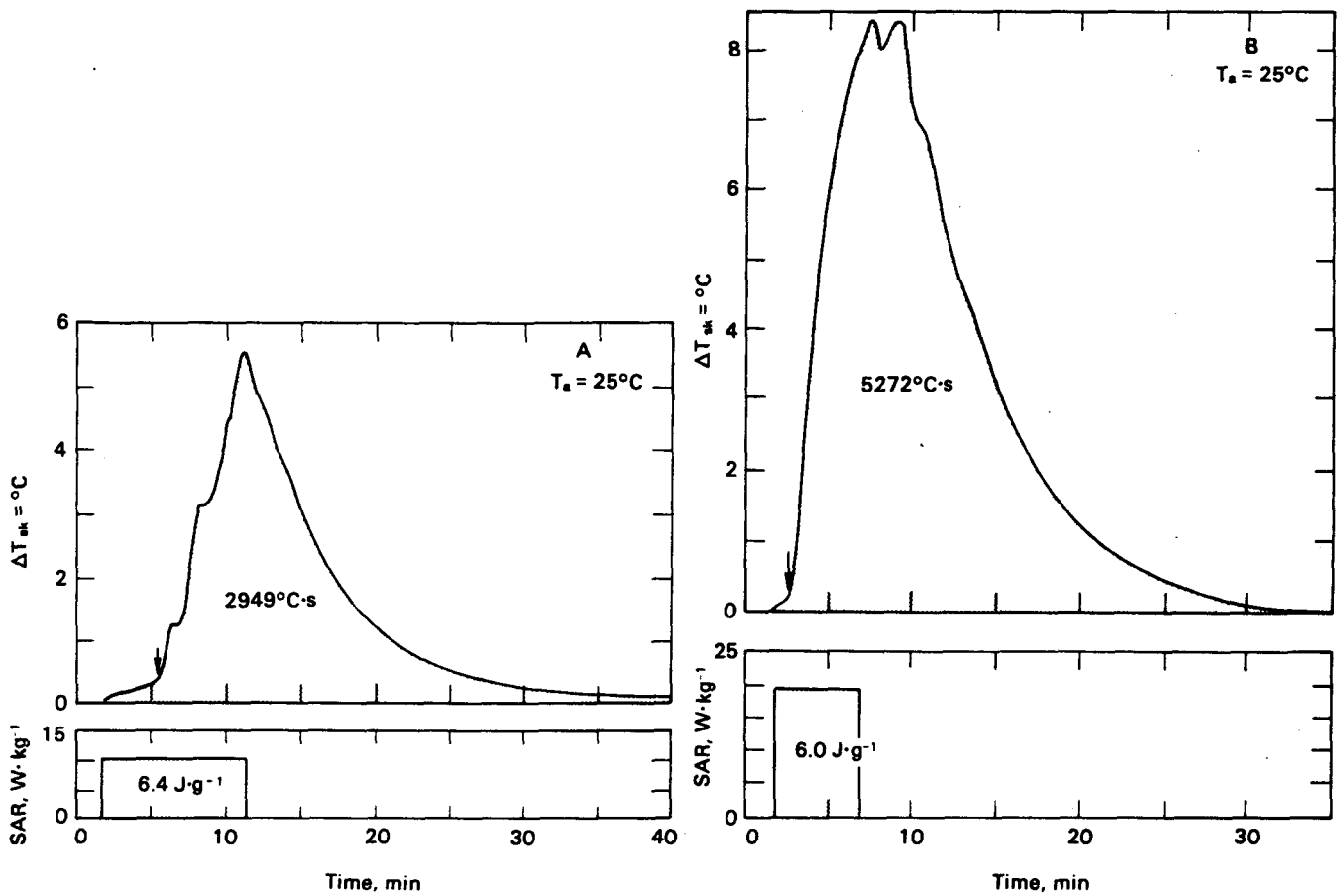
Adair and Adams (1980a) found that RF-radiation exposure in the squirrel monkey at 2450 MHz and 8 to 10 mW/cm^2 (SAR = 1.5 W/kg) at a T_a of 26°C promoted vasodilation in the tail without any change in rectal temperature. Furthermore, it was shown that an equivalent power density from an infrared heat source, which has a much shorter wavelength and is absorbed on the skin surface, was ineffective in promoting vasodilation.

Exposing the squirrel monkey to RF radiation promotes vasomotor responses similar to direct heating of the preoptic area/anterior hypothalamus, an extremely thermally sensitive area of the brainstem considered to be an integrative center for the control of body temperature (Sec. 4.1.1.3). The conclusion was that RF-induced vasodilation was caused by the activation of warmth-sensitive neural sites in and/or outside the CNS, which in turn affect the central neural control of heat-dissipating motor outputs, including the dilation of the peripheral vasculature (Adair and Adams 1980a).

4.1.2.2 Evaporative Heat Loss

Gordon (1982a) measured whole-body evaporative water loss (EWL) in mice exposed in a waveguide to 2450 MHz over a 90-min exposure period at a T_a of 20°C (Figure 4-15A). EWL remained stable up to an SAR of 29 W/kg. Above 29 W/kg EWL increased abruptly. In the same animal EWL was measured at a T_a of 20, 25, 30, 33, and 35°C (Figure 4-15B).

Figure 4-14. Examples of change in tail skin temperature (ΔT_{sk}) in restrained mice exposed to 2450 MHz at 25°C and specific absorption rate (SAR) of 10.6 W/kg (A) and 20.0 W/kg (B). Note that the absorbed heat load (J/g) is similar in both cases (data from Gordon 1983b).

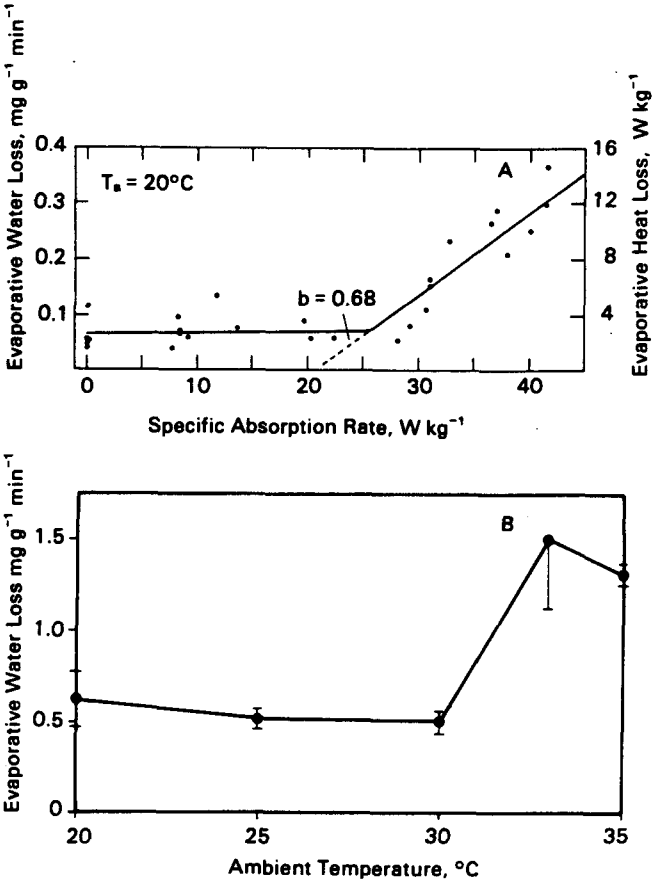


Between 20 and 30°C EWL remained at the same level as observed at SARs of 0 to 29 W/kg. EWL increased significantly at T_a's of 33 and 35°C. The mouse increased EWL at an SAR of 29 W/kg and at a T_a of 20°C and at T_a's of 30 to 33°C at an SAR of 0 W/kg. These data allow one to relate the effects of RF exposure and T_a on the activation of a thermoregulatory effector (EWL). Heat-stressed rodents can actively increase EWL by raising their ventilatory frequency (e.g., Hart 1971) and by applying saliva to the fur (Stricker and Hainsworth 1971). These two mechanisms are no doubt responsible for the rise in EWL which occurred in mice exposed to SARs above 29 W/kg or above a T_a of 30°C.

Michaelson *et al.* (1961) demonstrated the importance of evaporative cooling in the thermoregulatory response of dogs to high-intensity RF exposure (100 or 165 mW/cm² at 2790 MHz). During exposure dogs will pant to increase EWL. If the animal is dehydrated its rectal temperture reaches a critical level much faster than in hydrated dogs. With exposures lasting 4 h (165 mW/cm², SAR unknown) the dogs lose body mass while hematocrit increases, which indicates a depletion of body water.

The rate of heating, or SAR, is also a critical factor in the control of EWL. Gordon (1982c) exposed mice to 2450-MHz radiation in a waveguide for brief periods of time while continuously monitoring EWL at a T_a of 30°C. EWL was converted to evaporative heat loss (EHL) by assuming that 1.0 g of evaporated water was equal to a heat loss of 2426 joules. After an episode of exposing the mice, total EHL normalized to body mass in dimensions of J/g was calculated. The total heat load absorbed from RF exposure was calculated by integrating SAR over time, which yields the dimension of J/g. The open-loop gain (OLG) of EHL was calculated by dividing the integrated EHL response by the RF heat load. The OLG_{EHL}, a dimensionless number, describes the sensitivity of the control of evaporative water loss (Gordon 1982b).

Figure 4-15. Evaporative water loss (EWL) of mice exposed to 2450 MHz for 90 min: (A) Relationship between EWL and SAR of mice exposed at a T_a of 20°C; (B) effect of T_a on EWL of mice (data from Gordon 1982a).



At a T_a of 30°C the OLG_{EHL} increased nearly threefold by doubling SAR. Thus, the mice responded not only to the absorbed heat load but also to the rate the heat load was absorbed. This finding is important because it indicates that biological sensitivity can be defined not only in terms of a dose *per se* (i.e., J/g) but also in terms of the dose rate (i.e., J/(g·s)). A similar pattern was observed when skin temperature of mice was measured during 2450-MHz exposure (Sec. 4.1.2.1).

Using the same methods as described above, Gordon and White (1982) exposed mice to whole-body heat loads of 12 to 13 J/g by exposure to 2450 MHz at SARs of 19, 68, or 194 W/kg while recording the OLG_{EHL}. The OLG_{EHL} at a T_a of 32.5°C displayed a saturation at an SAR of approximately 160 W/kg. The large change in OLG_{EHL} over an order of magnitude change in SAR demonstrated a high degree of rate sensitivity at a low range of SARs.

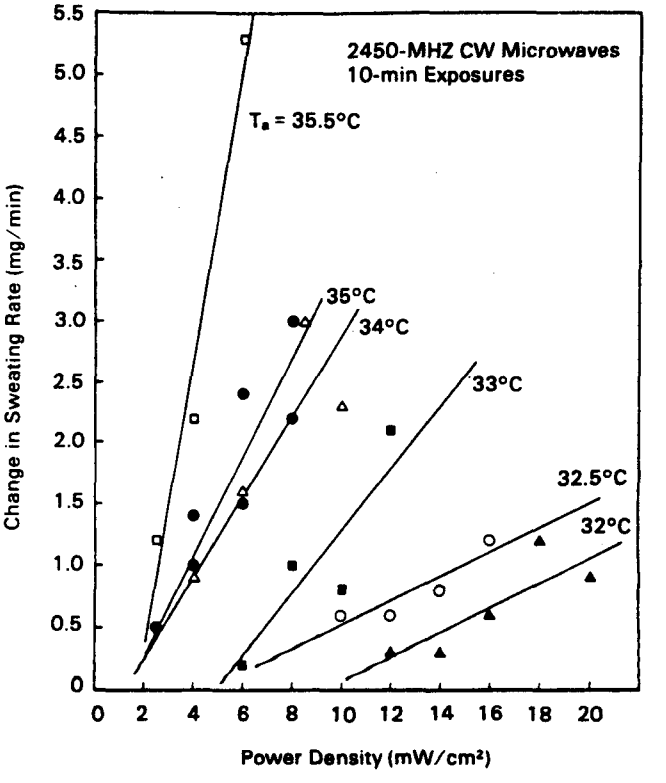
Adair (1981) measured the rate of sweating from the foot of squirrel monkeys exposed to 2450 MHz at a T_a of 33°C (just below the monkey's upper critical temperature). Sweating was activated consistently with 10-min exposures at power densities of 6 to 8 mW/cm² (SAR ~ 1.1 W/kg) (Figure 4-16). Lowering T_a led to an increase in the threshold SAR for activating sweating and a decrease in the sensitivity of sweating (i.e, Δ sweating/Δ power density).

4.1.2.3 Metabolism

When a homeotherm is exposed to a T_a below its lower critical temperature it must increase metabolism above the basal level to maintain a normal deep-body temperature (Sec. 4.1.1.4). If a homeotherm is exposed to RF radiation at a T_a below its thermoneutral zone one would expect a decrease in metabolic rate as the animal substitutes RF heat for metabolic heat. On the other hand, RF exposure at a T_a above the upper critical temperature of the thermoneutral zone should lead to an increase in metabolic rate as the RF radiation causes additional heat stress to the animal.

Ho and Edwards (1977b) exposed mice to 2450 MHz at a T_a of 24°C in a waveguide while recording metabolic rate by indirect calorimetry (i.e., oxygen consumption). They found a decrease in metabolic

Figure 4-16. Change in the rate of sweating from the foot of a squirrel monkey exposed for 10 min to 2450 MHz. The parameter is ambient temperature. Data are from Adair (1981).



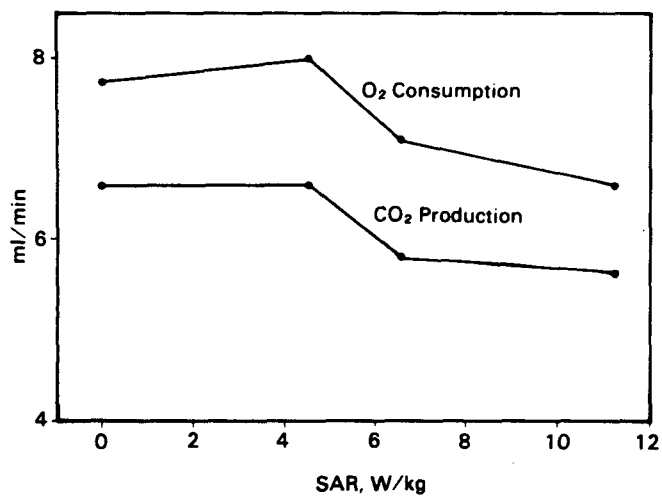
rate when SAR for a 30-min exposure exceeded 10 to 23 W/kg. In another study (Ho and Edwards 1979) mice were exposed to 2450 MHz at T_a's of 20, 24, 30, and 35°C. Exposure at SARs greater than 10 W/kg at T_a's of 20 and 24°C caused depressions in metabolic rate. However, the decrease in metabolic rate never reached the level of the sham irradiated group maintained at a T_a of 30°C (i.e., thermoneutral temperature for the mouse). At a T_a of 35°C metabolic rate increased during microwave exposure.

Phillips *et al.* (1975b) measured oxygen consumption and carbon dioxide production in rats immediately after being exposed to 2450 MHz for 30 min at SARs of 0 to 11.1 W/kg at a T_a of 24°C. Oxygen consumption was not affected at an SAR of 4.5 W/kg. At SARs of 6.5 and 11.1 W/kg oxygen consumption decreased and did not recover for at least 300 min following microwave exposure (Figure 4-17). Carbon dioxide production followed a pattern similar to that of oxygen consumption.

Adair and Adams (1982a) recorded metabolic rate at T_a's of 15, 20, or 25°C in restrained squirrel monkeys exposed to 2450 MHz in an anechoic chamber. Reductions in metabolic rate were achieved with 10-min exposures at power densities of 4 to 6 mW/cm^2 (SAR = 0.6 to 0.9 W/kg). In a 10-min exposure period the metabolic response was vigorous with a nearly 2.5-W/kg decrease in metabolic rate for a 1.0-W/kg increase in SAR. However, with prolonged exposure (90 min) metabolic rate adapted to a level where there was an approximate 1:1 substitiution of microwave energy for metabolic energy.

To summarize briefly, the metabolic rate of three species has been measured at a T_a below the thermoneutral zone during exposure to 2450 MHz. For the 0.032-kg mouse at a T_a of 24°C, metabolic rate is reduced reliably when SAR exceeds 10 to 12 W/kg; for the 0.43-kg rat at a T_a of 24°C, metabolic rate is reduced at an SAR of 6.1 W/kg; and for the 1.0-kg squirrel monkey at a T_a of 20°C, metabolic rate is reduced at an SAR of 0.9 W/kg.

Figure 4-17. Oxygen consumption and carbon dioxide production of rats immediately after a 30-min exposure to 2450 MHz at a T_a of 24°C (data from Phillips *et al.* 1975b).



4.1.2.4 Thermoregulatory Behavior

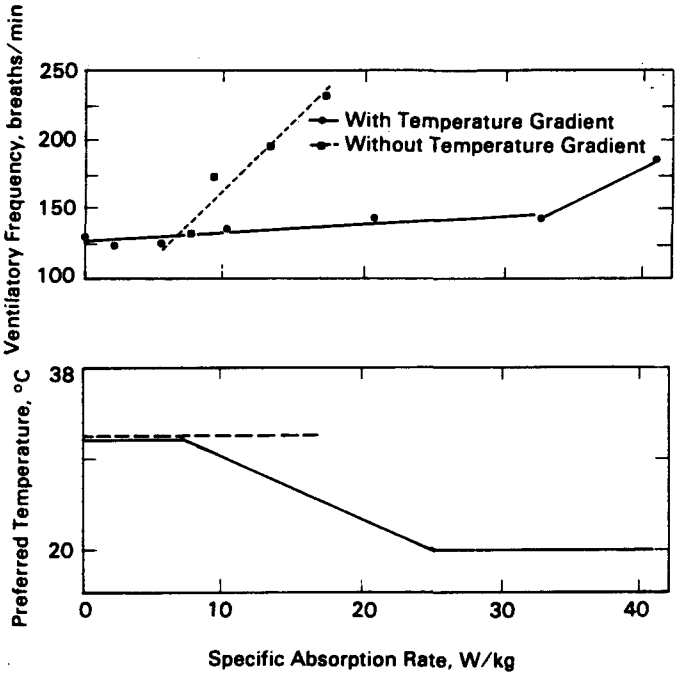
Artificially raising the temperature of the hypothalamus (Cabanac and Dib 1983; Gale *et al.* 1970), spinal cord (Carlisle and Ingram 1973), and rectum (Adair 1971) will activate behavioral thermoregulatory responses leading to a reduction in the preferred T_a. These changes in behavior can be initiated before there is a change in skin temperature. Hence, it is not surprising to find that deeply penetrating RF radiation can similarly affect behavioral thermoregulation as does local, artificial warming of thermosensitive areas described above.

Gordon (1983c) measured thermoregulatory behavior of unrestrained CBA/J mice in a combined waveguide-temperature gradient system during exposure to 2450 MHz. Without microwave exposure, the mice selected a preferred ambient temperature (PTA) of 31.5°C. The mice did not select a lower PTA until SAR exceeded 5.3 W/kg. After a 1-h exposure at 18 W/kg, the mice selected a PTA that was 9.5°C cooler than during the sham treatment. Then, 30 min after the termination of RF exposure, the mice returned to the warm end (~ 30°C) of the temperature gradient.

Using a waveguide-temperature gradient system similar to that described above, Gordon (1983a) measured PTA and ventilatory frequency of BALB/c mice during exposure for 60 min to 2450 MHz. The mice did not select a cooler PTA until SAR exceeded 7.0 W/kg. At an SAR of 25 W/kg the mice selected the coolest part of the temperature gradient (19°C). There were slight increases in ventilatory frequency at 20.5 W/kg when the mice could behaviorally select a cooler PTA. However, if the mice were forced (while unrestrained) to remain at their normal PTA of 31°C, ventilatory frequency increased significantly at SARs of 9.6 W/kg and above (Figure 4-18). Thus, mice will preferentially activate a behavioral thermoregulatory response (selecting a cool PTA) rather than activate an autonomic effector (ventilatory frequency) during RF exposure.

Stern *et al.* (1979) trained rats to bar press for infrared heat in the cold and then exposed them to 2450-MHz RF radiation for 15-min periods. They found a decrease in the rate of bar pressing at a power density of 5 mW/cm^2 (SAR ≃ 1.0 W/kg) compared to bar-pressing activity at 0 mW/cm^2. This power density, as well as exposure to 10 and 20 mW/cm^2, did not produce any increase in rectal temperture under similar environmental conditions (T_a = 5°C, fur of rat clipped from body). Thus, behavioral thermoreg-

Figure 4-18. Ventilatory frequency and preferred T_a of mice during exposure to 2450 MHz inside a waveguide-temperature gradient system. Responses without temperature gradient were measured in mice exposed to RF radiation at their preferred T_a of 31°C. Data are from Gordon (1983a).



ulation was offset by RF-radiation exposure in the absence of a change in rectal temperature.

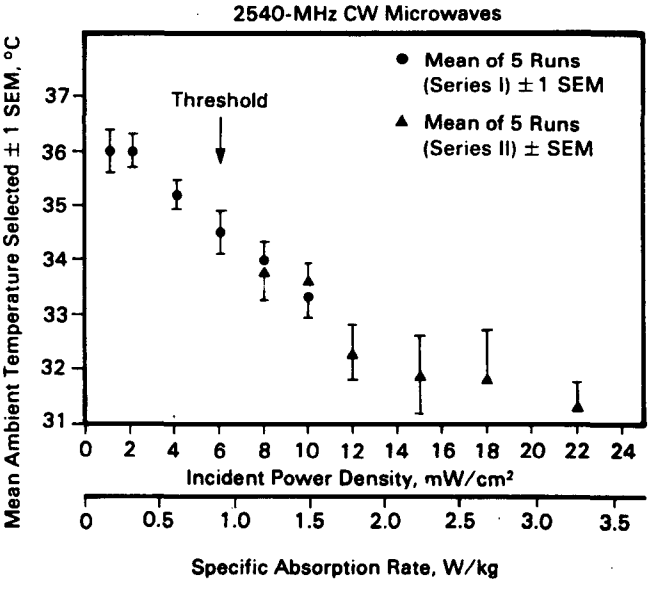
Adair and Adams (1980b) trained squirrel monkeys to control their T_a while being exposed for 10 min-periods to 2450 MHz in an anechoic chamber. Without microwave exposure the monkeys selected a T_a of approximately 35 to 36°C. Power densities below 6 to 8 mW/cm² (SAR ~ 1.1 W/kg) had no effect on the controlled T_a. Increasing power density above 6 to 8 mW/cm² led to a decrease in the controlled T_a (Figure 4-19). For example, at an exposure level of 22 mW/cm² (SAR ~ 3.2 W/kg), preferred T_a was reduced by 5°C while rectal temperature remained constant. Exposure to infrared radiation at the same power densities as RF exposure elicited no change in thermoregulatory behavior.

Using a similar experimental apparatus, Adair and Adams (1982b) exposed squirrel monkeys to 2450 MHz for 5 to 150 min while observing changes in thermoregulatory behavior. Exposure to 4 mW/cm² (SAR ~ 0.6 W/kg) had no effect on controlled T_a no matter how long the exposure lasted. Exposure to 10 and 20 mW/cm² (SAR ~ 1.5 and 3.0 W/kg) resulted in a lowering of the controlled T_a by 1.5 and 3.0°C, respectively. With few exceptions, the duration of RF-radiation exposure had no significant effect on the controlled T_a.

Postural adjustments in an RF field can be used to modify energy absorption, as well as the rate of heat loss, resulting from an RF-radiation heat load. Although rectal temperature was not measured, this behavior may still be viewed as a form of behavioral thermoregulation (Sec. 4.1.1.7). Monahan and Ho (1977) exposed mice to 2450 MHz inside a waveguide while measuring SAR. They found that at sufficiently high intensities the mice would reduce their absorption of RF power, presumably by postural adjustments. For example, at a T_a of 30°C the percent power absorbed did not decrease until SAR equalled or exceeded 25.8 W/kg. At a T_a of 20°C, changes in RF absorption were not seen until SAR equalled or exceeded 43.6 W/kg.

Gage *et al.* (1979) monitored the orientation of mice and rats exposed to 2450 MHz for 1 h in the far field at a power density of 15 mW/cm². Depending on the type of animal cage, by reorienting their position in the RF field, mice could change their SAR by a ratio of 1:1.2 to 1:2. However, because of their large size relative to the RF wavelength, the rats could not change SAR by reorientation. At T_a's of 22 and 28°C, exposure for 1 h elicited no significant change in orientation for the mouse or rat (maximum SAR ~ 3.6 W/kg for rat and 11.1 W/kg for mouse). The lack of effect in mice may be due to the relatively low intensity of exposure. Monahan and Ho (1977) did not observe a change in absorption until SAR equalled 25.8 W/kg at a T_a of 30°C. The lack of effect in the rat is probably due to the inability of this species to

Figure 4-19. Mean T_a selected by one squirrel monkey exposed to 2450-MHz RF radiation (data from Adair and Adams 1980b).



reduce SAR regardless of orientation in the far field at 2450 MHz.

4.1.2.5 Endocrine Systems

The thyroid and adrenal glands are two principal endocrine glands that are highly sensitive to thermal stimulation from RF radiation, as well as to other sources of thermal stimuli. For example, reducing T_a or direct cooling of the preoptic/anterior hypothalamic area (POAH) leads to an increase in the serum level of thyroid-stimulating hormone (TSH) and thyroxine (Gale 1973). Prolonged exposure to heat or cold leads to hypertrophy of the adrenal cortex, along with increased secretion of glucocorticoids. Local heating of the POAH leads to a rise or fall (species dependent) in glucocorticoids and a rise in serum levels of antidiuretic hormone. Hence, thermally sensitive neurons in the POAH and perhaps other sites in the CNS mediate some control over the thyroid gland, pituitary gland, and the cortex of the adrenal gland (Gale 1973).

Parker (1973) exposed rats to 2450 MHz at 0 and 15 mW/cm^2 for durations of 4, 16, or 60 h at a T_a of 22°C. Plasma-bound iodine (PBI) and thyroxine in the serum were significantly reduced at 15 mW/cm^2 for the 60-h exposure (SAR ~ 5 W/kg, assuming a conversion factor of 0.3 W/kg per mW/cm^2; Durney *et al.* 1978). These parameters were not affected at 10, 20, or 25 mW/cm^2 for the 16-h exposures. Lu *et al.* (1981) found a decrease in serum TSH in the rat following exposure to 2450 MHz for 1 h at 10 mW/cm^2 at a T_a of 24°C (SAR = 2.5 W/kg). The changes in serum thyrotropin were significantly correlated with RF-radiation effects on body temperature. Lu *et al.* (1977) found decreases in serum thyroxine in rats after exposure to 2450 MHz at 20 mW/cm^2 for 4 or 8 h at a T_a of 24°C (SAR = 5 W/kg). There was a transitory stimulation of thyroid function in rats exposed for 1 h to 1 mW/cm^2 (SAR = 0.25 W/kg).

Lu *et al.* (1977) found an increase in serum corticosteroid levels in rats exposed to 2450 MHz at 20 mW/cm^2 for 8 h (SAR = 5 W/kg). Lotz and Michaelson (1978) found a positive correlation between serum corticosterone and colonic temperature in rats exposed to 2450 MHz for 30, 60, or 120 min at a T_a of 24°C. This relationship has also been reported in humans exposed to extreme ambient heat stress (Follenius *et al.* 1982; see Sec. 4.1.10). No significant increases in plasma corticosterone for the 30- and 60-min exposures were observed below power densities of 50 mW/cm^2 (SAR ~ 8.0 W/kg). However, the 120-min exposure elicited a significant increase in plasma corticosterone at a power density of 20 mW/cm^2 (SAR ~ 3.2 W/kg). Lu *et al.* (1981) found a significant increase in plasma corticosterone in rats exposed to 2450 MHz for 1 h at 50 mW/cm^2 (SAR ~ 10.5 W/kg) and for 4 h at 40 mW/cm^2 (SAR ~ 8.4 W/kg).

Many of the above data indicate an accumulative thermal effect of RF-radiation exposure on the activity of the endocrine systems. The general trend is that longer exposure times are needed to elicit significant changes in hormone levels as SAR is reduced. In addition, the RF-radiation-induced activation of thyroid and adrenal cortical systems is intimately related to RF-radiation effects on body temperature. In general, hormone levels in the blood increase or decrease in unison with significant changes in core temperature. RF-radiation effects on the endocrine system are addressed in more detail in Sec. 5.7.1.

4.1.3 Body Temperature Regulation During RF-Radiation Exposure

Referring to the heat balance equation in Sec. 4.1.1.2, it can be seen that when heat gain (from metabolism or RF-radiation exposure) exceeds heat loss there will be positive heat storage and, consequently, an increase in average body temperature. Note the use of the term "average body temperature," meaning the average temperature of all tissues in the body (Sec. 4.1.10). Changes in the average body temperature represent imbalances between heat gain and heat loss that cannot always be detected by measuring rectal temperature alone. For example, rectal temperature may remain fixed while subcutaneous temperature increases and results in an increase in the average body temperature.

In a steady-state condition during RF-radiation exposure, if the thermoregulatory effectors described above (blood flow, evaporation, and behavior) cannot dissipate the RF heat load, then the average body temperature will rise. If we assume that during temperature regulation deep-body temperature (e.g., rectal, colonic, or core) should be regulated within a restricted range (see Glossary), in a first approximation, it can then be said that when the core temperature rises above the normal mean temperature by at least one standard deviation (defined as hyperthermia by Bligh and Johnson 1973) the regulatory system is no longer capable of maintaining the regulated variable, core temperature, within normal limits. However, this conservative view of defining the characteristics of the regulatory system may need to be compromised because of peculiarities of temperature regulation during RF-radiation exposure (see below).

Principal factors that influence the ability of a species to thermoregulate (i.e., maintain core temperature within one standard deviation of the normal mean level) during RF exposure are (i) species characteristics, (ii) degree of restraint, (iii) wake-sleep state (including anesthesia), (iv) ambient temperature, (v) relative humidity, and (vi) air velocity. Certain species are better able to maintain a constant body temperature in warm environments than others. For example, in hot desert conditions a rodent weighing 100 g would

have to dissipate 15 percent of its body weight in water per hour to thermoregulate, whereas a 70-kg man need only evaporate 1 to 2 percent per hour. Since a water loss of 10 to 20 percent per hour is lethal, small rodents in the desert burrow in the earth to avoid the heat during the day, whereas relatively large homeotherms, such as the human, can survive direct exposure from the desert heat (Schmidt-Nielsen 1964). Based on these examples one would predict tremendous species differences in thermoregulatory capacity during RF-radiation exposure. However, there are problems in relating ambient heat stress to RF-radiation heat stress (Sec. 4.1.4.3).

Restraint has a large impact on the ability to thermoregulate. Restrained animals have a reduced thermoregulatory capacity (e.g., Frankel 1959). The effect of anesthesia on thermoregulatory capacity at different ambient temperatures has already been discussed (Sec. 4.1.1.8). Generally, anesthetics reduce the ability of homeotherms to defend body temperature in the heat and cold.

Ambient temperature (T_a), relative humidity (RH), and air velocity (V) affect the capacity of homeotherms to thermoregulate. As T_a increases, the temperature gradient between the skin and air is reduced, thereby causing a reduction in passive, nonevaporative heat loss. Thus, with increasing T_a, homeotherms rely more on evaporative heat loss to balance heat gain and heat loss. The efficiency to evaporate is dependent on the partial pressure of water in the air (which is, of course, related to RH). The ability to evaporate water from a surface is reduced as the partial pressure of water of the surrounding air increases.

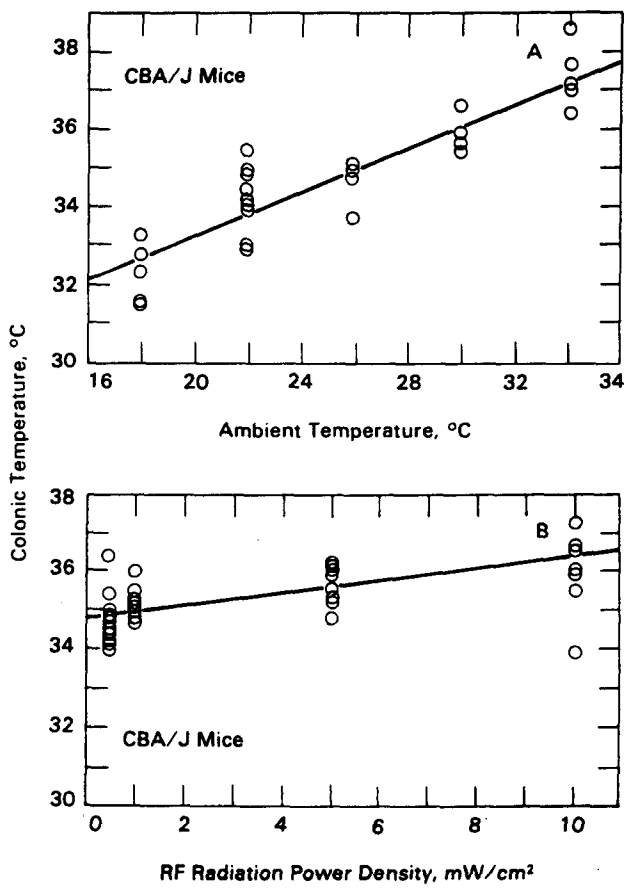
4.1.3.1 Mouse

CD-1 mice exposed 100 min to 2450 MHz (far field) at 28 mW/cm² (SAR ~22.2 W/kg) at T_a = 20°C and RH = 50 percent underwent a 0.8°C increase in rectal temperature, when compared to the post-treatment shams (Berman *et al.* 1978). AJ mice restrained in a waveguide and exposed for several minutes to 2450 MHz at a T_a of 32.5°C (dry air) underwent an abrupt increase in colonic temperature at SARs of 20 to 205 W/kg (Gordon and White 1982). The rate of body heating was 0.021°C/min per W/kg increase in SAR.

Gordon (1982d) exposed hypothermic (body temperture equalled 17 to 30°C) CD-1 and AJ mice to very intense 2450-MHz radiation inside a waveguide at SARs of 200 to 1800 W/kg. The resultant warming rate of colonic temperature of the restrained mice ranged from 0.05 to 0.65°C/s. Provided that body temperature did not exceed the lethal limit (~43°C) the mice could survive any warming rate up to 0.65°C/s. Thus, the rate of warming does not affect the tissue *per se*, but it does have a large impact on the degree of activation of thermoregulatory effectors (Secs. 4.1.2.1 and 4.1.2.2).

Smialowicz *et al.* (1981b) used a unique form of hypothermia as an assay for detecting the thermal effects of low level RF-radiation exposure. Below the thermoneutral zone, mice injected intraperitoneally with 5-hydroxytryptamine (5-HT) became hypothermic, the decrease in body temperature being inversely related to T_a (Figure 4-20). The 5-HT-induced hypothermia was attenuated in a dose-related response by exposure to 2450-MHz radiation at 1 to 10 mW/cm². The linear regression of colonic temperature after 5-HT vs. T_a calculates to a slope of 0.30°C colonic temperature/°C T_a. Plotting the 5-HT colonic temperature against power density yields a slope of 0.15°C colonic temperature/1.0 mW/cm². Dividing the T_a response by the RF-radiation response, we obtain

Figure 4-20. Effects of 5-HT injections on mice (data from Smialowicz *et al.* 1981b). (a) Linear regression of colonic temperature after an intraperitoneal injection of 5-HT at various T_a's. The drop in body temperature increases with decreasing T_a. (b) Linear regression of 5-HT-induced hypothermia for various power densities at 2450 MHz. Similar to ambient temperature, the magnitude of hypothermia is less with an increasing power density.



$$\frac{0.30\ \dfrac{\text{°C colonic temp}}{\text{1.0°C ambient temp}}}{0.15\ \dfrac{\text{°C colonic temp}}{\text{1.0 mW/cm}^2}} = 2\ \text{mW/cm}^2/\text{°C}$$

That is, for the mouse a 2-mW/cm² increase in the power density (2450 MHz) is equivalent to a 1°C increase in T_a when tested at a T_a of 22°C. This study is one of the very first attempts to relate ambient temperature and RF-radiation exposure.

4.1.3.2 Hamster

Berman *et al.* (1982) exposed Syrian (Golden) hamsters to 2450-MHz (CW, far field) at a 22°C T_a and 50-percent RH. The change in rectal temperature before and after 100 min of exposure was -0.8°C ± 0.4 at 0 mW/cm², -0.4°C ± 0.5 at 20 mW/cm² (SAR ~ 6 W/kg), and + 0.8°C ± 0.7 at 30 mW/cm² (SAR ~ 9 W/kg). Considering just the rectal temperatures at the end of RF-radiation exposure, an SAR of 9 W/kg induced a temperature of 39.8°C, compared with 38°C for the controls.

4.1.3.3 Rat

A majority of the data on temperature regulation during RF exposure has been collected from rats. Phillips *et al.* (1975b) measured colonic temperature in restrained rats immediately after they were exposed to 2450 MHz at a T_a of 24°C for 30 min. Colonic temperature was elevated by 0.6°C and 0.7°C immediately after exposure to 4.5 and 6.5 W/kg, respectively. Immediately after exposure to 11.1 W/kg, core temperature was 1.7°C above the control group. Within 30 min after RF-radiation exposure the colonic temperature of all exposed groups had returned to the unexposed level. However, during the course of recovery (over 5 h) the colonic temperature of the exposed animals undershot the control group. For example, the colonic temperature of the 11.1-W/kg group was nearly 1°C below the controls 2 h after the termination of RF-radiation exposure.

Several investigators have measured rectal or colonic temperature of unrestrained rats following RF-radiation exposure. Berman *et al.* (1981) exposed rats to 2450 MHz for 100 min (T_a = 22°C, RH = 50 percent) at a power density of 28 mW/cm² (SAR ~ 4.2 W/kg) and found colonic temperature to increase from 38.2 to 40.3°C. Berman and Carter (1984) exposed unrestrained rats to 2450-MHz RF radiation for 100 min (T_a = 22°C, RH = 50 percent) to 40 mW/cm² (SAR ~ 6.0 W/kg) and found an increase in colonic temperature from 37.6 to 39.6°C. Lotz and Michaelson (1978) found a significant increase in colonic temperature (0.27°C) of unrestrained rats following a 30-min exposure to 2450 MHz at a power density of 13 mW/cm² (SAR ~ 2.1 W/kg) at a T_a of 24°C and RH of 40 to 60 percent. Increasing the duration and power density led to a further increase in colonic temperature. From the same laboratory, Lu *et al.* (1977) found a 0.7°C increase in colonic temperature after 120 min of exposure to 2450 MHz (T_a = 24°C, RH = 40 to 60 percent) at a power density of 20 mW/cm² (SAR ~ 5.0 W/kg). Under similar environmental conditions, Lu *et al.* (1981) found a significant (0.5°C) increase in colonic temperature after 60 min of exposure to 2450 MHz at a power density of 20 mW/cm² (SAR ~ 4.2 W/kg).

D'Andrea *et al.* (1977) found a significant rise in colonic temperature (~ 0.04°C/min) in unrestrained rats (T_a = 21°C, RH = 27 percent) exposed to 600 MHz for 55 min at a power density of 10 mW/cm² but not at 7.5 mW/cm² (SAR ~ 7.5 and 5.7 W/kg, respectively). In the same study, rats were exposed to RF frequencies of 400, 500, 600, and 700 MHz at a power density of 20 mW/cm² while the rate of increase of colonic temperature was measured. A frequency of 600 MHz was found to have the greatest thermal effect. Changing frequency in 100-MHz increments above or below this point resulted in lower rates of warming. Thus, 600 MHz appears to be the resonant frequency for the rat (body weight ~ 350 g). The *Radiofrequency Radiation Dosimetry Handbook* (Durney *et al.* 1978) also predicts 600 MHz to be resonant for the rat, as based on a prolate spheroid model.

Phillips *et al.* (1973) assessed the effects of repeated RF-radiation exposure on metabolic rate and on skin (tail) and colonic temperature immediately after a 30-min exposure to 2450 MHz at an SAR of 11.1 W/kg. One group of rats was exposed for 10 days to 30 min/day of 2450 MHz (11.1 W/kg). The control group was subjected to 9 sham exposures followed by a 30-min exposure to 2450 MHz on the 10th day. The group that was exposed every day showed acclimation to RF-radiation exposure. For example, the group exposed only once to RF radiation had a 3.9°C elevation in colonic temperature, whereas the group exposed to RF radiation on 10 consecutive trials had a temperature elevation of 3.1°C. Skin temperature and colonic temperature followed similar patterns. Both rat groups had similar depressions in metabolic rate following exposure. This study shows that rats can apparently acclimate to repeated exposures of 2450 MHz. Acclimation to RF-radiation exposure appears to enhance heat-dissipatory mechanisms, since the acclimated group had a lower body temperature following exposure.

The variability in temperature regulation of rats reported in the above studies is of interest. At 2450 MHz Berman *et al.* (1981) found a 2.1°C rise in colonic temperature after 100 min of exposure at 4.2 W/kg, whereas Lu *et al.* (1977), using similar environmental conditions, found that a 120-min exposure to 5.0 W/kg led to only a 0.7°C increase in colonic temperature. D'Andrea *et al.* (1977) did not

observe significant colonic warming at 600 MHz until SAR equalled 7.5 W/kg. The variation in methodology (e.g., airflow, degree of restraint, animal training) used at different laboratories appears to have a large impact on the results of temperature regulation during RF-radiation exposure.

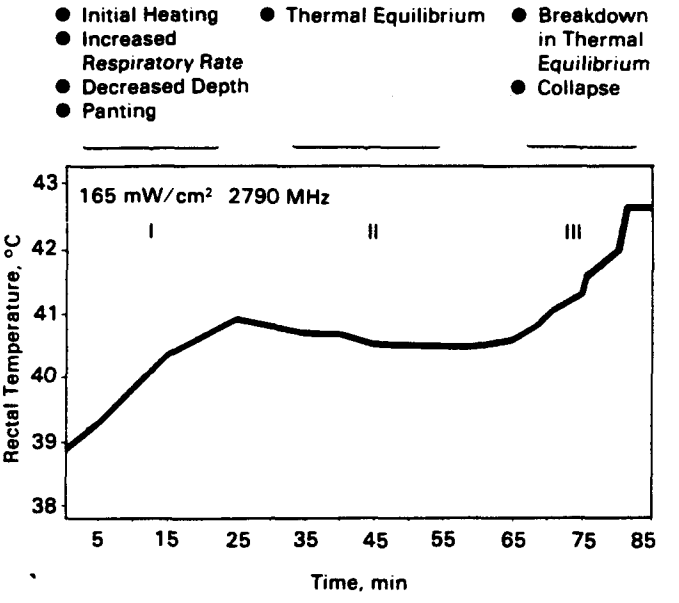
4.1.3.4 Rabbit and Dog

Ely and Goldman (1956) exposed restrained rats, rabbits, and dogs to 2884-MHz (PW) radiation. A rectal thermistor probe was connected in a closed-loop feedback to the RF generator such that the average power for maintaining rectal temperature at a given level could be constantly delivered to the animal. They found for each species that a power density of ~ 25 mW/cm² was required to maintain rectal temperature 1°C above normal. At this power density the estimated SAR was 5.0 W/kg for the 0.2-kg rat, 1.6 W/kg for the 4.0-kg rabbit, and 0.9 W/kg for the 10-kg dog. This SAR value for a 1°C rise in the temperature of the rat is similar to the data obtained at 2450 MHz that have been reported more recently by other investigators. (See citations above.) It should be noted that the metallic temperature probe may have affected the measurement of rectal temperature in the rat (Ely and Goldman 1956).

Michaelson *et al.* (1961) exposed confined dogs to 2790 MHz (PW) while recording rectal temperature at a T_a of 23 to 41°C. Exposure for 1 to 2 h at power densities of 100 or 165 mW/cm² (SAR ~ 3.7 to 6.1 W/kg) caused elevations in rectal temperature of approximately 1.5°C at a T_a of 22°C. The change in rectal temperature with time had three principal phases (Figure 4-21): (I) during the first 25 min of exposure the rectal temperature rose rapidly, with the dogs increasing their ventilatory frequency (panting); (II) for the next ~ 40 min rectal temperature was relatively constant at the hyperthermic level; and (III) after approximately 1 h of exposure there was a breakdown in the capacity of the dogs to dissipate heat, and rectal temperature increased rapidly, approaching lethal limits. Anesthetizing the dogs with pentobarbital sodium or chlorpromazine greatly reduced the capacity to maintain body temperature during RF-radiation exposure. (See also Ely *et al.* 1964).

The response of RF-exposed dogs to have a relatively constant but hyperthermic body temperature (Phase II; see Figure 4-21) might suggest that the animals are thermoregulating normally since rectal temperature is maintained at a steady level below lethal limits. However, as discussed at the beginning of this section, when core temperature exceeds the normal mean by more than 1 standard deviation, the animal is classified as hyperthermic. Conservatively, one can view any increase in body temperature that occurs during Phase II as a failure to maintain normal body temperature; however, the rise in body temperature may also be viewed as a response of the dog to better

Figure 4-21. Example of the triphasic rectal temperature response of a dog exposed to 2790-MHz RF radiation at a power density of 165 mW/cm² (data from Michaelson *et al.* 1961).



survive the thermal effect of RF-radiation exposure. For example, if the average body temperature of a 10-kg dog is allowed to rise by 2°C, a considerable amount of water is saved that would normally be used to dissipate the additional heat. The water savings would be calculated as:

$$\text{Water saved (g)} = \frac{(\Delta\overline{T}_b)\,(\text{Specific heat of body})\,(\text{body mass})}{\text{latent heat of vaporization}}$$

Thus, the approximate amount of water saved would be

$$\text{Water saved} = \frac{(2°\text{C})\,(3.47\ \text{J/g/°C})\,(10{,}000\ \text{g})}{2426\ \text{J/g}} = 28\ \text{g}$$

This concept is introduced here only to show that seemingly clear terminology such as "hyperthermia" and "regulation" vs. "failure of regulation" may become obscure. In other words, a rise in body temperature during RF exposure may not necessarily be classified as a failure of regulation but rather a normal response of the animal that occurs during heat stress. This phenomenon has been well documented in water-deprived camels exposed to desert heat (Schmidt-Nielsen *et al.* 1957).

4.1.3.5 Primate (Infrahuman)

Work on primates has been restricted primarily to the squirrel monkey and rhesus monkey. De Lorge (1979) showed a linear relationship between the logarithm

of power density at 2450 MHz to achieve a 1°C rise in rectal temperature of the rat, squirrel monkey, and rhesus monkey and the logarithm of body mass (cf. Figure 4-13). The approximate SAR was 5.8 W/kg for the rat, 2.5 to 4.5 W/kg for the squirrel monkey, and 4.7 W/kg for the rhesus monkey (T_a = 22.5 to 24°C). Adair and Adams (1982b) found very slight increases in rectal temperature of squirrel monkeys exposed to 2450 MHz at SARs from 1.5 to 3.0 W/kg (initial T_a ~ 35°C). However, in these experiments the monkeys could control their T_a. The animals appeared to counter the rise in core temperature by selecting a cooler T_a.

Lotz and Podgorski (1982) recorded rectal temperature in restrained rhesus monkeys exposed for 8 h to 1290 MHz at power densities of 0, 20, 28, and 38 mW/cm^2 (SAR ~ 0 to 4.1 W/kg) at a T_a of 24°C and RH of 55 percent. Rectal temperature increased an average 0.5°C at 2.1 W/kg, 0.7°C at 3.0 W/kg, and 1.7°C at 4.1 W/kg. It is of interest to compare these results to that of the de Lorge (1979) experiment with monkeys working for food at a frequency of 2450 MHz. At 2450 MHz and a T_a of 24°C, a 1°C rise in rectal temperature of the rhesus monkey was observed at an SAR of ~ 4.7 W/kg (de Lorge), compared with a 1.7°C rise when exposed to 1290 MHz at 4.1 W/kg (Lotz and Podgorski).

Lotz (1982) compared the effects of 225-MHz (near resonance) and 1290-MHz (supraresonance) RF-radiation exposure on the rectal temperature of rhesus monkeys at a T_a of 24°C. Monkeys were generally exposed for 4 h at either frequency. At 1290 MHz a 0.5 to 0.6°C rise in rectal temperature was achieved at a power density of 28 mW/cm^2 (3.0 W/kg). During exposure to 225 MHz, a similar rise in rectal temperature was achieved at a power density of only 2.5 mW/cm^2 (1.2 W/kg). Thus, as the frequency approached resonance the efficacy to raise rectal temperature of the rhesus monkey improved. Overall, for the rhesus monkey at 2450 MHz, rectal temperature rose 0.21°C per W/kg increase in SAR; at 1290 MHz the conversion factor was 0.24 to 0.41°C per W/kg; and at 225 MHz the conversion factor was 0.45 to 0.78°C per W/kg increase in SAR. It was estimated that the rhesus monkey could not thermoregulate within reasonable limits (42°C rectal temperature) for longer than 1 h at an SAR of 2.4 W/kg at a frequency of 225 MHz.

4.1.3.6 Lethality

Heretofore this section has discussed the following points: (i) relatively low levels of RF-radiation exposure lead to the activation of thermoregulatory effectors such as peripheral vasodilation, evaporation, metabolism (decrease), and behavior (selection of a cool T_a), which together increase heat loss from the body to the environment; and (ii) as the level of RF-radiation exposure exceeds the capability of the species to dissipate the RF heat load, heat gain exceeds heat loss, and there is a rise in average body temperature. If the exposure reaches the level whereby body temperature cannot be controlled, then thermal death will occur. Therefore, it is appropriate to review briefly the levels of RF-radiation exposure that cause thermal death.

In general, the lethal core temperature of homeotherms is approximately 6°C above the average normal core temperature (Table 4-2). These data are derived from work done at high T_a's, not RF-radiation exposure. The information is provided only to familiarize the reader with the general upper limits of body temperature of homeotherms.

Table 4-2. Approximate Normal and Lethal Core Temperatures of Some Birds and Mammals*

Animal	Normal Core Temperature (°C)	Lethal Core Temperature (°C)
Marsupials	35-36	40-41
Eutherian mammals	36-38	42-44
Man	37	43
Birds, nonpasserine	39-40	46
Birds, passerine	40-41	47

*Compiled by Schmidt-Nielsen (1979).

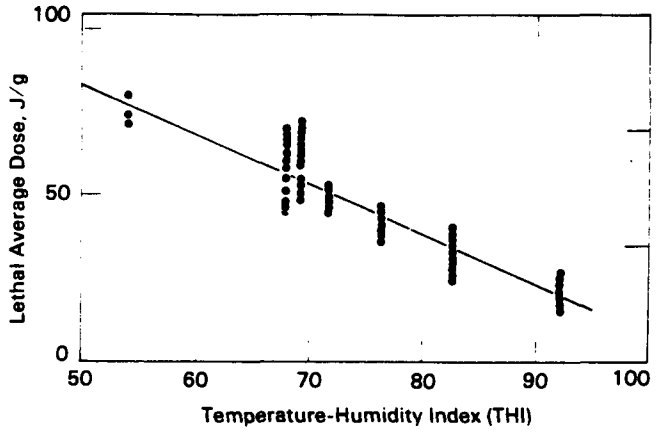
Rugh *et al.* (1974) measured lethality in mice exposed to 2450 MHz in a waveguide for various durations up to 5 min. The forward or incident power into the waveguide was 7.37 W. Assuming an average absorption efficiency of 42 percent (Ho and Edwards 1977), the estimated SAR was approximately 99 W/kg. The lethal dose, calculated in dimensions of J/g body mass, was measured at various air temperatures (15 to 40°C) and relative humidities (25 to 70 percent). The temperature-humidity index (THI) was used to assess the influence of the interaction between temperature and relative humidity on lethality (THI = 1.41T + 0.1RH + 30.6). The lethal dose at 2450 MHz varied from 20 to 77 J/g and was inversely related to THI (Figure 4-22).

In a similar experimental protocol Rugh (1976b) measured the lethal dose of RF radiation and the final rectal temperature at the time of death in mice exposed to 2450 MHz. The average lethal dose for 1-month-old weanlings, 2-month-old animals, and adults more than 12 months of age was approximately 40 to 45 J/g. The mean rectal temperatures at the time of depth for male and female mice of all ages was 46.6°C; however, in isolated cases, body temperature rose as high as 50°C before death occurred. The average lethal temperature is substantially higher compared to previous reports (Table 4.2).

4.1.4 Effect of Body Size on Thermoregulatory Sensitivity to RF Radiation

Few data exist on the whole-body thermoregulatory effects of RF-radiation exposure in humans. Detailed

Figure 4-22. Effect of an increasing THI on the lethal dose of RF radiation (2450 MHz) in mice (data from Rugh *et al.* 1974).



information on the dose response of humans to whole-body RF-radiation exposure may never be collected. Thus, we must rely on data collected on laboratory mammals.

Extrapolation of RF-radiation effects in laboratory mammals to humans has been attempted (Michaelson and Schwan 1973; de Lorge 1979; Ely *et al.* 1964). A degree of uncertainty exists in predicting the response of humans to RF-radiation exposure by extrapolation from the known bioeffects data collected in laboratory mammals. An obvious disadvantage to such extrapolations is the large difference in body size between experimental mammals and adult humans. For example, the mass of a laboratory rodent or a primate is 1.0 to 3.4 orders of magnitude smaller than the mass of a human (assuming an average adult male human body weight of 70 kg).

In many respects, the thermoregulatory physiologic processes of laboratory mammals and humans differ markedly. A prime example is the physiologic mechanism of heat dissipation during thermal stress. At high T_a's, primates rely principally on sweating to dissipate excess body heat, whereas rodents are unable to sweat but can dissipate heat through insensible evaporative water loss from the skin and respiratory tract (Sec. 4.1.1.6). Primates commonly used for RF-radiation experiments, such as squirrel monkeys (which sweat only on feet and hands) and rhesus monkeys sweat when subjected to heat stress, but these mammals are considerably smaller than humans (~ 1 and 5 kg, respectively). Hence, physiologic data collected on laboratory primates during RF-radiation exposure may aid in predicting human responses, but the dose-response differences between humans and primates may be very large.

Computer models of the human response to RF-radiation exposure are useful for estimating the probable magnitude of the threshold SAR capable of activating physiologic responses (Sec. 4.2). Modelers attempt to compensate for the problems mentioned above by using appropriate physiologic responses of adult humans to heat stress, for which abundant data exist, to calculate human responses to RF-radiation exposure. The physiologic responses incorporated into the computer models are those of humans exposed to high T_a's and/or exercise, but not to RF-radiation. Thus, these models can be used to calculate a dose-response relationship to RF-radiation exposure if the physiologic responses are the same as those of humans subjected to natural forms of heat stress (e.g., exercise and/or radiant or convective heat). However, the similarity of response between RF-radiation exposure and heat stress from exercise or exposure to high T_a's is currently under debate because of the uniqueness of RF-energy absorption.

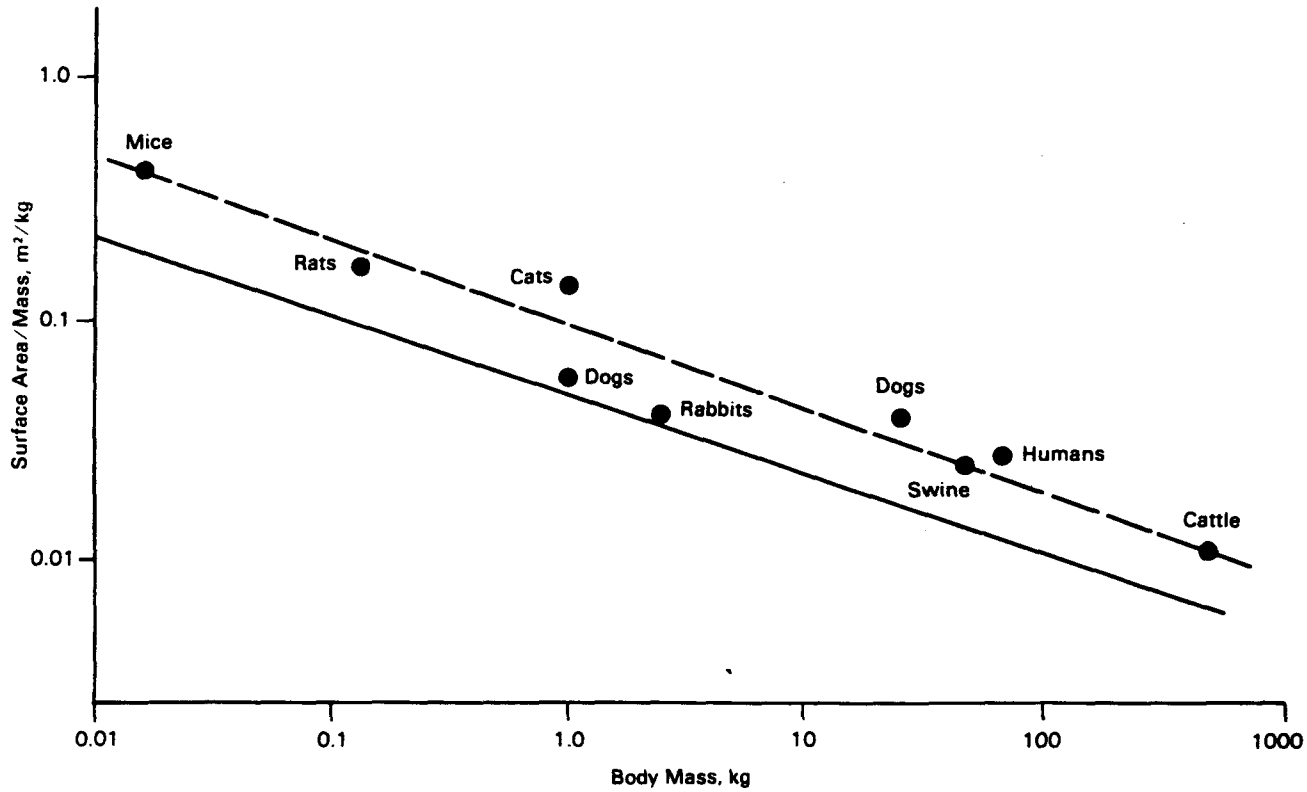
The purpose of this section is to demonstrate that a comparative analysis of the bioeffects of RF-radiation exposure on laboratory mammals may be useful in predicting SAR thresholds for exposed humans, if the effect is assumed to be due only to heating of tissue. Heretofore, data on the physiologic and behavioral effects of RF-radiation exposure have been presented for various laboratory mammals with body masses ranging from 0.02 to 7.0 kg, the largest body mass being 350 times greater than the smallest. If a relationship exists between an animal's mass and its sensitivity to thermalizing levels of RF-radiation, then an analysis of the known physiologic effects and their corresponding threshold SARs over such a wide span in body mass should allow a reliable extrapolation to a body mass of 70 kg. This would be an extrapolation of only a tenfold increase in mass and could give an estimation of SAR thresholds for humans.

4.1.4.1 Effect of Body Mass on Thermal Physiology of Mammals

An animal's weight, mass, and volume are proportional to the cube of its radial dimension, whereas its total surface area is proportional to the square of its radial dimension (for discussion, see Schmidt-Nielsen 1975). Thus, an animal's total surface area increases by approximately the 0.67 power with increasing body mass. Also, the surface area:mass ratio decreases logarithmically with increasing body mass. A regression line based on mammalian body mass vs. surface area/body mass has a slope of -0.33 (Figure 4-23).

The importance of the surface area:mass ratio in the physiology of homeothermic animals can be illustrated by comparing the metabolism of two species with large differences in body mass, such as a 70-kg human and a 0.03-kg mouse. In Figure 4-23,

Figure 4-23. **Relationship between the surface area:body mass ratio and the body mass of various mammals (data from Altman and Dittmer 1972). The solid line represents the same relationship for a sphere of density 1.0.**



the surface area:mass ratio of a 30-g mouse is approximately 0.35 m^2/kg, and that of a 70-kg human is 0.025 m^2/kg. If both species maintain the same body temperature at a given T_a then the rate of heat loss from the body to the environment, normalized to body mass, is expected to be 14 times greater in mice than in humans. Thus, metabolic activity in most mammals is inversely related to body mass.

The metabolic rate of mammals is a key example of a physiologic function that decreases in activity with increasing body mass. Studies on mammalian metabolism have shown that the rate of heat loss as a function of body mass does not follow the surface area:mass relation intrinsically, but instead has a slightly less steep slope of -0.24 (Schmidt-Nielsen 1975; see Figure 4-24). This significant discrepancy between slopes has prompted numerous discussions (for reviews, see Schmidt-Nielsen 1972 and Kleiber 1975). Regardless of the difference in slopes, the surface area:mass relationship has a direct effect on many physiologic parameters in mammals regardless of species.

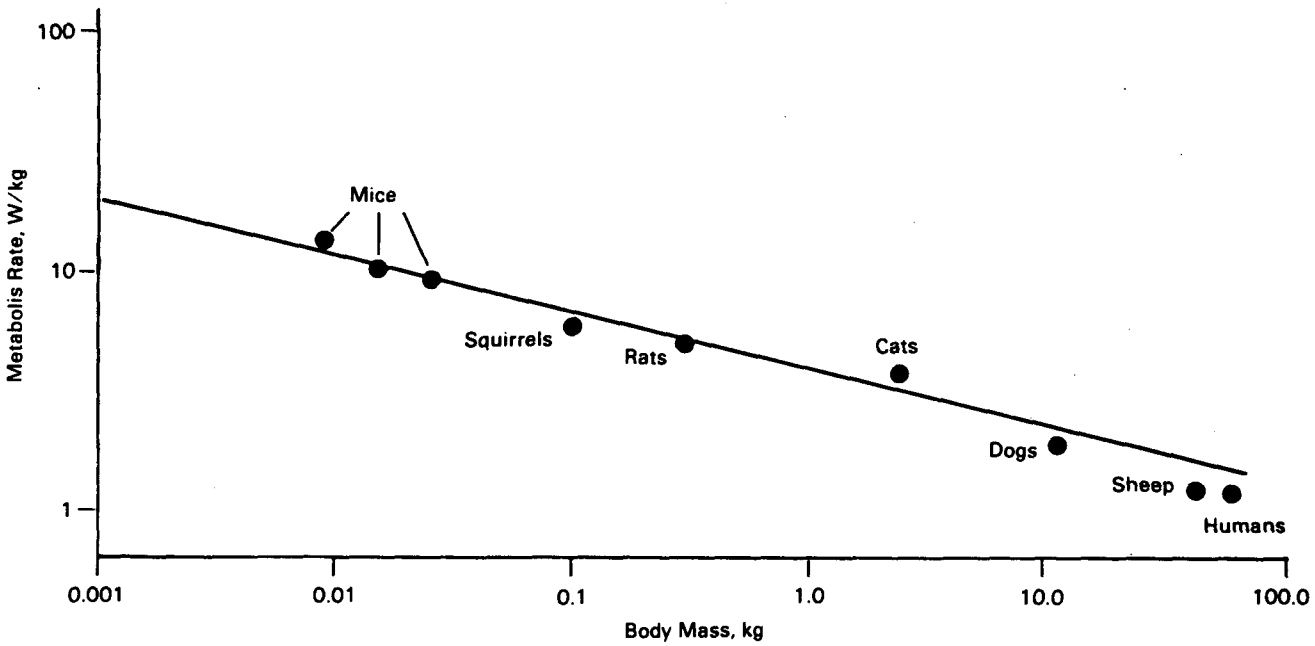
4.1.4.2 Physiologic Effets of RF-Radiation: Consequences of Body Mass

The metabolic rate vs. body mass curve in Figure 4-24 was calculated from the resting metabolic rate of mammals at a thermoneutral T_a. For the following analysis, a 0.03-kg mouse and a 70-kg human are at a thermoneutral T_a (~ 30°C), and each has a constant deep-body temperature of 37°C. Although the body temperatures of these mammals may not be exactly 37°C, this approximation simplifies the following general calculations.

At thermoneutrality, the metabolic rate is 9.0 W/kg for the mouse and 1.39 W/kg for the human (Figure 4-24). Thus, at the same T_a these two species use very different rates of energy production to maintain their deep-body temperatures of approximately 37°C. This difference in energy expenditure is due in large part to the relatively large surface area:body mass ratio of mice compared to that of humans (Schmidt-Nielsen 1979).

If a mouse and a human are exposed to resonant RF radiation (2450 and 80 MHz, respectively) at an SAR of 1.0 W/kg, and both dissipate the excess heat load with appropriate thermoregulatory responses, the whole-body heat loss of the mouse will increase from 9.0 to 10.0 W/kg (an 11 percent increase), and the human's heat loss will increase from 1.39 to 2.39 W/kg (72 percent increase). Thus, based on the percent change in whole-body heat loss, a small mammal will be less affected by a given SAR than a

Figure 4-24. Relation between metabolic rate and body mass of mammals (data from Schmidt-Nielsen 1975). All measurements were made on resting animals under thermoneutral conditions.



larger mammal. The 72-percent increase in a human represents slightly less than a doubling of metabolic rate.

The relation between body mass and percent increase in heat loss necessary to maintain normothermic temperature during exposure to RF radiation at SARs of 0.1, 0.4, and 1.0 W/kg is shown in Figure 4-25. An SAR of 0.4 W/kg represents the recently suggested exposure guideline recommended by ANSI (1982). Because of the logarithmic relationship between surface area and body mass, the percent heat loss increases exponentially with body mass.

Data from exercise physiology research provide valuable insight into the influences of body mass on the threshold percent heat loss necessary for activating a physiologic response. In a comparative analysis of these data, Taylor (1977) calculated the maximum rate of passive heat, or nonevaporative heat, which mammals can dissipate as a function of body mass. An inverse relationship was shown to exist between body mass and magnitude of nonevaporative heat loss (Figure 4-26). For example, a 0.02-kg animal can dissipate 9 times its metabolic heat production with nonevaporative heat loss, whereas a 100-kg animal can dissipate only 4.5 times its metabolic heat production (assuming a 20°C gradient between body and ambient temperature). If an increase in evaporative heat loss is used as a biological end point, the total heat loss of 0.02-kg animal would have to exceed 90 W/kg before it was observed, whereas that of a 100-kg species would have to exceed only 6 W/kg. Of course, the thermal load from exercise and RF-radiation exposure cannot always be equated physically or physiologically. However, Taylor's analysis is presented here to show that because of surface area:body mass relationships, a small mammal can passively dissipate heat at a far greater rate than a larger mammal.

Ambient temperature is critical in determining a homeotherm's sensitivity to a heat load. For example, at a T_a of 20°C, humans exercising at a work load of 40 W experience a 2.5-W/kg increase in heat production (and loss) and a slight elevation in evaporative heat loss. However, when the same work is performed at 30°C, the increase in evaporative heat loss is 5 times the magnitude of heat loss at 20°C (Sec. 4.1.1.6).

It would not be surprising to find, given the above analysis, that relatively high SARs are required to promote a thermoregulatory response in small experimental animals. Figure 4-27 is a plot of the SARs necessary to either activate a thermoregulatory effector or raise body temperature in the mouse, hamster, rat, squirrel monkey, and rhesus monkey. The data points essentially represent all the data discussed in Secs. 4.1.1.1, 4.1.2, and 4.1.3. The data include SARs required to raise skin temperature,

Figure 4-25. Relation between mass and percent increase in whole-body heat loss necessary to maintain normothermia in mammals exposed to RF radiation at SARs of 0.1, 0.4, and 1.0 W/kg. The calculations are based on the assumption of resting metabolic rate at a thermoneutral T_a, as in Figure 4-24. Percent heat loss was calculated as [SAR/(SAR + metabolic rate)] X 100.

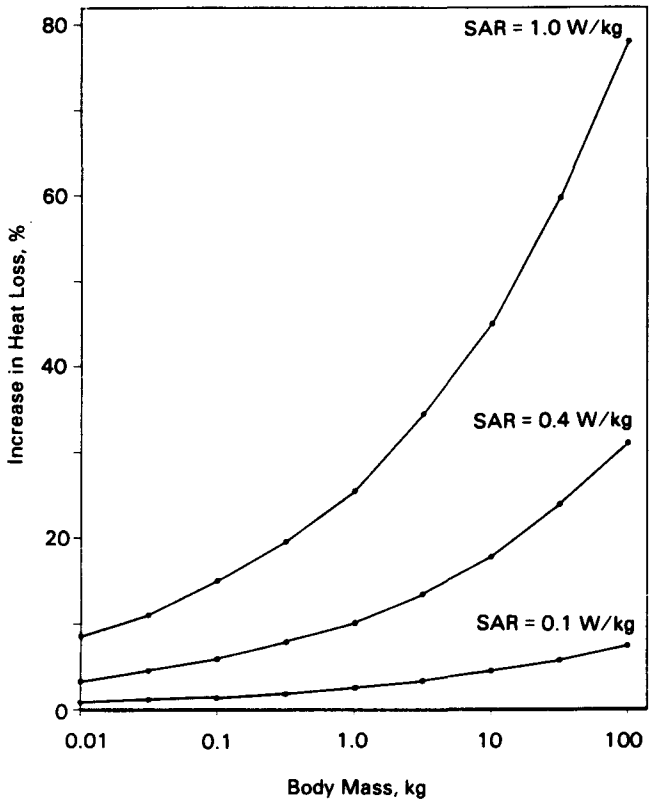


Figure 4-26. Effect of body mass on the maximum rate of nonevaporative heat loss relative to resting metabolism in mammals during exercise at a T_a of 20°C (data from Taylor 1977). The calculations are based on the assumption that thermal conductance is a constant 1 cal $(cm^2 \cdot h \cdot °C)^{-1}$.

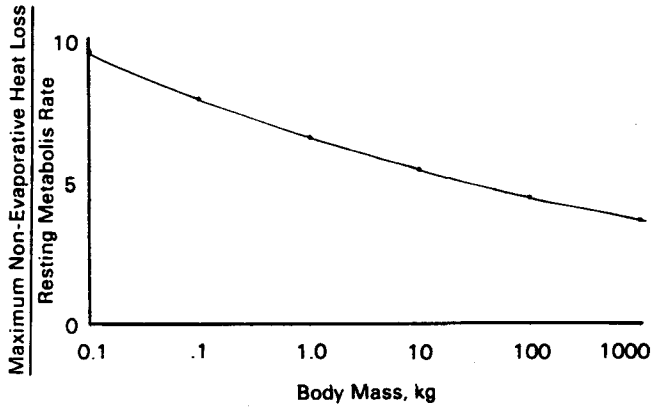
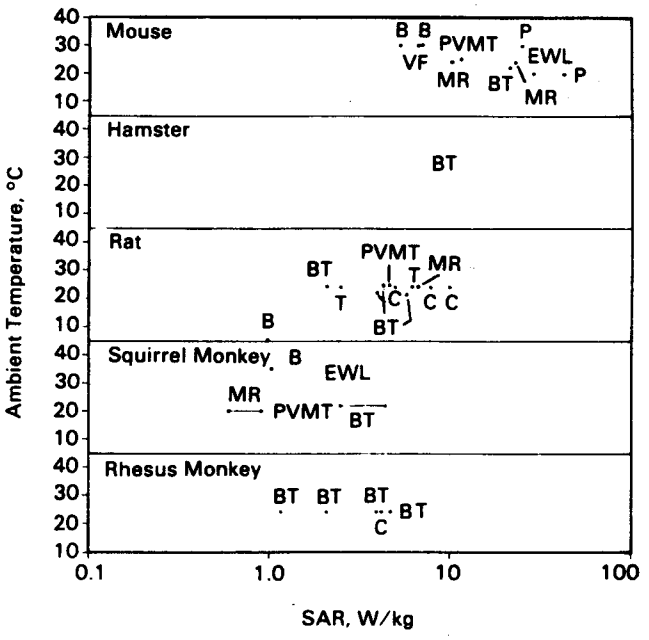


Figure 4-27. Relationship between SAR and T_a on the activation of various thermoregulatory effectors and elevation in body temperature in the mouse, hamster, rat, squirrel monkey, and rhesus monkey exposed to RF radiation. Data points represent those discussed in Secs. 4.1.2 and 4.1.3. Explanation of code: B—threshold for change in preferred T_a, BT—elevated colonic temperature (0.3 to 2°C), C—elevated serum corticoids, EWL—threshold for increasing evaporative water loss, MR—threshold for lowering metabolic rate, P—threshold for altering posture, PVMT—threshold for altering peripheral vasomotor tone (i.e., vasodilation), and VF—threshold for elevating ventilatory frequency. Note logarithmic scale of abscissa. RF—radiation frequency was 2450 MHz for all species except rhesus monkey (1290 and 225 MHz).



elevate evaporative water loss, lower metabolic rate, alter behavioral temperature regulation, and raise deep-body temperature by 0.3 to 2.0°C. The data are also plotted as a function of the T_a at which the thermoregulatory parameters were mesured. A trend is evident in Figure 4-27, despite the variations in T_a and RF frequency; that is, the SAR required to activate a thermoregulatory effector or raise body temperature decreases with increasing mass of the species.

The lowest SAR shown in Figure 4-27 at which body temperature of rhesus monkeys was elevated (Lotz 1982) is important because exposure occurred at a near-resonant frequency of 225 MHz. Resonant exposure, in which the energy is deposited very deep in the body, may be a worst-case situation. Similar SARs at a supraresonant frequency of 1290 MHz caused less severe rises in body temperature of the rhesus monkey. The mouse body temperature data in

Figure 4-27 were also collected at a near-resonant frequency (2450 MHz). For a 0.03-kg mouse exposed to resonant RF radiation at a T_a of 22°C, an SAR of 22 W/kg was required to raise the body temperature 0.5 to 1°C. For a comparable temperature rise in a 4-kg rhesus monkey at a T_a of 24°C, an SAR of only 1.2 W/kg was required. Assuming that large species follow a pattern similar to that of small species, an animal having 17 times the mass of the rhesus monkey (e.g., 70 kg, the mass of an adult human) exposed to a resonant RF radiation would be expected to undergo a similar rise in temperature at an SAR less than 1.0 W/kg.

4.1.4.3 Relating Heat Stress from RF-Radiation and Ambient Temperature Exposure

To some, there is a paradox in the hypothesis of the foregoing discussion concerning an inverse relationship that exists between body mass and the threshold SAR for activation of a thermoregulatory response. As mentioned earlier (Sec. 4.1.1.6), humans are well adapted to warm environments and are able to survive high T_a's much longer than smaller homeotherms such as rodents, rabbits, and infrahuman primates. There is an abundance of research on the functioning of humans in hot environments (Dill *et al.* 1964; Hardy and Bard 1974). However, one must be very careful in relating the adaptability of humans to survive high T_a's to that of thermoregulating during RF-radiation exposure.

The problem with such a comparison is that the data on human thermoregulation in hot environments are reported in terms of T_a(°C), relative humidity (percent), wind velocity (m/s), etc. In the study of RF radiation the whole-body dose rate is commonly measured in W/kg. The dimensions °C and W/kg have no relationship to each other. Simply stated, an RF-radiation field represents a heat source (i.e., M increases in the heat balance equation; see Sec. 4.1.1). On the other hand, increasing T_a does not represent a heat source (provided T_a is less than T_{re}) but rather impedes the dissipation of metabolic heat (i.e., raising T_a lowers K, C, and R in the heat balance equation). One can be misled by a prediction of an animal's response to a W/kg dose rate if the prediction is based only on the animal's response to ambient conditions. For example, in Sec. 4.1.1.9 it was shown that a human exposed to a very hot environment of 55°C T_a underwent a positive change in the rate of heat storage of 0.6 W/kg. A small rodent could not possibly survive this T_a exposure for very long, mainly because its surface area/mass ratio is so much larger than the human that the rodent will heat at a tremendously faster rate. On the other hand, the small rodent, because of the surface area/mass relation, can tolerate a much larger dose rate of RF energy (W/kg). A mouse with a body mass of 30 g has a metabolic rate of 10 W/kg, which is more than 16 times greater than the increase in the rate of heat storage of the human exposed to a T_a of 55°C.

Another way of viewing this problem is to look at the change in heat production during exercise. The maximal increment in metabolism of mammals with a mass of 0.018 to 25 kg is approximately 7 times greater than the basal metabolic rate (Hart 1971). Well-trained athletes can endure 10 times the basal metabolic rate. This implies that the 0.03-kg mouse can endure an overall increase of approximately 50 W/kg, which is 3 times greater than the maximal increase of a well-trained athlete (~ 15 W/kg). Thus, it is apparent that heat tolerance measured in °C (T_a) is not a valid indication of tolerance in terms of the rate of tissue energy absorption by the whole body (W/kg). The relationship in Figure 4-27 only affirms this deduction. Small homeotherms generally have much higher threshold SARs than larger species during exposure to RF radiation.

4.1.5 Unresolved Issues

At least three major issues in thermal physiology remain unresolved: (i) the effect of various thermal environments (exogenous or endogenous) encountered by most human beings that might affect their sensitivity to RF-radiation exposure, (ii) the validity of extrapolating the known bioeffects data in laboratory animals to humans, and (iii) the effect of RF-radiation frequency on thermoregulation. These issues are discussed below.

(i) Elevating T_a above thermoneutrality places a greater strain on the capacity of the thermoregulatory system to dissipate body heat. In such a situation an organism's normal thermoregulatory response to RF radiation is compromised. Most of the data concerning RF-radiation effects on thermoregulation have been collected in experiments with animals at a T_a below their thermoneutral zone. At a T_a below the thermoneutral zone the thermoregulatory system has a substantial capacity to dissipate the RF heat load. At T_a's above the thermoneutral zone homeotherms rely mostly on evaporation to dissipate heat. One can visualize the potentially stressful situation of a human exposed to 0.4 W/kg, or ~ 25 percent of the resting metabolic rate, at a T_a of 35°C (96°F). At this T_a, at least 90 percent of the heat lost is dissipated by evaporation (Sec. 4.1.1.9). Assuming that a human must evaporate 1 g of water for each 2426 J dissipated, in an environment of a T_a of 35°C in which the human is absorbing 0.4 W/kg RF radiation, the amount of evaporative water loss would increase by ~ 25 g/h·m^2 over the base-line level of 50 g/h·m^2. If the exposure took place at a T_a below the thermoneutral zone, most RF heat could be dissipated by radiation and convection or by lowering metabolic rate.

Either hot and dry or warm and humid environments are commonly encountered by much of the human

population during the summer. In addition to these ambient heat loads, one must consider altered thermal states created by exercise and fever. These conditions raise body temperature, which makes the effects of RF radiation on thermoregulation more apparent than in the nonworking or afebrile subject. Overall, combinations of abiotic factors (ambient temperature, relative humidity, solar radiation, "wind chill," and insulation) and biotic factors (fever, exercise, and the presence of medication or pathological conditions that impair thermoregulation) clearly make predicting the thermoregulatory capacity of a human population a very difficult task.

(ii) Can the thermoregulatory data collected in laboratory animals be used to predict how human beings might respond to RF-radiation exposure? In Sec. 4.1.4 a discussion is presented of how body mass influences the sensitivity of homeotherms to thermalizing levels of RF radiation. On this basis it may be possible to extrapolate the known bioeffects data of laboratory mammals to humans. However, it should be noted that this concept of extrapolation is not universally accepted in the scientific community. For example, Adair *et al.* (1983) were strongly critical of the attempt by Gordon (1982a) to extrapolate the known bioeffects data from laboratory mammals to humans based on body mass. It was stated by Adair *et al.* (1983) "Since we understand the thermoregulatory responses of man far better than the responses of any other species, and can quantify them more accurately, it is clear that no relation as that depicted in Fig. 5 (i.e., the graph showing an inverse relation as between body mass and threshold SAR) of Gordon (1982a) can possibly exist." Accordng to Adair, in the area of thermoregulation it is impossible at this time to extrapolate from animals to humans (E.R. Adair, personal communication).

However, Gordon (1983e) countered these criticisms by stating that our understanding of human thermoregulatory physiology is based on research of exposure to conventional heat sources (e.g., high T_a, infrared heat, and exercise), not to whole-body RF-radiation exposure. Thus, in the study of the effects of RF radiation on thermoregulation we understand the thermoregulatory responses of laboratory animals far better than those of human beings (Gordon 1983e). Because nearly all research in the study of RF radiation has been performed on infrahuman species, it is essential to have a means of extrapolating the animal data to humans. The use of body mass as an independent parameter for scaling the bioeffects of RF radiation may be useful.

(iii) Because of the nonuniformity of RF-energy deposition, the frequency of RF radiation (at a given SAR) has a large impact on the thermoregulatory system. Resonant frequencies appear to be a worst-case situation (e.g., see discussion on primates in Sec. 4.1.2). Average whole-body SAR *per se* may not adequately define the potential thermal effect of RF-radiation exposure because the frequency relative to the size of the animal (that is, infraresonant, supraresonant, or resonant) must be considered in evaluating the thermoregulatory effects of RF radiation.

4.2 Numerical Modeling of Thermoregulatory Systems in Man

Ronald J. Spiegel

This section reviews the models for calculating the thermal response of human beings exposed to RF fields. From this review the following generalizations can be drawn:

- The models predict that an exposure to a plane-wave field at 80 MHz (the whole-body resonant frequency for the adult human) will produce the highest temperatures in the legs.
- An exposure to a plane-wave field at 200 MHz (partial-body resonance in the arms) produces the highest temperatures in the arms.
- Elevated temperatures tend to occur where the localized SARs are the largest.
- Higher localized temperatures are produced at whole-body resonance because the body absorbs more energy from the incident field.

The limitations of the numerical models are discussed in Sec. 4.2.4, Unresolved Issues.

4.2.1 Heat-Transfer Models

It is important to develop accurate mathematical models to predict the absorption of electromagnetic energy and the thermal response of biological subjects. Mathematical modeling can provide a method for gaining qualitative and quantitative information that may be valuable in explaining and understanding many of the effects measured in experimental animals. More important, experimentation on human subjects is often unethical. Thus, to extrapolate RF-field results in experimental animals to equivalent effects in man, one must know thoroughly the dosimetry for both species. This knowledge can be achieved by the application of a sophisticated and realistic numerical simulation of the energy absorption and subsequent thermal response of subjects exposed to RF fields.

Several investigators have developed mathematical models to calculate the thermal response of the human body when it is subjected to different environmental conditions or levels of exercise. The same basic approach can be taken to develop a model to simulate the thermal response to RF radiation. However, this model must take into account that RF fields deposit energy nonuniformly in the human. The simple one-dimensional heat transfer models used in the past do not accurately simulate this condition. However, a short review of these previous attempts to model man in one dimension provides a good background for developing a more general model.

One of the earliest attempts at modeling the human body was made by Pennes (1948), who developed a cylindrical model of a human limb. This model was first used to simulate the human forearm but was later applied to the general case of limbs. The following factors were included in this model: (1) radial conduction, (2) metabolic heat generation, (3) convection to the blood, and (4) environmental exchange by convection, radiation, and evaporation.

Machle and Hatch (1947) introduced the concept of a core-and-shell model by comparing measured values of rectal and skin temperatures representing the core and shell temperatures used in the model. Empirical correlations for radiation, convection, and evaporation were experimentally developed for inclusion in this model. A modification by Kerslake and Waddell (1958) extended the model to include the case of complete skin wetness due to sweating.

Wyndham and Atkins (1960) further extended the core-and-shell model by introducing several concentric cylinders representing the various body layers. This model used a finite-difference technique to solve a set of resulting first-order differential equations by an analog computer.

A more rigorous analytical approach was taken by Hardy (1949), who applied the laws of thermodynamics and heat transfer to the human system. This analysis included radiant exchange with the environment, thermal conduction through concentric cylinders, natural and forced convection, and evaporation from the skin and lungs. The analysis was accompanied by experimental verification of several of the calculated responses.

Wissler (1961, 1964) modified the models of Pennes and Wyndham and Atkins and combined them to obtain a model of the entire human body. This model sub-divided the body into six elements: head, torso, two arms, and two legs. Each of these elements was assumed to have the following: (1) a uniformly distributed metabolic heat generation, (2) a uniformly distributed blood supply, (3) a composition of homogeneous materials, and (4) a geometry of isotropic cylinders. The effects of heat loss through the respiratory system and countercurrent heat exchange between the arteries and veins were also included.

In contrast to the models based on concentric cylinders, Crosbie *et al.* (1963) used an infinite-slab model to represent an element of the body. These investigators argued that the physics and physiology of the human system could be better understood if based on this configuration and that many uncertainties in previous analyses could be clarified. This model was programmed on an analog computer and verified by experimental observation.

Smith and James (1964) developed another analog model to study thermal stress in man. This model had the following characteristics: (1) metabolic heat production in the working muscles, (2) muscles insulated by a layer of subcutaneous tissue, (3) blood

flow from the muscles to the skin, and (4) blood flow between various elements of the body and heart. This model considered radial conduction through three concentric cylinders and countercurrent exchange between the arteries and veins, and it was verified experimentally.

The next major effort at modeling the entire human body was made by Stolwijk and associates at the John B. Pierce Foundation Laboratory. The initial effort by Stolwijk and Hardy (1966) was a model composed of three cylindrical segments, one each for the head, trunk, and extremities. The trunk was divided into three concentric layers: skin, muscle, and core. The head and extremities were divided into two concentric layers: skin and core. In this work, the concept of the body being composed of a controlled system and a controlling system was suggested. These investigators also did a rigorous review to determine accurate thermal properties of the constituents of the human body. This model was then programmed for analysis by an analog computer and compared to experimentally developed parameters.

The 1966 Stolwijk-Hardy model was expanded (Stolwijk and Cunningham 1968; Stolwijk 1969, 1971; Stolwijk and Hardy 1977) to include six segments: head, trunk, arms, hands, legs, and feet. All these segments were composed of four layers: skin, fat, muscle, and core. The geometry of each was cylindrical except for the head, which was spherical. This model was programmed for analysis by a digital computer and included high metabolic heat production, sweating, blood flow to all layers, and convective and radiant exchange with the environment. Stolwijk's model is one of the most comprehensive programs to date, and has been used to investigate a variety of heat stress situations. For example, for better understanding of the effect of local hyperthermia, heat has been deposited in local areas such as the brain (Stolwijk 1980). In addition, several investigators have adapted it to special cases; e.g., Montgomery (1972; 1974a,b; 1975) used the model to study the effects of man immersed in water.

Gordon *et al.* (1976) extended and improved the basic ideas formulated by Stolwijk (1971) and Wissler (1964) to model the human temperature regulatory response after exposure in a cold environment. This model characterized the human body as 14 cylindrical and spherical segments with a cold exposure control system. The control of metabolism, skin blood flow, and muscle blood flow was achieved by feedback controller signals consisting of the head core temperature, mean skin temperature, and mean skin heat flux. The heat flux control signal was not included in previous models, but the results of this study indicate that it is important when modeling the human thermoregulatory response in cold environments.

4.2.2 RF-Radiation/Heat-Transfer Models

As discussed earlier, there exist reasonably realistic RF-energy deposition models (Sec. 3.2.3, Analytical and Numerical RF Electromagnetic Interaction Models) and heat transfer models (see above discussion) for the human body. However, few attempts have been made to combine the two models to predict the body's thermal response under exposure to RF fields. In one study, Emery *et al.* (1976) determined the thermal effects of a uniform deposition of RF energy for a one-dimensional model of heat conduction. Although this model may yield realistic values for whole-body temperatures, the heating pattern produced by nonuniform deposition of energy may deviate substantially from that produced by uniform absorption; this deviation may occur if various parts of the body (head, arms, legs, etc.) selectively absorb energy from the incident field because of whole- and partial-body resonance. In another study, Guy *et al.* (1978) used thermographic determinations of the distribution of RF energy in phantom models of man, which were subsequently used to provide input for Emery's one-dimensional thermal model. This method certainly accounted for the nonuniformity in the RF-energy deposition, but it apparently did not account for heat flow along the major axis of the body. This factor is important, because the primary nonuniformity in the RF-energy deposition will occur along the body's major axis, since the body is much longer than it is thick. Thus, this model will tend to overestimate the temperature profile in the body because the model allows heat flow to occur only from the core to the skin. In reality, as a result of localized RF-energy deposition, heat flow must also occur along the major length of the body.

The most general attempt to date has been the work of Spiegel *et al.* (1979, 1980a), who have used block models to calculate the RF-energy deposition in the body with a two-dimensional extension of Stolwijk's model to determine the resulting thermal response of the body. This model allows heat flow from the core to the skin as well as along the major axis of the body. The authors used a transient heat conduction model with internal heat generation and heat dissipation. The internal heat generation is caused by metabolism and absorption of RF energy. The internal dissipation is caused by convective exchange with the cardiovascular system and a combined convective and radiant exchange with the surrounding environment at the surface of the skin. The equation simulating the response is, therefore,

$$\rho c \frac{\partial T}{\partial t} = \nabla(k\nabla T) + \frac{1}{V}(QEM + QM - QE - QR) \quad (4\text{-}1)$$

where ρ = tissue density
c = tissue specific heat
T = local tissue temperature

t = time
V = tissue volume
k = tissue thermal conductivity
QEM = electromagnetic energy deposition
QM = metabolic heat generation
QE = evaporative heat dissipation in the skin
QR = respiratory heat loss in the lungs

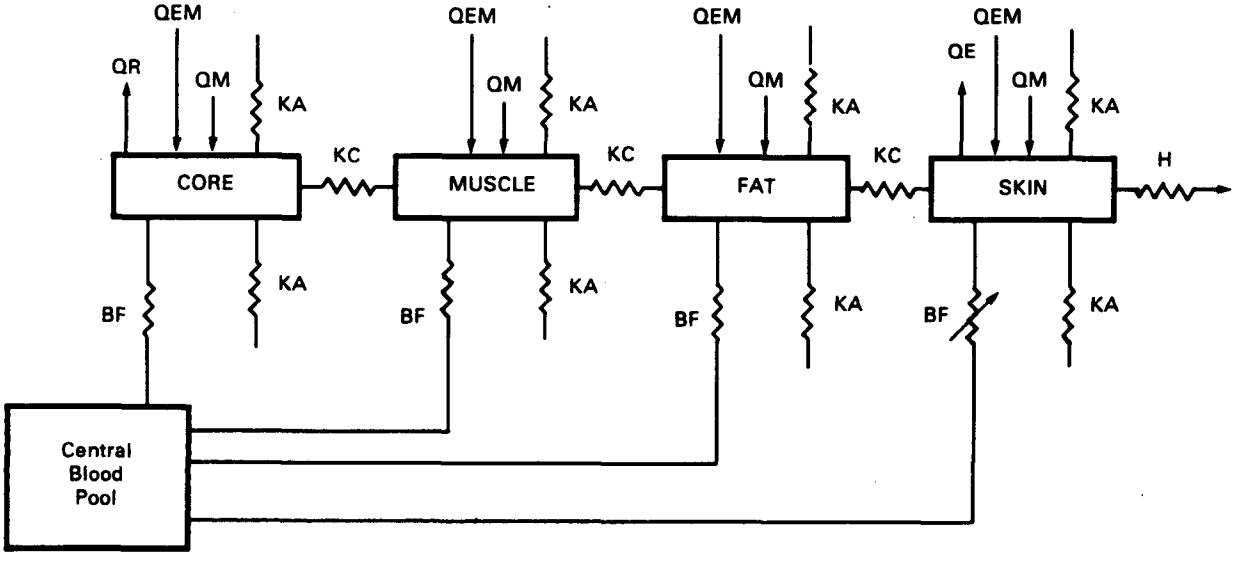
To solve Equation 4-1, the body is divided into several finite elements and this relationship is applied to each element or node. The body is represented by 15 segments, with each segment subdivided into 4 concentric layers — core, muscle, fat, and skin. The head is modeled by a sphere; the neck, hands, and feet are approximated as single cylindrical segments; the arms and legs are each divided into four cylindrical segments, and the trunk is divided into three cylindricl segments. The radius and length of each of these cylindrical segments are based on dimensions for a standard man (Diffrient *et al.* 1974). Calculations of heat capacitance, thermal conductance, and density are based on the type of tissue, the surface area, and the volume for each segment and layer.

In this model, the time and spatial derivatives are represented by finite difference approximations, and the resulting system of equations is solved by an iterative procedure in which the initial temperatures are used to compute the temperatures a short time later. These new temperatures are then used to compute the temperatures at the new time and so on until thermal steady-state conditions are reached.

Figure 4-28 shows the relationship of the various thermal conductances for a typical segment that includes four nodes in the finite element analysis. Each lumped conductance represents heat exchange with the other nodes. The quantities KC and KA represent the radial and axial conductances, respectively, the values of which are determined by layer and segment geometry and by tissue thermal conductivity (Carslaw and Jaeger 1959). Heat exchange between the skin and surrounding environment by convection and radiation is represented by the quantity H, which is determined in the standard engineering manner as described by Stolwijk (1971). The BF terms designate the amount of heat exchanged by each node and the central blood pool, and are a function of blood flow. Blood flow rates to all segments, except the skin, are set to basal values (Stolwijk 1971). The skin-blood flow rate is controlled by vasodilatation, which is a function of the temperature difference between the local skin temperature and the skin set-point temperature, as well as the difference in temperature between the hypothalamic temperature and its set-point temperature. It is believed that all tissues respond to local temperatures in excess of 40°C by an increase in blood flow. However, the literature does not appear to provide enough information to include this response for all 100 compartments of the model.

The other heat exchange modes shown in Figure 4-28 include metabolic heat production QM; heat loss by sweat evaporation on the skin QE; respiratory heat loss in the lungs QR; and electromagnetic heat input QEM. The respiratory loss is determined according to Stolwijk, and the model assumes that the expired air has come to thermal equilibrium with the upper trunk

Figure 4-28. Block diagram for one segment of the thermal model.



core temperature and is saturated. This term enters the equation for thermal balance (Equation 4-1) only at the node that represents the core of the upper trunk segment. Several mathematical models have been proposed to calculate the heat lost by sweating (Emery *et al.* 1976). All are empirical and attempt a best fit to experimental data for various conditions, such as for a sedentary subject or for various levels of exercise. This model is based on the detailed work of Stolwijk (Stolwijk 1971, Stolwijk and Hardy 1977). Evaporation basically is controlled by the sweating rate. As with the rate of blood flow, the term that simulates sweating is a function both of the temperature difference between the local skin temperature and the skin set-point temperature and of the difference between the hypothalamic temperature and its set-point temperature. The body develops its own source of heat as a result of metabolic heat production QM. For a sedentary subject, this value can be at the basal level or can be accelerated by shivering. Shivering is initiated when the body is subjected to a low ambient temperature (< 28°C for a nude subject) and experiences a chill. Since the air temperature for this study is always in excess of 28°C, the effects of shivering and vasoconstriction are not included in the analysis. The RF energy input term QEM is calculated by a block model comprised of 180 cubical cells of various sizes (Hagmann *et al.* 1979a).

4.2.3 Numerical Results

To illustrate the model used by Spiegel *et al.* (1980a), Table 4-3 shows the resulting steady-state temperature distribution in a resting, nude, 70-kg, 170-cm-high man in a thermally neutral environment (air temperature = 30°C; relative humidity = 30 percent) exposed to a plane wave at 80 and 200 MHz. The electric field vector is oriented parallel to the major axis of the body (i.e., E polarization). Whole-body resonance occurs for the 80-MHz field, and partial-body resonance occurs in the arms for the 200-MHz field. For the 80-MHz case, an incident power density of 10 mW/cm² is used (SAR = 2.25 W/kg). For the 200-MHz field, incident power densities are 10 and 32.5 mW/cm² (SARs = 0.58 and 1.9 W/kg, respectively). As mentioned above, the RF-energy deposition term QEM is inserted into Equation 4-1 in a manner prescribed by the 180-cell model.

The distribution of temperatures is quite different in the two cases. For the 80-MHz field, a thermal hot spot (a temperature of around 41.6°C) is generated in the lower thigh; for the 200-MHz field the hot spot tends to occur in the arms. In addition, for the 200-MHz case there is an elevated temperature (40.6°C) in the neck. Another difference is that the hot spot occurs for an incident power density of 10 mW/cm² for the 80-MHz field, whereas 32.5 mW/cm² was required to produce a hot spot for the 200-MHz case. This difference occurs because the whole-body SAR is at least four times greater for the 80-MHz field.

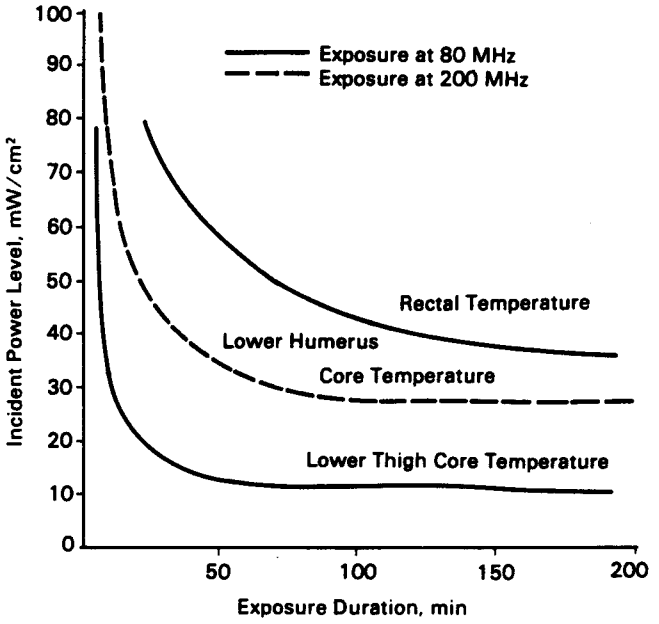
Table 4-3. Steady-State Temperatures (°C) in a Human Body After Exposure to 80- and 200-MHz RF Fields

		80 MHz		200 MHz			
		10 mW/cm²		10 mW/cm²		32.5 mW/cm²	
Segment	No.	Muscle	Core	Muscle	Core	Muscle	Core
Head	1	36.3	37.4	36.1	37.0	37.0	37.2
Neck	2	38.3	38.9	37.7	38.2	40.6	40.6
Upper trunk	3	37.7	37.3	36.9	36.9	37.6	37.1
Middle trunk	4	38.8	37.5	37.2	37.0	39.3	37.2
Lower trunk	5	38.9	37.8	37.1	37.0	38.4	37.2
Upper humerus	6	34.5	35.9	35.3	36.5	37.0	38.4
Lower Humerus	7	34.6	36.0	36.9	38.0	41.2	42.9
Upper forearm	8	34.4	35.7	36.3	37.5	39.8	41.4
Lower forearm	9	34.0	35.0	35.1	36.1	36.9	38.4
Hand	10	36.4	36.6	36.0	36.2	36.4	36.6
Upper thigh	11	39.5	40.3	35.7	37.0	35.8	37.1
Lower thigh	12	40.3	41.6	35.5	36.7	35.7	37.0
Upper calf	13	39.9	41.2	35.7	36.9	36.7	37.9
Lower calf	14	38.4	40.0	35.5	36.4	36.7	37.9
Foot	15	36.4	36.8	35.6	35.8	35.9	36.1

As another useful method to present the data, Figure 4-29 graphically shows the time it takes to obtain a hot spot for a given level of incident power density level for the two frequency conditions. The production of a hot spot can be viewed in terms of a strength-duration model; for example, Figure 4-29 shows that the time required to create a hot spot in the lower thigh for an 80-MHz field takes only a few minutes at 50 mW/cm², but at 10 mW/cm² it will take an hour or more of exposure. In addition, different minimum levels of power density are required to produce hot spots at various body locations. For instance, the rectal temperature profile has an asymptote at a level just above 35 mW/cm², but the lower-thigh core temperature asymptote occurs around 10 mW/cm². For 200-MHz radiation, the lower humerus core temperature was considered, and the intensity-duration curve for this case is shown by the dashed curve.

Based on these results the most critical temperature elevations evidently occur at whole-body resonant frequencies, as might be expected. In fact, the rise in temperature is sufficient to produce a hot spot (41.6°C) in the legs for an incident power density of 10 mW/cm². The increased blood-flow response (based on the calculated results) for tissue temperatures in excess of 40°C was not included in the model. Therefore, the model most likely overestimates the magnitude of the temperature rise in the thigh.

Figure 4-29. Incident power density vs. exposure duration to obtain a hot spot (41.6°C).



4.2.4 Unresolved Issues

Although the combined RF-heat-transfer model reported here is realistic enough to predict gross effects and trends, the model could be further refined. The most obvious refinement is the extension of the two-dimensional heat transfer model to a three-dimensionl simulation. Although this extension is numerically straightforward, problems might arise in computer storage requirements and in the computational time needed to generate the heating patterns. In addition, altered tissue blood flow for temperatures in excess of approximately 40°C has not been implemented in the model. This modification would be simple, but its implementation would require experimentation to quantify the altered blood flow rates.

Another problem is that little is known about the effects of RF energy on the predominant heat-dissipating mechanisms of sweating and vasodilatation. Although the empirical models yield results that compare well with experimental measurements from a human subject placed in a room at a controlled temperature and relative humidity, it is certainly open to question whether good agreement between measured and calculated results would likewise be obtained when the thermal load is caused by an RF field. This problem could be resolved by experimental verification of the model with animal models.

Section 5
Biological Effects of RF Radiation

5.1 Cellular and Subcellular Effects

John W. Allis

The investigation of RF-radiation effects on cellular and subcelluar systems is principally an attempt to elucidate specific biochemical mechanisms for the interaction of the radiation with macroscopic biological systems. This approach takes advantage of the relative simplicity of *in vitro* systems, the ability to control variables, the rapid and economical way with which results may be obtained, and the perceived ease of mechanistic interpretation of the results. In practice, however, these advantages are not always realized.

The divisions between molecular, subcellular, and cellular systems are somewhat arbitrary, but for convenience, results presented in this section will be discussed in this format, illustrated in Table 5-1. When investigating molecular and subcellular systems, one normally looks at a single key structure or function where, one hopes, all other variables may be held constant. In these cases, thorough understanding of the end point under study allows the investigator to interpret results more easily in terms of a detailed biochemical mechanism. For instance, if a change in the kinetics of an enzyme-catalyzed reaction is found, the type of inhibition can be determined, the particular molecules involved can be identified, and a hypothesis for the effect can be constructed.

In some experiments on intact cells, these conditions can also be approached. An example of this is sodium (Na^+) and potassium (K^+) transport across the red-blood-cell (RBC) membrane. The RBCs limited metabolic activity is geared primarily to performing its main function of transporting oxygen from lungs to tissue. In this case, ion transport across the membrane is linked to the mode of energy production in the cell and to very little else, and studies on this system are relatively simple to interpret.

Experiments on most living cells are complicated by complex biochemical systems, many of which have multiple or alternate pathways. Rather than isolated functional changes, broad end points such as growth or genetic changes are often assayed. Here, the investigator tries to use "biological amplification" where, for example, the cell's growth is highly sensitive to disruptions of a critical but unspecified metabolic step, or where a mutant appears that must reproduce over several generations before sufficient numbers are present to be measurable. The investigator also recognizes that the redundancies in a complex system like a living cell may negate any efforts to detect the putative effect.

This inherent complexity makes it difficult to ascribe a detailed biochemical mechanism to effects found. Such effects must be viewed as a starting point from which a mechanism may eventually be deduced. On the other hand, effects on cells can also be used to

Table 5-1. Classification of Cellular and Subcellular Experiments

Classification	Type of System Studied	Examples of Experimental Measures
Molecular	Purified enzyme preparations	Enzyme activity, binding to small molecules
Molecular	Purified DNA preparations	DNA melting
Subcellular organelles	Membrane-bound enzymes	Enzyme activity
Subcellular organelles	Cell membranes, phospholipid vesicles	Infrared, Raman spectra
Subcellular organelles	Isolated mitochondria	Mitochondrial function
Cellular	Red blood cells	Ion transport
Cellular	Bacteria	Growth, survival, infectivity
Cellular	Isolated neurons	Neuronal firing, membrane potential

rationalize or interpret—perhaps even predict—effects in the intact animal.

Dosimetry for *in vitro* systems presents problems to the researcher that are in many respects unique to the study of RF-radiation interactions. In general, average SAR in the sample is relatively easy to measure and has become the standard dose-rate measurement in this research area. The most convenient methods are thermal measurements, i.e., analysis of heating and/or cooling data (Allis *et al.* 1977), and electrical measurements, where forward, transmitted, and reflected power are recorded in a closed exposure system. (See Sec. 3.4.) Thermal measurements have become much more convenient and accurate since the development of temperature probes that do not perturb the RF field. A third commonly used dosimetric method is calculation of SAR based on incident power or power density. This approach is less satisfactory than the methods mentioned above because simplifying assumptions must normally be made to model the exposure geometry. In this section on cellular and subcellular systems, the SAR given for each study is the average for the sample unless otherwise noted.

In most *in vitro* as well as *in vivo* exposures, the distribution of absorbed energy in the sample is not constant throughout the sample. Most researchers in the field recognize this fact, and the standard approach for treating the problem is to stir or agitate the solution if possible. Normally this is an effective way to eliminate thermal gradients produced by inhomogeneous absorption patterns. When stirring is not possible, and occasionally even when it is, potentially serious problems arise because the end points measured for *in vitro* systems are often very sensitive to temperature. Inhomogeneities in temperature within the sample can give misleading results (Livingston *et al.* 1979, for example). The potential for this problem exists in some of the work discussed later in this section.

Because of temperature sensitivity of biological end points measured in many *in vitro* systems, researchers are generally careful about maintaining temperature control of the exposed sample and matching it to the control or sham-exposed sample. Two methods are normally used. In one, the researcher establishes a steady-state temperature in the presence of the RF radiation and then begins the assay. In this case, the exposed sample is cooled to (or experiences an ambient temperature) below the temperature at which the assay is conducted, with the RF energy making up the temperature difference. The sham or control sample is matched to the steady-state temperature and remains at thermal equilibrium with its surroundings. Because the exposed sample is at a higher temperature than its surroundings, a temperature gradient necessarily exists in the RF-exposed sample that does not exist in the control. The magnitude of the gradient depends on the energy absorbed from the field and the sample geometry. Among the more conventional methods of heating, infrared exposure mimics most closely the heating patterns for *in vitro* samples exposed to RF radiation. The second method of temperature control often used is to allow the temperature of the exposed sample to rise during exposure and then to mimic the rise in the control sample by applying conventional heating techniques. This method has the same difficulty with a gradient in the exposed sample as just described; also, it is difficult to match precisely the kinetics of the temperature rise due to exposure to RF radiation using conventional techniques. However, properly designed experimental apparatus and good techniques can significantly reduce the difficulty.

One must also recognize that generally *in vitro* systems are primarily made up of a solvent medium in which the cells or subcellular systems are suspended. Temperature probes are macroscopic and necessarily measure the temperature of the solvent, whereas the measurement desired is that of the temperature experienced by the cell, or by the immediate environment about the subcellular systems. On the other hand, a more detailed analysis of the thermal properties of a sample, and more precise and accurate data, can be obtained from *in vitro* systems than can be achieved with *in vivo* experimentation.

The foregoing discussion has presented the major problems with dosimetry for *in vitro* systems. In general, however, these problems are less severe than those encountered with *in vivo* work. The investigation of mechanisms of interaction of RF radiation with biological systems is critical to a basic understanding of the biological effects and is best accomplished using *in vitro* techniques. If careful attention is paid to dosimetry and if the difficulties presented here are addressed, dosimetry need not be a principal concern in the interpretation of the experimental results.

The general conclusions that can be made at this time concerning the effects of RF radiation on cellular and subcellular systems are:

- No consistent biological effects have been demonstrated for molecular or subcellular systems exposed *in vitro* that can be attributed to RF-specific interactions.
- No consistent effects have been demonstrated on growth and colony-forming ability of single cells that can be attributed to RF-specific interactions.
- There is an indication that sodium and potassium ion transport across red blood cell membranes can be affected by exposure *in vitro* to RF radiation in a manner different from generalized heating.
- The electrophysiological properties of single cells, especially the firing rate of neurons in isolated

preparations, may be affected by RF radiation in a manner different from generalized heating.

5.1.1 Effects on Molecular Systems

To obtain insights into possible direct interactive mechanism(s) of microwave radiation at the molecular level, several investigators have attempted to measure changes in biologically important macromolecules exposed *in vitro* (Table 5-2). Enzyme kinetics studies form a majority of the reports, but a few examine changes in macromolecular structure. In sum, these reports do not demonstrate consistent effects on molecular systems exposed *in vitro* to RF radiation that can be attributed to RF-specific interactions.

In one study of macromolecular structure, Hamrick (1973) measured DNA melting curves after exposure of calf thymus DNA to 2.45-GHz (CW) radiation for 16 h (SAR = 67 W/kg) and at dose rates to 160 W/kg for 1 h. Temperature was controlled during all exposures, usually at 37°C, but for some experiments it was maintained at 40, 45, and 50°C. The intent of the study was to determine whether microwaves disrupted hydrogen bonding between the DNA strands of the double helix and thus affected the melting curve. The assay was carried out after exposure. In one experiment the investigators preserved any disruption of hydrogen bonding between the strands by performing the microwave exposure with formaldehyde in the buffer. However, all melting curves were virtually identical to those of unexposed, temperature-matched controls.

In another report concerning macromolecular structure (Allis 1975), the protein bovine serum albumin (BSA) was exposed to 1.70- and 2.45-GHz (CW) radiation (SARs ranging from 30 to 100 W/kg). The author recognized that structural changes due to microwave exposure may be reversible. In this study, he attacked the problem by developing an exposure apparatus in which ultraviolet (UV) and visible spectrophotometric measurements could be performed during exposure. The difference in UV absorption between the exposed and unexposed samples was measured directly by a double-beam spectrophotometer. Differences of this type reflect small changes in the surroundings of certain UV-absorbing amino acids and, in this case, could be interpreted as changes in the structure of the protein. The temperature of the exposed samples was controlled during exposure, and it was matched by the temperature of the control sample. Temperatures ranged from 24 to 32°C, depending on the SAR value. Spectra were measured immediately upon beginning exposure, and again 30 min later with continuous exposure. The study results showed that no changes in the UV spectrum could be found over a variety of structural states of protein, so that structural changes due to microwave exposure could not be inferred.

The ability of microwave radiation to alter enzyme activity has been studied by several workers. Measurements were performed during microwave exposure by two groups, each using spectrophotometric measures of enzyme activity. Ward *et al.*

Table 5-2. Summary of Studies Concerning RF-Radiation Effects on Molecular Systems

End Point Measured/ Effects	Experimental System	Exposure Conditions: Frequency (GHz)	Duration (min)	Exposure Facility (type)	SAR (W/kg)	Reference
No change in UV difference spectra measured over pH range 2.5-5.5	BSA*	1.70 (CW) 2.45 (CW)	30	Waveguide	30-100	Allis (1975)
UV spectra and binding constants for mononucleotides showed no difference from controls	Ribonuclease	1.70 (CW) 2.45 (CW)	30	Waveguide	39	Allis *et al.* (1976)
No change in enzyme activity	Glucose-6 phosphate dehydrogenase; adenylate kinase; NADPH cytochrome C reductase	2.45 (CW)	5	Waveguide	42	Ward *et al.* (1975)
No difference in melting curves	DNA	2.45 (CW)	60, 960	Far field	67, 160	Hamrick (1973)
Inactivation of enzyme; probably temperature inhomogeneity effect at very high doses	Horseradish peroxidase	2.45 (CW)	5, 10, 20, 30, 40	Waveguide	62,500-375,000	Henderson *et al.* (1975)
Heat inactivation of enzymes found at highest SAR (T = 50 °C) corresponded closely to heat-treated controls	Glucose-6-phosphate dehydrogenase; lactate dehydrogenase; acid phosphatase; alkaline phosphatase	2.8 (PW)	4.5, 18.5	Waveguide	~200-500	Belkhode *et al.* (1974a,b)
Heat inactivation of enzyme found at SARs > 165 W/kg	Lactate dehydrogenase	3.0 (CW)	20	Waveguide	33-960	Bini *et al.* (1978)

*BSA = bovine serum albumin.

(1975) examined three enzymes (glucose-6-phosphate dehydrogenase, adenylate kinase, and NADPH-cytochrome c reductase) exposed to 2.45-GHz (CW) radiation (SAR = 42 W/kg). All exposed and control samples were maintained at 25°C. Exposure durations were ~5 min, during which the enzyme activity was measured. No differences between exposed and control samples were found. Bini *et al.* (1978) followed the activity of lactate dehydrogenase exposed to 3.0-GHz (CW) radiation (SARs between 33 and 960 W/kg). They demonstrated that the changes found in the enzyme activity were entirely consistent with calculations of thermal inactivation of the enzyme at the temperatures attained. The sample exposed at 33 W/kg was not different from the unexposed control; all other exposures (SARs ranging from 165 to 960 W/kg) showed evidence of enzyme inactivation.

Belkhode *et al.* (1974a,b) reported the effect of 2.8 GHz square-wave modulated (1-kHz) radiation on four enzymes: glucose-6-phosphate dehydrogenase, lactate dehydrogenase, acid phosphatase, and alkaline phosphatase. Enzyme preparations were analyzed after exposures (SARs ~ 200 to 500 W/kg on average). Exposures were conducted at 37, 46.7, and 49.7°C; enzyme activities were compared to the activity of sham-exposed samples at the same temperatures. Activities of the exposed enzymes at each temperature were indistinguishable from the shams.

Henderson *et al.* (1975) reported a change in enzyme activity that was interpreted as an indicator of direct interaction on the enzyme by microwaves. In this experiment, horseradish peroxidase was subjected to 2.45-GHz (CW) radiation (SARs between 62,500 and 375,000 W/kg) with the sample exposed in a tube (4.7-mm ID) that protruded through a waveguide. The sample tube was surrounded by a concentric cooling jacket, through which an organic coolant was pumped continuously to maintain the temperature at 25°C. Thermocouples were placed in the sample tube so that the sample temperature could be monitored from positions just outside the waveguide. The total volume of the exposed sample was ~0.8 ml. A marked decrease in enzyme activity was found at 62,500 W/kg after 30 min of exposure, and at 187,500 W/kg after 20 min of exposure, even though the temperature was reported never to exceed 35°C. It is possible that the very high fields present at these SARs could produce field-specific effects. However, it appears likely that very high local heating occurred in the sample that was responsible for enzyme inactivation. This likelihood is substantiated by the work of Harrison *et al.* (1980), who performed liquid-crystal thermography under similar exposure conditions. Temperature rises of as much as 0.3°C were recorded within a micropipette suspended in a waveguide and cooled with water circulating through the waveguide. Henderson *et al.* (1975) exposed their samples at 5 to 10 times the levels used by Harrison *et al.*; also, the latter researchers used water as a coolant, which would attenuate the energy reaching the sample much more strongly than would the organic solvent used by Henderson *et al.* A study by Livingston *et al.* (1979) graphically illustrates the effect of temperature gradients during microwave exposure.

The binding of small substrate-like molecules to the enzyme ribonuclease was studied to determine whether the binding relationship between an enzyme and substrate could be affected by microwaves (Allis *et al.* 1976). In this work, UV-absorption spectra were measured during exposure to 1.70- and 2.45-GHz (CW) radiation (SAR = 39 W/kg). Measurements were performed immediately upon beginning irradiation and after 30 min of exposure. Neither structural changes in the enzyme-substrate complex nor changes in the binding constants were found.

5.1.2 Effects on Subcellular Organelles

There has been relatively little research on the effects of microwave radiation on subcellular organelles (Table 5-3). The reports included in this document range from work with phospholipid bilayers (i.e., synthetic analogs of cell membranes) to experiments on intact mitochondria, the energy-producing system in eukaryotic (e.g., mammalian) cells. Most of the work to be discussed here has not demonstrated effects of microwave exposure at dose rates ranging from 1 to 430 W/kg. Two reports that have indicated an effect do not meet all criteria for inclusion here and are therefore discussed with other reports that present unresolved issues.

Two reports describe work with enzymes bound to biological membranes. The study by Ward *et al.* (1975), discussed above, focused on the enzyme NADPH-cytochrome c reductase, which is loosely bound to the membrane of the endoplasmic reticulum of rat liver cells. Allis and Fromme (1979) studied adenosine triphosphatase (ATPase) in RBC membranes and cytochrome oxidase in the inner mitochondrial membrane of rat liver cells. The latter two enzymes are thought to be integral parts of membranes. Conditions of the exposure were identical for all three enzymes in that the essay was performed spectrophotometrically during exposure to microwaves. In the latter study the dose rate was 26 W/kg, and the 2.45-GHz radiation was sinusoidally modulated at 16, 30, 90, and 120 Hz. Enzyme activity was not measurably affected by these exposures; a 10- to 15-percent change in enzyme activity would have been required to detect a reliable microwave effect.

Ismailov (1977) investigated the infrared (IR) absorption spectra of proteins in RBC membranes exposed to 1.009-GHz fields (SARs up to 45 W/kg) and maintained at 25°C. The samples were exposed

for 30 min in aqueous suspension in a stripline and were then dried to a thin film to obtain the IR spectra. No change in α-helix or β-sheet content of the membrane proteins was noted. However, when D_2O (heavy water) was added to the suspension before beginning exposure, application of microwaves was found to increase the degree to which strongly bound amide hydrogens were exchanged. This effect was pronounced at SAR = 45 W/kg but disappeared when the SAR was below 10 W/kg. The increase in accessibility of the poorly exchangeable amide hydrogens indicates that the microwaves disturb the relationship of the protein to its neighboring membrane lipid.

IR spectra of *Escherichia coli* after exposure to microwaves were also measured (Corelli *et al.* 1977). After 12 h of exposure to 3.2-GHz (CW) radiation (SAR = 20 W/kg), *E. coli* were dried to a film, and spectra were measured in the protein and nucleic acid absorption regions. No differences were found. These results are comparable with those of Ismailov (1977), which indicated no changes, but they do not address the conditions for which Ismailov did report effects.

The functional properties of the microtubule assembly system extracted from rabbit brain cells were studied after exposure to 3.1-GHz fields by Paulsson *et al.* (1977). The binding of the drug colchicine to the microtubule precursor protein tubulin was measured after exposure to PW microwaves for 15 min at average dose rates of 112 and 243 W/kg (pulse-repetition rate of 200 Hz, pulse duration of 1.4 μs). Colchicine normally blocks the formation of microtubules, which halts cell division. The normal assembly of microtubules from tubulin exposed for 10 min to PW microwaves, as above, at 430 W/kg was also studied. No noticeable effect on either process was found. The data indicate that a change of about 15 percent in the colchicine binding and about 10 percent in the microtubule assembly measurement would have been noted. Paulsson *et al.* also studied the migration of proteins within the axonal membrane of the rabbit's vagus nerve. In this case the samples were exposed for 24 h (the SAR estimated from their data was 10 to 100 W/kg) at a pulse-repetition rate (PRR) of 100 Hz and a pulse duration 1.4 μs. The distribution of tritium-labeled protein in the axonal membrane was found to be the same in exposed and control samples. A difference of > 20 percent would have been required for detection in this experiment.

Two papers (Elder and Ali 1975; Elder *et al.* 1976) present results of exposure of rat liver mitochondria to microwave radiation. Both papers examine oxygen utilization by measuring respiratory activity (e.g., respiratory control ratio, ADP to oxygen ratio) under

Table 5-3. Summary of Studies Concerning RF-Radiation Effects on Subcellular Systems

End Point Measured/ Effects	Experimental System	Exposure Conditions: Frequency (GHz)	Duration (min)	Exposure Facility (type)	SAR (W/kg)	Reference
Increase in exchange of strongly bound amide hydrogens in membrane protein measured by IR† spectra for SAR > 10 W/kg; no change in α-helix or β-sheet content of proteins	RBC membrane*	1.0 (CW)	30	Stripline	5-45	Ismailov (1977)
No change in activity of membrane bound enzymes measured spectrophotometrically	RBC membrane; mitochondrial inner membrane	2.45 (SW#)	10	Waveguide	26	Allis and Fromme (1979)
No change in activity of membrane-bound enzyme measured spectrophotometrically	Endoplasmic reticulum	2.45 (CW)	5	Waveguide	42	Ward *et al.* (1975)
No difference in respiratory activity	Mitochondria	2.45 (CW)	30 to 210	Anechoic chamber far field	17.5, 87.5	Elder and Ali (1975)
No difference in respiratory activity	Mitochondria	2-4 (Swept) 3.4 (CW)	10	Coaxial airline	1.6-2.3 41	Elder *et al.* (1976)
No change in formation of microtubules	Tubulin (rabbit brain)	3.1 (PW)	15	Far field	112-430	Paulsson *et al.* (1977)
No change in migration of proteins within axonal membrane	Vagus nerve cell	3.1 (PW)	24 h	Far field	~10-100	Paulsson *et al.* (1977)
No changes in IR spectra of proteins and nucleic acids in E. *coli* exposed before drying	Dried film of *E. coli* cells	3.2 (CW)	8, 10, 11 h	Waveguide	20	Corelli *et al.* (1977)

*RBC = Red blood cell.
†IR = Infrared.
#SW = Sine-wave modulated.

various conditions. These parameters are functional indications of the energy production system in eukaryotic cells. The earlier paper tested mitochondria kept at 0°C, or inactive state, during exposure in the far field at 2.45 GHz. The mitochondrial functions were examined after exposure in the active state at 25°C. (Exposures for periods up to 3.5 h were conducted at SARs of 17.5 and 87.5 W/kg.) No changes in mitochondrial activity were seen. In the later paper, the disadvantage of exposing inactive mitochondria was overcome by use of a novel flow-through system that coupled a coaxial airline and an oxygen electrode. The mitochondrial suspension was cycled continuously between the airline, where exposure was accomplished, and the oxygen electrode. Samples were exposed to 2.45-, 3.0-, and 3.4-GHz (CW) radiation (SAR = 41 W/kg) and also to radiation at swept frequencies between 2 and 4 GHz (SARs from 1.6 to 2.3 W/kg). As in the earlier work, no effects of microwave exposure were detected under any condition. In general, a five-percent change would have been sufficient for detection. Other workers have presented data on microwave exposure of mitochondria, either in a form too incomplete for inclusion or in oral presentations. Their findings do not differ from those described here.

5.1.3 Effects on Single Cells

Effects on single cells have been investigated by several researchers (Table 5-4). Most of the work discussed in this section falls into three classes: studies of ion transport into or out of red blood cells, growth or colony-forming ability of various lines of cells, and responses of single neurons exposed to RF radiation. In the ion transport studies two papers have demonstrated effects, but one of them has not been replicated despite two attempts. Only one of the reports involving cell growth reported an effect, but sample heating may have been responsible for the result. The potentially most significant effect is that of the response of neurons. Two papers from one laboratory are discussed in this section, and a third report from a second laboratory is discussed under Unresolved Issues (Sec. 5.1.4). All show very similar results for the firing rate of neurons exposed to RF radiation. In sum, for cellular systems, effects have been found that may prove significant and should provide leads for elucidating a new mechanism of action. However, at present, these effects require additional documentation.

Transport and related properties of RBC membranes have been studied by five groups. In each case Na^+ or K^+ transport was used as an end point. In the RBC, active (or energy requiring) Na^+ and K^+ transport across the membrane is by the enzyme Na^+-K^+ ATPase (the same enzyme discussed in Sec. 5.1.2, Effects on Subcellular Organelles), and passive transport is through channels in the membrane. Ismailov (1971) exposed human RBCs to 1.0-GHz (CW) microwaves at 45 W/kg and found an increased efflux of K^+ and a concomitant increased influx of Na^+. The Na^+ influx was twice as large, ion per ion, as the K^+ efflux. Exposures were carried out in a coaxial stripline for 30 min, with analysis of the ion content of the supernatant performed afterwards. These results indicate either a reversal of the normal action of the Na^+-K^+ ATPase, or an inhibition of the enzyme, which permitted ion leakage across the membrane to change the Na^+/K^+ ratio. Hamrick and Zinkl (1975) and Peterson *et al.* (1979) have performed similar experiments by exposing RBC's at 2.45 GHz in the far field (SAR's were 3 to 57 W/kg, and ~ 200 W/kg, respectively). Neither study found a difference between the K^+ efflux from microwave-exposed RBC's and conventionally heated RBCs with similar histories of temperature elevation, although Peterson *et al.* did find a difference between unexposed rabbit cells maintained at 25°C compared with those maintained at 37°C. This difference did not occur with human cells. Ismailov also used temperature controls but did not describe the solution parameters for the cell suspensions. Under certain conditions of chemical concentration, it is possible to reverse the Na^+-K^+ ATPase; however, Ismailov's controls behaved normally, which would indicate that chemical concentrations in the controls were not unusual. The origin of the discrepancy between these studies is not clear.

Hamrick and Zinkl (1975) and Peterson *et al.* (1979) measured other end points as well. The former looked at osmotic fragility of the RBC's and concluded that there was no difference. The latter paper gives data on hemoglobin release from RBC's, an indicator of membrane fragility. Again, no differences were found between irradiated and heat-treated RBCs; however, as for K^+ efflux, the unexposed rabbit cells released less hemoglobin at 25°C than at 37°C.

Liu *et al.* (1979) also studied K^+ efflux, hemoglobin release, and osmotic fragility in red blood cells. Exposure to RF radiation was conducted in a waveguide system at frequencies of 2.45, 3.00, and 3.95 GHz. A 1.2-cm-diameter polystyrene tube containing a 0.6-ml suspension of RBCs was inserted through the center of the waveguide with the long axis of the tube parallel to the electric field. Temperature was measured before and after exposure by insertion of a thermistor. The temperature of the exposed sample was allowed to rise, and heat-treated controls were placed in a water bath at the temperature equivalent to the maximum exposure temperature. Time of treatment was the same for exposed and heat-treated samples. No statistically significant differences were found between exposed and heat-treated samples in any of the measurements performed. Experiments included exposure of rabbit RBCs at SARs of 22 to 200 W/kg (equilavent to 5.2 to 22°C rise in temperature); ouabain treatment of the

rabbit RBCs to block the Na^+-K^+ ATPase; and a comparative study of rabbit, human, and dog RBCs exposed at 3.00 GHz and an SAR of 173 W/kg.

In a separate paper, Ismailov (1978) reported increases in the electrophoretic mobility of human RBCs exposed under conditions identical to those in his previously discussed study. The electrophoretic mobility was measured at 10-min intervals after cessation of exposure. The mobility was found to peak 30 min after exposure and to return to base line ~60 min after exposure. The peak mobility decreased with shorter exposure durations (30, 15, 8, and 4 min). Also, the mobility change decreased as a function of dose rate and disappeared altogether between 5 and 10 W/kg. Although a change in the counter-ion distribution around the cell and possible conformational changes in the membrane proteins were discussed or suggested as possible causes, it remained unclear why these phenomena peaked 30 min after exposure.

Passive ion transport was examined by Olcerst *et al.* (1980) after they exposed rabbit RBCs to 2.45-GHz (CW) radiation (SARs at 100, 190, and 390 W/kg). The cells were treated wth ouabain to inhibit active transport of Na^+ and K^+ by Na^+-K^+ ATPase, the important enzyme discussed previously in several papers. Exposures took place in a waveguide system in which the sample was placed parallel to the E-field in a cylindrical tube. An organic coolant of low dielectric constant was circulated around the sample

Table 5-4. Summary of Studies Concerning RF-Radiation Effects on Single Cells

End Point Measured/ Effects	Experimental System	Exposure Conditions: Frequency (GHz)	Duration (min)	Exposure Facility (type)	SAR (W/kg)	Reference
Increase in RBC electrophoretic mobility 30 min post-exposure (SAR ≥ 10 W/kg)	RBC*	1.0 (CW)	4, 8, 15, 30	Stripline	5-45	Ismailov (1978)
Increase in K^+ efflux and Na^+ influx	RBC	1.0 (CW)	30	Stripline	45	Ismailov (1971)
K^+ transport no different from heat-treated controls; no change in osmotic fragility	RBC	2.45 (CW)	60, 120, 180, 240	Monopole far field	3-57	Hamrick and Zinkl (1975)
K^+ transport no different from controls at corresponding temperatures; no difference in hemoglobin release	RBC	2.45 (CW)	45	Anechoic chamber far field	200	Peterson *et al.* (1979)
Passive transport of Na^+ and Rb^+ increased at transition temperature	RBC	2.45 (CW)	60	Waveguide	100, 190 390	Olcerst *et al.* (1980)
No significant changes in K^+ efflux, hemoglobin release, or osmotic fragility	RBC	2.45 (CW) 3.00 (CW) 3.95 (CW)	20, 180	Waveguide	22-200	Liu *et al.* (1979)
Rapid response in change of firing rate of pacemaker neurons which does not correlate with temperature changes in minority of trials	Isolated neuron from *Aplysia*	1.5, 2.45 (CW and PW)	3	Stripline	1-100	Wachtel *et al.* (1975); Seaman and Wachtel (1978)
No change in growth or CFU† of exposed cultures	*E. coli* *P. aeruginosa*	2.45 (CW)	720	Far field	29-320	Hamrick and Butler (1973)
No change in growth, CFU, of various strains of exposed cultures under several growth conditions	*E. coli*	2.45 (CW)	240	Anechoic chamber far field	0.0075-75	Blackman *et al.* (1975)
No change in survival curves (measuring CFU) of exposed cultures	*E. coli* *B. subtilis* spores	2.45	1	Microwave oven	~400	Goldblith and Wang (1967)
Growth rate slowed; morphological changes found	Chinese hamster lung cells, V79	2.45 (CW)	20	Waveguide	1059	Chen and Lin (1978)
No change in light emission of photoactive bacterium	*P. fischeri*	2.6-3.0 (CW)	~22	Waveguide	660 to 5300	Barber (1962)
No effect on colony-forming ability	*E. coli*	2.6-4.0 (CW)	8 h	Waveguide	29	Corelli *et al.* (1977)
Temporary decrease in virulence (> 6 h) of bacteria for its host cells; recovery within 24 h at 37 °C	*A. tumefaciens*	10 (CW)	30, 60, 230	Cavity	~1	Moore *et al.* (1979)

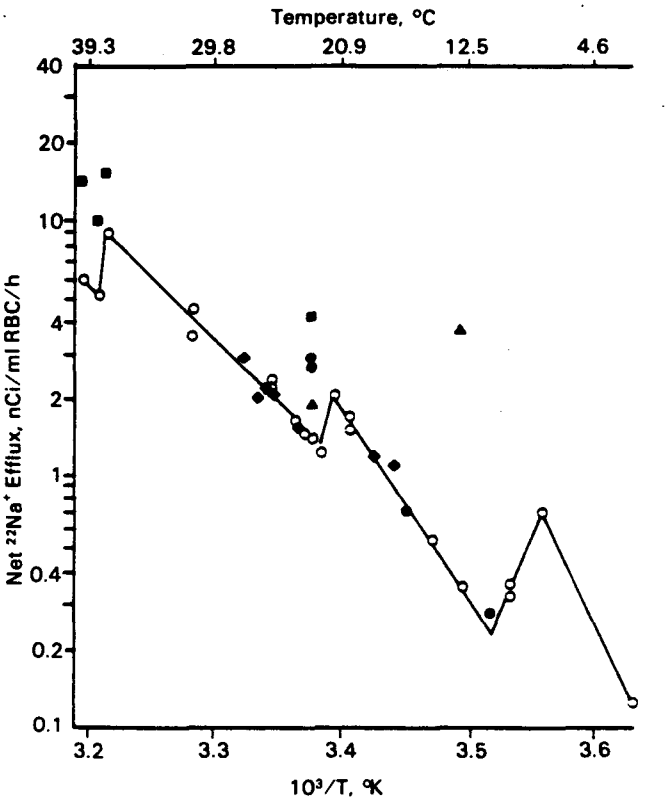
*RBC = Red blood cell.
†CFU = Colony forming unit.

in a larger concentric cylinder to maintain the temperature of the sample under exposure. The SARs were computed from readings of forward and reflected power. The RBCs were pre-incubated with radioactive Na^+ or Rb^+. (The latter is a K^+ substitute.) Samples were exposed or heat-treated for 1 h, and the suspending medium was analyzed for radioactivity. Graphs of the logarithm of the efflux vs. inverse temperature were identical except at three transition temperatures, where the slope of these plots changes sharply (Figure 5-1). At these points, the exposed samples exhibited considerably higher efflux than the heated samples; however, no consistent difference between exposure levels could be established. These results imply that the cell membrane structures responsible for passive ion transport are sensitive to microwave exposure at temperatures at which transitions between two states are taking place. Living cells depend on closely regulated ion concentrations for many processes, and serious disruption of these balances could be lethal. It should be noted that none of the previously discussed studies of Na^+ or K^+ transport in RBCs were conducted at the temperatures at which transitions were found in this report.

Many studies focus on a major function of a cellular species as a generalized end point. The reasoning for this approach is that if microwaves disrupt an important metabolic step, the result will be a decline in the ability of the cell to perform its major function. As mentioned earlier, this reasoning assumes that no compensating mechanism will operate. A broad spectrum of such end points has been investigated for cells exposed *in vitro.* Some of them are discussed elsewhere: phagocytosis and blastic transformation in lymphocytes in Sec. 5.2, Hematologic and Immunologic Effects; and the induction of the antibiotic colicin, along with point mutations in single cells, in Sec. 5.8, Genetics and Mutagenesis.

Perhaps the ultimate test of a cell's functional ability is growth and survival. Several workers have concentrated on this end point and have investigated the frequency range between 1 and 4 GHz. In general, the results have proved negative. Far-field exposures were conducted (Hamrick and Butler 1973; Blackman *et al.* 1975) on several strains or mutants of *E. coli* and on *Pseudomonas aeruginosa.* Samples were exposed in T-flasks or petri dishes, principally to 2.45-GHz (CW) radiation. Growth was measured by assays of colony-forming units (CFUs). In both experiments the duration of exposure was sufficiently long (12 and 4 h) for the average cell to divide at least once. Blackman *et al.* examined several growth conditions such as lag, log and stationary phases of growth, rich and minimal media, and a "normal" as well as a mutant amino-acid-requiring strain. In each case, no differences between the exposed samples and temperature-matched control samples were found. Hamrick's SARs ranged from 29 to 320 W/kg with

Figure 5-1. Arrhenius plot of Na^+ efflux. Unirradiated temperature controls are represented by open symbols; irradiated samples are represented by darkened symbols. Specific absorption rates are expressed as watts per kilogram (● = 100, ■ = 190, ▲ = 390). Control samples had an average standard error of 0.98 percent. Irradiated samples had an average standard error of 4 percent (Olcerst *et al.* 1980).



power densities of 60 to 600 mW/cm², and Blackman's from 0.0075 to 75 W/kg with power densities of 0.005 to 50 mW/cm².

Corelli *et al.* (1977) exposed *E. coli* at the end of a waveguide to microwaves swept from 2.6 to 4.0 GHz for 8 h at a dose rate of 29 W/kg. No effect of the microwave exposure was found on colony-forming ability of the bacteria. Goldblith and Wang (1967) exposed *E. coli* and *Bacillus subtilis* spores in a microwave oven at 2.45 GHz for periods to 1 min (SAR estimated at 400 W/kg). In this case, microwave irradiation and conventional heating were found to have identical effects on survival.

Chen and Lin (1978) exposed Chinese hamster lung cells, V79, in a waveguide fitted with a micropipette that contained the cell suspension. Temperature was regulated by circulation of cooling water through the waveguide around the micropipette. Samples were exposed to 2450-MHz (CW) radiation for 20 min, and the cells were allowed to grow in cultures for 12 days after exposure. The exposed cells were observed to divide at a lower rate and to exhibit a fibroblastic type

of growth, in contrast with the controls. These cells were exposed at 400 mW/cm² (SAR = 1059 W/kg) under conditions similar to those in which Harrison *et al.* (1980) found temperature elevations in the sample that were as much as 0.3°C higher than the cells in the cooling bath. Chen and Lin (1978) state that temperature-treated controls at 38°C (1°C higher than the coolant temperature during microwave exposure) did not display the changes observed in the microwave-exposed cells. However, it is not entirely clear whether the changes in the microwave-treated cells were caused by elevated temperatures within the micropipette.

The emission of light by a photoactive bacterium, *Photobacterium fischeri,* has been used as the end point of one study (Barber 1962), where the bacterial suspension was circulated through a waveguide. The bacteria were undergoing exposure in the waveguide for approximately half the time during a typical 43-min experiment. Bacteria were exposed at several frequencies between 2.6 and 3.0 GHz; the assay was performed 24 h later. In spite of extremely high dose rates, 660 to 5300 W/kg, there were no differences between microwave-irradiated and conventionally heated samples that received parallel treatment.

In the single experiment conducted at 10-GHz frequency, a transient effect was found in the virulence of *Agrobacterium tumefaciens* towards its normal hosts, potato and turnip disks (Moore *et al.* 1979). This bacterium produces a plasmid, which it injects into the host cells and which is responsible for turning these cells into uncontrolled tumor cells. In this experiment, a suspension of *A. tumefaciens* was exposed in a petri dish for 30, 60, and 230 min. The longer exposures produced a decrease of virulence near 60 percent with no essential change in the number of viable cells. The effect was unchanged 6 h post-exposure, but virulence returned to normal 23 h post-exposure when the bacteria were maintained at 27°C. An additional experiment, in which treated and untreated cells were added to the host simultaneously, indicated that the exposed cells were able to compete effectively with untreated cells for binding sites on the host cells. The treated bacteria were always maintained at or below 27°C during irradiation. From the temperature data in the paper, a dose rate of ~ 1 W/kg and power density of 0.58 mW/cm² can be estimated. A possible explanation for this effect, which was not offered by the original authors, is that the plasmid DNA of the *A. tumefaciens* was incorporated into the major DNA of the bacteria during microwave exposure, preventing injection into the host. Normal growth may have subsequently allowed the plasmid to return to its original state and activity.

In two papers, Wachtel and co-workers (Seaman and Wachtel 1978, Wachtel *et al.* 1975) have examined the effects of microwave irradiation on the firing rate of isolated neurons from the marine gastropod *Aplysia.* Neurons were exposed in a stripline to 1.5- and 2.45-GHz (CW and PW) fields (0.5- to 10-μs duration, 1000 to 15,000 pulses/s). The firing rate of pacemaker neurons and the burst rate of bursting cells were measured during microwave exposure at dose rates between 1 and 100 W/kg. Glass capillary electrodes filled with 0.5 M KCl were used to inject current and measure the firing rate of the cells. The electrodes had artifactual DC potentials of less than 1 mV and currents of less than 10 pA during exposure; these values were judged by the authors to be too small to affect the performance of the cells. In the majority of cases, the firing rate of pacemaker cells increased with an increase in temperature, and decreased with a decrease in temperature. In a minority of cases, 13 percent, for the pacemaker cells, the microwave irradiation reversed the normal change in firing rate; i.e., the rate decreased or stopped with a microwave-induced increase in temperature. The authors were able to detect slow and rapid components. The slow component, occuring in 30 to 60 s, was correlated with the slow rise of temperature associated with exposure. The rapid component, occurring within 1 s, appeared to correlate with the presence of the microwave field. The rapid component was always found to be a decrease in firing rate in the presence of the field and was never produced by convective heating. Similar but more variable effects were found for the bursting cells. The threshold for the slow component was ~ 7 W/kg, but in one case the rapid component was found at an SAR as low as 1 W/kg. For all cases in which effects were found, the firing rates returned to normal when the radiation was terminated and when the temperature was returned to normal. The authors hypothesized that at a dose rate of ~ 1 W/kg, conversion of 0.1 percent of the microwave energy into a polarizing current density across the cell membrane would be sufficient to affect the firing rate of pacemaker neurons.

5.1.4 Unresolved Issues

Several issues remain unresolved in the area of cellular and subcellular effects of microwave radiation. Nearly all of the relevant research is concentrated in a narrow frequency band, between 1.0 and 4.0 GHz. No acceptable studies have been reported for a large portion of the frequency spectrum of concern, 0.5 MHz to 100 GHz.

An active area of research at present is concerned with the role of structured water in the cell. Questions such as how much water in a cell is structured to a greater degree than "bulk" water, and whether this structure plays an important role in cell metabolism, are as yet unanswered. Three monographs (Alfsen and Berteaud 1976; Drost-Hansen and Clegg 1979; Grant *et al.* 1978) summarize knowledge in this area. Experiments attempting to establish the presence and extent of structured water within biological

systems are described, and the dielectric data indicating a possible frequency range for the structured-water resonance are presented. According to the limited information now available, RF radiation is most effective in modifying the state of structured water at frequencies below 1 GHz (Grant *et al.* 1978, pp. 160-165). As yet no experiments have been conducted that define whether absorption of RF energy by structured water leads to a measurable change in a biological system.

Three of the reports discussed in Sec. 5.1.3, Effects on Single Cells, also raise questions. The explanation offered by Ismailov (1978) for the change in electrophoretic mobility of exposed RBCs is speculative and does not account for the peaking of the phenomenon 30 min post-exposure. These results must be considered an effect of unknown origin until more information is available. The results of experiments by Moore *et al.* (1979), in which the virulence of *A. tumefaciens* was decreased for more than 6 h after exposure to microwave radiation, suggest reversible functional changes in the organism. In this case, the implications for cellular function after microwave exposure would be broad. However, no other worker has noted a similar effect with other single-cell organisms, and this experiment has not been independently confirmed. Therefore, its significance is unknown at this time.

The results of Wachtel and co-workers (Seaman and Wachtel 1978; Wachtel *et al.* 1975) are potentially highly significant because they indicate the possibility of a direct interaction between the microwave field and the functioning of the pacemaker neuron (i.e., the rapid effect). Three other workers have obtained supportive results. The documentation in these reports is not sufficiently complete for inclusion in the preceding sections, but they bear mentioning here.

Yamaura and Chichibu (1967) found results strikingly similar to those of Wachtel in ganglia of crayfish and prawn exposed at 11 GHz. The regular firing rate of the ganglia decreased rapidly during microwave exposure, rebounded to a higher than normal rate when the radiation was removed, and then returned to normal. Temperature controls showed only an increased firing rate as the temperature was increased. The authors stated that the SAR was ~ 100 W/kg but did not describe the method of measurement.

Arber (1976) found a hyperpolarization of the resting potential of giant neurons of the mollusk *Helix pomatia* during exposure to 2.45-GHz (CW) radiation. In this experiment, the ganglion was isolated and mounted in a stripline. The cell potential was measured, as in Wachtel's experiment, by insertion of microelectrodes into the neuron. Exposure to microwaves (SAR near 15 W/kg) for 1 h produced a 5- to 10-percent increase in resting potential, followed by a stabilization or slight additional increase over 1 h post-exposure. This result is presumably caused by a change in the Na^+-K^+ balance in the cell. When Arber treated the cells with ouabain (post-exposure), which inhibits Na^+-K^+ ATPase, he found that part of the hyperpolarization could be accounted for by the action of this enzyme under the influence of microwaves. The remainder was attributed to changes in passive ion transport.

Pickard and Barsoum (1981) have recently presented results in which single cells from *Chara braunii* and *Nitella flexilis,* plants from the family Characeae, exhibited a large step increase in voltage when exposed to 0.1- to 5-MHz (PW) radiation (pulses were of 250-ms duration, pulse interval was 6.3 s). These authors also found a fast and slow component. The slow component correlated with a temperature rise in the sample; the fast component was frequency dependent and disappeared abruptly at ~ 10 MHz. The authors suggest that the fast component was produced by rectification of the oscillating electric field by the cell membrane. The fast component disappeared into noise at ~ 667 V/m and may have been an effect of intense fields.

The results of these four studies indicate a possibility of a direct microwave interaction with the electric potential across the cellular membrane of all living cells. This kind of interaction would have broad significance in the functioning of all cells and, in particular, cells of the nervous system.

Additional studies have been conducted recently that have not yet been sufficiently documented to include in the previous sections. However, because of their potential importance, they are discussed here. The first two reports concern microwave effects on phospholipid bilayers, whereas the third is concerned with changes in growth of the yeast *Saccharomyces cerevisiae* exposed at frequencies between 41 and 42 GHz.

Tyazhelov *et al.* (1979a) have exposed a phospholipid membrane formed between two chambers containing solutions of NaCl or KCl. An antibiotic that forms pores through the membrane was added to facilitate passage of Na^+ or K^+. Conductance was measured across the membrane while 4-s pulses of 900-MHz radiation were delivered at between 125 and 280 V/m (field strength in the aqueous medium). The results showed a change in conductance under exposure that is consistent with temperature rises of 12°C, but the temperature of the NaCl or KCl solutions did not vary by more than 0.5°C. However, insufficient information concerning the exposure system makes it difficult to judge whether serious inhomogeneities in energy deposition, and thus similar inhomogeneities in the temperature distribution, were likely. One cannot estimate an SAR from the information presented.

Sheridan *et al.* (1979) have presented at meetings, but so far have not published, results of Raman spectroscopy of single- and multilamellar phospholipid vesicles exposed to 2.45-GHz (CW) radiation. No change was found in the Raman bands of single-layered vesicles. In contrast, the data for multilamellar vesicles indicate that the hydrocarbon tails of the phospholipids were undergoing a temperature-dependent phase transition at a point at which the bulk temperature was too low for the transition to have begun. The change was reported to be equivalent to a temperature difference of ~ 2°C at an exposure of 25 mW/cm^2. The bulk temperature of the sample in these experiments was measured by a unique method. Small ruby crystals were suspended in the sample, and the shifts in the Raman bands of the crystal were measured and compared with calibration curves. This appears to be an accurate method for temperature determination. The origin of this effect is unknown, but if a similar effect were found in naturally occurring membranes, it could have an impact on the functioning of the biological membrane.

Keilmann and co-workers (Grundler *et al.* 1977; Keilmann 1978; Grundler and Keilmann 1980) have demonstrated that *S. cerevisiae* exhibits an enhanced or inhibited growth rate when exposed at certain closely spaced frequencies between 41.60 and 41.80 GHz. For instance, they found a 10- to 15-percent increase in growth rate at 41.64 and 41.68 GHz, and a 20-percent decrease at 41.66 GHz. The experiments were conducted with a unique waveguide termination that was dipped into a suspension of yeast cells. In a typical experiment, 24 W was dissipated in the yeast-cell suspension, and the authors estimated a maximum exposure intensity of about 10 mW/cm^2. However, because of the unusual nature of the waveguide termination and the high attenuation of high-frequency radiation by aqueous samples, SAR values cannot be determined. Sample temperature was monitored and was within 0.5°C of the desired 32°C. Equivalent temperature controls were performed, and the authors believe that changes of the observed magnitude could not be purely temperature effects. This contention appears reasonable, since the growth rate both increased and decreased at the same levels of incident energy but at different exposure frequencies. The decrease is difficult to explain, based on the authors' reports of no observable temperature rise. However, if a localized temperature > 37°C (> 5°C above the controlled temperature) were attained close to the waveguide termination, then the decrease could be explained solely on the basis of temperature. There are scanty reports from the Soviet literature that present results similar to those of Keilmann and co-workers. These studies are important because they are suggestive of a specific interaction mechanism between RF radiation and a biological system.

In summary, the available literature on cellular and subcellular effects of microwaves does not yet definitely establish whether effects unrelated to elevation of temperature exist at dose rates on the order of 1 W/kg. Several investigators have reported effects, but a majority have not found effects unrelated to temperature variations. In some cases, the results conflict. In other cases, the effects found are equivocal. Effects of elevated temperature may not be clearly eliminated, or, as in the case of neuronal firing rate, the change in the rate may occur only in a minority of cases (Seaman and Wachtel 1978). The question of microwave-induced temperature rises must always be carefully considered when one is dealing with the biological effects of exposure to microwave radiation. In cellular systems, a principal effect is to increase the *rates* of all biochemical reactions, including the rate at which denaturation of proteins and DNA occurs (Lehninger 1975), at which bases are removed from DNA (Lindahl and Nyberg 1974), and at which mutations occur in DNA (Bingham *et al.* 1976). When temperature is raised to a certain level, often ~ 43°C, cell functions become so disrupted that the cell's capacity to repair the damage is exceeded and the cell dies. The effect of a rapid heating rate is less clear. Some disruption of cell function may be expected from a rapid temperature rise, even if the critical temperature (e.g., 43°C) has not been reached. Whether this disruption is fully reversible has not been well documented. RF-radiation exposure can produce such high heating rates, especially from high-peak, low-average power pulses. Effect of nonuniform heat deposition is probably the most difficult aspect to account for when one is evaluating the effects of exposure of RF radiation.

The effects presented in this section are sufficiently well established to warrant continued concern and effort. The effects of microwave radiation on the electrical properties of the cell are potentially the most significant. Four separate experiments have demonstrated these effects. All cells use the electrical potential across the cell membrane in their life functions, and perhaps the most important cells are those of the nervous system. Microwave effects have been found in the functioning of the nervous system and in behavior, as will be discussed in the following sections.

At this time, nearly all the effects documented for cellular and subcellular systems are observed in intact cells. This finding could imply that a living cell is required for the necessary interaction with microwave radiation to occur; or, it may be that the right questions are not being asked about the subcellular level, perhaps because the levels of understanding and instrumentation capabilities are as yet too limited. Although the primary mechanism(s) of interaction other than heating the water medium

have not yet been defined, some useful directions are indicated by the results reviewed here. One might also conclude that some of the effects noted at the cellular level, particularly the changes in nerve cell function, may be correlated with effects at higher levels of organization.

5.2 Hematologic and Immunologic Effects

Ralph J. Smialowicz

Over the years, a considerable number of reports has appeared in the literature dealing with the effects of RF radiation on the hematologic and immunologic systems of animals. For the most part, the responsible investigators have been motivated by a concern for the possible adverse health effects of exposure to RF radiation. Studies in which animals have been exposed at various frequencies and intensities have shown inconsistent changes in elements of both biological systems. In some instances, a thermal burden to the exposed animal has been credited with the observed changes, whereas in others, a "nonthermal" (i.e., lack of measurable elevation of temperature) or direct (i.e., athermal or field-specific effect) interaction of RF radiation with the blood and blood-forming systems has been suggested as the causative mechanism for the observed effects. In any case, the final interpretation of RF-induced changes must consider many variables that affect the interaction of RF radiation with the biological entity. As has been noted previously, variables such as body shape and mass, radiation frequency, duration of exposure, field intensity, specific absorption rate, energy distribution, orientation of the body in the field, ambient environmental conditions, area of the body exposed, and field modulation may all influence the final results. Variability of response among species and strains as well as between sexes must also be considered.

This section critically reviews the reported effects of RF radiation on the hematologic and immunologic systems of laboratory animals. On the whole, direct comparisons between many of these studies are difficult to make because of differences in species, in exposure parameters, and in the biological end points examined. Furthermore, as mentioned above, the reported responses are inconsistent and highly variable, with general trends in the data not readily apparent. Nevertheless, from this review the following generalizations may be formulated:

- Partial or whole-body exposure of animals to RF radiation may lead to a variety of changes in the hematologic and immunologic systems. Depending upon the exposure conditions, species, and parameters measured, the changes may be stimulatory or suppressive.
- Transient changes in peripheral blood composition, possibly caused by redistribution of blood cells and hemoconcentration, have been reported.
- In those cases where the reversibility of RF radiation effects on the immune system have been examined, the effects have proven to be transient.
- Some of the reported effects of RF radiation on the hematologic and immune systems are similar to those (a) resulting from a stress response involving the hypothalamic-hypophyseal-adrenal axis, or (b) following administration of glucocorticoids.
- Several reports show an association between RF-induced thermal loading or increased core temperature and hematologic and immunologic changes. Conversely, there is a lack of convincing evidence for a direct interaction of RF radiation with hematologic and immunologic systems in the absence of some form of thermal involvement.
- That an increase in rectal temperature is not observed after exposure to RF radiation does not preclude a thermal interaction that the animal is able to compensate for and control.
- There is presently no convincing evidence from animal studies for adverse alterations in the hematopoietic or immune systems at RF-radiation intensities comparable to average environmental levels, i.e., 0.01 to 0.1 $\mu W/cm^2$ in the frequency range of 54 to 900 MHz, which encompasses the resonant frequencies for human beings.

For convenience, this section is divided into two general topics: hematologic effects and immunologic effects. These two topics are further subdivided into reviews of studies in which cellular components of these systems have been exposed *in vitro* and of studies dealing with *in vivo* exposures to RF radiation.

5.2.1 Hematology

Hematology is the study of the anatomy, physiology, and pathology of the blood and blood-forming tissues. The hematopoietic system is comprised of a variety of cells and cell products. In fetal life, the production of blood cells occurs in the liver, spleen, and bone marrow. After birth this function is limited largely to the bone marrow, which produces red cells (erythrocytes), white cells (neutrophilic, eosinophilic, and basophilic granulocytes; lymphocytes; and monocytes), and platelets. Each of these cell types performs specific functions that are essential to life. For example, mature erythrocytes transport O_2 and CO_2 to and from tissues, granulocytes and monocytes phagocytize invading microorganisms, and lymphocytes are involved in immune responses. These functional cells are all descendants of progenitors (stem cells) that reside within the bone marrow. Blood-cell formation consists of two essential processes, proliferation and differentiation; bone marrow progenitor cells proliferate and differentiate into red and white cells. As the process of differentiation progresses, the capacity for cellular proliferation decreases. Impairment of either of these

processes may lead to dysfunctions in the hematologic system that may be life threatening.

5.2.1.1 *In Vivo* Studies

A paucity of information on the health effects of RF-radiation exposure from clinical and epidemiological studies has led to studies of effects on the hematologic systems of laboratory animals (Table 5-5). Many of the early investigations on the blood-forming system of laboratory animals employed power densities of 10 mW/cm^2 and higher. For example, Deichmann *et al.* (1964) reported significant leukocytosis, lymphocytosis, and neutrophilia in rats following 7 h of exposure to 24,000-MHz (PW) microwaves at an average power density of 20 mW/cm^2 (SAR estimated at 3 W/kg). One week following exposure, peripheral blood values returned to normal. Rats exposed for 3 h at 10 mW/cm^2 displayed the same changes and returned to normal after 2 days (SAR estimated at 1.5 W/kg). Increases in circulating erythrocytes, hemoglobin concentration, and hematocrit were observed in two of three strains of rats (Osborne-Mendel and CFN) exposed to 24,000-MHz fields at 10 or 20 mW/cm^2. However, in Fischer rats exposed under the same conditions, there was a reduction in the number of circulating erythrocytes and a reduction in hematocrit and hemoglobin concentration. These differences in Fischer rats are difficult to reconcile in light of the hematologic responses to thermal loads displayed by the Osborne-Mendel and CFN rats. In another experiment, Deichmann *et al.* (1963) exposed two dogs to 24,000-MHz (PW) fields at an average power density of 24 mW/cm^2 (SAR estimated at 1 W/kg). One dog was exposed for 20 months, 6.7 h/day, 5 days/week; the second dog was exposed for 20 months, 16.5 h/day, 4 days/week. No significant changes were observed in blood volume, hematocrit, hemoglobin, erythrocytes, total and differential leukocytes, blood cholesterol, or protein-bound iodine. The only finding attributed to the exposure was a slight loss of body mass.

Kitsovskaya (1964) exposed rats to 3000-MHz (PW) radiation at 10, 40, or 100 mW/cm^2 for various periods of time (SAR estimated at 2, 8, and 20 W/kg, respectively). No changes were found in rats exposed at 10 mW/cm^2; at 40 and 100 mW/cm^2, however, the absolute number of peripheral blood erythrocytes, total leukocytes, and lymphocytes decreased, and granulocytes increased. These blood changes did not return to normal until several months after cessation of exposure.

The apparent discrepancy between the results of Deichmann *et al.* (1964) and Kitsovskaya (1964) may be partially explained by the work of Michaelson *et al.* (1964). These investigators reported that the hematopoietic effects of 2800- and 1280-MHz (PW) fields depend on the frequency, intensity, and duration of exposure. For example, dogs exposed to 2800-MHz fields showed a marked decrease in circulating lymphocytes and eosinophils after 6 h at 100 mW/cm^2 (SAR estimated at 4 W/kg). This exposure resulted in a 1°C mean increase of rectal temperature. Neutrophils remained slightly increased at 24 h; eosinophils and lymphocyte values returned to normal levels. After a 2-h exposure at 165 mW/cm^2 to 28,000-MHz fields (SAR estimated at 6 W/kg), there was a slight leukopenia, neutropenia, and definite hemoconcentration. These changes were accompanied by a rectal temperature rise of 1.7°C. Eosinopenia was still evident 24 h after this exposure. Changes in leukocyte counts were more apparent following exposure of dogs to 1280-MHz (PW) fields or to 200-MHz (CW) radiation. After exposure of dogs at 1280 MHz for 6 h at 100 mW/cm^2 (SAR estimated at 4.5 W/kg), a leukocytosis and neutrophilia were observed. After 24 h the neutrophil level was still increased above pre-exposure levels. Lymphocyte and eosinophil values were slightly depressed following exposure, but at 24 h they were slightly higher than initial values. A 6-h exposure to 200-MHz (CW) fields at 165 mW/cm^2 (SAR estimated at 25 W/kg) caused a marked increase in neutrophils and a slight decrease in lymphocytes. After 24 h this trend was more evident. Michaelson *et al.* (1964) suggested that the results indicated a stress response of the exposed animals in the hypothalamic and/or adrenal axis that was brought about by a thermal stimulation from RF-radiation exposure.

Spalding *et al.* (1971) exposed mice to 800-MHz fields at an average power density of 43 mW/cm^2 (SAR estimated at 10.7 W/kg) for 2 h/day, 5 days/week, for a total of 35 weeks. These investigators found no changes in blood erythrocytes, leukocytes, hematocrit, or hemoglobin concentrations. It is interesting that these investigators did not detect changes in the peripheral blood picture of exposed mice, despite the thermal burden that was being placed on these animals. Failure to detect changes may have been due to the animal's ability, over the prolonged period of exposure, to adapt to the RF-induced thermal load. Four mice died from "thermal effects" following the 33rd and 34th RF-radiation exposures.

Effects produced at levels at or below 10 mW/cm^2 (SAR estimated at 0.5 to 2.0 W/kg) have also been reported. For example, Barański (1971, 1972a,b) exposed guinea pigs and rabbits to 3000-MHz (CW and PW) microwaves at an average power density of 3.5 mW/cm^2 (SAR estimated at 0.5 W/kg) for 3 months, 3 h daily. At this power level, the body temperature of the animals was not elevated. Observations were made of increases in absolute lymphocyte counts in peripheral blood, abnormalities in nuclear structure, and mitosis in the erythroblastic cell series in the bone marrow and in lymphoid cells in lymph nodes and spleen. No changes were observed

Table 5-5. Summary of Studies Concerning Hematologic Effects of RF-Radiation Exposure*

Effects	Species	Exposure Conditions: Frequency (MHz)	Intensity (mW/cm^2)	Duration (days x min)	SAR (W/kg)	References
Increased: WBC, lymphs, PMN, RBC, Hct, and Hgb	Rat	24,000 (PW)	10 20	1 x 180 1 x 420	 3.0†	Deichmann *et al.* (1964)
No change	Dog	24,000 (PW)	24	400 x 400-900	1†	Deichmann *et al.* (1963)
No change Decreased: RBC, WBC and lymphs Increased: PMN	Rat	3,000 (PW)	10 40 100	216 x 60 20 x15 6 x 5	2† 8† 20†	Kitsovskaya (1964)
Decreased: lymphs and eosin Decreased: WBC, PMN, and eosin Decreased: WBC, lymphs, and eosin Increased: PMN Decreased: lymphs Increased: PMN	Dog	2,800 (PW) 2,800 (PW) 1,280 (PW) 200 (CW)	100 165 100 165	1 x 360 1 x 120 1 x 360 1 x 360	4† 6† 4.5† 25†	Michaelson *et al.* (1964)
No change	Mouse	800	43	175 x 120	12.9†	Spalding *et al.* (1971)
Increased: lymphs and mitotic index of lymphoid cells	Guinea pig	3,000 (CW or PW)	3.5	120 x 180	0.5†	Baranski (1971 and 1972a)
Increased: RBC, Hct, and Hgb	Rat	2,400 (CW)	10	30 x 120	2†	Djordjevic and Kolak (1973)
No change	Rat	2,400 (CW)	5	90 x 60	1†	Djordjevic *et al.* (1977)
Increased: eosinophils	Rabbit	2,450 (CW)	10	180 x 1380	1.5	McRee *et al.* (1980a)
Increased: WBC, CFU Decreased: ^{59}Fe uptake	Mouse	2,450 (CW)	100	1 x 5	70†	Rotkovska and Vacek (1975)
Accelerated recovery following x-irradiation; increased erythropoiesis and myelopoiesis	Mouse	2,450 (CW)	100	1 x 5	70†	Rotkovska and Vacek (1977)
Accelerated recovery from x-irradiation	Dog	2,800 (PW)	100	1 x 3600	4†	Michaelson *et al.* (1963)
Increased: PMN and RBC Decreased: lymphs Accelerated recovery from x-irradiation	Chinese hamster	2,450 (CW)	60	1 x 30	28†	Lappenbusch *et al.* (1973)
Increased: lymphs Decreased: PMN (Not reproduced consistently)	Rat (Perinatal exposure)	425 (CW)	10	47 x 240	3-7	Smialowicz *et al.* (1982)
No change	Rat (Perinatal exposure)	2,450 (CW)	5	57 x 240	1-5	Smialowicz *et al.* (1979a)
No change	Rat (Perinatal exposure)	100 (CW)	46	57 x 240	2-3	Smialowicz *et al.* (1981a)
No change	Quail egg	2,450 (CW)	30	1 x 1440	14	Hamrick and McRee (1975)
Decreased: Hct, WBC, and lymphs	Rat (young)	2,736 (PW)	24.4	35 x 240	5-25†	Pazderova-Vejlupkova and Josifko (1979)
No change	Mouse	2,450 (CW)	30	22 x30	22	Smialowicz *et al.* (1979b)
Decreased: lymphs Increased: PMN	Mouse	26 (CW)	8610		13†	Liburdy (1977)
Decrease in CFU for erythroid and granulocyte-macrophage series	Mouse	2,450 (CW)	15	9 x 30	10	Huang and Mold (1980)
Reduction in CFU granulocyte-macrophage precursors exposed *in vitro*	Mouse	2,450 (CW)	60-1000	1 x 15	120-2000	Lin *et al.* (1979b)

*WBC = white blood cell, PMN = polymorphonuclear leukocytes, RBC = red blood cell, Hct = hematocrit, Hgb = hemoglobin, and CFU = colony-forming unit.
†SAR estimated.

in the granulocytic series in peripheral blood. Shifts in peripheral blood cells were found to correlate with changes in the cellularity of the spleen and lymph nodes. An increase in the mitotic index and in the percentage of cells incorporating ^{3}H-thymidine was observed in the spleen and lymph nodes of exposed animals.

Djordjevic and Kolak (1973) exposed rats to 2400-MHz (CW) fields at 10 mW/cm^2 (SAR estimated at 2 W/kg) 2 h/day for 10 to 30 days. Body temperature in rats exposed under these conditions increased by 1°C within the first 30 min of exposure and remained at this level throughout the exposure period. Hematocrit, hemoglobin concentration, and circulating erythrocytes increased during the 30-day exposure. Fluctuations in the various leukocyte populations were also observed. The authors suggested these changes were caused by the thermal effect of microwaves. In a more recent study, Djordjevic *et al.* (1977) found no significant difference in any of several hematologic end points for rats exposed to 2400-MHz (CW) microwaves at 5 mW/cm^2 (SAR estimated at 1 W/kg) for 1 h/day during a 90-day period.

Recently, McRee *et al.* (1980a) reported significant decreases in eosinophils and a lowering of albumin and calcium in blood from rabbits immediately following chronic exposure to 2450-MHz fields. In this study, rabbits were exposed 23 h daily for 180 consecutive days to 2450-MHz (CW) radiation at a power density of 10 mW/cm^2 (SAR = 1.5 W/kg). No change in hematologic parameters was observed 30 days after termination of exposure (i.e., depression in eosinophils seen immediately following exposure had normalized); however, a significant decrease in albumin/total globulin ratio was observed in the blood of exposed rabbits at this time. The authors contend that, because only 3 of the 41 blood-chemistry parameters measured immediately after exposure were significantly different ($p < 0.05$), and because this observation is close to that expected by chance, further validation of these changes is warranted.

Rotkovska and Vacek (1975) reported changes in hematopoietic cell populations of mice following a single 5-min exposure to 2450-MHz (CW) radiation at an intensity of 100 mW/cm^2 (SAR estimated at 70 W/kg). The response of microwave-exposed mice was compared with that of mice placed in a warm-air chamber at an ambient temperature of 43°C for 5 min. Both treatments caused a rise in rectal temperature > 2°C. A leukocytosis occurred in mice under both conditions; however, the time course for the leukocytosis and the response of hematopoietic stem cells differed between the two treatments. Following RF-radiation exposure, a decrease in the total cell volume of the bone marrow and spleen was observed, and the number of hematopoietic stem cells in bone marrow and spleen, as measured by the colony-forming unit (CFU) assay, increased. Incorporation of ^{59}Fe in the spleen decreased 24 h after RF-radiation exposure. On the other hand, the exposure to heat caused a decrease in the CFU's in bone marrow and spleen and an increase in the percentage of ^{59}Fe incorporation. Rotkovska and Vacek concluded that the different effects of RF radiation and externally applied heat on the hematopoietic stem cells indicate that biological effects caused by high intensities of RF radiation may not necessarily be related only to increases in internal temperature. They indicated that their results suggest a possible "direct" effect. This study is significant because it demonstrates a marked difference in the kinetic response of the hematopoietic system to two forms of heat stress. Consequently, these differences must be considered in the interpretation of RF-radiation-induced changes in the hematopoietic system.

Subsequently, Rotkovska and Vacek (1977) studied the effect of microwaves on the recovery of hematopoietic tissue following exposure to x-irradiation. Mice exposed to X rays at 300 to 750 rads were then exposed to 2450-MHz (CW) microwaves for 5 min at 100 mW/cm^2 (SAR estimated at 70 W/kg). The combined treatment resulted in an accelerated recovery of hematopoietic tissue, a heightened erythropoiesis and myelopoiesis, and an increased survival rate compared with x-irradiated mice. The increase in the number of endogenous hematopoietic colonies in the spleens of the x-irradiated mice after microwave exposure supports Rotkovska and Vacek's earlier (1975) observation of an elevation in the number of stem cells in the spleens of intact mice after microwave exposure alone. These investigators suggested that RF radiation may influence the mechanisms that activate the pool of stem cells, either by improving the repair of sublethal radiation damage or by increasing the proliferative capacity of stem cells that survive x-irradiation. The authors concluded that this acceleration of the processes of repairing radiation damage in hematopoietic cells after thermogenic doses of RF radiation depended on the stage of intracellular repair at the time of RF-radiation exposure. In earlier work, Michaelson *et al.* (1963) reported that simultaneous exposure to X rays and microwaves (2800 MHz, PW modulated, 100 mW/cm^2, SAR estimated at 4 W/kg) caused an accelerated recovery of the hematopoietic function in dogs. Thomson *et al.* (1965) reported that pretreatment of mice with RF radiation (2800 MHz, PW modulated, 100 mW/cm^2, SAR estimated at 70 W/kg) reduced the mortality after x-irradiation (800 rads). The 30-day lethality was 40 to 55 percent among mice given single or multiple RF treatment prior to x-irradiation, compared with 76 percent lethality in mice not pretreated with RF radiation. Exposure of Chinese hamsters to RF radiation (2450 MHz, CW, 60 mW/cm^2, SAR estimated at 28 W/kg, for 30 min) 5 min after X irradiation (725 to 950 rads)

significantly increased the X-ray LD_{50}^{30} dose compared with exposure of animals to X rays only or with exposure to RF radiation before irradiation (Lappenbusch *et al.* 1973). Lappenbusch *et al.* reported that the radio-protective effect of RF radiation appears to be associated with a delayed decrease in the number of circulating white blood cells, reduced period of decreased cell density, and complete replenishment of white blood cells within 30 days following the dual treatment. Exposure to RF radiation either alone or combined with X-ray exposure increased the relative number of neutrophils, reduced the relative number of lymphocytes, and slightly increased the number of circulating red blood cells. On the other hand, animals exposed first to RF radiation and then to X rays demonstrated a more severe leukocyte picture than hamsters x-irradiated only; in these animals, leukocyte counts decreased faster, and the animals developed leukopenia.

The effect of exposure to RF radiation on circulating blood cells of developing rats has been studied by Smialowicz *et al.* (1979a, 1982). Rats were exposed pre- and postnatally to 425-MHz (CW) fields at 10 mW/cm², 4 h daily up to 41 days. Because the animals were growing, SARs ranged from 3 to 7 W/kg. No consistent changes in blood values were observed in exposed compared to sham-irradiated control rats (Smialowicz *et al.* 1982). Rats exposed under the same regimen but to 2450-MHz (CW) fields at 5 mW/cm² (SAR estimated at 1 to 5 W/kg) also showed no difference in circulating erythrocyte count, leukocyte and differential counts, or hematocrit and hemoglobin concentration compared with sham-irradiated controls (Smialowicz *et al.* 1979a). Rats exposed to 100-MHz fields at 46 mW/cm² (SAR estimated at 2 to 3 W/kg) pre- and post-natally as above showed no change in blood parameters compared with controls (Smialowicz *et al.* 1981a).

Pazderová-Vejlupková and Josifko (1979) reported decreases in the hematocrits, number of leukocytes, and absolute numbers of lymphocytes in young rats exposed to 2736-MHz (PW, 395 Hz, 2.6-μs pulse width) microwaves at 24.4 mW/cm² for 7 weeks (5 days/week, 4 h/day). The means of body mass of rats at the beginning and at the end of the 7-week exposure period was 65 and 350 g, respectively (SAR estimated at 5 to 25 W/kg). These changes disappeared within 10 weeks after termination of exposure. The activity of alkaline phosphatase in neutrophils increased during the first week of irradiation but decreased transiently after the irradiation. In a similar experiment by the same authors (data not given), in which adult rats were exposed for 14 weeks to 3000-MHz (PW, 300 Hz, 2.5-μs pulse width) microwaves at 1 mW/cm² (SAR estimated at 0.2 W/kg), no difference was observed in hematologic parameters between exposed and control rats.

Hamrick and McRee (1975) examined the effect of RF radiation on developing birds. Quail eggs were exposed for 24 h during the second day of incubation to 2450-MHz (CW) fields at 30 mW/cm² (SAR = 14 mW/g). At 24 to 36 h after hatching, quail chicks were examined for gross deformities, changes in organ weight, and hematologic changes. No significant effects due to RF exposure were detected.

In another study, Smialowicz *et al.* (1979b) exposed mice to 2450-MHz (CW) fields at 30 mW/cm² (SAR = 22 W/kg) for 30 min on 22 consecutive days. These mice showed no significant difference in circulating-erythrocyte count, leukocyte and differential counts, or hematocrit and hemoglobin concentration compared with sham-irradiated controls. In this experiment, mice were maintained in an environmental chamber in which temperature, humidity, and air flow were continuously controlled. Under the conditions of this study, the RF radiation did not significantly elevate rectal temperatures of exposed mice. In contrast, when mice were exposed to thermogenic levels (2 to 4°C rise in rectal temperature) of 26-MHz (CW) radiation, 8610 mW/cm² (SAR estimated at 13 W/kg), a decrease in the number of circulating lymphocytes and an increase in circulating neutrophils was observed immediately after exposure (Liburdy 1977). These mice were held in a chamber that lacked a continuous turnover of air. Liburdy (1977) reported that this shift reached its peak 3 h after exposure. The number of circulating lymphocytes and neutrophils was reported to return to normal, pre-exposure levels 55 to 96 h after exposure. On the other hand, mice exposed at high ambient temperatures (79°C) in a vented, dry-air oven showed an increased number of circulating lymphocytes and neutrophils for a 12-h period after exposure. The response of circulating leukocytes to exogenous thermal loading thus depends on the means by which the body is heated. These results are similar to those reported by Rotkovska and Vacek (1977) and indicate that the heating properties of RF radiation differ from those of conventional modes of tissue heating.

Recently Huang and Mold (1980) reported that bone marrow (cultured *in vitro*) from mice exposed to 2450-MHz (CW) fields at 15 mW/cm² (SAR = 10 W/kg) for 30 min on 9 consecutive days had significantly fewer ($p < 0.05$) CFUs of both the erythroid and granulocyte-macrophage series. No data were presented on the peripheral blood counts of any of these blood cells that would confirm or expand the information gathered in the CFU assay.

5.2.1.2 *In Vitro* Studies

Lin *et al.* (1979b) reported a reduction in the number of CFU's (granulocyte and macrophage precursor cells) formed by bone marrow cells exposed *in vitro* to 2450-MHz fields at 60 to 1000 mW/cm² (SARs at 120 to 2000 W/kg). This reduction in colony

formation was reported to be dose dependent and occurred without a significant rise in the temperature of the cell suspension. The authors indicate that their results point to a direct effect of microwave radiation on these hematopoietic precursor cells. Although these results are interesting, the *in situ* application of fields as intense as those required to produce the observed effects would certainly cause gross thermal injury to the tissue.

In summary, levels of RF radiation that cause an increase in body temperature elicit changes in the hematopoietic system that can for the most part be ascribed to a thermal stress response. Changes in the blood of animals exposed to RF radiation at intensities below those that cause an increase in core temperature suggest a similar stress-response mechanism. The failure to record an increase in core temperature does not preclude the possibility that the animal is compensating for the added thermal energy by thermoregulatory mechanisms. Indeed, lack of a temperature change indicates that thermoregulation is operating. The response elicited by RF-radiation-induced heating, however, appears to differ from that of conventional heating because of the differing internal heating patterns of this form of radiation.

5.2.2 Immunology

The immune system is comprised of myriad mechanical, cellular, and humoral components that act as the body's defense against various pathogenic microorganisms, viruses, and neoplasias. The immune system is divided into the humoral element, i.e., antibodies and complement, and the cellular elements, which are composed of the lymphoid and phagocytic cells. The cellular elements of the immune system are also part of the hematologic system. The phagocytic cells responsible for engulfing and digesting certain microorganisms are the neutrophils or polymorphonuclear leukocytes (PMNs) and the monocytes or macrophages. In the presence of antibodies and complement, neutrophils are aided in engulfing and digesting invading organisms. The monocyte is also a phagocytic cell. Monocytes move into an area in which an infection has begun and then differentiate into macrophages. Macrophages can be "activated" to kill certain microorganisms (e.g., intracellular, facultative bacteria such as *Mycobacteria tuberculosis* and *Listeria monocytogenes,* viruses, and fungi) through the interaction of certain subpopulations of lymphocytes, such as the T lymphocytes.

The other cellular components of the immune system are the lymphocytes. These cells are broadly divided into two groups, the B lymphocytes and the T lymphocytes. Although these cells are similar morphologically, they are different functionally; B and T lymphocytes can be distinguished by the presence of unique antigens or receptors on their membrane surface. Both T and B lymphocytes are believed to originate in the bone marrow and then to proceed through various stages of development and differentiation, maturing into functional cells of the immune system.

The B lymphocyte, or bursa-equivalent lymphocyte, is responsible for humoral immune responses. The B lymphocytes, after appropriate stimulation by antigens, proliferate and undergo morphological changes and develop into plasma cells that actively synthesize and secrete antibodies.

The T lymphocyte, or thymus lymphocyte, is processed through the thymus after leaving the bone marrow. Classically cell-mediated or T-lymphocyte responses include protection against viruses, fungi, and several bacteria. T lymphocytes are also involved in reactions such as delayed hypersensitivity or contact hypersensitivity and rejection of tumors and foreign tissues such as transplants (allografts). Cell-mediated reactions are so named because these reactions, which operate by specifically sensitized T lymphocytes, can be transferred by these cells to normal animals. B-lymphocyte-mediated humoral responses, in contrast, are transferable by serum.

The recent availability of monoclonal antibodies has made the typing of lymphocyte subpopulations possible on a routine basis. Various functional categories of T cells can be recognized: "helper" (inducer/amplifier) T cells, "suppressor" T cells, "cytotoxic" T cells, and NK (natural killer) cells. Immature thymocytes may be identified by surface antigens distinct from mature peripheral T cells. Cellular interactions between the various T-cell subtypes and other immunocompetent cells are vital to the modulation of the immune response. Because of their pivotal role in enhancing antigen-mediated immune responses, disorders involving T-cell subsets may result in immunodeficiency syndromes involving either cell-mediated or humoral immunity.

Each element of the immune system—the T and B lymphocytes and macrophages—plays a cooperative role in defending the host against infection and disease. A delicate balance exists to prevent the immune system from reacting to its own tissues so that autoimmune reactions are avoided. The alteration or dysfunction of any of these elements may lessen the host's ability to combat infection or may lead to autoimmune disease. However, because of adaptability and redundancy in the immune system, the host can generally survive subtle perturbations. Consequently, although subtle effects on the immune system may be generated by physical

or chemical agents, all such effects may not lead to clinically significant immune dysfunctions.

5.2.2.1 *In Vivo* Studies

A summary of *in vivo* studies concerning immunologic effects of RF-radiation exposure is presented in Table 5-6.

Effects on adult animals—One of the most consistently found RF-radiation-induced changes in the hematopoietic system is the increase in lymphocyte formation and activity following exposure of animals of several species to RF radiation at various frequencies (Barański 1971, 1972a,b; Czerski 1975). There have been several studies of the effects of RF radiation on lymphocytes and the immune system. In a study reported by Czerski (1975), mice were exposed 2 h daily to 2950-MHz (PW modulated) microwaves at 0.5 mW/cm² (SAR estimated at 0.5 W/kg) for 6 to 12 weeks. After 6 weeks, there was a large increase in the relative number of lymphoblasts in the lymph nodes of exposed mice. In another series

Table 5-6. Summary of Studies Concerning Immunologic Effects (*In Vivo*) of RF-Radiation Exposure

		Exposure Conditions				
Effects*	Species	Frequency (MHz)	Intensity (mW/cm²)	Duration (days x min)	SAR (W/kg)	References
Increase in lymphoblasts in lymph nodes and increased response to SRBC	Mouse	2950 (PW)	0.5	42 x 120	0.5†	Czerski (1975)
Increase in "spontaneous" lymphoblast transformation of cultured lymphocytes	Rabbit	2950 (PW)	5	24-48 x 120	0.8†	Czerski (1975)
Increase in lymphoblasts in spleen and lymphoid tissue	Mouse	3105 (PW)	2	6-8700	2†	Miro *et al.* (1974)
Increased transformation of unstimulated cultured lymphocyte and decreased mitosis in PHA-stimulated lymphocyte cultures	Chinese hamster	2450 (CW)	5, 15, 30 or 45	5 x 15	2.3, 6.9, 13.8 or 20.7	Huang *et al.* (1977)
Transient decrease and increased response of cultured lymphocytes to PHA, Con A, and LPS	Mouse	2450 (CW)	5 or 15	1-17 x 30	3.6 or 10	Huang and Mold (1980)
Increased mitosis of PHA-stimulated lymphocytes	Rhesus monkey	10-27 (PW)	1320	1 x 30	0.4-2.0†	Prince *et al.* (1972)
Increase in CR^+, Fc^+, and Ig^+ spleen cells. Increased response to B-cell mitogens. Decrease in primary response to SRBC	Mouse	2450 (CW)	—	1 or 3 x 30	14	Wiktor-Jedrzejczak *et al.* (1977a, b, c)
Increase in CR^+ and Fc^+, spleen cells	Mouse	2450 (CW)	—	1 x 15 1 x 30	11.8 5	Sulek *et al.* (1980)
Increase in CR^+ spleen cells, strain specificity	Mouse	2450 (CW)	—	1 x 30	10-19	Schlagel *et al.* (1980)
Increase in CR^+ spleen cells	Mouse	2450 (CW)	40	1 x 30	28	Smialowicz *et al.* (1981c)
Increased lethality to endotoxin	Mouse	2450 (CW)	20, 30	1 x 120	12, 18	Riddle *et al.* (1982)
Increase in response of cultured lymphocytes to T- and B-cell mitogens	Rat	2450 (CW) 425 (CW)	5 10	57 x 240 47 x 240 (Perinatal exp)	1-5 3-7	Smialowicz *et al.* (1979a, 1982)
No change	Mouse	2450 (CW)	5-35	1-22 x 15 or 30	4-25	Smialowicz *et al.* (1979b)
No change	Rat	100 (CW)	46	57 x 240	2-3	Smialowicz *et al.* (1981b)
Increase in T and B lymphocytes in spleen Decrease in DTH	Mouse	26 (CW)	800	1 x 15 or 10 x 15	5.6†	Liburdy (1979)
Reduction of lymphocyte traffic from lung to spleen	Mouse	2600 (CW)	5 or 25	1 x 60	3.8 or 19	Liburdy (1980)
Decrease in NK activity, increase in macrophage phagocytosis	Mouse	2450 (CW)	30	2 or 9 x 90	21	Smialowicz *et al.* (1983)
Decrease in NK activity	Hamster	2450 (CW)	25	1 x 60	13	Yang *et al.* (1983)
Increase in macrophage viricidal capacity	Hamster	2450 (CW)	25	1 x 60	13	Rama Rao *et al.* (1983)
Decreased response to PWM	Rabbit	2450 (CW)	10	180 x 1380	1.5	McRee *et al.* (1980a)
No change	Quail	2450 (CW)	5	12 x 1440	4.03	Hamrick *et al.* (1977)
Decrease in tumor development	Mouse	2450 (CW)	— (near-field application)	11-14 day of gestation or 11-14 & 19-45 x 20	35	Preskorn *et al.* (1978)

Table 5-6. (Continued)

Effects*	Species	Exposure Conditions: Frequency (MHz)	Intensity (mW/cm²)	Duration (days x min)	SAR (W/kg)	References
Decreased granulocytic response	Rabbit	3000 (CW)	3	42 to 84 x 360	0.5	Szmigielski *et al.* (1975)
Tumor regression and increase in antitumor antibodies and anti-BSA	Rabbit	13.56	(near-field application)	1 x 10-15	(local hyperthermia)	Shah and Dickson (1978b)
Tumor inhibition and immune stimulation	Rat	2450 (CW)	200W	3 or 6 x 45	(local hyperthermia)	Szmigielski *et al.* (1978)
Increased tumoricidal activity in lymphocytes and macrophages	Mouse	1356	600-900	1 x 5	(local hyperthermia)	Marmor *et al.* (1977)
Tumor regression	Mouse	3000 (CW)	40	1-14 x 120	28†	Szmigielski *et al.* (1977)
Increase in lung cancer colonies and inhibition of contact sensitivity to oxazolone	Mouse	2450 (CW)	50	4, 7, 10 or 14 x 120	36†	Roszkowski *et al.* (1980)
Decrease in response to BSA	Rabbit	1356	(near-field application	3 x 60	(local hyperthermia)	Shah and Dickson (1978a)

*SRBC = sheep red blood cells, PHA = phytohemagglutinin, Con A = concanavalin A, LPS = lipopolysaccharide, CR^+ = complement-receptor positive, Ig^+ = immunoglobulin positive, Fc^+ = Fc portion of immunoglobulin, DTH = delayed-type hypersensitivity, PWM = pokeweed mitogen, BSA = bovine serum albumim.
†SAR estimated.

of experiments (Czerski 1975), rabbits were exposed 2 h/day, 6 days/week for 6 months to 2950-MHz (PW) microwaves at 5 mW/cm² (SAR estimated at 0.8 W/kg). After culturing for 7 days *in vitro,* peripheral blood lymphocytes from these animals were found to undergo an increase in "spontaneous lymphoblastoid transformation." Maximal increases occurred after 1 to 2 months of exposure; the transformation rate then returned to base line and rose again 1 month after an irradiation had been terminated. Miro *et al.* (1974) continuously exposed mice to 3105-MHz (PW) microwaves over a 145-h period at an average power density of 2 mW/cm² (SAR estimated at 2 W/kg). No description was given of how animals were fed or watered. An increase in lymphoblastic cells in the spleen and lymphoid areas of exposed mice was observed. A somewhat similar response was observed (Huang *et al.* 1977) in lymphocytes cultured from Chinese hamsters that were exposed to 2450-MHz (CW) microwaves for 15 min on 5 consecutive days at 5 mW/cm² (SAR = 2.3 W/kg) without a detectable rise of rectal temperature. Increased transformation to lymphoblastoid forms in the absence of mitogens was maximal in cultures from hamsters exposed at 30 mW/cm² (SAR = 13.8 W/kg). Irradiation at this power density caused a 0.9°C rise in rectal temperature of exposed hamsters. Mitosis of lymphocytes cultured in the presence of the mitogen phytohemagglutinin (PHA), however, was depressed in cells obtained from hamsters exposed at 5, 15, 30, or 45 mW/cm². These effects were reported to be transient and reversible; control levels were again observed after 5 to 10 days (Huang *et al.* 1977).

More recently, Huang and Mold (1980) reported an oscillating response of spleen cells to PHA, concanavalin A (Con A), and lipopolysaccharide (LPS) from mice exposed to 2450-MHz fields at 15 mW/cm² (SAR = 10 W/kg) for 30 min. Mitogen responsiveness decreased significantly after 2 days of exposure, returned to normal after 4 days of exposure, and was significantly increased for all mitogens after 9 days of irradiation. Responsiveness to mitogens tended to return to normal or to fall to subnormal levels after 17 days of exposure. In contrast, when mice were exposed at 5 mW/cm² for 30 min on 5 consecutive days, a significant increase in the response to LPS was observed, whereas no change was observed in LPS responsiveness to exposure at 15 mW/cm² for 5 days. When macrophages were removed from spleen-cell suspensions of mice irradiated at 15 mW/cm² for 9 days, the responsiveness to LPS was greater than the already increased spleen-cell responsiveness without macrophage removal. However, addition of macrophages from the RF-irradiated mice to spleen-cell cultures from nonirradiated mice caused a significant decrease in responsiveness to LPS. The authors suggest that macrophage activation (macrophages from irradiated mice displayed increased spreading and increased phagocytosis of latex particles *in vitro*) by microwaves may be responsible for inhibiting LPS responsiveness.

Prince *et al.* (1972) reported the opposite effect in rhesus monkeys. These investigators found an enhanced mitotic response of peripheral blood lymphocytes stimulated *in vitro* with PHA from monkeys 3 days following a 30-min exposure to 10.5-MHz (PW) radiation at 1320 mW/cm² (SAR estimated at 0.4 W/kg). Enhancement of mitosis of cultured lymphocytes from monkeys similarly exposed to 19.27- and 26.6-MHz were also reported. Also reported were increases in circulating lymphocytes that ranged from 4 to 47 percent above pre-exposure levels. At a frequency of 26.6 MHz (SAR estimated at

2 W/kg), the rectal temperature of monkeys following exposure was reported to increase by 2.5°C above pre-exposure levels.

The particular susceptibilities of lymphocytes to RF radiation have led to an examination of the effects of this form of radiation on the immune response. For example, Czerski (1975) reported that mice exposed for 6 weeks to 2950-MHz (PW) microwaves at 0.5 mW/cm^2 (SAR estimated at 0.5 W/kg) had significantly greater numbers of antibody-producing cells and higher serum antibody titers following immunization with sheep red blood cells (SRBCs). Interestingly, mice that were exposed for 12 weeks did not show this increased responsiveness. This return to normal responsiveness may have resulted from the animal's ability to adapt to the RF exposure after 12 weeks. More recently, Wiktor-Jedrzejczak *et al.* (1977a,b,c) exposed mice in a rectangular waveguide to 2450-MHz radiation for 30 min at an average dose rate near 14 W/kg. At 3, 6, 9, and 12 days after a single or multiple exposures, mice were tested for (1) the relative frequency of T and B splenic lymphocytes, (2) the functional capacity of spleen cells to respond to T- and B-cell-specific mitogens, and (3) the ability to respond to SRBCs (a T-dependent antigen) or dinitrophenyl-lysine-Ficoll (DNP-lys-Ficoll, a T-independent antigen). A single 30-min exposure induced a significant increase in the proportion of complement-receptor-positive (CR^+) lymphocytes in mouse spleens that peaked 6 days after exposure. This effect was further enhanced by repeated (three) exposures, which also produced a significant increase in the proportion of immunoglobulin-positive (Ig^+) spleen cells (Wiktor-Jedrzejczak 1977a). A significant increase in the proportion of Fc-receptor-positive (FcR^+) cells in the spleens was also observed 7 days after a single 30-min exposure (SAR = 13.7 W/kg). However, no change in the number of Ig^+ cells in spleens of these mice was observed (Wiktor-Jedrzejczak 1977c). The type and combination of surface receptors (CR, Ig, Fc) expressed on splenic B cells represent different maturational stages in B-cell development. Wiktor-Jedrzejczak *et al.* (1977a,b,c) were unable to demonstrate any change in the total number of theta-antigen-positive (θ^+) T cells in the spleens of mice following a single or multiple exposure to 2450-MHz microwaves. No change was detected in the *in vitro* spleen-cell response to stimulation by the T-cell-specific mitogens PHA and Con A or by pokeweed mitogen (PWM), which stimulates both T and B cells (Wiktor-Jedrzejczak *et al.* 1977a). However, the response to the B-cell-specific mitogens lipopolysaccharide (LPS), polyinosinic polycytidylic acid (Poly I C), and purified protein derivative (PPD) of tuberculin was significantly increased over controls following a single exposure. These results clearly correlate with the observed changes in the proportion of cells bearing different surface markers. Wiktor-Jedrzejczak *et al.* (1977a) noted that RF irradiation did not stimulate lymphoid-cell proliferation *per se* but rather appeared to act as a polyclonal B-cell activator, which led to an early maturation of noncommitted B cells. They also found a significant decrease in the primary immune response to SRBCs, a thymus-dependent antigen, in mice that had been immunized just prior to the first exposure to RF radiation. They suggested that this decreased response may result from the nonspecific stimulation of some cells by RF radiation to mature before they are activated by antigen (SRBCs), so that the proportion of unresponsive cells was increased.

Recently, Sulek *et al.* (1980) corroborated this increase in CR^+ and Fc^+ spleen cells in mice 6 days following a 30-min exposure to 2450-MHz fields (average SAR = 12 W/kg). The kinetics for increased frequency of CR^+ cells in the spleens of irradiated mice showed an initial increase 3 days following exposure that persisted for 5 to 6 days and then returned to normal within 9 to 10 days. The authors determined the threshold for this effect by varying the time of exposure with a constant forward power (0.6 W), or by maintaining a constant time of exposure while varying the forward power (0.1 to 0.78 W). It was shown that a minimum of a single 15-min exposure (11.8 W/kg) or a single 30-min exposure (5 W/kg) caused significant increases in CR^+ cells 3 or 6 days after exposure. The effect of absorption of multiple subthreshold quantities of microwaves was found to be cumulative only if the exposures occurred within 1 h of one another. The increase in CR^+ cells was found at dose rates ranging from 10 to 18 W/kg for mice within a weight range of 18 to 25 g. The rectal temperature of exposed mice was found to be elevated no more than 0.6°C above that of sham-irradiated mice. No change in θ^+ (T lymphocytes) cells was observed. In contrast, Huang and Mold (1980) reported a significant increase in θ^+ cells but no change in B cells (Ig^+) of mice exposed to 2450-MHz fields at 15 mW/cm^2 (SAR at 10 W/kg) for 30 min on 9 consecutive days.

Smialowicz *et al.* (1979b) exposed BALB/c mice (H-2^d) to 2450-MHz (CW) fields under far-field conditions for 15 or 30 min daily for periods to 22 consecutive days at power densities from 5 to 35 mW/cm^2 (SARs at 4 to 25 W/kg). Splenic lymphocyte function was assayed by the *in vitro* mitogen-stimulated response as measured by ^{3}H-thymidine incorporation after culture in the presence of T (PHA, Con A, PWM) or B (LPS, PWM, PPD) mitogens. The proportions of T (θ^+) and B (CR^+) splenic cells and the primary immune response of mice to SRBCs were also studied. No difference in the response to mitogens or to SRBCs or in the frequency of T or B cells in spleens was observed in RF-irradiated compared with sham-irradiated mice.

Subsequent to the report by Smialowicz *et al.* (1979b), Schlagel *et al.* (1980) reported that

sensitivity to RF-induced CR^+ cell increases was under genetic control. Mice that were responsive were found to be of the $H\text{-}2^k$ haplotype (i.e., CBA/J), while other mouse strains of the $H\text{-}2^a$, $H\text{-}2^b$, $H\text{-}2^d$ (i.e., BALB/c) and $H\text{-}1^{i5}$ haplotypes did not display increased CR^+ cells following RF exposure. The age of the mice was also found to be critical for expression of increase CR^+ cells following 2450-MHz (SAR ≈ 14 W/kg) RF-radiation exposure. Mice less than 12 weeks old did not respond.

In light of the findings by Schlagel *et al.* (1980) that indicated that RF-induced increases in CR^+ cells were under genetic control, Smialowicz *et al.* (1981c) re-examined the effect of RF radiation on CR^+ cells in CBA/J mice ($H\text{-}2^k$). Increases in the frequency of CR^+ spleen cells of CBA/J mice 6 days following a single, 2450-MHz exposure (SAR = 28 W/kg), under far-field conditions in an anechoic chamber, were reported by Smialowicz *et al.* (1981c). This increase in CR^+ cells was observed only in 16-week-old mice and not in younger mice, a result similar to that reported by Schlagel *et al.* (1980). However, unlike the results of Schlage *et al.* (1980), an increase in CR^+ cells was accompanied by a significant decrease in the number of nucleated cells in the spleens of these mice that were obviously under thermal stress. No increase in CR^+ cells was observed in mice irradiated at SAR values of 10, 14, or 21 W/kg, SARs at which Schlagel *et al.* (1980) observed effects. Smialowicz *et al.* (1981c) concluded that the age and strain of the mouse, the RF-exposure characteristics (waveguide vs. far field), and the environmental conditions are all sources of variation that affect CR^+ cell appearance.

Evidence that exposure of mice to far-field 2450-MHz RF radiation at an SAR ≥ 12 W/kg is thermogenic was provided by Riddle *et al.* (1982). Mice were injected with various doses of lipopolysaccharide (LPS) and exposed to 2450-MHz CW RF radiation, and the 50-percent lethal dose (LD_{50}) of LPS was determined. A significant decrease in the LPS LD_{50} dose was observed at SAR values of 12 and 18 W/kg. High ambient temperature (37°C) also potentiated the lethal effect of endotoxin, indicating that RF heating was responsible for the observed effect. The SAR values used in this study were comparable to those used in studies by Wiktor-Jedrzejczak *et al.* (1977a,b,c), Schlagel *et al.* (1980), and Sulek *et al.* (1980) in which augmented CR^+ spleen cells were observed. This further supports the hypothesis that increases in CR^+ spleen cells following RF exposure may be due to an RF-induced thermal response.

Further evidence for an RF-induced thermal mechanism in spleen cell changes comes from Liburdy (1979), who reported that changes in splenic lymphocyte populations similar to those observed by Wiktor-Jedrzejczak *et al.* (1977a,b,c) can be produced by exposure of mice to thermogenic levels of 26-MHz radiation. When mice were exposed to 26 MHz at an intensity (800 mW/cm², SAR at 5.6 W/kg) that produced a 2 to 3°C rise in rectal temperature, a relative increase in splenic T and B lymphocytes was observed. Similar responses (i.e., increase in T and B cells) were induced following administration of the synthetic glucocorticoid methyl prednisolone sodium succinate. These results indicate that these RF-radiation-induced changes might represent some form of stress. It is difficult to understand how a 2 to 3°C rise in rectal temperature would occur in mice irradiated for 15 min at an SAR of 5.6 W/kg. A possible explanation is that these mice were restrained in perforated acrylic cages and held in an exposure chamber in which the air was not circulated during this period of irradiation.

In examining further possible mechanism(s) for the shift in lymphocyte populations in the spleens of mice exposed to RF radiation, Liburdy (1980) examined the circulation of lymphocytes in microwave-exposed mice. Mice injected with ^{51}Cr-labeled syngeneic spleen cells were exposed for 1 h at either 5 or 25 mW/cm² to 2600-MHz fields (SAR at 3.8 and 19 W/kg, respectively). Controls included sham-irradiated mice, mice held in a 63°C warm-air oven for 1 h, and mice injected with methyl prednisolone sodium succinate. The distribution of injected cells was determined for the lung, liver, spleen, and bone marrow at 1, 6, and 24 h after exposure. Exposures at 25 mW/cm² caused a 2.0°C increase in core temperature. This regimen led to a 37-percent reduction in lymphocytes leaving the lung and migrating to the spleen. Also, a threefold increase in spleen lymphocytes entering the bone marrow occurred in this group of mice. A similar pattern of lymphocyte circulation was observed in the steroid-treated group. No change in lymphocyte traffic was observed in mice of the 5-mW/cm² or warm-air groups. Liburdy (1980) concluded that these results suggest that steroid release associated with thermal stress and attempts by the animal to thermoregulate during exposure to RF radiation are responsible for effects on the immune system.

More recently, further evidence for an association between RF-induced thermal stress and effects on the immune system has been reported. Thermogenic doses of RF radiation were found to suppress the natural killer (NK) cell activity of mice (Smialowicz *et al.* 1983). Exposure of CBA/J mice to 2450-MHz (CW) RF radiation at an SAR of 21 W/kg for 90 min on 2 or 9 days caused a significant reduction splenic NK activity as determined using *in vitro* or *in vivo* assays. No effect on NK activity was observed at SAR values of 3.5 or 10.5 W/kg. NK activity returned to normal levels within 24 h following the last exposure at 21 W/kg. Treatment of mice with hydrocortisone also caused suppression of NK cell activity measured *in vitro* and *in vivo*. Paradoxically, a concomitant increase in macrophage phagocytic ability was

observed in mice exposed to RF radiation at an SAR of 21 W/kg. These results were essentially in agreement with work reported by Yang *et al.* (1983) and Rama Rao *et al.* (1983). Yang *et al.* (1983) reported that a single, 2450-MHz exposure of hamsters at an SAR of 13 W/kg caused a significant suppression of splenic NK activity that returned to normal levels by 8 h. This exposure also caused a 2.0 to 3.5°C increase in colonic temperatures, as well as elevated serum glucocorticosteroid levels. Exposure of mice at 8 W/kg caused no demonstrable effect on NK cell activity. In another study Rama Rao *et al.* (1983) reported that exposure of hamsters to thermogenic levels (13 W/kg) of 2450-MHz RF radiation resulted in activation of peritoneal macrophages. Macrophages from irradiated hamsters were found to be significantly more viricidal to vaccinia virus as compared to that from sham-irradiated hamsters. In all of these studies (Smialowicz *et al.* 1983; Yang *et al.* 1983, Ramo Rao *et al.* 1983) a strong association exists between RF-radiation-induced immune system effects and RF-induced thermal stress.

Effects on young animals—RF-radiation effects on the development of the immune response have been studied. Smialowicz *et al.* (1979a) exposed rats on day 6 of gestation through 41 days of age to 2450-MHz (CW) fields at 5 mW/cm^2 (SAR at 1 to 5 W/kg). The young animals absorbed microwaves at a higher rate (5 W/kg) than the adults (1 W/kg). In this study the exposed rats had lymphocytes that responded to a significantly greater extent than those from control animals following *in vitro* stimulation by T- or B-cell mitogens. A similar increase in lymphocyte responsiveness was seen in another study in which rats were exposed pre- and postnatally to 425-MHz radiation (SAR at 3 to 7 W/kg, with the neonates absorbing at the latter SAR) for periods to 41 days postpartum (Smialowicz *et al.* 1982). However, lymphocytes from rats exposed perinatally to 100-MHz fields at 46 mW/cm^2 (SAR at 2 to 3 W/kg) showed no change in mitogenic responsiveness (Smialowicz *et al.* 1981b). The results of the two former studies indicate that long-term exposure of developing (especially neonatal) rats to RF radiation at absorption levels higher than those achieved in the latter study may give rise to increased responsiveness of cultured lymphocytes. These results are similar to other reported changes in mammalian lymphocyte responsiveness following RF-radiation exposure (Czerski 1975; Prince *et al.* 1972; Wiktor-Jedrzejczak *et al.* 1977a,b,c). Increases in lymphocyte activity can also be elicited by conventional heating (Roberts 1979). Although the benefits are not known concerning this increased responsiveness to mitogens by lymphocytes from animals exposed perinatally to RF radiation, a recent report by Preskorn *et al.* (1978) indicates that irradiation at this time during development may be beneficial for increased immunosurveillance against tumors. These investigators exposed mice to 2450-MHz fields (SAR = 35 W/kg) for 20 min either on days 11 through 14 of gestation, or on days 19 through 45 postpartum, or during both periods. On the 16th day postpartum, all mice were implanted with a lymphoreticular cell sarcoma. Mice irradiated *in utero* only (colonic temperature increase of 2.2°C in dams) showed a lower incidence of tumors (13 percent vs. 46 percent for sham-irradiated mice) 93 days postpartum. In mice irradiated *in utero* and postnatally, tumors initially developed at a lower rate compared with controls; however, after 2.5 months, no difference was observed in tumor incidence between groups. At the end of 4 months, the tumor incidence in irradiated mice was slightly greater than controls (46 vs. 40 percent, respectively). An interesting finding, however, was that both tumor-bearing and tumor-free animals that had been irradiated only *in utero* lived longer on the average than their respective controls. This result is somewhat similar to that reported by Prausnitz and Susskind (1962), who found that mice briefly irradiated hundreds of times by a highly thermogenic level of RF radiation survived longer than controls.

McRee *et al.* (1980a) reported that 30 days after termination of a 6-month 23-h daily irradiation to 2450-MHz fields (SAR = 1.5 W/kg) spleen cells from rabbits showed a decreased responsiveness to PWM. Decreased responsiveness to PHA and Con A by these spleen cells was also reported, but responses to PHA and Con A were not statistically different from those of controls. Although these results are interesting, they are not conclusive and are of questionable value, because only four exposed and four sham-irradiated rabbits were employed. Also, both irradiated and sham-irradiated rabbits were transported from one laboratory to another (University of Washington to the National Institute of Environmental Health Sciences in Research Triangle Park, N.C.) between the termination of RF exposure and spleen-cell assay.

Hamrick *et al.* (1977) examined the avian humoral-immune response in Japanese quail exposed to RF radiation during embryogenesis. Fertile quail eggs were continuously exposed to 2450-MHz (CW) radiation at 5 mW/cm^2 (SAR = 4.03 W/kg) throughout the first 12 days of development. At 5 weeks of age, quail were immunized with SRBCs, and the levels of anti-SRBC antibodies were determined. No difference was observed in the antibody titers of exposed and sham-exposed quails. The masses of the bursa of Fabricius (site of B-cell production in birds) and spleen were not altered significantly by exposure to RF radiation.

Effects on phagocytosis—RF-radiation-induced effects on phagocytic leukocytes of animals have been reported by Szmigielski *et al.* (1975). Rabbits were exposed to 3000-MHz fields for 6 h daily for 6 to

12 weeks at 3 mW/cm^2 (SAR estimated at 0.5 W/kg). After the last exposure to RF radiation, rabbits were infected with an intravenous injection of virulent *Staphylococcus aureus*. At periods before and after infection, functional tests of granulopoiesis were performed. The investigators reported a decreased production of mature granulocytes in infected, RF-radiation-exposed rabbits, which was manifested as a more serious illness in these animals.

Summary—Exposure of laboratory animals to RF radiation can lead to changes in the functional integrity of lymphocytes. These cells play an important role in the immune-defense system of man and animals. The significance of the changes caused by RF radiation is difficult to interpret. Although some studies indicate that RF radiation causes an increased responsiveness of lymphocytes (Czerski 1975; Smialowicz *et al.* 1979a, 1982; Prince *et al.* 1972; Wiktor-Jedrzejczak *et al.* 1977a,b,c) and a potentiation of the immune response to antigen (Czerski 1975), others indicate a depression in responsiveness (Huang *et al.* 1977; Wiktor-Jedrzejczak *et al.* 1977a; Liburdy 1979; Szmigielski *et al.* 1975). In most cases these alterations can be attributed to a stress response, since qualitatively similar but quantitatively more pronounced changes are observed at obviously stressful thermogenic levels of RF radiation (Huang *et al.* 1977; Huang and Mold 1980; Prince *et al.* 1972; Liburdy 1979; Riddle *et al.* 1982; Smialowicz *et al.* 1981b) or after administration of glucocorticoids or detection of increased levels of glucocorticoids (Liburdy 1979; Smialowicz *et al.* 1983; Rama Rao *et al.* 1983; Yang *et al.* 1983). It is well known that stress alters physiological systems that regulate immunological function. Both immunosuppression and immunoehancement have been observed to result from stress (Monjan 1981; Blecha *et al.* 1982; Bradley and Michell 1981; Palmbald 1981; Rogers and Matossian-Rogers 1982), which is not inconsistent with the reported effects of RF radiation on the immune system. However, stress-induced modulation of the immune system is still imperfectly understood. Recent data suggest that the mechanisms by which stress affects the immune system are more complex than previously recognized and that, in addition to adrenal-dependent phenomena, adrenal-independent effects, which are as yet poorly understood, may be operative (Keller *et al.* 1983). The role of stress as a possible mediator of observed RF effects on the immune system remains speculative, although useful heuristically, at the present time. Critical experiments (especially, with careful consideration of other environmental stressors and proper controls—i.e., adrenalectomized animals) examining the relationship between stress and RF-radiation effects have yet to be done.

Effects caused by RF-induced hyperthermia—Alterations in the immune system can be produced by RF-radiation-induced hyperthermia. Whole-body microwave-induced hyperthermia has been reported to serve a therapeutic role either alone (LeVeen *et al.* 1976) or in combination with ionizing radiation (Nelson and Holt 1978). In many cases, the direct destruction of malignant tissues by RF-radiation-induced heating is the ultimate goal. However, in some cases, hyperthermia has led to changes in the immune response. For example, Shah and Dickson (1978b) reported that following local heating of VX2 (carcinoma) tumor-bearing rabbits by a 13.56-MHz field, tumor regression and host cure were observed in 70 percent of the rabbits. Intratumoral temperatures of 47 to 50°C were achieved within 30 min. Along with tumor regression, cell-mediated immunity—as measured by skin reactivity to tumor extract and dinitrochlorobenzene—markedly increased. A hundredfold increase in serum levels of antitumor antibody and increased response to the antigen bovine serum albumin (BSA) were also observed. In contrast, whole-body hyperthermia led to temporary reduction of tumor growth, followed by a return to an exponential increase in tumor volume and rapid death of the rabbit. This course of events following whole-body hyperthermia was accompanied by abrogation of the enhanced cellular and humoral immune responsiveness, observed following local RF-induced heating.

Szmigielski *et al.* (1978) reported that local heating (43°C) of the Guerin epithelioma in Wistar rats by 2450-MHz (CW) radiation inhibited tumors and stimulated the immune reaction against the tumor. Other immune reactions stimulated by this treatment were the antibody response to BSA, high reactivity of spleen lymphocytes to the mitogen PHA, and increased serum lysozyme levels as a measure of macrophage activity. Tumor-specific reactions observed were increased cytotoxicity of spleen cells and peritoneal macrophages to cultured tumor cells. Similar results were reported by Marmor *et al.* (1977), who exposed tumors in mice to focal 1356-MHz radiation. The EMT-6 tumor was found to be extremely sensitive to RF heating. The cure rate was a function of temperature and duration of exposure. A 5-min exposure at 44°C reduced the tumors by almost 50 percent. To determine the effectiveness of RF-induced heating on tumor regression, tumor-cell survival was studied by the treatment of EMT-6 tumors *in situ*. Cell inactivation by RF-radiation-induced heating was similar to that for heating by a hot water bath. The results indicated that direct cell killing could not account for the observed cures, and these investigators suggested that hyperthermia (RF or convection-induced) may stimulate a tumor-directed immune response.

Szmigielski *et al.* (1977) exposed mice bearing transplanted sarcoma-180 tumors to 3000-MHz radiation, 2 h daily on the 1st through 14th day after transplantation, whole-body at 40 mW/cm^2 (SAR

estimated at 28 W/kg). This exposure led to a 3 to 4°C increase in rectal temperature and resulted in a reduction of tumor mass by ~40 percent, a reduction enhanced when microwave hyperthermia was combined with Colcemide, Streptolysin S, or both. Colcemide enhances the inhibiting effect of hyperthermia on proliferation of cells *in vitro* (Szmigielski *et al.* 1976), and Streptolysin S is an antineoplastic agent. Szmigielski *et al.* (1978) suggested that immunostimulation is important in the complex inhibition of tumor growth by increased temperature.

Although many investigators see local and systemic hyperthermia as a possible cancer treatment, either alone or in combination with drugs or ionizing radiation, there is evidence that hyperthermia may enhance the dissemination of certain cancers and abrogate the immune response. For example, Roszkowski *et al.* (1980) reported that exposure of mice to 2450-MHz radiation at 50 mW/cm^2 for 4, 7, 10, or 14 days, 2 h daily (SAR estimated at 36 W/kg) caused an increased number of lung-cancer colonies and an inhibition of contact sensitivity to oxazolone (a measure of T-lymphocyte activity) with increased duration of hyperthermia. Shah and Dickson (1978a) exposed normal rabbits either to RF-radiation-induced (13.56 MHz) or to watercuff-local hyperthermia of thigh muscles, which are maintained at 42°C for 1 h on 3 consecutive days. No alteration in the response to dinitrochlorobenzene challenge was observed. However, the humoral immune response to BSA was significantly depressed. This response was independent of the method and degree of heating. The results indicate that B lymphocytes might be more susceptible to hyperthermic damage than are T lymphocytes.

The above results indicate that if the applied microwaves are of sufficient intensity to cause heating of tissue or of the whole animal, changes in the immune system will follow. With heating to any extent, the hypothalamic-hypophyseal-adrenal axis plays a major role in the responses elicited. It is well known that endogenous or exogenous adrenal glucocorticoid hormones affect the immune response. In addition, heat alone may affect immune function. For example, heat has been shown to affect the response of mitogens *in vitro* (Ashman and Nahmias 1978; Roberts and Steigbigel 1977; Smith *et al.* 1978; Gutman and Chang 1982), which suggests that elevation of temperature *per se* may mediate some of the observed RF-radiation-induced changes. But what of the RF-induced responses reported in the absence of measurable temperature increases or at rates of energy absorption well below that of the resting or basal metabolic rate? Observed changes in the immune response under these conditions are more difficult to explain on a thermal-stress basis, primarily because of a lack of sensitive techniques to detect subtle stress responses. However, no increase of rectal temperature after exposure to RF radiation does not mean that the animal might not compensate for added thermal energy by thermoregulatory mechanisms. RF radiation may also cause focal heating (thermal "hot spots") in organs critical to the immune response.

5.2.2.2 *In Vitro* Studies

Among the studies in this area (Table 5-7), several have involved attempts to determine if *in vitro* exposure of lymphocytes to RF radiation leads to "direct" changes in the metabolic or functional state of these cells. In an early study, Stodolnik-Baranski (1967) exposed human lymphocytes in culture to 3000-MHz (PW) microwaves at 7 or 14 mW/cm^2. Some lymphocytes were irradiated 4 h/day at 7 mW/cm^2 for 3 to 5 days, while those exposed at 14 mW/cm^2 were irradiated 15 min daily for 3 to 5 days. After 5 days in culture, the microwave-exposed cells were found to have undergone a fivefold increase in lymphoblastoid transformation compared with controls. Czerski (1975) attempted without success to repeat this experiment. But, in a more recent study, Baranslki and Czerski (1976) reported that exposure of human lymphocytes to 10,000-MHz fields at power densities between 5 and 15 mW/cm^2 could induce lymphoblastoid transformation (SAR not given). At power densities below 5 mW/cm^2, this effect was not observed, whereas at power levels above 20 mW/cm^2, cell viability decreased. The induction of blastic transformation depended on termination of irradiation (5 to 15 mW/cm^2) at the moment when the temperature of the medium reached 38°C. These results indicate that the microwave-induced blastic transformation might be caused by a thermal mechanism.

Similar increases in the lymphoproliferative response of cells exposed to temperatures > 37°C have been reported. As mentioned, Ashman and Nahmias (1978) reported that human lymphocytes, when cultured at 39°C with the mitogens PHA or Con A, showed an enhancement and earlier onset of ^{3}H-thymidine incorporation compared with cultures incubated at 37°C. In a similar study, Roberts and Steigbigel (1977) reported that the *in vitro* human lymphocyte response to PHA and the common antigen streptokinase-streptodornase was enhanced at 38.5°C relative to 37°C. Smith *et al.* (1978) reported that the *in vitro* response of human lymphocytes to PHA, Con A, PWM, and allogeneic lymphocytes was markedly enhanced by culture at 40°C compared with 37°C. These studies demonstrate the need to monitor and to control the temperature of cultures exposed to RF radiation. Without adequate temperature data, it is virtually impossible to accept *in vitro* effects as due to RF radiation itself.

The proliferative response of lymphocytes exposed *in vitro* to RF radiation appears to be related to culture

Table 5-7. Summary of Studies Concerning Immunologic Effects (*In Vitro*) of RF-Radiation Exposure*

Effects	Species	Exposure Conditions: Frequency (MHz)	Intensity (mW/cm^2)	Duration (days x min)	SAR (W/kg)	References
Increased blastogenesis of exposed lymphocytes *in vitro*	Human lymphocytes	3,000 (PW)	7 14	3-5 x 240 3-5 x 15	†	Stodolnik-Baranska (1967)
Increased blastogenesis	Human lymphocytes	10,000	5-15	Observed effect only when culture temperature approached 38 °C	†	Barański and Czerski (1976)
No change in mitogen response to PHA, Con A or LPS	Mouse spleen cells	2,450 (CW)	10	1 x 60, 120, or 240	19	Smialowicz (1976)
No change in mitogen response to PHA	Rat blood lymphocytes	2,450 (CW)	5, 10 or 20	1 x 240, 1440, or 2640	0.7, 1.4 or 2.8	Hamrick and Fox (1977)
No change in viability or growth	Human lymphoblast cell lines (Daudi and HSB_2)	2,450 (CW)	10-500	1 x 15	25-1200	Lin and Peterson (1977)
Decreased macrophage phagocytosis	Mouse macrophage	2,450 (CW)	50	1 x 30	15 J/min	Mayers and Habeshaw (1973)
Liberation of intracellular hydrolytic enzymes and increased death	Rabbit granulocytes	3,000 (CW)	1 or 5	1 x 15, 30, or 60	†	Szmigielski (1975)

*PHA = phytohemagglutinin, Con A = concanavalin A, and LPS = lipopolysaccharide.
†Unable to calculate SAR.

temperature. Smialowicz (1976) exposed murine splenic lymphocytes to 2450-MHz (CW) radiation for 1, 3, or 4 h at 10 mW/cm^2 (SAR = 19 W/kg). Immediately after irradiation the temperature of the exposed cultures did not differ significantly from that of controls, and cell viability was unchanged. These cells were then cultured for 72 h in the presence of T- or B-cell mitogens, and the proliferative response was measured by ^3H-thymidine incorporation. No difference was found in the blastogenic response of microwave-exposed and sham-exposed spleen cells to any of the mitogens employed. In a similar experiment, Hamrick and Fox (1977) exposed rat lymphocytes to 2450-MHz (CW) radiation for 4, 24, or 44 h at 5, 10, or 20 mW/cm^2 (SARs at 0.7, 1.4, or 2.8 W/kg, respectively). The transformation of unstimulated or PHA-stimulated lymphocytes was measured with ^3H-thymidine. No significant differences were found in the proliferative capacity of lymphocytes from exposed and control cultures. The effects of RF radiation on the growth and viability of cultured human lymphoblasts was studied by Lin and Peterson (1977). Human lymphoblasts (cell lines Daudi and HSB_2) were exposed to 2450-MHz (CW) radiation in a waveguide for 15 min at incident power densities of 10 to 500 mW/cm^2; the corresponding SARs were 25 to 1200 W/kg. No temperature increase was observed, even at the highest power density in the capillary tube that held the cell suspension in the waveguide. No change was observed in the viability or growth of microwave-exposed lymphoblasts compared with controls. These studies provide further evidence that no change in lymphocyte activity occurs following RF-radiation exposure *in vitro* when proper control of culture temperature is achieved.

In vitro exposure of macrophages to 2450-MHz fields has been reported by Mayers and Habeshaw (1973) to depress phagocytosis. Monolayer cultures of mouse peritoneal macrophages were perfused with suspensions of human erythrocytes while being exposed to 2450-MHz radiation at 50 mW/cm^2. The rate of energy absorption in the sample was 15 J/min. The phagocytic index of exposed cultures was significantly lower than that of the control after a 30-min exposure. Macrophage phagocytic activity returned to normal levels if RF irradiation was discontinued. During irradiation, a 2.5°C temperature increase was observed; however, the final temperature in the culture vessel in any given experiment reportedly did not exceed 36.2°C. The investigators concluded that the observed depression of phagocytosis in the irradiated cultures was not thermally induced. The 2.5°C rise in temperature during irradiation, according to the authors, would have been expected to enhance rather than depress phagocytosis, since it is optimal at 38.5°C. The mechanism by which the observed effect occurs is not known; however, heating effects are difficult to dismiss because of an observed 2.5°C rise in culture temperature. Although the temperature of the suspension medium did not exceed 36.2°C, thermal gradients of much higher temperature would be expected at the macrophage-glass interface.

An RF-induced effect on granulocyte integrity and viability was reported by Szmigielski (1975). Rabbit granulocytes were exposed *in vitro* to 3000-MHz (CW) radiation at 1 or 5 mW/cm² (SAR not given) for 15, 30, or 60 min. Cultures exposed at 5 mW/cm² for 30 to 60 min showed increased numbers of dead cells as demonstrated by an increase in nigrosine staining and an enhanced liberation of lysosomal enzymes. Exposure at 1 mW/cm² did not cause increased cell death but did lead to a partial liberation of hydrolase enzymes. No change was observed in the temperature of the irradiated cultures. The liberation of acid phosphatase and lysozyme from granulocytes was observed in cell suspensions exposed at 1 or 5 mW/cm²; both suspensions exhibited a time- and dose-dependent response.

In summary, exposure of laboratory animals to RF radiation may lead to changes in the functional integrity of leukocytes, which play important roles in the immune-defense system. The significance of the changes caused by RF radiation is difficult to interpret, since many observed effects are transient and reversible. Furthermore, some studies indicate that RF radiation causes immunopotentiation, whereas others indicate immunosuppression. In many cases the observed alterations in the immune system can be attributed to thermal stress, because qualitatively similar but quantitatively greater changes are observed at obviously stressful (highly thermalizing) levels of RF radiation or following the administration of glucocorticoids. A possible explanation for the immunomodulating effects of RF radiation arises from the timing of the meausrements of immune responsiveness after an animal is subjected to stress. For example, corticoid-induced impairment of immune responsiveness is commonly followed by homeostatic recovery, then subsequent overcompensation, which may be associated with immunoenhancement.

As for reports in which measurable elevations of temperature from RF-radiation-induced heating are not detected, a possible role by RF-radiation-induced thermogenesis cannot be dismissed. The failure to detect a measurable increase in tissue or core temperature in RF-irradiated experimental animals through the use of conventional techniques indicates that the animal was able to compensate for the added energy. The role that thermoregulating mechanisms play in affecting the immune response needs further study. There is at present no convincing evidence for a direct effect of RF radiation on the immune system in the absence of a thermal (heating) effect.

5.2.3. Unresolved Issues

Several issues relating to the effects of RF radiation on the hematologic and immunologic systems remain unresolved. Perhaps the most perplexing question is what to make of the many Soviet reports on these systems. In most cases these reports lack sufficient technical detail for adequate critical assessment of reported results. Alterations in the hematopoietic and immunologic systems have been reported in animals exposed to RF radiation at and below 10 mW/cm² over periods of weeks to months. Nevertheless, no convincing evidence has been presented to demonstrate a direct effect of RF radiation in the absence of thermal involvement; well-defined and planned, chronic (months to years), low-level (< 1 mW/cm²) studies have not been carried out to investigate Soviet claims of possible immune alterations including induction of autoimmune reactions following chronic exposure. Investigations of the possible hematologic and immunologic effects of PW vs. CW irradiation have not been undertaken in response to the claims by Eastern European investigators that PW modulation is more effective than CW irradiation in causing alterations in these systems.

Investigations are lacking that would define possible synergistic effects of other agents or drugs with RF radiation on the hematopoietic and/or immune systems. RF radiation (at hyperthermic doses) has been shown to provide a protective effect against damage by ionizing radiation to the hematologic system. Although this is a beneficial effect of RF radiation, it is not known whether the combination of drugs or other physical agents with RF radiation is detrimental.

Another issue is based on the recent work of Szmigielski *et al.* (1980, 1982) who described the increased incidence of cancer development in mice exposed chronically to 2450-MHz (CW) fields. After exposing the animals for several months at either 5 or 15 mW/cm² (SAR = 2 to 3 and 6 to 9 W/kg, respectively), these investigators reported an increased incidence of spontaneously arising mammary tumors in C3H/HeA mice and increased skin tumors in BALB/c mice whose skin was painted with 3,4-benzopyrene. These workers also reported that chronic stress (i.e., overcrowding of mice) produced an acceleration in tumor development comparable to that found in mice irradiated at 5 mW/cm², with still greater acceleration in tumor development in mice exposed at 15 mW/cm². These results suggest that RF radiation at 15 mW/cm² was more stressful (i.e., via thermal-induced stress) than at 5 mW/cm². Szmigielski *et al.* (1982) suggest that the acceleration in tumor development in mice irradiated at 15 mW/cm² may be due to local thermal effects or RF-induced "hot" spots. Acceleration of cancer development in these mice was suggested by Szmigielski *et al.* to be accompanied by a lowering of natural antineoplastic resistance, in particular effects on immunocompetent cells. These investigators conclude that the effects on immunocompetent cells may be due to a direct interaction of RF radiation with the immune system or via a stress response. Based

on the results obtained from other laboratories (Rama Rao *et al.* 1983; Yang *et al.* 1983; Liburdy 1977, 1979, 1980; Smialowicz *et al.* 1981, 1983; Smialowicz 1979; Riley 1981), as well as the results in the Szmigielski *et al.* (1980, 1982) studies with mice stressed by overcrowding, it appears that the latter hypothesis (i.e., RF-radiation stress-induced effects) is the most plausible explanation. Nevertheless, this effect warrants corroboration because of its potential significance. Studies should be undertaken that strive to determine the threshold for RF-radiation-induced accelerated tumor growth. Strict control of both the RF-exposure parameters and ambient environmental parameters is essential in any future studies. Several species should be employed to determine whether this phenomenon occurs across species.

5.3 Reproductive Effects

Ezra Berman

This section on the reproductive effects of RF radiation is organized into three categories: Teratology (5.3.1), where the treatment is administered to the pregnant dam and observations are then made on the embryo, fetus, neonate, or older offspring; Reproductive Efficiency (5.3.2), where the end point of the experiment occurs in the primary and secondary sex organs of the parent; and Testes (5.3.3), where testicular morphology and function of testes are examined for alterations.

RF radiation has been examined intensively for its potential reproductive effects for a variety of reasons: (1) many reproductive toxicologic tests can be carried out in a simple and inexpensive experimental design after insult by RF radiation, (2) the laboratory techniques used are conventionally acceptable as toxicologic assays, and (3) detrimental reproductive changes carry not only an emotional impact but have potential for early and long-term consequences of a serious nature.

5.3.1 Teratology

The science of teratology and its underlying principles must be kept in mind if we are to make judgments on the potential of RF radiation for teratologic manifestations. Wilson (1973) has developed general principles of teratogenesis. These principles are rephrased here to familiarize the reader with the guidelines one should keep in mind when evaluating the available literature, so that their relevance to RF radiation teratologic investigations may be more easily understood.

(1) Susceptibility to RF radiation teratogenesis depends on species, strain, and stage of development at the time of exposure.

(2) There are four indications of abnormal development: death, malformation, retarded growth, and deficient function.

(3) These indications increase in incidence and degree with increasing dosage.

Teratology was initially confined to the study of birth malformations, monstrosities, and serious deviations from normal. As teratology has matured into a branch of toxicology, included now in teratology are toxic manifestations in the fetus with lesser symptoms than gross morphologic changes. Such fetotoxic symptoms may be decreased fetal or birth weight, as well as changes in function observed well after birth. In this discussion, the terms "teratogenesis" or "terata" refer to gross morphologic or monstrous changes. Subteratogenic doses are those just below teratogenic doses and are not expected to cause terata. Fetotoxic symptoms include body-weight changes without terata. Functional changes are fetotoxic symptoms not readily apparent in the fetus, or even at birth, but are often seen later as postnatal maturation occurs. This discussion posits that the list of possible deviations caused in the conceptus is an order of decreasing degree of severity (death $>$ malformation $>$ growth retardation $\geq$ functional changes). The significance of any laboratory animal or system as a model of human exposure may not be universally accepted among scientists.

An attempt is made to derive from available data three aspects of teratologic toxicology of RF radiation: the presence of a teratologic effect, the generalization of that effect across species, and the dose-response character of that effect. From the evidence presented, we believe that the reader will agree with the following statements:

(1) RF radiation can cause teratogenesis in all the mammalian species studied adequately so far if sufficiently high power densities or SARs are obtained.

(2) Reduced fetal weight seems to occur consistently in rodents exposed gestationally to teratogenic doses of RF radiation, or to doses somewhat smaller than those which cause death or malformation.

(3) There is evidence that gestational exposure to RF radiation may cause functional changes later in life.

5.3.1.1 Nonmammalian Models

The potential for human teratology is usually sought in mammalian models. But other models that are lower on the phylogenetic scale or cell-culture models are also often informative. Workers at the Bureau of Radiological Health of the Food and Drug Administration have used an insect to demonstrate the reproductive alterations due to RF radiation. Pay *et al.* (1978) examined the egg production of female fruit flies *(Drosophila melanogaster)* in response to RF radiation. Using a 2450-MHz waveguide exposure system housed in an environmentally controlled chamber (24°C, 50 percent relative humidity), these workers determined the survival rate of *D. melanogaster* pupae at SARs ranging from 400 to 800 W/kg. Approximately 70 percent of the pupae did not survive a 10-min exposure when the rate of energy absorption was 640 W/kg; the temperature of the agar surface on which the pupae rested was 45°C. If pupae were incubated instead in a 44°C environment without RF radiation, the death rate was less severe (50 percent).

The potential for RF-radiation-induced teratology in birds has been examined by use of the fetal form of

birds, the egg, as a model. This is a reasonably popular model since use of bird eggs is more economical than use of mammals. Study of the bird egg can provide insight into fetal effects independent of maternal influence. The egg is an object that can be placed in almost any desired position by the experimenter; it will remain there, a distinct advantage over free-ranging mammals. The egg is symmetrical externally and so lends itself more easily to estimates of local and total absorption of RF energy.

In theory, mammalian models have no advantage over avian models in the study of teratogenic potential of RF radiation because concepts of organogenesis apply equally to avian and mammalian fetuses. It would be a mistake to dismiss the considerable research on the teratologic effects of RF radiation in birds' eggs because the avian egg is poikilothermic and the mammal's egg is homeothermic. The mammalian conceptus is also poikilothermic; it has little, if any, control of its own temperature since it is entirely surrounded by placental fluids. It can dissipate thermal energy only by radiating into surrounding maternal tissues because its capacity to rid itself of thermal energy depends entirely on the gradient between itself and surrounding tissues. If the temperature of the mammalian conceptus tissue is increased because of RF-radiation absorption, it also must radiate that absorbed energy into its surroundings (dam), just as the egg in similar exposure conditions must radiate energy into the air of its incubator. If air or maternal temperatures are detrimentally high, then the loss of thermal energy from the egg or mammalian fetus is affected similarly.

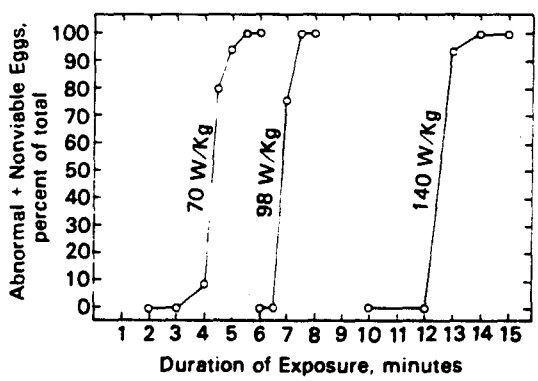
Carpenter *et al.* (1960a) have studied RF radiation as an inducer of cataracts. These investigators have also likened the growth in the lens to the process of embryonic development and growth, where proliferation and differentiation take place concurrently. To further understanding of the RF-radiation-induced effects that appear in the lens, Carpenter *et al.* performed experiments on the egg of the domestic chicken. They irradiated almost 500 chick embryos at the 48-h stage and examined the eggs 48 h after irradiation, scoring incidences of survival and structural abnormalities. The irradiation was conducted in an anechoic chamber at 2450 MHz and at power densities of 200, 280, and 400 mW/cm^2. Estimates of SARs for these power densities are 70, 98, and 140 W/kg, respectively (Durney *et al.* 1978). Power densities were determined by calorimetry with a saline-filled egg. The exposure durations ranged from 1 to 15 min. The eggs were incubated at 39°C air temperature before, during, and after irradiation. However, the temperatures of the eggs are not mentioned in the report. At the 96th hour of development, all eggs were opened, and the embryos were removed, fixed, stained, and examined as whole-mounts.

Experimental results relevant to this section are presented in Table 3 of the Carpenter *et al.* 1960a publication. We have used the data in that table to calculate the relative summed incidences of dead and abnormal 96-h egg embryos for each experimental group (power density: time) and present the incidences in Figure 5-2.

The teratologic end points observed by Carpenter *et al.* (1960a) were death and abnormal morphology, which can be viewed as a continuum of the same effect, interference with the normal processes of development. When abnormal structure is so severe as to interfere greatly with the continuation of development, the embryo cannot develop or maintain sufficiently normal structural and physiologic systems. The relationships between these systems collapse and the embryo dies. As stated earlier, indications of abnormal development increase in incidence and degree as the dosage increases. One mechanism for the increase in death is that as the dosage increases, more embryos undergo more changes in more systems, which results in more deaths.

Figure 5-2 contains three curves, one for each group of eggs exposed at dose rates of 140, 98, or 70 W/kg for varying durations. The data are plotted against the summed relative incidence of affected (dead or morphologically abnormal) eggs. The slopes of the curves are steep, so that small increases in the exposure duration cause disproportionate increases of effect. For example, the incidence in the group exposed for 4 min at 140 W/kg was 9 percent. An increase of only 30 s in exposure time caused a ninefold increase (80 percent) in incidence. An additional characteristic of these slopes is the disproportionate spacing of the three curves along the axis of exposure duration.

Figure 5-2. Summed incidence of abnormal and nonviable chick embryo eggs (percent of total) exposed to 2450-MHz radiation for varying durations at 70, 98, or 140 W/kg (from data in Carpenter *et al.* 1960a).



Studies of RF radiation effects in the Japanese quail have been conducted exclusively by workers at the National Institute of Environmental Health Sciences. In their first attempt to induce terata in the quail egg, Hamrick and McRee (1975) exposed fertilized eggs in an anechoic chamber to 2450-MHz (CW) fields, producing an SAR of 14 W/kg in the egg. The eggs were exposed for 24 h beginning 2 days after laying, then were returned to their incubators until 24 to 36 h after hatching. Several experimental replications occurred; the sample numbers were 102 in the control group and 110 in the RF-irradiated group. After hatching, observations were made of cellular elements of blood and of selected organ weights. No significant differences between the two groups were seen in hatchability, blood cell parameters, body weights, or organ weights.

The same authors also reported a similarly designed experiment on Japanese quail eggs, in which the eggs were exposed during the first 12 days of development at SARs of 4.03 W/kg (McRee and Hamrick 1977). As before, the eggs were allowed to hatch and were than examined for teratologic alterations and blood-cell parameters. When the experiment was conducted at an environmental temperature of 35.5°C, there were no significant changes in body weights, organ weights, or blood-cell parameters.

The authors also demonstrated the importance of ambient temperature in experiments in which RF radiation is the agent under investigation. Absorption of RF radiation energy produces increased temperature. In most studies of reproductive effects reviewed in this document, fields were at sufficiently high power densities to cause significant depositions of energy. Temperatures in the animal subjects were usually increased by 0.5°C or more. Therefore, the ambient temperature in which the subject is maintained or treated can be a significant determinant of a resulting trend.

Levels of ambient temperature can be especially relevant to experimental subjects that have no significant thermoregulatory capability. For example, the report by McRee and Hamrick (1977) included the results of an experiment in which Japanese quail eggs were in an environment at a temperature only slightly higher (+1.5°C) than in the experiment discussed above (35.5°C). The authors began their study at an ambient temperature of 37°C because that is the temperature at which quail eggs are conventionally incubated. But this ambient temperature, with the addition of a 4 W/kg SAR, was sufficient to cause a 93 percent death rate of the fertilized eggs. The eggs that were irradiated at the same SAR, but at an ambient temperature lower by 1.5°C, sustained only a 42 percent death rate. The results of this seemingly slight (1.5°C) increase in incubation temperature during RF irradiation shows that for this poikilothermic model, the quail egg, the temperature at which the egg is maintained during experimentation is critical.

5.3.1.2 Mammalian Models

Morphologic teratology—The mouse is commonly used in the determination of the teratogenic potential of toxic agents and also appears to be a useful model for determining the teratogenic potential of RF radiation. The mouse's size is conducive to this kind of experimentation because the apparent resonance of mice is 2450 MHz, a frequency at which irradiation equipment is commonly and economically available.

Rugh *et al.* (1974, 1975) conducted several experiments on the mouse at 2450 MHz with a waveguide exposure system to expose individual pregnant CF1 mice at air temperature of 25°C and 50 percent relative humidity. All mice were exposed once on the 8th day of pregnancy to CW fields at 2450 MHz for 2 to 5 min at a forward power that delivered a measured average energy dose ranging from 2.45 to 8 cal/g; there were no control or sham-irradiated mice in this study.

These and a few other authors have reported dose parameters in calories or Joules per gram, which we have converted to the SAR unit (W/kg) used in this document. Each of the texts of the two papers by Rugh *et al.* (1974, 1975) refers the reader to the other for more detailed methodology, but neither adequately describes exposure factors to convert accurately the dose values to dose rate (SAR). Our best solution was to convert to a range. The range of doses given by Rugh *et al.* is 10.3 to 33.5 J/g delivered over 2 to 5 min. The four possible combinations (Table 5-8) of two extremes of dose (10.3 and 33.5 J/g) and two extremes for exposure duration (2 and 5 min) result in SARs ranging from 34 to 280 W/kg for this study. The most probable range of values is 85 W/kg (10.3 J/g for 2 min) to 112 W/kg (33.5 J/g for 5 min).

The authors clearly demonstrated the teratogenicity of RF radiation in mice, especially the potential for death and generation of anomalies. By determining the energy dose in each pregnant mouse, and

Table 5-8. Conversion of J/g to W/kg*

Average Dose (J/g)	Exposure Duration (min)	SAR (W/kg)
10.3	5	34
10.3	2	85
33.5	5	112
33.5	2	280

*W/kg = J/g x 1000 ÷ seconds (data from Rugh *et al.* 1974, 1975).

because varying doses were absorbed during the 2 to 5 min of exposure, the effect observed in each litter could be assigned to a definite whole-body average dose. These are the strong points in the Rugh *et al.* studies.

Rugh *et al.* (1974, 1975) showed that resorption of fetuses is a characteristic response to RF-radiation exposure. Resorptions appeared at a dose rate of approximately 85 W/kg. Both the incidence of resorptions within litters and the incidence of litters with resorptions increased as the average dose increased. Near the maximum dose (33.5 J/g, approximately 110 W/kg) almost all the litters were affected. Even at 25 J/g, there were litters with 100 percent resorption rates.

Anomalies "...were various, but the one used for this study, and which occurred most frequently, was exencephaly (brain hernia)..." The report also included data on resorptions, dead, and stunted fetuses. In lieu of numerical data, the incidences of brain hernia (also termed encephalocele, exencephaly, or cranioschisis) are given by the authors in one figure. Data, as percentage of affected litters, were grouped into cells 8.4 J/g in width that ranged from 10.9 to 35.9 J/g. Approximately 30 percent of the litters given an average dose of 15 J/g (approximately 90 W/kg) had fetuses with brain hernias. Of those litters given an average dose of 31.8 J/g (estimated as 109 W/kg) almost all contained fetuses with some form of brain herniation.

Though sham, cage-control, or historical control value for the incidence of brain hernia in this mouse strain (CF1) is not given, the authors state "...since this aberration rarely if ever occurs without trauma, it is significant when even a single exencephaly occurs." However, one report of the incidence of spontaneous brain hernia in CF1 mice showed an occurrence of 11 exencephalic litters in a total of 90, approximately 12 percent of litters (Flynn 1968). Apparently, spontaneous incidences of anomalies are quite variable.

A report by Rugh and McManaway (1977) included data on mice exposed once for 4 min to 2450-MHz RF radiation (SAR = 100 to 114 W/kg) on days 0 to 11 (10 mice per day). In this group of mice (we cannot differentiate these data from those reported in Rugh *et al.* 1975 and Rugh 1976a,b) are uneven incidences of stunted fetuses (irradiated on day 4 of gestation) and death (irradiated on day 3, 8, or 10 of gestation). Rugh considers small fetuses as stunted and believes that this is a teratologic symptom.

Rugh's experiments included using a single, but high field intensity for a very short time (i.e., 4 min on the 8th day of gestation). A longer period (100 min daily) was used by Berman *et al.* (1978) in the exposure of pregnant CD1 mice to 2450-MHz CW fields at power densities of 0 to 28 mW/cm^2 in an anechoic chamber. Between 15 and 25 mice were irradiated simultaneously, each in a small ventilated container. Mean rectal temperature was 38.2°C at the end of exposure to the highest power density (28 mW/cm^2). SARs were determined by twin-well calorimetry and averaged 2.0 W/kg at 3.4 mW/cm^2, 8.1 W/kg at approximately 14 mW/cm^2, and 22 W/kg at 28 mW/cm^2.

This study incorporated the examination of several variables of fetal response to toxic agents. Values were tabulated by power density for pregnancy rates, incidences of live and dead fetuses, live fetal weights, and incidences of anomalies. Values were expressed that used the litter as the experimental unit. This is a conservative approach in experiments in which the potential fetal toxicity of an agent is determined (Atkinson 1975). Berman *et al.* (1978) also "corrected" the mean fetal weight of each litter by a factor representing the potential influence that litter size had upon fetal weight. The technique is also endorsed by Atkinson, because it allows greater confidence in the interpretation of data.

The study by Berman *et al.* (1978) demonstrated that daily exposure to 2450-MHz fields at intensities producing an SAR of 22 W/kg during the entire period of organogenesis caused a 10-percent decrease in body weight of mouse fetuses. The practical significance of this result is difficult to determine without experimental confirmation of the permanency or lack of reversibility of the smaller fetal weight. Until it can be shown that the effect is permanent (stunting) or temporary (delayed growth), the effect remains hygienically unresolved. The effect will have more practical significance if it can be shown that stunting is the result.

Berman *et al.* (1978) also reported on the incidences of anomalies. There did not appear to be a significant increase of individual or total anomalies at any SAR.

The C3H-HeJ strain of mouse was used by Chernovetz *et al.* (1975) in an attempt to determine the effects of fetal irradiation with 2450-MHz RF radiation. Pregnant mice were irradiated in a multimodal cavity for 10 min on the 11th, 12th, 13th, or 14th day of gestation at an SAR (determined by calorimetry) of 38 W/kg with or without the administration of cortisone, or given cortisone without irradiation. The fetuses were examined near term (near the end of the gestation period) without any difference seen between the RF-irradiated and the sham-irradiated groups of fetuses. The variables observed in these fetuses related to the morphologic and the lethal aspects of the RF irradiation. Fetal body weights were not observed in these animals.

The scientific reports on the teratologic potential of RF radiation in the rat represent the major fraction of

rodent work. Perhaps the main reason is that many of the studies that have looked for morphologic changes have also included functional teratology as one of the end points. For that kind of study, especially behavioral studies, the rat appears to be preferred over the mouse.

Chernovetz has probably published most on the teratologic potential of microwaves in the rat. She reported (Chernovetz *et al.* 1977) the results of exposures of pregnant rats to 2450-MHz fields in a multimodal cavity (most likely the same device used to irradiate mice in experiments discussed above in Chernovetz *et al.* 1975) at an SAR calculated by calorimetry of approximately 31 W/kg. Exposures were conducted during 1 of 7 days, from the 10th through 16th day of gestation, and the fetuses were examined on the 19th day of gestation. Each single exposure lasted 20 min. The experiment included a total of 74 time-bred female rats, each assigned to 1 of 7 days of gestation and to 1 of 3 treatment groups (RF-irradiated, infrared-irradiated, or sham-irradiated). The result is an experimental design with 21 different cells into which 74 rats were distributed.

By the end of the 20-min exposure period, the mean rectal temperature in the surviving pregnant rats was 42°C. Of the original group of 30 bred females that were used in the RF-irradiation group, 7 (or 23 percent) died; none died in the sham-irradiated group. Therefore, the application of 2450-MHz RF radiation to bred rats for this duration at this SAR was lethal for a significant portion of the animals involved.

No numerical data on the gross teratologic consequences of this RF irradiation were given in the paper. However, comments were made in the text regarding the lack of any structural abnormalities. The number of resorptions was significantly higher (approximately 6 times) in the RF-irradiated than in the sham-irradiated fetuses, especially in the dams that had been irradiated on the 11th day of gestation. Fetal weights were also altered by the irradiation regimen; there was a small but statistically significant decrease in fetal weight. The alterations seen in the fetuses, in this case decreased fetal weights and death (in the form of resorptions), reflect the teratogenic potential of RF radiation exposure in the rat. These fetal alterations were found from RF-radiation exposure regimens where rectal temperatures in the dam rose above 40°C.

Chernovetz *et al.* (1979) reported on the effect of 2450-MHz RF radiation in pregnant rats, this time at SARs of 0, 14, or 28 W/kg. The same multimodal cavity was used, through which air at 22 ± 1.5°C flowed at 0.75 m/s. Pairs of bred female rats were exposed for a 20-min period on the 8th, 10th, 12th, or 14th day of gestation and then were examined on the 18th day of gestation. With cage controls added to each of these cells, the complete experimental design used 4 different days of treatment and 4 treatments (cage control, 0 W/kg [shams], 14 W/kg, and 28 W/kg), and 6 bred females per cell, for a total of 72 bred females. Those rats irradiated at 28 W/kg developed rectal temperatures of approximately 42°C, temperatures that were similar to the authors' previous experiments in which bred female rats were dosed at 31 W/kg. The rats irradiated at 14 W/kg had a mean peak rectal temperature near 40°C.

The values used by the authors in the statistical analyses were individual fetal values, not litter mean values. At the higher SAR level (28 W/kg), only ~ 10 percent below the sublethal level used in their previous report, the authors did not demonstrate lethality in the dams due to RF-radiation exposure. The 20-min exposure period at other levels of SAR produced no gross morphologic alterations in the fetuses or any severely edematous fetuses; there were also no statistically significant changes in resorption rates.

The results of fetal weights are most interesting. In the previous study (Chernovetz *et al.* 1977), the authors reported that exposure for 20 min at approximately 31 W/kg on odd-numbered days of gestation produced a significant decrease in fetal weight. In the 1979 study, a similar result was also obtained from exposure at 14 W/kg on even-numbered days (12 and 14), or 28 W/kg on the 8th day of gestation. Unexpectedly, exposure at 28 W/kg on the 12th or 14th day produced an increased body weight. The unexpected increased body weight is an interesting observation, especially when it is viewed against the decreased fetal body weight documented in the same authors' previous paper and other reports of RF-radiation-induced fetal alterations in rats and mice.

Berman *et al.* (1981) were not able to elicit any fetotoxic or teratologic responses (body weight; numbers alive and dead; external, visceral, or skeletal morphology) in fetal rats irradiated daily (100 min/day) during gestation, even with a large number of litters. The dams were exposed to 2450-MHz radiation at power densitites of 0 or 28 mW/cm^2 (4.2 W/kg). These conditions caused a mean rectal temperature of 40.3°C by the end of the 100-min exposure.

Kaplan (1981) did not find differences in the survival of squirrel monkeys up to 10 months of age after daily *in utero* and postnatal exposures to 2450-MHz in multimodal cavities. Pregnant squirrel monkeys were irradiated for 3 h daily, beginning in the first trimester; after birth, the daily irradiation of the dams and their young were continued, and from 6 to 10 months of age only the young monkey was irradiated. The SAR was determined by calorimetry to be 3.4 W/kg. In 21 irradiated and 22 sham live-born, differences were not seen in sex ratio, the number dead by 10 months of age, or in the mean age at death. Postmortem examinations did not reveal any

tendency to specific causes for death. The results of this study did not confirm the results of suspected increased lethality in squirrel monkeys from a previous study (Kaplan *et al.* 1982).

Functional teratology—Functional teratology is a branch of reproductive toxicology that has allowed increasingly greater insight into the toxicology of environmental agents. The field contains a wide variety of specialists who examine the functional capacity of neonatal or growing animals after *in utero* exposure. Except for the following discussion of viability and of body weight, assays of functional teratogenesis after *in utero* exposure to RF radiation are discussed in the section dealing with each relevant discipline.

The survival rate of fetuses can be used as an indicator of immediate effects on the fetus. The rate of survival of neonatal, infant, or older off-spring can be also used as an indicator of delayed alterations in functional capacity long after insult during the fetal stage. For example, Kaplan *et al.* (1982) reported a study of the postnatal effects of *in utero* exposure (at dose rates to 3.4 W/kg) to 2.45-GHz RF radiation in squirrel monkeys. One effect the authors observed was an increase in neonatal deaths. However, after a more intensive examination, Kaplan (1981) did not demonstrate any change in death rate and could not confirm the results of the study done earlier (but reported later).

A simple test to determine whether RF irradiation *in utero* would alter the survival of mice after birth was conducted by Rugh (1976a). In this experiment, pregnant CF1 mice were exposed on the 9th, 12th, or 16th day of gestation to a regimen of approximately 4 min of irradiation at 2450 MHz, which resulted in a mean dose of ~ 25 J/g (104 W/kg). The survivors of this sublethal exposure were allowed to give birth and their young to mature to 2 months of age. At that time, the offspring were again irradiated in the same device until each one was dead. The time-to-kill and the mean dose-to-kill was determined as a measure of the radiosensitivity of the offspring irradiated originally as fetuses. In this waveguide system, measurement of absorbed dose was monitored by power meters and calculated by the difference of forward power, transmitted power, and reflected power. While the subject in the waveguide was alive, the values of transmitted and reflected powers were constantly changing. When the subject died, these values became constant. At the time of death, the rectal temperatures of these mice, measured just after the waveguide was opened, ranged from 40 to 51°C.

Because of body weight differences in the sexes at 2 months of age, the analyses were carried out by sex. Time-to-kill was shortened in males irradiated originally during the 12th or 16th day of gestation. The males irradiated originally on the 12th day of gestation had a lower mean dose-to-kill. Therefore, Rugh (1976a) has shown that RF irradiation on select days *in utero* can alter later (sometimes much later) effects of re-irradiation with microwaves.

As noted, one effect observed commonly in fetuses exposed to RF radiation is decreased body weight. There are difficulties associated with interpreting altered fetal weight as an indicator of toxicity, especially when the permanency of decreased fetal weight (delayed growth vs. stunting) is not yet determined. But Rugh (1976a) gives evidence that mice irradiated as fetuses weigh less at 2 months of age. In that study, the mean weights of 2-month-old male offspring of dams irradiated during the 9th, 12th, or 16th day of gestation were all lower than concurrent sham-irradiated males ($p < 0.05$). Females irradiated during the 16th day of gestation were also smaller than their controls ($p < 0.05$), but not females from the 8th or 12th day groups. These results are evidence of a permanent change (stunting) in mice caused by RF irradiation.

Chernovetz *et al.* (1975) carried out an experiment to observe alterations in functional capabilities after *in utero* irradiation. Pregnant mice were exposed once during the 14th day of gestation at an SAR of 38 W/kg, and the offspring were examined until weaning for survival. The RF-irradiated and sham-irradiated groups each contained 15 dams. The statistical analyses, done by litters, show that there was a slight (approximately 12 percent) increase in the survival rate of the RF-irradiated litters as compared to the sham-irradiated controls.

Some experimental protocols continue irradiation past birth. In one example of chronic adminsitration at 2450 MHz, reported by Smialowicz *et al.* (1979a), pregnant rats were irradiated daily for 4 h/day at a power density of 4 mW/cm^2 from the 6th day of gestation to term; irradiation of the offspring continued through 40 days of age. The SARs were determined by twin-well calorimetry for several ages of the animals. Pregnant rats weighing 300 to 350 g had a mean SAR of 0.7 W/kg; offspring 1 to 5 days of age and 6 to 10 g in weight absorbed approximately 4.7 W/kg. There was no significant difference between the mean body weights of the males (female offspring were not used in this experiment) in the 12 sham-irradiated litters when compared to the mean body weights of the males in the 12 RF-irradiated litters.

Shore *et al.* (1977) reported decreased body weight and decreased brain weight in postnatal rats exposed *in utero* to 2450-MHz RF radiation. In this experiment, pregnant rats were exposed at an average power density of 10 mW/cm^2 (SAR estimated, from Durney *et al.* 1978, to be 2.2 W/kg) for 5 h per day repeatedly on days 3 through 19 of gestation. Rats were allowed to deliver naturally and were observed frequently thereafter. Rats were grouped by E- or H-field orientation during exposures; only the 3-day-old

offspring that had been exposed parallel to the E-field were significantly different, having lowered body and brain weights. We cannot easily explain this preferential decrement on the basis of either age or orientation during exposure except that the data were repeatedly analyzed using unadjusted *t*-tests. Our expectation is that there is no significant difference due to orientation in wholebody SAR in rats at this frequency (Gage *et al.* 1979).

In experiments conducted by Michaelson *et al.* (1978), some apsects of functional teratology of RF radiation were explored in Long-Evans rats. In these experiments, rats were exposed to 2450-MHz RF radiation at power densities of 10 mW/cm^2 for 1 h on the 9th and 16th day of gestation, or 40 mW/cm^2 for 2 h on the 9th, 13th, 16th, or 20th day of gestation. According to data based on water-calorimetry, an exposure at 40 mW/cm^2 produced an SAR of approximately 10 W/kg and approximately 2.5 W/kg at 10 mW/cm^2. Exposure at 40 mW/cm^2 caused an increase in the mean of rectal temperature of approximately 1 to 2°C over that of the sham-exposed animals. The exposure at 10 mW/cm^2 (2.5 W/kg) on the 9th or 16th day of gestation caused a significant increase (approximately 0.5 to 1°C) in temperature of dams at the 16th day of gestation. There were no statistical differences in the sizes of litters as a consequence of exposure during gestation. There also appeared to be no difference in the growth rates up to 21 days of age of the rat pups that were exposed to RF radiation as compared with shams, nor in their relative brain weights.

At the symposium where Michaelson described his work, Johnson *et al.* (1978) reported on a study, then in progress, on the functional teratologic effects in rats exposed to 918 MHz for 20 h per day for 19 days of gestation at a power density of 5 mW/cm^2. The experiment is especially interesting because it was conducted at a frequency close to the resonance of the experimental subject (rat) and because it is the only reported study conducted with almost continuous exposure. The SAR in this study is approximately 2.5 W/kg, determined by calculations from thermographic scans. The eight RF-irradiated and eight sham-irradiated bred dams were maintained in the waveguide exposure apparatus under environmental conditions of 22°C, 45 percent relative humidity, and *ad libitum* access to rat chow and water. The exposure was begun on the first day of pregnancy, the day on which the copulatory plug was first seen. In this experiment, the dams remained in individual waveguides or sham condition until day 20 of gestation, at which time they were removed and placed in delivery cages. At 4 days of age, the litters were culled to four males and four females per litter, which were then observed through 91 days of age.

There appeared to be no differences in the litter means for the number of pups born or for number dead during the first day after birth. There were no pups in any of these litters (including RF-irradiated, sham-irradiated, and cage-controls) with any visible physical defects. Body weights at birth, at 28 days of age, and at 91 days were analyzed for significant differences on an individual pup basis. The only statistically significant differences in body weights were found between the RF-irradiated and cage-control females at 28 days of age. A difference also existed in males at 91 days of age, when the RF-irradiated and the sham-irradiated males weighed less than the cage-control males.

Another parameter of development used as an assay of functional teratology in this study was the age at eye-opening. The phenomenon of eye-opening is a little-understood but frequently used indicator of developmental maturation. There appeared to be a significant shift to earlier eye-opening in animals exposed to RF radiation during gestation, and this maturation was earlier by approximately 1 day.

Jensh reported a series of experiments designed to examine pre- and postnatally the effects of 915-MHz, 2450-MHz, and 6-GHz irradiation of rat fetuses (Jensh *et al.* 1979; Jensh 1979, 1980). These studies included irradiation up to 8 h daily during most of gestation with power densities not sufficient to cause increased core temperatures (915 MHz, 10 mW/cm^2, 2 W/kg; 2450 MHz, 20 mW/cm^2, 3 W/kg; 6 GHz, 35 mW/cm^2, 3.5 W/kg; SAR estimates from Durney *et al.* 1978, p. 96). Offspring were examined pre- and postpartum in a complex series of observations meant to locate behavioral or morphological alterations. None was noted.

In lieu of any other workable hypothesis supportable by experimental data, the most plausible available theory that can account for RF radiation effects is that, upon absorption, microwaves deposit energy that is converted to thermal energy. There remain differences among theories that attribute individual effects to a general input of energy, or the heating of local (hot-spot) areas, or some more subtle contribution of microwaves not characteristic of conventional methods of heating animals with infrared radiation, convective heating, or immersion in water or oil baths.

Comparisons between RF heating and infrared or convective heating have been conducted in the study of hyperthermia as a teratogenic agent. Edwards is a frequently cited investigator of the effects of hyperthermia on the development of mammals. His extensive work on this agent as a cause of congenital malformations is perhaps best summarized in one of his reviews (Edwards 1974), which describes his experiments on the teratologic manifestations of hyperthermia in the guinea pig. The guinea pig is an unusual laboratory animal in its long gestational development, approximately 65 days. During the latter two thirds of gestation in the guinea pig, the

unborn offspring is in a stage of development similar to that which occurs after birth in the mouse and the rat. A long gestation period does not in itself prevent use of the guinea pig as a model for teratogenesis. But as far as teratologic experimental methodology is concerned, the administration of the agent at 40 or 50 days of gestational age in the guinea pig has no equivalent in rodent fetuses; this stage of development occurs postpartum in mice and rats.

Studies of the teratogenic potential of conventionally induced hyperthermia in almost all the species used show some general changes that can be seen in RF-radiation-treated animals as well. The symptom of hyperthermia, whether induced by RF radiation or otherwise, causes varied anomalies (such as kinked tail, microphthalmia, exencephalia, cleft palate, general edema). This is evidence that hyperthermia is a general teratogen. Perhaps the only case where RF-radiation-induced and conventionally induced teratogenesis is not the same is in the development of smaller brain weights in fetuses heated by non-RF-radiation-heating agents. Except for Shore *et al.* (1977), perhaps the literature in RF-radiation-induced teratogenesis has not been sufficiently developed to show this effect of decreased brain weight.

Conventionally induced hyperthermia, like RF-radiation hyperthermia, appears to affect most species if sufficient energy is applied and proper timing of the agent is obtained. A sufficiency is usually manifested by a rise in maternal rectal temperature, usually over 40°C, but often in a range of 41 to 43 or even 44°C. At these temperatures, the teratogenic potential of heat applied by conventional means or by RF radiation does not appear to show any significant differences. The authors of one study attempted to differentiate teratogenic effects of microwaves from the more conventional methods of heating (in this case, infrared irradiation). Chernovetz *et al.* (1977) exposed pregnant rats to 2450-MHz fields at an SAR of approximately 31 W/kg, or to infrared radiation. The rectal temperatures of the RF-irradiated and the infrared-irradiated groups were similar (approximately 42°C). The results of the exposures showed little difference in effects due to infrared heating or RF-radiation heating.

The symptom of decreased body weight of fetuses is a general developmental effect. This response to microwaves is commonly seen in experiments, even those experiments that have not otherwise demonstrated specific morphologic changes (e.g., O'Connor 1980). Body weight changes alone have also been seen in mice fetuses at temperatures <40°C (Berman *et al.* 1978).

Body temperatures reported in the above studies were those of the dam, usually measured in the dam's large intestine. Measurements of fetal temperatures after RF-irradiation have not been reported. A report by Morishima *et al.* (1975) provides some understanding of the physiologic changes that occur in the fetus as a result of conventionally induced hyperthermia. Morishima *et al.* used pregnant baboons and simultaneously monitored temperature and physiologic changes in the dam and the fetus during hyperthermia. The temperatures in these dams were raised to 41 to 42°C by infrared lamps and warming pads. While the pregnant dam was maintained in an analgesic state using nitrous oxide inhalation anesthesia and intravenous succinylcholine chloride infusions, thermistors and catheters were placed at comparable positions in the dam and the fetus. Two groups of animals were used: one group was kept at 38°C; the temperature of the other was allowed to elevate gradually to 41 or 42°C. At the more normal temperature, 38°C, there was a slight (0.5°C) but steady increment in the temperature of the fetus over that of the dam. When the temperature was increased to 40°C in the dam, the fetal temperature rose accordingly and remained 0.75°C higher than the dam's temperature. The hyperthermia produced increased uterine activity and some acidosis in the dam, and a profound acidosis and hypoxia in the fetus. If conditions comparable to those seen in the baboon are also seen in the mouse, then we might expect the mouse fetus to have temperatures greater than that of its dam.

That the teratogenic potential of RF radiation might depend only on the deposition of energy as heat was shown experimentally by Rugh and McManaway (1976). They exposed pregnant mice to highly teratogenic (high incidence of fetal death) levels of RF radiation with and without pentobarbital anesthetic. The mice exposed during anesthesia had normal rectal temperatures and normal incidences of fetal death. Therefore, the anesthetic protected against the primary temperature effect of the radiation by reducing "...the body temperature to a degree equivalent to the rise in temperature expected from the conditions used." This result is clear evidence that the increased fetal abnormalities are strongly, if not solely, associated with increased maternal temperature.

Further evidence for a direct relationship between fetal effects and hyperthermia induced by RF radiation is shown in several reports (Dietzel and Kern 1970; Dietzel *et al.* 1972; Dietzel 1975). In these experiments, groups of pregnant rats were subjected to 27-MHz radiation to raise rectal temperature to 42°C. From these data, the thresholds for increased malformation rates appear to be between core temperatures of 39.0°C. maintained for 5 min and 40.5°C for 10 min.

Observed teratological effects are summarized in Table 5-9.

Table 5-9. Summary of Studies Concerning Teratologic Effects of RF-Radiation Exposure

Effects	Species	Exposure Conditions* Intensity (mW/cm^2)	Duration (days x min)	SAR† (W/kg)	Reference
30% survival of pupae	*D. melanogaster*		1 x 10	640	Pay *et al.* (1978)
Embryonic LD_{50}	Chicken	200	1 x 12	70	Carpenter *et al.* (1960a)
		280	1 x 7	98	
		400	1 x 4	140	
Decreased postnatal survival	Mouse		1 x 4	104	Rugh (1976a)
Teratogenesis	Mouse		1 x 2-5	85-112	Rugh *et al.* (1974, 1975)
No change in teratogenesis	Mouse		1 x 10	38	Chernovetz *et al.* (1975)
Increased postnatal survival	Mouse		1 x 10	38	Chernovetz *et al.* (1975)
Maternal lethality, resorptions, decreased fetal weight	Rat		1 x 20	31	Chernovetz *et al.* (1977)
Decreased fetal weight	Mouse	28	12 x 100	22	Berman *et al.* (1978)
No change post-hatching: hatchability, hemogram, body or organ weights	Japanese quail		1 x 1440	14	Hamrick and McRee (1975)
No change	Rat		1 x 20	14	Chernovetz *et al.* (1979)
No change	Rat	40	1 x 120	10	Michaelson *et al.* (1978)
No change	Mouse	3. 4-14	12 x 100	2-8	Berman *et al.* (1978)
Teratogenesis	Japanese quail		12	4	McRee and Hamrick (1977)
No change	Rat	5	Many x 240	0.7-4.7	Smialowicz *et al.* (1979a)
No change	Rat	28	12 x 100	4.2	Berman *et al.* (1981)
No change	Squirrel monkey		Many x 180	3.4	Kaplan (1981)
No change	Rat	10-35	Many	1-3.5	Jensh *et al.* (1979) Jensh (1979, 1980)
No change	Rat	5	19 x 1200	2.5	Johnson *et al.* (1978)
Decreased body and brain weight	Rat	10	16 x 300	2.2	Shore *et al.* (1977)

*Frequency used was 2450 MHz, except for Jensh (914, 2450, and 6000 MHz), and Johnson *et al.* 1978 (918 MHz).
†From report or estimated from Durney *et al.* (1978)

5.3.2 Reproductive Efficiency

This section discusses aspects of reproduction where the conceptus is not "insulted" directly by the agent, although the fetus may be involved in demonstrating the effect. Generally, reproductive efficiency is the capacity of the dam or sire to effect conception and to bear and rear offspring. Changes in this capacity might be due to alterations in behavior, physiology, or morphology. For example, reproduction efficiency might be affected by changes in maternal cyclical hormone secretions. Tests for reproductive efficiency are not conducted as frequently as those for teratologic effects, usually because the male and female reproductive systems require considerable alteration by a toxic agent to cause significant fetal wastage or increased reproductive efficiency. The testes as factors in reproductive efficiency are discussed separately in the next section.

We have previously discussed the effects of 2450-MHz RF radiation on *D. melanogaster* reported by Pay *et al.* (1978). The fruit flies that were the subjects of that study were irradiated before production of ova. The SAR used in the study ranged from 400 to 800 W/kg. Reproductive efficiency, in this case the production of eggs, was significantly reduced in both conventionally heated and RF-irradiated females as compared with the shams. But there appeared to be no significant difference in the production of ova from females exposed to RF radiation compared with those exposed to the conventional source of thermal energy.

The egg production of chickens can also be used to provide an index of reproductive efficiency or reproductive wastage. A single intense exposure of day-old chicks was made in the experiment reported by Davidson *et al.* (1976). In one of four experiments they describe the reproductive efficiency of 28-week-old hens that had been irradiated as chicks on day 1 of age for 4.5 s at a power density of 800 W/cm^2 in a multimodal cavity. The estimated SAR was 2770 W/kg. No differences appeared between the control group and the irradiated group in the production of eggs during 100 days of laying. The authors also stated that a dose rate of 2500 W/kg for 9 s at 2450 MHz is a lethal dose in day-old chicks and that 42 percent of the chicks dosed for 6 s at 2810 W/kg died. The animals that survived were unconscious for up to 5 min. The day-old chicks had approximately the same sublethal SAR (2770 W/kg for 4.5 s) used in the examination for latent reproductive effects, but there were no deaths that could be directly attributed to the RF-radiation exposure. From these experiments, it is concluded that the massive doses of this experimental regimen left no latent alterations in reproductive efficiency.

Rugh *et al.* (1975) reported an experiment in which they examined differences in average lethal dose of RF radiation (2450 MHz) during the estrous cycle of CF1 mice. The weights of the mice ranged from 29 to 31 g. There was a prior 20-min acclimation to the waveguide exposure chamber, and environmental conditions were 23.5°C, 50 percent relative humidity, and an airflow of 38 liters/min (0.38 km/h). There

was a significant decrease in the average lethal dose for females in estrus as compared to the average lethal dose for those in diestrus ($P < 0.01$). The forward power was 8.24 W. This experiment shows that changes brought about during the reproductive cycle can affect radiosensitivity.

In summary, it appears that the efficiency of the female reproductive system is not easily altered. Only irradiation at extremely high dose rates has made changes in reproductive patterns. Small alterations from normal values, though detectable by modern scientific and statistical methodology, do not seem able to sway the general outcome of the reproductive cycle. Observed reproductive effects are summarized in Table 5-10.

5.3.3 Testes

Considerable scientific work has been done to determine effects of RF radiation on the testes. The testes are so placed anatomically that they can be conveniently irradiated without irradiation of the remainder of the body. Tests for testicular function are also conducted easily. Quantitative changes in sperm concentration can be conveniently assessed by repeatable laboratory techniques. It is known that when the mammalian testes, which have a normal temperature of 33 to 35°C, are heated to temperatures approaching abdominal temperature (37-38°C), sterility can occur. Sterility consequent to high testicular temperatures can be viewed as a purposeful contraceptive agent or as an unintended toxic agent.

Table 5-10. Summary of Studies Concerning Reproductive Effects of RF-Radiation Exposure

		Exposure Conditions*		
Effects	Species	Duration (day x min)	SAR (W/kg)	Reference
Decreased ova production	*D melanogaster*		400-800	Pay *et al* (1978)
No change in egg production	Gallus	1 x 0 08	2770	Davidson *et al* (1976)
Lethality changes with estrous cycle	Mouse			Rugh *et al* (1975)

*Frequency has 2450 MHz in all cases

A report by Muraca *et al.* (1976) describes the results of irradiation of rat testicles with 2450-MHz radiation. Each animal was anesthetized, placed in an anechoic chamber, then irradiated in a free field at a power density of 80 mW/cm^2. The SAR for adult rats was 16 W/kg (Durney *et al.* 1978).

In the experiment, the authors irradiated rat testes to produce increases of intratesticular temperature to 36, 38, 40, and 42°C; the testes were then maintained at these temperatures. The technique of irradiation included implantation of a thermistor into one testis of the anesthetized male, with the temperature of that testis acting as the control of the on-off-on sequence of the RF irradiator. Both testicles were irradiated until the temperature of the testes was within ±0.5°C of the levels mentioned above. The duration of each irradiation at a power density of 80 mW/cm^2 varied from 10 to >70 min. The animals were irradiated once or repeatedly during 5 consecutive days. Five days after the treatment ended, the animals were killed and their bodies were infused with solutions to preserve the testis that was not "invaded" by the thermistor. The microscopic appearance of the testicular tissue was categorized as follows: apparently normal; appearance of early inflammatory or degenerative changes in the spermatogenic epithelium without well-developed necrosis; or severe degeneration of the majority of seminiferous tubules with coagulated cellular elements.

When male rats were exposed once (80 mW/cm^2; 2450 MHz; 10 to 73 min; temperature of the testis maintained at 40°C), no significant change was observed in the incidence of apparently abnormal testicular tissue. After a single exposure of 10 min, during which the temperature of the testis was allowed to reach 42°C, the number of animals that had some abnormal changes tripled. Multiple (five) exposures, even where the temperature reached only 36°C for 60 min, caused all the testes to have some changes in the spermatogenic epithelium. When temperatures were allowed to reach 40°C in the testes for repeated short periods (10 to 27 min, five times), severe degeneration in the spermatic tubules was seen in all the testicular samples.

This study points to two important factors of irradiation of the testes with 2450-MHz RF radiation: that a minimum temperature (>40°C) must be reached in an acute exposure, and that repetitive treatments are much more effective than single ones. These two factors also interplay, so that an acute temperature excursion, even as high as 40°C for over 70 min, is not as deleterious as a lower temperature (36°C) reached repeatedly (five times).

Fahim *et al.* (1975) conducted an experiment to compare the contraceptive capability of microwaves with that of other methods of heating. The authors used male Sprague-Dawley rats (Holtzman strain) and irradiated them with 2450-MHz radiation (from a diathermy unit of maximum output of 100 W) during pentobarbital anesthesia. The applicator of the diathermy unit was 7.5 cm from the testicles of the rat and provided near-field exposures that do not allow a good estimate of the associated SAR. By varying the power output of the unit and by varying the exposure time from 1 to 15 min, the authors developed four subgroups of animals: those in which testicular temperature reached 65°C for 5 min, 45°C for 15 min, and 39°C for 1 or 5 min. The males were allowed to mate with normal females 24 h after treatment, and every 5 days thereafter until pregnancy was observed in the females. "The endpoint for fertility was the amount of time required for every surviving male in the treatment group to impregnate a female." Later,

the sexual organs were weighed, and histological examinations were made of the testes and secondary sex organs.

Raising the temperature of the testes to 65°C for 5 min or to 45°C for 15 min caused complete infertility in the males for 10 months. When these testes were examined histologically, there was no observable spermatogenesis. When the temperature was raised to only 39°C, 70 percent of the males retained normal breeding capability, whereas the remaining 30 percent recovered their fertility within 2 wk. Histological sections indicated normal spermatogenesis. There appeared to be no differences in testicular weights or secondary sex-organ weights, even in the group (45°C, 15 min) that was sterile 10 months after the RF-radiation exposure had ended.

This experiment demonstrates that a temperature of 45°C caused by RF-radiation exposure must be attained in the rat testes to produce permanent sterility. Temperatures that ranged to 39°C, somewhat above rectal temperature, for only a short period (5 min) were not effective and produced only temporary, if any, infertility. Along with the permanent sterility induced by the high temperatures (minimum of 45°C), there was damage to the tubules and a lack of spermatogenesis.

Sterility can occur in rats following RF-radiation exposure. At high temperatures, epithelial and tubular structures of the testes can be damaged permanently. At lower temperatures (approximately normal body temperature) for short durations, the temperature in the testicles due to RF-radiation exposure resulted in temporary sterility. This last condition implies that the spermatogenic cells themselves are not damaged permanently. The rat's spermatogenic cycle has a duration of about 10 weeks, i.e., it takes about 70 days from the first meiotic divisions of sperm generation in the germinal epithelium until the time when the sperm are fully matured, in place, and ready for ejaculation. During the last 2 weeks of spermatogenesis, sperm are located in the tubules of the testes and in the epididymis and require very little additional maturation. There is a constant stream of maturing sperm, because various seminiferous tubules are in different stages of this long cycle. The most mature stages of the spermatogenic cycle are most sensitive to heat (Van Demark and Free 1970). The permanent (10-month) sterility seen in the experiment above is due not only to loss of the most mature and most heat-sensitive stages, but also to the loss of sperm at all stages, including the stages involving the germinal epithelium. The 2-week temporary infertility seen in the less affected males was caused by the loss of only the most mature and most heat-sensitive sperm.

A study to demonstrate an alteration in functional fertility was conducted by Berman *et al.* (1980). The authors' report concentrated on chronic exposures of rats to 2450-MHz radiation in an anechoic chamber. There were three separate experiments:

(1) exposure at a power density of 5 mW/cm^2 for 4 h/day, daily, from the 6th day of gestation through 90 days of age postpartum;
(2) exposure at a power density of 10 mW/cm^2 for 5 h/day for 5 days, beginning on the 90th day of age postpartum; and
(3) exposure at 28 mW/cm^2 for 4 h/day, 5 days a week, for 4 continuous weeks, beginning on the 90th day of age postpartum.

The main purpose of the experiments was to evaluate potential mutagenic effects of RF radiation on the germ cells of the male rat. Male rats were bred to untreated female rats shortly after the end of the treatment period. No mutagenic effect was demonstrated. The breeding data of the assays used in these experiments were used to evaluate the effects on the spermatogenic function in rats.

In the first experiment, the animals were exposed daily from the 6th day of gestation to 90 days of age, at a power density of 5 mW/cm^2. In this experimental group, the SAR varied inversely with the growth of the animals, i.e., from approximately 4.5 W/kg in neonates to approximately 0.9 W/kg at 90 days of age. Twin-well calorimetry was not used in the other two experiments, and SARs are estimated at 2 W/kg at a power density of 10 mW/cm^2, and 5.6 W/kg at 28 mW/cm^2.

In this study, temperatures of the testes of rats exposed up to 90 min to 2450-MHz fields at 28 mW/cm^2 showed an increase from a pre-exposure level of 34°C to almost 38°C after exposure. Simultaneously recorded rectal temperatures were ~ 3°C higher than temperatures of the testes during the entire period. Sham-irradiated animals had testicular temperatures ranging from almost 32°C to approximately 35°C. The exposure at 28 mW/cm^2 during the 90-min period produced a temperature in the testis equivalent to the normal rectal temperature.

Chronic exposure at 5 mW/cm^2 from the 6th day of gestation through 90 days of age appeared to have no effect on the reproductive efficiency of the male rats when bred with normal females. Also, exposure at a power density of 10 mW/cm^2 (SAR ~ 2 W/kg) at 90 days of age for a period of 5 days had no effect on the reproductive efficiency of the males. It was only the most severe regimen, the exposure of adult male rats at 28 mW/cm^2 for ~ 4 weeks (estimated SAR ~ 5.6 W/kg), that caused any alteration in reproductive function. This exposure produced a severe decrease in the reproductive ability of the males; only 50 percent of the females that were available to the males for breeding became pregnant during the week immediately following the exposure period. The breeding returned to normal beginning at the third week after irradiation (the next period of test breeding).

The animals bred normally thereafter. No examination was made of the testes of animals exposed at 28 mW/cm^2. The temperatures reached in the testes at the highest power density (28 mW/cm^2) were similar to those reported by Fahim *et al.* (1975), where histological changes were seen.

Varma and Traboulay (1975) exposed anesthetized male mice to 1.7-GHz or 3.0-GHz radiation at power densities up to 200 mW/cm^2 for up to 100 min. The results of the reported experiments are (frequency in GHz; power density in mW/cm^2; SAR in W/kg, and estimated from Durney (1978); exposure duration in minutes; and effects observed): 1.7 GHz, 10 mW/cm^2, 15 W/kg, $<$ 100 min, no effect; 1.7 GHz, 10 mW/cm^2, 15 W/kg, 100 min, necrotic germinal and tubular tissue, and intact interstitial and Sertoli cells; 1.7 GHz, 50 mW/cm^2, 75 W/kg, 30 to 40 min, all tissues necrotic; 1.7 GHz, 200 mW/cm^2, 300 W/kg, 20 min, skin burns; 3.0 GHz, 50 mW/cm^2, 50 W/kg, 20 min, minimal (sic) injuries. In this experiment, as in the earlier work described in the document, acute effects are very dependent on the combination of exposure duration and field strength.

Cairnie *et al.* (1980a) used oil-bath immersion to modify core and testis temperature. When conscious mice were immersed in oil baths at temperatures from 34 to 42°C, both core and testicular temperatures appeared to be physiologically regulated, paralleled the bath temperature, and reached equilibrium. Anesthetized mice, on the other hand, did not appear to demonstrate any core or testicular temperature modification, but appeared, instead, to increase temperatures equally with the temperature of the oil. This study assumes importance because it clearly demonstrates that the temperature in the testes is not normally regulated in anesthetized animals. The investigators also studied the effects in mouse testes after a range of whole-body exposures of up to 30 days for 16 h/day at 2450 MHz and power densities of up to 36 mW/cm^2 (average whole-body SAR = 7 W/kg; average testicular SAR = 14 W/kg). These exposures caused no measurable increase in testicular temperature. No changes were seen in the number of dead testicular cells, the number of epididymal sperm, or in the percentage of abnormal sperm after exposure, even up to 8 weeks after exposure. Four strains of mice were used, and no strain susceptibility was observed.

Cairnie *et al.* (1980b), in preparation for their future work in the RF-radiation effects in the testes, determined the dosimetry of 2.45 GHz in mouse testes. They found that the absorption in the abdomen in the area of the liver was 11 times greater than in the testes when the body is oriented parallel to the electric-field vector. They also found that though abdominal temperature may have been increased by exposure to 50 mW/cm^2 for 16 h, testicular temperature was not.

Cairnie and Leach (1980) examined the viability of testicular and sperm cells and the morphology of sperm cells after exposure to hot-water baths of the posterior torso in mice. Unanesthetized mice were partly immersed in water at temperatures of 32 to 43°C for up to 4 h. The results of this experiment are appropriate to this discussion in that they may reflect the type of response that testicular tissue and sperm would give to exposure to RF radiation; however, caution should be used in attempting to equate durations of water immersion and RF radiation exposure, as the site and time-profile of heat deposition may not be equivalent. Cairnie and Leach observed that heat-damaged testicular cells are evident within 2 h after exposure (41°C, 30 min), that the incidences of the damaged cells are at a maximum from 4 to 12 h after exposure, and that the incidences of damaged testicular cells are related to combinations of exposure duration and bath temperature. They also observed that a 30-min immersion in 43°C water, but not lower temperatures, significantly decreased total epididymal sperm counts during a 10-week-long postexposure period, and that the incidences of abnormal-appearing sperm followed a similar pattern.

In the studies reported by Ely *et al.* (1964), 2880-MHz (PW) radiation was used to irradiate only the testicular area in groups of dogs. The animals were anesthetized during exposures while temperatures were measured in the testis by a thermistor in a metal needle. Irradiation of the testicular area continued until a peak temperature was reached; the RF radiation was then turned off manually so that the testes could cool, at which point the RF radiation was turned on once again. This cycling of exposure was completed many times so that the animal's testes could be kept at a "steady" temperature for a considerable length of time. The normal temperature of the testes of the dogs was ~33°C, 5°C lower than that of the rectum.

According to this report, exposure of the testes caused an elevated testicular temperature of 36°C at 20 mW/cm^2, 38°C at 33 mW/cm^2, and up to 40°C at 45 mW/cm^2. As 38°C is the approximate body temperature in the dog, bringing the testes to body temperature can expect to produce sterility if the elevation is sufficiently chronic. It appears, then, that 45 mW/cm^2 is required to produce this type of effect.

There is a large body of literature on the fertility effects caused by temperature increases, such as when the testicles are clothed to prevent the normal thermal radiation. Even high environmental temperatures, when sustained, can produce infertility in male rats. One example of this is a report (Pucak *et al.* 1977) describing deaths in a large rat-production colony in which room temperatures accidently reached as high as 31.6°C for 2 days and as high as

37.7°C in individual cages. Under these conditions, approximately 3,000 of 14,000 Sprague-Dawley rats died from heat prostration. When examined 18 days after the incident, 25 percent of the surviving males showed bilateral atrophy of the testicles, which were approximately half the normal size. Histological examination showed atrophy of the spermatic tubules and failure of spermatogenesis. The proportion of affected testicles ranged from 50 to 75 percent. Five weeks after the incident the animals with small testes were still sterile. In comparison with the temperatures seen in this study, raising the temperatures of testes to 42°C by RF-radiation exposure appears to be an extreme experimental regimen. Observed testes effects are summarized in Table 5-11.

5.3.4 Unresolved Issues

5.3.4.1 Teratology

A threshold of teratogenic effects due to RF radiation has not been determined. The measurement of threshold will have to include the entire range of teratogenic effects: lethality, anomaly production, decreased body weight in fetuses, and alteration of postnatal function. Even at this stage of development of the data relating to RF-radiation-induced teratogenesis, a picture is appearing in which the degree of response depends on the level of whole-body SAR, the duration of exposure, the timeliness of the exposure, and the species, all of which complicate the threshold determination. It is not yet clear whether threshold can be based on a finite whole-body SAR for all species or whether some adjustment or proportion will be necessary for species size, metabolic rate, thermoregulatory capacity, etc. So far, the only physiologic variable that can be supportably associated with teratogenic effects is the colonic temperature of the dam during or at the end of exposure. The mouse and rat, two extensively studied species, show a minimum temperature of approximately 40°C in the dam is associated with teratologic symptoms. However, whole-body SARs required to cause temperature excursions like this are much higher in the mouse than in the rat. Therefore, an adequate relationship of teratogenesis to SAR alone is not apparent. The maternal colonic temperature, then, is the only available indicator of a threshold for teratogenesis in mammals.

Published reports that meet the criteria for consideration in this document have limited their examination of the fetal results of gestational exposure to a gross morphological change or one that might be seen under low magnification (15X). There has been no organized attempt to examine in histologic detail fetuses that have been irradiated *in utero*. Authors of one study (McRee *et al.* 1980b), however, made a detailed examination of embryonic hearts but could not demonstrate changes in morphologic, ultrastructural, or enzymatic activity. The subjects were Japanese quail which had been exposed daily for 8 days to 2450-MHz radiation at SARs of 4 and 16 W/kg.

There are classifications of fetal changes that represent no gross structural deficit, but nevertheless represent some variation of structure. An example of a variation that may not be considered by all teratologists as a "deficit" is a small but normal fetus. However, if the incidence of this variation is consistently increased by the application of a toxic agent, it could be considered an expression of embryotoxicity. The decreased body weight so often seen in offspring exposed to RF radiation (Berman *et al.* 1978; Chernovetz *et al.* 1977, 1979; Rugh 1976a) might otherwise be considered as a lesser category of "structural variation without deficit" if decreased weight were not so consistent in these experiments. Whether this decreased fetal weight is temporary (i.e., only a delayed growth that will disappear in the neonatal stage) or permanent (i.e., a stunting of the fetus that will persist) has not yet been resolved.

There is one aspect of the literature on the teratogenic potential of RF radiation that deserves further discussion. More than half the papers in this document on teratogenesis report experiments with

Table 5-11. Summary of Studies Concerning Effects of RF-Radiation Exposure in Testes of Mice and Rats

		Exposure Conditions				
Effects	Species	Frequency (GHz)	Intensity (mW/cm^2)	Duration (days x min)	SAR (W/kg)	Reference
No change	Mouse	1.7	10	1 x < 100	15	Varma and Traboulay (1975)
Abnormal germinal cells, normal interstitial cells			10	1 x 100	15	
All tissue necrotic			50	1 x 30-40	75	
Scrotal skin burns			200	1 x 20	300	
"Minimal" injury	Mouse	3.0	50	1 x 20	50	
No change in tissue, sperm	Mouse	2.45	<37	many x 16 h	<8	Cairnie *et al.* (1980a)
Abnormal spermatogenic tissue	Rat	2.45	80	1 x 10-73	16	Muraca *et al.* (1976)
				5 x 10-73	16	
No change	Rat	2.45	5	many x 240	0.9-4.5	Berman *et al.* (1980)
No change			10	5 x 360	2	
Temporary sterility			28	20 x 240	5.6	

the rat. Chernovetz *et al.* (1977) raise an interesting point about using the rat in determining the teratogenic potential of RF radiation. The authors argue that because levels of microwave exposure which are associated with high mortality rates of dams do not also produce fetal structural abnormalities in the rat, "...that the teratogenic threshold of microwave radiation is higher than the dam's threshold of mortality," and hence"... that maternal mortality is more probable than malformation of the fetus, irrespective of the dose."

The problem of using animal models in determining teratogenic potential in humans is that there is no assurance that any of these models is a real estimate of effects in humans. The concepts supporting the use of animals as models of human beings require that the response be demonstrated in a number of species, so that the resultant generality can be more confidently extended to humans. Therefore, we seek among species some generality of effects of microwaves on the fetus. Mice and rats are the two laboratory animals upon which rest almost all of the data of RF-radiation-induced teratogenesis. Any difference between the two species in their teratogenic response to RF radiation, therefore, becomes important.

5.3.4.2 Reproductive Efficiency and Testes

The testes contain, besides sperm-producing tissues, interstitial cells that secrete testosterone, the male hormone. Gunn *et al.* (1961) described the effect of 24-GHz radiation on the morphology and function of the interstitial cells in rats. They exposed rats once at this frequency for a period of 5 min at a power density of 250 mW/cm^2, which caused the temperature to rise to 41°C in the testes. As a result, there were scrotal burns, severe edema, and spermatic tubular degeneration, but not interstitial-cell pathology.

The testosterone secreted by the interstitial cells of the testes regulates zinc uptake by the dorsolateral prostate. When Gunn examined zinc uptake in RF-irradiated rats that had no interstitial cell pathology, he found a decreased uptake. Gunn related the decreased function of this secondary sex organ to decreased testosterone secretion.

The effects seen by Gunn were produced at a frequency at 24 GHz. At such a short wavelength there should be no significant penetration to affect the dorsolateral prostate directly. The tests using the dorsolateral prostate as an indicator of sexual function in the rat have been commonly used by Gunn and others in other types of experimental situations.

It is not known why and how the dorsolateral prostate lost its capacity to function normally when there was no observable change in the interstitial tissues, the other testicular damage appeared to be minimal, and the energy could not reach the prostate. This appears to deserve additional attention and exploration.

The literature we have cited does not lend itself to extrapolation of effects of RF radiation that cause only small increases in the temperature of the testes. The lack of data on RF-radiation effects at lower power densities (which cause lower testicular elevations of temperature than have been cited in the articles above) is especially important in light of suggestions in the popular media that thermal energy, in the form of absorbed RF radiation, can be used as a contraceptive in men.

One report by Rugh (1976a) contains data on survival in RF-radiation fields that are different in males and females. In this study, mice of both sexes and of three ages (weanlings, young mature, and aged) were irradiated with 2450-MHz RF radiation until dead. Of the three variables (age, sex, body weight) examined for their contribution to RF-radiation lethality, Rugh found that "The overall conclusion would be that no matter at what age...absorbed dose to death...is different for the two sexes. Females are slightly more radiosensitive..." These results are not explained easily. Although they are not apparently related to sexual function, they were included here on the basis of sexual differences.

5.4 Nervous System

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Communication with the external environment and modification of the operation of other organ systems are functions of the nervous system. Signals from stimuli in the external environment, such as chemicals, pressure, temperature, or radiant energy, are received by specialized receptor cells and transduced into nerve impulses that are measured as a complex pattern of electrical and chemical events. These impulses are combined with other signals from the internal environment, such as chemical secretions or feedback from intermediate neurons or neurons in efferent paths of the nervous system, at junctions called synapses. Information is thus transmitted through the nervous system until some effector change occurs (usually a chemical event at a site called a neuromuscular junction) that activates or modifies some gland or muscle tissue, and brings about an integrated response to changes in the internal and external environment of an organism. Detailed descriptions of the organization and functioning of the nervous system are available (Crosby *et al.* 1962, Kandel and Schwartz 1981; Carlson 1980; Cooper *et al.* 1982; *Scientific American* 1979).

Two types of cells are found in the nervous system, neurons and glia. Neurons consist of cell bodies and two types of peripheral processes known as dendrites and axons. They are considered responsible for carrying the information throughout the nervous system. The glia (of which there are several types) are considered to support the neurons, to nourish them, and react to damage of nearby neurons.

The nervous system can be divided into several anatomical subsystems, that are not mutually exclusive but have been formulated to unify a particular function or anatomical similarity. One such division is the central nervous system (CNS, i.e., the brain and spinal cord), as opposed to the remainder of the nervous system called the peripheral nervous system (PNS). The brain may be subdivided into areas which may be further subdivided into nuclei or cortices (the gray matter containing the cell bodies and frequently the dendrites of neurons) and tracts (the white matter containing the axons which are covered with a white fatty tissue called myelin and in the PNS are wrapped by Schwann cells). Neurons in nuclei and cortices and axons in tracts are positioned so that each area contains a topographic projection of the part of the peripheral location connected by the neurons.

There is much redundancy within the nervous system. Multiple pathways carry similar information between the periphery and the brain, as well as within the brain itself. Some of these paths, such as primary sensory tracts, have few neuronal connections; others, such as the reticular formation, have many intermediate (or internuncial) neurons. Input neurons synapse with intermediate and output neurons at numerous levels in the nervous system.

At synapses specific chemicals known as neurotransmitters function in complex series of reactions to carry signals between neurons. Packets of neurotransmitter substance are released at the synapse by one neuron and taken up at the postsynaptic membrane of an adjoining neuron. Much evidence indicates that norepinephrine, dopamine, acetylcholine, serotonin, and γ-aminobutyric acid (GABA) are neurotransmitters. The reactions at synaptic connections are different from another type of chemical activity that takes place at the membrane along the axon at breaks in the myelin cover called nodes, enabling conduction of electrical impulses along the axon. At these nodes influx and efflux of ions of potassium, sodium, and calcium establish changes in electrical potentials.

The fine topographic organization throughout the nervous system, coupled with multiple connections and pathways between input and output and the transmission of specific chemicals at particular synaptic junctions, enables the specificity of response to ambient changes for which the nervous system is renown. This exquisite organization and complexity within small areas in the brain is also responsible for a variety of changes that might be seen if RF radiation were to affect the nervous system.

A review of the literature of the effects of RF radiation on the nervous system permits the following general statements to be made:

- Acute or chronic CW or PW radiation of animals at SARs $\geq$ 2 W/kg can produce morphological alterations in the central nervous system. These changes are qualitatively similar after acute or chronic exposure and at different SARs, but quantitatively more alterations occur in the affected neuronal structure after exposure at higher SARs and after chronic exposure. The changes are found less frequently if the animals are allowed to survive several days to weeks after exposure. Acute exposures above 2.5 W/kg alter electrophysiological responses in the thalamus of the cat brain.

- Currently, no information conclusively shows RF radiation affects the blood-brain barrier (BBB) at SARs below 2 W/kg. Initially it appeared that RF radiation at low power densities altered the permeability of the BBB in experimental animals.

Later experiments indicated such alterations were due to thermal effects. Effects formerly attributed to changes in BBB permeability are now thought to be due to increased blood flow in the brain.

- RF radiation appears to have a potentiating effect on drugs that affect nervous system function. Most of the relevant studies have used pulse-modulated waves only. Whether RF radiation also has an inhibiting effect on neuropharmacologic drugs is not certain.

- There are no data on the effects of RF radiation on neurotransmitters at SARs < 2 W/kg. However, after exposure at SARs > 8 W/kg the release of neurotransmitters appears to be affected. Whether there is an increased or a decreased release depends on the specific neurotransmitter.

5.4.1 Morphological and Physiological Observations

The nature of morphologic changes in the nervous system of exposed animals depends on the frequency, power density, duration, and modulation characteristics (e.g., PW or CW) of the radiation. Gordon (1970) and Tolgskaya and Gordon (1973) reported severe damage in the brain of rats after short exposure to RF radiation of various frequencies at high power densities (> 40 mW/cm^2, SAR estimated > 8 W/kg, assuming the worst case condition which would occur if the rats had their long body axis parallel to the E-field vector) which produced rectal temperatures of 42 to 45°C. These changes consisted of hemorrhages, edema, and vacuolation of neurons after a 40-min exposure to 3,000 or 10,000 MHz PW or CW radiation at 40 to 100 mW/cm^2. At 20 mW/cm^2 similar but less severe effects were observed. Further, 3000-MHz radiation (SAR estimated about 4 W/kg) produced more marked changes than 10,000 MHz (SAR estimated about 3.2 W/kg) at equal power densities. However, Austin and Horvath (1954) did not observe similar changes in brains of rats that became convulsive and hyperthermic (rectal temperature increase of 2.3°C, or brain temperature increase to about 43.7°C) during a single, short irradiation. The exposure to 2450 MHz lasted for a maximum of 7 min or until the onset of convulsion (which was usually less than 2 min). Exposure was of high intensity and was presented only to the head (60 or 90 W applied 2.5 cm above or on the head). These authors observed only mild pyknosis and hyperemia in some areas of the brain, mostly in the pyramidal cell layer of the hippocampus.

Albert and DeSantis (1975) did not observe hemorrhage, gliosis, or focal necrosis in adult Chinese hamsters exposed to 2450 MHz (CW) at 50 mW/cm^2 (SAR estimated at 15 W/kg) in the far field in an anechoic chamber for 30 min or single periods lasting up to 24 h, but they did observe swollen neurons with frothy cytoplasm in the hypothalamic and subthalamic regions located near the center of the brain. Such observations were not seen in the cerebellum, pons, or spinal cord, which are located more posterior than the other areas. These changes were less severe in hamsters allowed to survive for 6 to 10 days after treatment. In a second study (Albert and DeSantis 1976) similar histologic changes were seen in the hypothalamus and subthalamus of Chinese hamsters following single 1700-MHz (CW) exposures lasting from 30 to 120 min at either 10 mW/cm^2 (SAR estimated at 3 W/kg) or 25 mW/cm^2 (SAR estimated at 7.5 W/kg) in the far field in an anechoic chamber. No lessening of the severity of these changes was seen in animals allowed to survive for 13 to 15 days following exposure.

Histologic changes in the rat brain have also been reported after multiple (35 or more) 30-min exposures to 3000 MHz at lower power densities (< 10 mW/cm^2, SAR estimated at 2 W/kg). The histological alterations included cytoplasmic vacuolation of neurons, axonal swelling and beading, and swelling in and decreased numbers of dendritic spines (Gordon 1970; Tolgskaya and Gordon 1973). These changes were seen to a lesser degree or not at all in animals allowed to survive for 3 to 4 weeks after exposure before sacrifice. Vacuolation of neurons but not glia was also seen in the hypothalamic region of Chinese hamsters exposed to 2450 MHz (CW) at 25 mW/cm^2 (SAR estimated at 7.5 W/kg) for 14 h on each of 22 days (Albert and DeSantis 1975).

Baraǹski (1972b) reported that exposure of groups of 30 guinea pigs to 3000 MHz (CW and PW at 400 Hz) in an anechoic chamber at 3.5 mW/cm^2 (SAR estimated at 0.53 W/kg) and exposure of 20 rabbits to 3000 MHz (CW or PW not indicated) at 5 mW/cm^2 (SAR estimated at 0.75 W/kg) for 3 h daily for 30 days resulted in myelin degeneration and increased proliferation of glial cells in both the cerebrum and cerebellum. More alterations were noted in the guinea pigs exposed to PW than those exposed to CW. Temperatures recorded at unspecified points in the body were reported never to increase more than 0.5°C. Single 3-h PW or CW exposures of guinea pigs at 3.5 mW/cm^2 had no effects, but single exposures at 25 mW/cm^2 (SAR estimated at 3.75 W/kg) produced edema, hyperemia, and small necrotic lesions indicative of damage due to heat.

Switzer and Mitchell (1977) found 3 times as many myelin figures in the dendrites of brain neurons of 15 female rats repeatedly exposed to 2450-MHz (CW) fields in a multimodal cavity than in the 14 sham-irradiated control rats. Exposures lasted 5 h, 5 days weekly for 22 weeks (a total of 550 h at an average

SAR calculated to be 2.3 W/kg, with $T_a = 24 \pm 1.5°C$, RH = 50 ± 10 percent) and were followed by a 6-week recovery period before the euthanasia. These authors did not observe other changes such as gliosis, perivascular edema, or synaptic pathology. However, the irradiated rats in this study exhibited marked disruptions of behavior during the exposure period (Mitchell *et al.* 1977; see also Sec. 5.5).

Qualitatively, the morphological effects on the CNS are similar in the range of 10 to 50 mW/cm² (SARs above 2 W/kg), but effects are quantitatively greater at the higher power densities. Many scientists would consider that irradiation at these power densities can raise body temperature. Soviet scientists have reported similar morphological changes at power densities less than 10 mW/cm² after chronic irradiation; they do not consider these alterations to be of thermogenic origin. Tolgskaya and Gordon (1973) and Baraǹski (1972b) further state that morphological effects are more marked after PW than after CW and after chronic exposure than after acute exposure. Most Eastern European studies claim full recovery of irradiated animals in 1 to 3 weeks after exposure at less than 10 mW/cm² (SAR of 2 W/kg). Albert and DeSantis (1975, 1976) found continued existence of neuronal cytopathology in animals 2 weeks after exposure. Perhaps a longer recovery period in the latter study would have shown complete reversibility. We can conclude that RF radiation causes morphological changes in the CNS of experimental animals following acute or chronic exposures at SARs of 2 W/kg. In most of the lower-intensity exposure studies, effects were rarely observed or were less severe in animals allowed to recover for 3 or more weeks after exposure.

Electrophysiological recordings from the brain and spinal cord of animals have been made during and following RF radiation when precautions have been taken to minimize artifact due to electrodes in the microwave field. Johnson and Guy (1972) have shown that a metal electrode of the type commonly used in neurophysiology can greatly increase the amount of energy absorbed in neighboring tissue by several orders of magnitude. However, saline-filled glass electrodes did not alter thermograms showing RF power absorption in brain tissue. Averaged evoked potentials were measured with glass electrodes in the thalamus to somesthetic stimulation of the contra-lateral forepaw (Johnson and Guy 1972). Cats (anesthetized with alpha-chloralose and immobilized with gallamine triethiodide) were exposed to 918 MHz (CW) for 15-min intervals at power densities ranging from 1 to 40 mW/cm² with a microwave applicator located 8 cm from the head and directed so maximum intensity was aimed at the thalamic region of the brain. The SAR in the thalamus of a live cat was 1.88 mW/cm³ (~ 1.88 W/kg) for an incident power density of 2.6 mW/cm². The exposures decreased latencies between the stimulus presentation and the peaks of the later components of the evoked potentials as a function of the power density (threshold of 2.5 to 5 W/kg). Latencies between the stimulus and initial thalamic response were not decreased by the RF radiation. This result indicates a change in the multisynaptic paths to the thalamus and within the brain with little change in the primary sensory pathway. Although microwave exposure produced increases in thalamic and body temperatures, similar increases in body temperature produced by a hot pad decreased latency of both initial and later components of the thalamic evoked potential.

Monosynaptic ventral root reflex responses of the spinal cord to electrical stimulation of the ipsilateral gastrocnemius nerve of cats anesthetized with pento-barbital and immobilized by gallamine triethiodide were measured with a polyethylene suction electrode during and after brief exposure to microwaves (Taylor and Ashleman 1975). Exposures of 3 min at 2450 MHz (CW) were delivered by a parallel-plate applicator surrounding the spinal cord. Decreases in latency and attenuation in amplitude to zero of the monosynaptic reflex occurred during exposures with an incident power of 7.5 W, resulting in an absorbed power of 1.6 W/cm³ (~ 1600 W/kg) at the spinal cord. The temperature in a bath surrounding the cord was 37.5°C. Similar but less marked changes were observed during 3.75-W exposures. These changes were reversible with the termination of exposure. Increased amplitude of the monosynaptic reflex produced by cooling the spinal cord was reversed by microwave radiation. Raising spinal cord temperature by heating the bath surrounding the cord produced effects similar to those seen during microwave radiation.

Takashima *et al.* (1979) exposed male rabbits between parallel plates to RF fields having carrier frequencies ranging from 1 to 30 MHz that were amplitude modulated at either 15 Hz or 60 Hz during a single 2-to 3-h exposure or during 4 to 6 weeks of chronic exposure. The electric field strengths ranged from 60 to 500 V_{rms}/m. Acute and chronic EEG readings were obtained from animals under sodium pentobarbital anesthesia. There was no temperature rise in the exposed animals. The EEG recordings after acute exposure at field strengths of 60 to 500 V_{rms}/m or after chronic exposure at strengths up to 70 V_{rms}/m showed no difference between control and experimental animals. However, chronic irradiation at higher field strengths was associated with abnormal patterns, consisting of bursts of high amplitude spindles at 90 V_{rms}/m, as well as suppression of activity at 500 V_{rms}/m. All brain activities returned to normal a few hours after irradiation. The results in this study appear to be free of electrode artifacts

because chronic exposures were made without electrodes, and all recordings were made when the fields were switched off. The effects of anesthesia are not clear, and the natural fluctuations of brain activity also complicate interpretation of the results. Although the occurrence of high-amplitude spindles in irradiated animals in this study is similar to that described by Bawin *et al.* (1973), comparison of the two results is difficult because in the latter study, chronically implanted electrodes may have interfered with the imposed fields. Takashima *et al.* (1979) confirmed the existence of artifacts during irradiation when implanted electrodes were used.

Bawin *et al.* (1973) exposed adult female cats previously implanted with steel electrodes and held in a fixed position by a wooden stereotaxic frame in a parallel-plate exposure system to 147-MHz fields amplitude modulated at frequencies ranging from 1 to 25 Hz at intensities of 1 mW/cm^2 or less (SAR estimated about 0.015 W/kg). Five cats were trained (by operant behavioral reinforcement techniques) to increase the percentage of time during which specific brain waves were within a narrow frequency band specified by the experimenter. Then reinforcement was discontinued for a series of sessions until the percentage of brain waves of the reinforced frequency returned to preconditioning operant levels. During these extinction sessions, three of the cats were exposed to the RF radiation modulated at 4.5 Hz for one cat, 3 Hz for the second, and 14 Hz for the third. The modulation frequency was within the range reinforced for each cat. Irradiated cats required more sessions for the brain activity to return to preconditioning levels than nonirradiated cats. Spectral analysis of the brain waves of irradiated cats showed a shift such that the predominant frequency centered around the modulation frequency of the RF radiation. No such spectra were seen in irradiated cats that had no behavioral training. In the same study two other cats were reinforced by amplitude-modulated radiation. The production of specified frequencies of brain rhythms was followed by irradiation. Increases in the number of bursts of the reinforced frequencies occurred, but the duration of these bursts did not increase. The number of bursts returned to preconditioning levels when the irradiation was discontinued.

5.4.2 Blood-Brain Barrier Studies

A separation between the blood and the central nervous system (including the ventricles containing the cerebrospinal fluid) limits the ready passage of certain substances from the blood into the nervous system. Such a separation acts to protect the brain from foreign and therefore toxic substances but allows entry of certain molecules necessary for metabolism. This separation is an anatomical entity consisting of special cells that have tight junctions between them, as well as a functional property of some glial cells. A thorough discussion of the blood-brain barrier has been presented by Rapoport (1976). In the past few years, contradictory reports have been published concerning the effects of RF radiation on the permeability of the BBB. (For reviews, see Albert 1979a and Justesen 1980).

Frey *et al.* (1975) were the first authors in the United States to report a permeability increase in the BBB of the rat after RF-radiation exposure. They observed that a 30-min 1200-MHz exposure (CW) at 2.4 mW/cm^2 (SAR estimated at 1.0 W/kg) resulted in a statistically significant increase in fluorescein in brain slices of experimental animals over controls. Most of the fluorescein appeared to be concentrated in the vicinity of the lateral and third ventricles. Some dye also was detected in the metencephalon. The authors also reported similar but heightened alterations in the permeability of the BBB when rats were irradiated with PW radiation at 2.1 mW/cm^2 peak and 0.2 mW/cm^2 average power density (SAR estimated at 0.8 W/kg). Their results also indicated that PW radiation was more effective in altering brain permeability than CW.

Merritt *et al.* (1978) were unable to replicate the fluorescein studies of Frey *et al.* (1975). However, increased brain permeation of fluorescein-albumin (mol. wt. 60,000) was produced in rats heated to 40°C by hot air or by RF radiation. They concluded that hyperthermia *per se,* and not field-specific effects of RF radiation, is the essential determinant of increased permeability. With sodium fluorescein and Evan's blue, Lin and Lin (1980) also found no change in BBB permeation after a single 20-min focal exposure within the rat head at 0.5 to 1000 mW/cm^2 (local SARs ranged from 0.04 to 80 W/kg) at 2450 MHz (PW). In 1982, these authors reported increased BBB permeability in the rat exposed similarly but at an SAR of 240 W/kg (in the brain); the brain temperature was 43°C (Lin and Lin 1982).

Electron microscopic tracer methodology has been used to follow the movement of horseradish peroxidase into Chinese hamster brains after 2450-MHz (CW) radiation in the far field at 10 mW/cm^2 (SAR estimated at 2.5 W/kg) for 2 h (Albert 1977; Albert and Kerns 1981), and into rat and Chinese hamster brains after 2800-MHz (CW) radiation at 10 mW/cm^2 (SAR estimated at 0.9 W/kg for rats and 1.9 W/kg for Chinese hamsters) for 2 h (Albert 1979b). Horseradish peroxidase is an enzyme (mol. wt. 40,000) that normally does not enter the brain. Focal areas of dark-staining material indicating increased permeability of peroxidase were seen in about 35 percent of the irradiated animals in contrast with about 10 percent of the controls. Dark-stained particles were seen in a variety of brain areas, but

appeared with greater frequency in the thalamus, hypothalamus, medulla, and cerebellum than in the cortex or hippocampus (Albert and Kerns 1981). In two of the above studies (Albert 1979b; Albert and Kerns 1981), fewer of the animals that were allowed to survive for 1 h following irradiation and almost no animals that were allowed to survive for 2 h following irradiation showed evidence of peroxidase in areas other than those that are leaky in all animals due to the normal absence of the BBB. This finding demonstrated complete reversibility of the RF-radiation effect. The increased permeability of the BBB appeared to be due to increased pinocytotic transport of the tracer rather than to opening of the endothelial tight junctions (Albert and Kerns 1981).

Sutton and Carroll (1979) produced a change in permeability of the BBB to intravenously administered horseradish peroxidase by 2450-MHz (CW) microwaves of sufficient power (10 to 20 W) to raise and maintain brain temperatures of male rats to 40, 42, or 45°C for periods lasting from 10 to 120 min. Exposures were limited to the head region by the use of type A or type B applicators and by shielding of the remainder of the body with an absorbent collar. Increased residual peroxidase activity in brain was found after 10-min exposure at 45°C, after 15 min at 42°C, or 60 min at 40°C. If body core temperature was maintained at 30°C during exposure by precooling the rat before head-only irradiation, peroxidase activity increased in the brain after 15 min at a brain temperature of 45°C, 30 min at 42°C, and 180 min at 40°C. Precooling the rats increased the exposure time needed to eliminate BBB integrity, and also increased the survival time of the rats irradiated at the lowest level from 2 to 3 h. This study indicates that severe hyperthermia induced by the radiation produces the disruption in the BBB and that this disruption can be prevented or retarded by perfusion of the brain by blood cooled in passage through the remainder of the body.

Oscar and Hawkins (1977) exposed rats injected with radioisotope tracers to 1300 MHz (CW or PW) radiation for 20 min. Using the technique of Oldendorf (1970), they found after CW irradiation at 1 mW/cm^2 (SAR estimated at 0.4 W/kg) a greater uptake of radiolabelled mannitol (mol. wt. 182) and inulin (mol. wt. 5000), but not dextran (mol. wt. 60,000), in brains of exposed animals. Similar, but greater, uptake of these compounds was observed after PW irradiation (average power density 0.3 mW/cm^2; SAR estimated at 0.1 W/kg) than after CW irradiation. Uptake of mannitol by the brain was dependent on power density, pulse width, and number of pulses per second. Merritt *et al.* (1978), who also used the Oldendorf technique, reported no significant change in uptake of mannitol or inulin in rats exposed to RF radiation under conditions similar to those used by Oscar and Hawkins (1977).

Preston *et al.* (1979) used the Oldendorf technique in a study of rats exposed to 2450-MHz (CW) fields for 30 min at zero or one of five power densities ranging from 0.1 to 30 mW/cm^2 (SAR estimated at 0.02 to 6 W/kg) in the far field in an anechoic chamber (T_a=22±1°C). No change in uptake of mannitol into the medulla, cerebellum, diencephalon, or cerebral cortex of the brian was found. Intracarotid infusion of propylene glycol, however, did increase brain uptake of mannitol. They speculated that the changes reported by Oscar and Hawkins (1977) may have been due to changes in blood flow. Later, Oscar *et al.* (1981) measured the blood flow in several brain regions during exposure to 2800-MHz (PW) fields at 15 mW/cm^2 (average) for 5 to 60 min and found increased local blood flow. They then suggested that previously reported BBB permeability changes (Oscar and Hawkins 1977) may be smaller than originally indicated.

A later report by Preston and Prefontaine (1980) described studies on BBB permeability in rats exposed to 2450-MHz (CW) radiation in both the near and the far field. The exposure in the far field in an anechoic chamber was at 1 or 10 mW/cm^2 (SAR estimated at 0.2 or 2.0 W/kg) for 30 min (T_a=22±1°C). In the near-field exposure, a microwave applicator was placed on the rat head for a single 25-min irradiation at 7, 28, or 140 mW forward power (SAR of the head, estimated as 12.64 W/kg for each watt of forward power, was 0.08 to 1.8 W/kg). In the near-field study the exposure took place after radiolabelled sucrose was injected into the animal so that BBB function during irradiation could be examined. No change in permeation was found in either study.

In summary, some initial reports indicated that direct effects of RF radiation in experimental animals might result in increased permeability of the BBB (Frey *et al.* 1975; Oscar and Hawkins 1977; Albert and DeSantis 1976; Albert 1979b). Other reports indicated that increased permeability might be mediated by hyperthermia induced by intense RF fields (Sutton and Carroll 1979; Merritt *et al.* 1978; Lin and Lin 1980). Preston *et al.* (1979) and Preston and Prefontaine (1980) reported negative findings at lower power densities. Some of these discrepancies may be attributed to differences in techniques employed to assess changes of permeability. These methodologies consisted of gross examination of brain slices, fluorescence observations, and measurement of single-passage isotopic tracers and electron microscopic tracers. All these techniques have some inherent shortcomings, either in quantitation or sensitivity. Some of the deficiencies of these methods have been recently reviewed

(Blasberg 1979; Segal and Magin 1983). Thus, unless the changes of permeability are diffuse and significant, positive results may not be readily apparent. Further complications with the interpretation of the data lie in reports that average power density, peak power, and pulse width may be important variables affecting the BBB permeability (Frey *et al.* 1975; Oscar and Hawkins 1977). Therefore, one must consider the limitations of the techniques and the exposure parameters before reaching conclusions regarding effects of RF radiation on the BBB.

5.4.3 Pharmacological Effects

RF radiation has been reported to alter effects of drugs that influence CNS functions. Baraǹski and Edelwejn (1968) noted altered EEG tracings and increased effects of Cardiasol, a CNS stimulant, in persons working in microwave fields. To understand these observations better they conducted experiments in rabbits. Administration of 4 mg/kg Phenactil (chlorpromazine), a depressant of cortical activity, followed by 3000-MHz (PW) irradiation at 20 mW/cm^2 (SAR estimated at 3.0 W/kg) for 20 min, resulted in desynchronization of the EEG, and reversal of the synchrony of the EEG seen after Penactil alone. According to Baraǹski and Edelwejn (1968) this result indicated that microwaves stimulated the brain-stem reticular formation (a path of multiple short neurons lying in the middle of the brain), which was inhibited by the chlorpromazine. Administration of 3 mg/kg Cardiasol (pentylenetetrazole, a CNS stimulant and convulsant) following irradiation or sham exposure of these rabbits resulted in an EEG change only in the exposed animals. The authors concluded that microwaves potentiated the effects of the pentylenetetrazole through pathways through the center of the brain. Chronic exposure of rabbits (Baraǹski and Edelwejn 1968, 1974) to 3000-MHz (PW) radiation at 7 mW/cm^2 (SAR estimated at 1.0 W/kg), 3 h/day for 23 to 26 days (a total of 70 to 80 h) resulted in convulsions that were more violent than after single exposures or in control rabbits. This result indicated that microwaves acted on the same thalamic reticular formation areas as did the pentylenetetrazole. Chronic RF exposure also resulted in desynchronization and high-amplitude recording potentials in the EEG. In these studies, thermal effects of microwaves were considered unlikely. However, it should be noted that the EEG records were obtained with screw electrodes implanted into the skull of the rabbits and that the pulse modulation characteristics were not specified in these experiments.

Servantie *et al.* (1974) investigated the convulsive effects of a 50-mg/kg intraperitoneal injection of pentetrazol (pentylenetetrazole) following chronic exposures of mice to 3000-MHz radiation (PW, peak power of 600 kW, average power of 350 W, pulse duration of 1 μs, repetition rate of 525 Hz). The mice were exposed in groups in the far field in an anechoic chamber in front of a horn antenna for either 8, 15, 20, 27, or 36 days (for an unspecified duration each day). The mean power density measured in the absence of the animals was 5 mW/cm^2 (SAR estimated at 5 W/kg). RF radiation affected the time to onset of convulsions and the mortality rate. Nonirradiated mice had a biphasic distribution of convulsion latency. Mice were equally distributed between groups with a short and long onset time. After 15 days of irradiation, a greater proportion of mice had longer latencies to start pentylenetetrazole convulsions. However, after 20, 27, or 36 days of exposure, a greater number of mice had shorter latencies to convulsion. Mice irradiated for only 8 days were not different from control populations. Increased incidence of mortality following convulsions was observed in the groups of mice irradiated for more than 8 days.

Servantie *et al.* (1974) also investigated the effect of curare-like drugs on rats and neuromuscular preparations of rats irradiated for 10 to 15 days, presumably under conditions described above (SAR would be 1 W/kg). They found that irradiated rats were less susceptible to the paralyzing drugs. Similar findings were noted in sciatic and phrenic nerve preparatons from exposed rats. Phrenic nerves isolated from irradiated rats were paralyzed to a lesser extent and recovered sooner than those from control rats.

Goldstein and Sisko (1974) investigated the gross behavior and EEG of rabbits given pentobarbital and then exposed for 5 min to 9300 MHz (CW) in an anechoic chamber at power densities ranging from 0.7 to 2.8 mW/cm^2 (SAR estimated at 0.1 to 0.3 W/kg, assuming the rabbits were oriented with the long axis of their body parallel to the E-field vector). Five minutes prior to irradiation or sham exposure the rabbits were injected intravenously with 4 mg/kg of sodium pentobarbital. No difference was seen in EEG patterns between control and irradiated rabbits during the 5-min exposure period. However, after a latent period lasting from 3 to 12 min following exposure, periods of EEG and behavioral arousal lasting as long as 16 min and followed by periods of sedation occurred in the animals exposed to RF radiation after the barbiturate, but not in the controls. Such effects were seen after the lowest power densities investigated but were more pronounced after exposure at 2 mW/cm^2. Similar effects of arousal after irradiation were also seen in rabbits injected with hallucinogens or morphine in place of the pentobarbital before exposure. In this study the EEG was recorded with the aid of stainless steel electrodes implanted before the irradiation.

A related finding, that of decreased sleeping time in rabbits following injections of 22 mg/kg sodium pentobarbital during 2450-MHz or 1700-MHz (CW) RF irradiations, has been reported (Cleary and Wangemann 1976). Exposures were in the far field in an anechoic chamber (T_a=22±0.6°C, RH=40 to 60 percent). The exposure level for this effect was 5 mW/cm² (SAR estimated at 0.8 W/kg) at 2450 MHz and 10 mW/cm² (SAR estimated at 1.3 W/kg) at 1700 MHz. Effective exposures were accompanied by increased rectal temperatures. However, pentobarbital-injected rabbits kept at an elevated room temperature (39°C), which resulted in similarly increased rectal temperatures (+1°C), showed an insignificant reduction in sleeping time.

Recently, Thomas *et al.* (1979) reported that acute, low-level (av 1 mW/cm²) 2450-MHz (PW) radiation in the near field (SAR estimated at 0.2 W/kg) potentiated the behavioral response to chlordiazepoxide (a tranquilizer) in rats. This and other behavioral studies are discussed in Sec. 5.5.5, Behavior, Interactions with Other Stimuli.

It can be concluded from pharmacologic studies that low-level microwaves may elicit a drug-specific interaction on the nervous system. Such interactions may prove to be potentially both useful and harmful as more information becomes available.

5.4.4 Effects on Neurotransmitters

Specific neural systems that contain various neurotransmitters are known to affect the inhibitory or excitatory states of the brain. The relative firing rates of these neuronal systems are reflected in the turnover of their neurotransmitters. Since RF radiation has been reported to stimulate and depress the CNS, several scientists have investigated the effects of RF radiation on CNS neurotransmitters.

Snyder (1971) made neurochemical measurements in rats exposed to 3000-MHz (CW) radiation. He observed that a 1-h exposure at 40 mW/cm² (SAR estimated at 8 W/kg) resulted in a significant increase of 5-hydroxyindolacetic acid (5-HIAA) and 5-HT (serotonin), indicating increased turnover rates of serotonin in the brain. The opposite effect (that is, reduced levels of 5-HIAA and 5-HT, indicating reduced turnover rates of serotonin) was found in rats exposed at 10 mW/cm² (SAR estimated at 2 W/kg) 8 h/day for 7 days. The body temperature in the rats exposed at 10 mW/cm² rose by 1 to 2°C during irradiation, and the animals showed signs of moderate heat stress. Control rats were similarly handled and restrained but not irradiated. The effects of the 10-mW/cm² exposure were compared to those of conventional radiant heat loads by elevation of body temperature of rats by 1 to 2°C (by placement in an incubator maintained at 34°C by thermostatically controlled incandescent lights) for 8 h/day for 7 days. No difference was found in the turnover rate of norepinephrine or 5-HT, or steady-state levels of 5-HIAA, between conventionally heated and control animals. Snyder concluded that exposure to RF radiation produced distinctly different effects on 5-HT and 5-HIAA in rat brains from effects produced by conventional heating.

Zeman *et al.* (1973) investigated the effects of acute and chronic exposure of rats to 2860-MHz (PW, peak power of 60 kW, average power of 300 W, pulse duration of 1 μs, repetition rate of 500 Hz) radiation on brain GABA. Chronic exposures at 10 mW/cm² (SAR estimated at 2 W/kg) lasted for 8 h daily for 3 or 5 days or lasted 4 h for 5 days per week for either 4 or 8 weeks. No significant increase in body temperature was measured in randomly selected rats immediately after exposure during the chronic series. Acute exposures at 40 mW/cm² (SAR estimated at 8 W/kg) lasted 20 min, and acute exposures at 80 mW/cm² (SAR of 16 W/kg) lasted 5 min. Rectal temperature increased by no more than 3°C, and signs of general hyperthermia were observed after exposures to either of these acute conditions. There were no significant differences in whole-brain GABA levels or in L-glutamate decarboxylase (the enzyme synthesizing GABA) activity between control and irradiated animals after either chronic or acute exposures.

Merritt *et al.* (1976) reported decreased norepinephrine, dopamine, and serotonin in discrete areas of rat brains after a whole-body exposure for 10 min to 1600-MHz microwaves at 80 mW/cm² (SAR estimated at 24 W/kg) that raised rectal temperatures 4.1°C. Hyperthermal control rats were kept at 78°C for 10 min, which was sufficient to raise rectal temperatures 3.7°C. Hypothalamic norepinephrine and dopamine were significantly decreased in irradiated rats and were decreased (although less severely) in hyperthermic control rats, as compared with normotheric controls. Levels of serotonin in the hypothalamus and striatum of the brain were unchanged, but serotonin levels in the hippocampus were decreased only in irradiated rats, and serotonin levels in the cerebellum and cortex (areas usually low in serotonin) were decreased only in hyperthermic control rats. Merritt *et al.* (1976) concluded that hyperthermia was responsible for these effects on neurotransmitters.

In a separate study, Merritt *et al.* (1977) observed a significant decrease in norepinephrine and an insignificant decrease in dopamine in the hypothalamus of rats exposed for 10 min to 1600-MHz (CW) radiation at 20 mW/cm² (SAR estimated at 6.0 W/kg), but not at 10 mW/cm² (SAR of 3 W/kg). The effective exposure produced increased brain and rectal temperatures, whereas exposure at the lower

power density did not. Serotonin in the hypothalamus was unaffected by exposures up to 80 mW/cm² (SAR of 24 W/kg).

Nervous-system effects are summarized in Table 5-12. There appear to be ample data that suggest effects of high power densities of RF radiation on the nervous system of animals. It may be that most of these effects are the result of thermal effects on the tissues. The effect of RF radiation on calcium ion efflux from brain and other tissues is discussed in Sec. 5.7.5.

5.4.5 Unresolved Issues

There are several difficulties in evaluating alterations in function of the nervous system that result from exposure to RF radiation. Minute changes in the energy distribution due to focusing or scattering effects could produce changes that may be reflected in various parts of the body. Electromagnetic energy may affect the nervous system in many ways. The electrical and magnetic fields surrounding the neurons might be directly alterable by externally imposed fields. Radiation may produce changes in chemical reactions that could result in a variety of effects. In addition, small differences in size and shape among individuals could result in quite different manifestations of exposure to a given power density of RF radiation. Observations of anatomical changes must be made at a time quite removed from the exposure. Moreover, it is labor intensive to localize where small anatomical damage might occur. Neurophysiologists typically record patterns of electrical activity in either individual neurons or groups of neurons by inserting metal electrodes in the nervous system or on the body and amplifying the small signals recorded by sophisticated electronic apparatus. The use of metal in electronic equipment precludes easy measurement of neuronal functioning in the presence of electromagnetic fields. Chemical measurements made by neurochemists are only just beginning to be understood as indicators of neuronal functioning. Techniques are only now becoming available by which minute chemical changes known to occur in the nervous system as it responds to specific inputs can be measured.

Investigations of effects of RF radiation on CNS development have usually examined behavior rather than the nervous system at the cellular and subcellular levels. Thus the effects of low-level exposure to RF radiation on the morphology and physiology of the adult and developing CNS have not been adequately studied to permit definitive conclusions to be drawn. Two morphological studies have been done by Albert *et al.* (1981a,b). In the first study, he reported permanent loss of cerebellar Purkinje cells in rat pups after exposure of pregnant dams to 2450-MHz (CW, SAR of 2 W/kg) and both the dams and their offspring to 100-MHz (CW, SAR of 2.77 W/kg) radiation. These authors also reported an apparent reversibility of a decrease in cerebellar Purkinje cells following irradiation of rat pups 6 to 10

Table 5-12. Summary of Studies Concerning RF-Radiation Effects on the Nervous System*

		Exposure Conditions				
Effects	Species	Frequency (MHz)	Intensity (mW/cm²)	Duration (days x min)	SAR (W/kg)	Reference
Desynchronized EEG	Rabbit	3000 (PW)	20 (av)	1 x 20	3.0 (est)	Barański and Edelwejn (1968)
Greater effect of CNS stimulating drugs	Rabbit	3000 (PW)	7 (av)	24-26 x 180	1.0 (est)	Barański and Edelwejn (1968)
Biphasic effect of latency to a convulsive drug effect	Mice	3000 (PW)	5	8-36 x Unknown	5	Servantie *et al.* (1974)
Decrease effect of paralyzing drugs	Rats	3000 (PW)	5	10-15 x Unknown	1	Servantie *et al.* (1974)
Changes in EEG patterns of anesthetized animals	Rabbits	9300 (CW)	0.7-2.8	1 x 5	0.1-0.3 (est)	Goldstein and Sisko (1974)
Potentiation of drug response	Male rats	2450 (PW)	1.0 (av)	1 x 30	0.2 (est)	Thomas *et al.* (1979)
Decreased hypothalamic NE, DA, and hippocampal serotonin in hyperthermic animals	Rats	1600 (CW)	80	1 x 10	24 (est)	Merritt *et al.* (1976)
Decreased hypothalamic NE, DA	Rats	1600 (CW)	20, 80	1 x 10	6-24 (est)	Merritt *et al.* (1977)
No effect on neurotransmitter levels	Rats	1600 (CW)	10	1 x 10	3.0 (est)	Merritt *et al.* (1977)
No effect on GABA content	Rats	2860 (PW)	80 40 10 10	1 x 5 1 x 20 5 x 480 40 x 240	16.0 (est) 8.0 (est) 2.0 (est)	Zeman *et al.*(1973)
Swollen neurons in hypothalamus and subthalamus	Chinese hamsters	2450 (CW)	50 25	1 x 30 22 x 840	15 (est) 7.5	Albert and DeSantis (1975)
Swollen neurons in hypothalamus and subthalamus	Chinese hamsters	1700 (CW)	10	1 x 30-120	3 (est)	Albert and DeSantis (1976)

Table 5-12. (Continued)

Effects	Species	Exposure Conditions: Frequency (MHz)	Intensity (mW/cm^2)	Duration (days x min)	SAR (W/kg)	Reference
Myelin figures in dendrites 6 weeks post-exposure	Female rats	2450 (CW; multimodal cavity)	10	110 x 300	2.3	Switzer and Mitchell (1977)
Increased permeability of BBB to fluorescein	Rats	1200 (CW) 1200 (PW)	2.4 0.2 (av)	1 x 30 1 x 30	1.0 (est) 0.08 (est)	Frey *et al.* (1975)
Myelin degeneration and metabolic alterations; glial cell proliferation	Guinea pigs Rabbits	3000 (CW;PW) 3000 (CW;PW) 3000 (CW;PW)	3.5 25 5	90 x 180 1 x 180 90 x 180	0.5 (est) 3.5 0.4 (est)	Barański (1972b)
Focal areas of increased BBB permeability to peroxidase	Chinese hamsters Rats	2800 (CW) 2800 (CW)	10 10	1 x 120 1 x 120	1.9 0.9	Albert (1979b)
Increased peroxidase in brain, absent after recovery period	Chinese hamsters	2450 (CW)	10	1 x 120	2.5	Albert and Kerns (1981)
Increased peroxidase in brain	Chinese hamsters	2450 (CW)	10	1 x 120	2.5	Albert (1977)
Brain temperature elevation (40-45°C); increased permeability of BBB	Rats	2450 (CW)	80 W	1 x 10-30	—	Sutton and Carroll (1979)
Increased permeability of BBB (mannitol and inulin)	Rats	1300 (CW) 1300 (PW)	1.0 0.3 (av)	1 x 20 1 x 20	0.4 0.1	Oscar and Hawkins (1977)
Decreased latency of late components of thalamic somatosensory evoked potentials	Cat	918 (CW)	2.6	1 x 15	2.5	Johnson and Guy (1972)
Attenuation of monosynaptic spinal reflex	Cat	2450 (CW)	3.75 W	1 x 3	800	Taylor and Ashleman (1975)
EEG effects seen after chronic but not acute exposures	Rabbit	1-10 (AM) 1-10 (AM)	60-500 V_{rms}/m 90-500 V_{rms}/m	1 x 120-180 20-30 x 120-180	10^{-5} -10^{-4} 10^{-4} -10^{-3}	Takashima *et al.* (1979)
Change of predominant EEG frequencies	Cat	147 (AM)	1.0	Varying	0.015 (est)	Bawin *et al.* (1973)
Reversible neuronal morphology alterations	Rat Rat	3000 3000	10 10	35 x 30 35 x 30	2 (est) 2 (est)	Gordon (1970) Tolgskaya and Gordon (1973)
Mild pyknosis of hippocampal neurons, increased brain and rectal temperature	Rat	2450	60-90 W	1 x 2.5-7	head only	Austin and Horvath (1954)
Increased brain serotonin turnover rate	Rat	3000	40	1 x 60	8.0 (est)	Snyder (1971)
Decreased brain serotonin turnover rate	Rat	3000	10	7 x 480	2.0 (est)	Snyder (1971)
No decrease in cerebellar purkinje cells in offspring	Squirrel monkey	2450	10	368 x 180	3.4	Albert *et al.* (1981a)
Decreased cerebellar purkinje cells after perinatal exposure	Rat	2450 100	10 46	5 x 1260 110 x 240	2.0 2.7	Albert *et al.* (1981b)

*AM = amplitude modulation, NE = norepinephrine, DA = dopamine.

days postnatally at 2450 MHz. Rats killed immediately after exposure had a 24-percent decrease in these cells, whereas those killed 40 days after the exposures had only an insignificant 7-percent decrease. No histological examination was made of other portions of the brains of these rats. In the second study (Albert *et al.* 1981b), no difference was observed in the number of Purkinje cells in the uvula of the cerebellum from seven squirrel monkeys exposed for 3 h, 5 days/week, both prenatally and for 9 months postnatally to a 2450-MHz (CW) field in a multimodal cavity (SAR calculated to be 3.4 W/kg), when compared to cell counts in seven control monkeys. Therefore, the extent of abnormal development and the conditions of exposure that lead to such development are still uncertain.

Synergistic and antagonistic effects of RF radiation with chemical agents that affect the nervous system have not been investigated in a systematic fashion. In addition, existing data are quite old, and experiments utilizing the latest neurochemical measurements and techniques are lacking. Information on the effects of chronic and low-level RF-radiation exposure on neurotransmitters is lacking. Data on microwave-produced alterations in BBB permeability are controversial; the effects may be simply due to increased brain temperature or increased blood flow.

In summary, the state of the art does not permit one to assume that exposure to low-level RF radiation produces a significant effect on nervous system

morphology, the blood-brain barrier, CNS-active drugs, or neurotransmitters. Reports of long-term, low-level exposure on the developing and adult nervous system are conspicuously absent from the Western European and the U.S. literature. Higher-level, acute exposure may alter nervous system structure and function, but the effects may not be specific to the nervous system and could be the consequence of body heating.

5.5 Behavior

Michael I. Gage

Behavior has been defined as "anything an organism does" (Catania 1968), or as "the actions or reactions of persons or things under specified circumstances" (Morris 1976). Behavior may also be defined as the actions of an organism in relation to its environmental stimuli.

Behavioral effects of RF radiation have been extensively studied for several reasons. The first is the reports of experiments (not fully documented with methods and detailed data analysis) from the Soviet Union and other East European countries that behavioral effects of microwaves are seen at relatively low levels, i.e., 500 $\mu W/cm^2$ and below at 2375 MHz in rats (Dumansky and Shandala 1974; Shandala *et al.* 1977). The second is that behavior can serve as an index of how the whole organism is functioning, displaying the status of the nervous system and many other organ systems of the body as they act together. Behavior has often been defined as the final common pathway of the nervous system. Moreover, behavior can be analyzed in a nonterminal fashion, without resort to surgically or biochemically invasive preparatory techniques.

Behavior may be separated into two major categories: naturalistic and acquired. Spontaneous or naturally occurring behavior may be innate and is often species-specific in frequency of occurrence. Examples of naturally occurring behavior include locomotor activity, eating, drinking, and mating. Elements of these behaviors are often acquired.

There are two general categories of acquired or learned behavior—respondent and operant, which are distinguished by the procedures used in the acquisition or conditioning of the behavior. Respondent conditioning occurs as a consequence of the temporal contiguity between stimuli. Stimuli paired in time with another stimulus, which reflexively elicits a response, gradually elicit the response. Examples of acquired respondent behavior are salivation and hunger pangs when one is passing a restaurant or eye blinks to acoustic stimuli. Responses conditioned by respondent procedures are usually measured by their occurrence and their magnitude.

Much complex behavior of human beings and other higher animals in the course of daily activities can be viewed as emitted or operant behavior. Operant conditioning occurs as a consequence of reinforcement that follows the emission of a response. Reinforcers may be positive (such as food or water), or negative (such as termination of electric shock or intense radiant energy). All reinforcers maintain or increase the frequency of response. By definition, a positive reinforcer is a stimulus that increases or maintains the probability of emission of an operant by its presentation. A negative reinforcer is a stimulus that increases or maintains this probability by its removal after emission of the operant. Reinforcement need not follow the occurrence of each response. It may be intermittent according to a schedule (i.e., a schedule of reinforcement). Responses are said to be conditioned when they have a highly predictable probability of occurrence. This probability is often expressed by the average occurrence within a period of time, or the response rate. Examples of operant behavior include eating with a knife and fork, driving a car, or writing a review on behavioral effects of microwaves.

Operant conditioning may be used to answer specific questions about behavior that are known to be similar across species. For example, by reinforcing the responses in the presence of light of one wavelength but not reinforcing responses in the presence of light of any other wavelength, animals can learn to respond selectively in the presence of light of the first wavelength. By presenting light at wavelengths close to the one that is reinforced, one can obtain the threshold for discriminability of colors.

Specific types of behaviors investigated in behavioral research are so numerous that no attempt can be made to describe them all here. Descriptions will be given of behaviors that have been studied as a function of microwave exposures. For a more complete description of behavior as studied by ethologists and psychologists, the reader is referred to several standard books (Brown 1975; Hinde 1970; Honig and Staddon 1977; Kling and Riggs 1971; Konorski 1967; Pavlov 1960; and Skinner 1953).

Some general statements can be made regarding the effects of RF-radiation exposure on behavior:

- Some microwave effects have been reported for a variety of animal behaviors. Most of the studies have used rats as subjects; only a few have used mice, squirrel monkeys, and rhesus monkeys.
- Changes in locomotor behavior have occurred after CW exposures at an SAR as low as 1.2 W/kg in rats (D'Andrea *et al.* 1979). Changes in food and water intake or body mass have not been consistently reported at such levels.
- Decreases in rates of ongoing operant behavior have been seen during exposures at SAR = 2.5 W/kg in rats (de Lorge and Ezell 1980), and cessation of operant behavior has been seen at an SAR of 10 W/kg in rats (D'Andrea *et al.* 1976).
- Alterations in operant performance measured after exposure was terminated also occurred with SARs of 2.5 W/kg or more in rats (Gage 1979a).
- The threshold for detection of microwaves may be as low as 0.6 W/kg in rats (King *et al.* 1971).

However, it is not certain that animals avoid or attempt to escape from CW microwaves, even at very high power levels.

- Drug effects on behavior in rats have been augmented after PW-radiation exposures lasting 0.5 h at average SAR = 0.2 W/kg (Thomas *et al.* 1979). Behavioral thermoregulation has been altered after only several minutes of exposure at SAR = 1.0 W/kg in the rat (Stern *et al.* 1979) and at SAR = 1.0 W/kg in the squirrel monkey (Adair and Adams 1980b).
- Although the same behavioral effects during or after microwave exposure of the same magnitude may not be consistently predictable, enough behavioral changes have been reported after similar exposures to warrant the conclusion that behavior is disrupted by microwaves with an energy input that approximates one quarter to one half of the resting metabolic rate of many animals.
- When the persistence of behavioral changes after the termination of exposure has been investigated, the behavioral alterations reported were reversible with time after the exposure ended.

5.5.1 Naturalistic Behavior

Spontaneous locomotor behavior has been studied with both acute- and chronic-exposure regimens in the rat. Hunt *et al.* (1975) found decreased initial exploratory activity by male Wistar rats after a 30-min exposure to 2450-MHz fields in a multimodal cavity (T_a = 24°C, RH from 20 to 40 percent), with power adjusted to produce an SAR of 6.3 W/kg. The activity of exposed animals returned to control values within a 2-h period. The decrease in initial exploratory activity was the same whether the rat was placed in the apparatus immediately after or 1 h after exposure was terminated. Core body temperature was increased to 40.3°C at termination of exposure but dropped to 37.8°C, within the normal range, 1 h after exposure. Decreased swimming speed in water at 24°C was also seen in rats that were practiced swimmers after 30-min exposures to 2450-MHz fields at SARs of either 6.3 or 11 W/kg. The effects were seen only after 1.2 km of swimming following a 6.3-W/kg exposure. After an 11-W/kg exposure, effects were seen immediately for the first few meters and again after 0.6 km of swimming despite the fact that water at 24°C would reduce persistence of a microwave-related hyperthermia.

Roberti *et al.* (1975), on the other hand, did not see changes in spontaneous motor activity, as measured in a glass cage, in male Wistar rats after four different exposure conditions in the far field of an anechoic chamber (T_a = 22 ± 1°C, RH = 50 ± 5 percent). The locomoter activity measured by Roberti *et al.* may not have required as much physical effort as continuous swimming. The four exposure conditions were (1) 10,700-MHz (CW) fields at 0.6 to 0.9 mW/cm² (SAR, based on single animal exposures, can be estimated at 0.15 W/kg) for 185 continuous hours (24 h daily for 7 2/3 days); (2) 3000-MHz (CW) fields at 0.5 to 1.0 mW/cm² (SAR can be estimated at 0.3 W/kg) for 185 continuous hours; (3) 3000-MHz (PW) fields, 769 pulses/s, at 1.5 to 2.0 mW/cm² (SAR estimated at 0.6 W/kg) for 185 continuous hours; or (4) 3000-MHz (PW) fields, 769 pulses/s at 24 to 26 mW/cm² (SAR estimated at 8.3 W/kg) for 408 continuous hours (24 h daily for 17 days). After this last exposure condition, no change was also observed in running speed during forced runway running by the rats.

Locomotor activity on a small platform was increased (as compared with five controls) in five female Sprague-Dawley rats during the course of repeated exposures to 2450-MHz (CW) fields in a multimodal cavity (Mitchell *et al.* 1977). Exposures of 5-h duration occurred 5 days weekly for 22 weeks (T_a = 24 ± 1.5°C). The average SAR was determined to be 2.3 W/kg, which is similar to the SAR at power density of 10 mW/cm² in a plane-wave environment. The activity increased within the first week of exposure and remained high throughout the course of the exposure period.

Decreases in activity, measured by visual observation, were reported during repeated exposures of eight Wistar male rats to 918-MHz (CW) fields in a circular waveguide (Moe *et al.* 1976). Each exposure lasted 10 h (from 2200 to 0800) and occurred nightly during the dark and usually more active period of the circadian cycle of a rat for 3 weeks for a total of 210 h (T_a = 21.8 ± 0.13°C). The range of whole-body average SARs was measured as 3.6 to 4.2 W/kg (10 mW/cm² average power density). Most of the decreased activity occurred shortly after the microwave field was activated. The exposed rats were stretched out in a prone position more frequently than control rats in the early morning hours. In addition, exposed rats were reported to consume less food than did the controls over the course of the exposure, even though their body mass was not different from that of controls. A repeat of this experiment, where eight male Wistar rats were exposed 10 h/night for 13 weeks at an average power density of 2.5 mW/cm² (average SAR = 0.9 to 1.0 W/kg; T_a = 21.1 ± 0.15°C), resulted in no differences in food consumption or in activity measured during the eleventh week (Lovely *et al.* 1977). The two studies indicate that a dose-rate-related threshold for these effects might be somewhere between 1.0 and 3.6 W/kg. Unfortunately, in the circular waveguide, the power density is twice the average on axis and falls off rapidly toward the wall, which may lead to fluctuating and uncertain quantitative description of SAR at specific times during exposure (Guy and Chou 1976).

Effects on spontaneous behavior of rats were reported in two other chronic-exposure experiments. Both experiments used 15 exposed and 15 control male Long-Evans rats irradiated during the illuminated portion of the circadian cycle from 0900 to 1700 (8 h), 5 days/week for 16 weeks in an anechoic chamber with a central monopole antenna and ground plane (T_a = 22 ± 2°C, RH from 20 to 40 percent). The rats were adapted to the exposure and testing apparatus for 4 or 8 weeks before irradiation. In one experiment (D'Andrea *et al.* 1979), exposures were to 2450-MHz (CW) fields at a power density of 5 mW/cm² (average SAR = 1.2 W/kg); and in the other (D'Andrea *et al.* 1980), exposures were to 915-MHz (CW) fields at a power density of 5 mW/cm² (average SAR = 2.5 W/kg).

In the study at 2450 MHz, rats showed decreases in activity as measured on a stabilimetric platform throughout the course of exposure but increased running-wheel activity overnight through the course of exposure. (This latter effect was not significant.) No significant differences were seen in food and water intake and in body mass. In the study at 915 MHz, exposed rats showed increased activity as measured both in the running wheels and on the stabilimeter. Again, no significant changes in food and water intake or body mass were observed.

Rudnev *et al.* (1978) reported effects of exposure of 25 male albino rats to 2375-MHz (CW) fields at 0.5 mW/cm² (SAR estimated at 0.1 W/kg for individual animal exposure) for 7 h daily for 1 month. Open field activity was measured in irradiated rats and in 25 controls as the number of squares crossed in 3 min on 2 successive days. The count on the first day was defined as exploratory activity, and on the following day, as motor activity. Shock-induced aggression was measured by observation of battles between an exposed and control rat. Maintenance of balance on a rotating treadmill (dynamic-load endurance) and on an inclined rod (static-load endurance) was measured, as was the amount of food consumed in 20 min after 23 h of deprivation. Electrodermal skin sensitivity was measured as the voltage of 100-Hz square-wave electrical stimulus that was needed to elicit paw withdrawal from the metal bars on the cage floor. The above measurements were made at the start of the series of exposures and again prior to irradiation periods on the 10th, 20th, and 30th days of exposure, and every 15 days for 3 months after exposure.

A significant reduction in food intake, time on the treadmill, and in time on the inclined rod was seen by the 10th day of exposure. Exploratory activity was significantly decreased, and shock sensitivity was increased after 20 days of exposure. At the end of exposure, exploratory and motor activity, time on the inclined bar, and shock sensitivity were significantly decreased. The latency to start eating when food was presented was increased for 30 days after exposure ended. Time on the treadmill was reduced for 15 days after the termination exposure. Exploratory activity was increased throughout the 3-month postexposure period. Sensitivity to electric shock was reduced significantly on the 30th and 60th day after exposure ended and was still below control levels on the 90th day.

5.5.2 Learned Behavior

5.5.2.1 Respondent Conditioning

Currently, there appear to be no reports by U.S. investigators of microwave exposure altering respondent behavior, although the description of an experiment that used RF radiation as an unconditional stimulus has been published. Some studies using respondent conditioning techniques that report changes in behavior as a consequence of microwave exposure appear in the Soviet literature (e.g., Dumansky and Shandala 1974; Lobanova 1974). Unfortunately, details regarding exposure conditions or behavioral methodology and results are too sketchy to permit inclusion in this review. An attempt was made to use microwave exposure as an unconditional stimulus in one experiment (Bermant *et al.* 1979). A 30-s presentation of a 525-Hz tone that preceded 2450-MHz sinusoidally modulated microwaves that were either presented for 10 s (SAR = 420 W/kg) or 30 s (SAR = 220 W/kg), or that preceded an electric shock to the tail, produced rises in rectal temperature of 0.7, 0.5, or 0.37°C, respectively, during a base-line period over the course of 10 conditioning sessions at an unspecified T_a. Control female Sprague-Dawley rats presented with the tone alone showed a decrease of 0.47°C in rectal temperature during this period. The microwave exposure itself was designed to produce an increase in rectal temperature of 1.5°C. Aside from this study there are no reports of microwaves altering respondently conditioned behavior in which exposure parameters allow clear determination of the SAR.

5.5.2.2 Operant Conditioning

There is a large body of literature that examines alterations of operant behavior produced by microwaves for which SAR values have been, or can be, determined.

Reduction in response rates on an operantly conditioned task has been observed during the course of microwave irradiation. Rats were trained to lever-press for food pellets on a random-interval, 30-s schedule. After behavior on this task stabilized, the rats showed a response rate that was in general linearly uniform and typical of random- or variable-interval schedule-controlled performance. The rats were then exposed to microwaves under each of several conditions in sessions lasting 25 min, or until the rat's response rate fell below one third of its base-line control rate. In an initial experiment (D'Andrea *et*

al. 1976), six male Long-Evans rats were exposed to 360-, 480-, or 500-MHz (CW) fields (T_a from 21.1 to 22.2°C, RH from 12 to 40 percent) in a parallel-plate apparatus at an incident power density of 25 mW/cm² with the long axis of the rat parallel either to the electric-field vector or to the vector of wave propagation. Responding was reduced only during exposures to 500-MHz fields when the long axis of the body was parallel to the electric-field vector. Behavior stopped abruptly after ~11 min of exposure, and upon removal from the apparatus the animals appeared flaccid, wet, and, according to the authors, heat stressed. At this exposure, the SAR was comptued from the measured 0.16°C/min rise in rectal temperature to be ~ 10 W/kg. Exposures that produced no change in behavior had SARs ranging from 5 to 6 W/kg.

In a second experiment (D'Andrea *et al.* 1977), these results were confirmed and extended. Exposures were conducted in a monopole-above-ground radiation chamber and lasted for up to 55 min, or until responding on the random-interval schedule fell below one third of the base-line rate. Exposures of five male Long-Evans rats for periods up to 55 min to 400-, 500-, 600-, and 700-MHz (CW) fields at 20 mW/cm² power density (T_a = 22± 1°C; RH = 50 ±1.5 perent) yielded a U-shaped function of time to the criterion reduction in rate, with the minimum of ~23 min at 600 MHz when rectal temperature increased 0.09°C/min (SAR estimated at 16.4 W/kg). At the time they stopped responding, all rats appeared heat stressed and were engaged in spreading saliva on their fur. Six additional rats, exposed to 600-MHz (CW) fields at power densities of 5, 7.5, 10, and 20 mW/cm², showed decreased times to stop their responding at power densities above 7.5 mW/cm² when rectal temperature increased 0.04°C/min or more. At 10 mW/cm² (SAR estimated at 7.5 W/kg) the rats stopped responding after ~45 min, and rectal temperature increased 0.04°C/min. Three rats exposed to PW microwaves with 170 mW/cm² peak and 5.1 mW/cm² average power density showed no change in performance. As in the earlier experiment of D'Andrea *et al.* (1976), response reduction was abrupt and was correlated with the rectal temperature increase.

A series of experiments by de Lorge (1976, 1979) also examined alterations in operant performance during exposure to microwaves. In most of these experiments, the schedule of reinforcement was used to measure observing and detection responses in an operant task. Two levers were present in a testing chamber or in front of a primate restraint chair made of Styrofoam and sheet plastic for optimal transparency to microwaves. Responses on the right lever, called observing responses, produced either a low- or a high-frequency acoustic signal. The high-frequency signal was scheduled to occur on a variable interval of either 30 or 60 s. If the animal made a response on the left lever when the high-frequency signal occurred—a detection response, it received a food pellet as a reinforcer. Observing responses occurred at fairly linear response rates, a pattern similar to that seen on variable interval schedules of reinforcement.

In the first experiment (de Lorge 1976) five male rhesus monkeys *(Macaca mulatta)* showed no change in behavior on this schedule during 1 or 2 h of exposure to 2450 MHz in the far field of an anechoic chamber (T_a from 21 to 24°C, RH = 70 ± 15 percent) when power densities ranged to 16 mW/cm² (SAR estimated at 1.2 W/kg). The field was 100-percent amplitude modulated at 120 Hz. Three of these monkeys showed reduced rates of observing response during 1-h exposure to this field at 72 mW/cm² (SAR estimated at 5.0 W/kg) but not at 32, 42, 52, or (in two monkeys) 62 mW/cm². At 72 mW/cm², rectal temperatures rose ~ 2°C and were still increasing at the end of the hour-long session. The animals moved more in their chairs after 20 min and were observed to take short naps after ~30 min at this power density. When observing responses decreased, reaction time to respond on the left lever increased.

In the second experiment (de Lorge 1979) four male squirrel monkeys *(Saimeri sciureus)* were tested and exposed to 2450-MHz 120-Hz modulated microwaves under conditions similar to those described above at 10, 20, 30, 40, 50, 60, and 70 mW/cm² (T_a = 22.5 to 23.2°C, RH = 57 percent during 0.5-h exposures and 74 percent during 1-h exposures). No reduction in the mean rate of right lever observing responses > 1 standard deviation below the mean of the control rate was seen at any power density during the 30-min exposures. But brief pauses in responding were seen at microwave onset and offset at 50 mW/cm² and above (SAR estimated at 2.75 W/kg). At this power density rectal temperature rose > 1°C. Three of the monkeys were also given 1-h exposures. Graphic representation of data from one monkey showed observing response rate decreased more, and this decrease began earlier, in sessions at the higher power densities (de Lorge 1979, Figure 6). One of the three monkeys exhibited an increase of response rate as power density increased. After microwave exposure, all monkeys also showed decreased responding that was directly related to the power density during the exposure. These decreases were apparent for a 30-min period following exposure but gradually returned to base-line values. All monkeys showed increases in frequency of incorrect responding on the left lever for food, which was a direct function of power density. Changes in behavior consistently occurred only at power densities of 40 to 50 mW/cm² at a time when rectal temperatures had risen by > 1°C.

In a third experiment (de Lorge and Ezell 1980), eight male Long-Evans rats were exposed in an anechoic chamber (T_a varied from 23 to 26.5°C, RH from about 50 to 52 percent) to 5620-MHz (PW) fields at 662 pulses/s, and then to 1280-MHz (PW) fields at 370 pulses/s. They were tested on the behavioral task of vigilance during exposures (SARs were reported at 0.19 W/kg per mW/cm² at 5620 MHz, and 0.25 W/kg per mW/cm² at 1280 MHz). Rates of observing responses during exposures to 1280-MHz fields decreased somewhat at 10 mW/cm² (average power density) and decreased markedly after 15 to 20 min during 15 mW/cm². At 5620 MHz, rates of observing responses decreased only during exposures at 26 mW/cm² and above. Behavior decrements occurred at SAR = 2.5 W/kg at 1280 MHz but required SAR = 4.9 W/kg at 5620 MHz.

In a related experiment (Sanza and de Lorge 1977), four male Sprague-Dawley rats were trained to respond on a fixed-interval 50-s schedule for food pellets as reinforcers. With this schedule, the first response emitted 50 or more seconds after arrival of the last food pellet produced another food pellet. Exposures for 60 min to 2450-MHz, 120-Hz modulated fields at 37.5 mW/cm² in the far field of an anechoic chamber (T_a = 24 ± 0.6°C, RH = 70 ± 5 percent) produced decreases in response rates that had a fairly abrupt onset. The response decrements were seen only in two rats that had high base-line rates and not in two rats with low response rates. Exposures at 8.8 and 18.4 mW/cm² produced no decrements in performance. All rats spent more time at the wall opposite the food cup during 18.4- and 37.5-mW/cm² exposures than during sham or 8.8-mW/cm² exposures. The SAR was not given but is estimated at 3.7 W/kg at 18.4 mW/cm² and 7.5 W/kg at 37.5 mW/cm².

Responding of three male rhesus monkeys trained to a high level of proficiency on a visual tracking task was not disrupted by exposures at 10 or 20 mW/cm² to 1200-MHz (CW) fields (reported SAR estimated at 0.8 and 1.6 W/kg; T_a = 27 ± 3°C, RH = 50 ± 3 percent) during behavior sessions lasting ~ 2 h (Scholl and Allen 1979).

Some other studies have looked at changes in previously learned operant behavior at the termination of single or multiple exposure periods. Thomas *et al.* (1975) trained four male Sprague-Dawley rats to respond on a multiple schedule. One component was fixed ratio 20 (FR20): Every 20th response on the right lever was reinforced by a food pellet. The other component was a differential-reinforcement-of-low-rate of 18 s with a limited hold of 6 s (DRL 18 LH 6): Responses on the left lever separated by at least 18 s, but by no more than 24 s, were reinforced. Components alternated on an irregular basis. Only one of the schedules was in effect during a given time period. Exposures to microwaves lasted for 30 min, and behavioral testing began 5 to 10 min after exposure. Exposure parameters were as follows: 5, 7, 15, and 20 mW/cm² to 2450-MHz (CW) fields; 5, 10, 15, and 20 mW/cm² to 2860-MHz (PW) fields at 500 pulses/s and 1-μs pulse width; and 1, 5, 10, and 15 mW/cm² to 9600-MHz (PW) fields at 500 pulses/s and 1-μs pulse width. All rats were exposed to all parameters while restrained in the far field of an anechoic chamber. In general, response rates increased on the DRL schedule and decreased on the FR schedule. Increased rates on the DRL schedule were seen following exposures to 9600-MHz fields at 5 mW/cm² and above (SAR estimated at 1.5 W/kg), to 2450-MHz (CW) fields at 7.5 mW/cm² and above (SAR estimated at 2.0 W/kg), and to 2860-MHz fields at 10 mW/cm² and above (SAR estimated at 2.7 W/kg). Decreased response rates on the FR schedule were observed following exposures to all frequencies at 5 mW/cm² and above (SAR estimated at 1.5 W/kg for 9600 MHz, and 1.4 W/kg for 2450 and 2860 MHz). Increased response rates during time-out periods between components were seen following exposures to all three frequencies at 5 mW/cm². Time-out responses peaked and then dropped after exposures at higher power densities.

In a second study, Thomas *et al.* (1976) trained four male Sprague-Dawley food-deprived rats on a fixed-consecutive-number-eight (FCN 8) schedule. With this schedule, at least eight presses had to be made on the right lever before depression of the left lever would yield a food pellet reinforcer. If the rat made fewer than eight consecutive responses on the right lever before switching, the count was restarted at zero. Well-trained rats were tested after 30-min exposures in the near field at 5, 10, and 15 mW/cm² to 2450-MHz (PW) fields at 500 pulses/s, and 1-μs pulse width. Because exposures were in the near field, SAR cannot be precisely estimated but may be assumed at 0.4 W/kg for each 1 mW/cm² (Durney *et al.* 1980). The percentage of eight or more consecutive responses on the right lever (reinforced runs) decreased, and the length of these runs decreased after all exposures. Those decreases were direct functions of power density. However, the overall rate of responding and the running rate (i.e., the rate after the first response following reinforcement) hardly decreased during these postexposure sessions.

Gage (1979a) reported decreases in response rates of eight adult male Sprague-Dawley rats trained to alternate between levers either 11 or 33 times for a food-pellet reinforcer. The decrements occurred in sessions following overnight, 15-h exposures (T_a = 22°C; RH = 50 percent) to 2450-MHz (CW) fields at 10, 15, and 20 mW/cm², but not after exposures at 0.5 and 1.0 mW/cm². Only very small decrements were seen after 55-min exposures at power densities up to 30 mW/cm². (The SAR measured in rats under similar exposure conditions was 0.3 W/kg for each 1 mW/cm².)

Discrimination was tested immediately after 30 min of irradiation in 10 well-trained, young adult male Wistar rats (Hunt *et al.* 1975). Exposures produced SARs of 0.0, 6.5, and 11.0 W/kg at 2450 MHz (modulated in a quasi-sinusoidal fashion at 120 Hz in a multimodal cavity at T_a = 24°C, RH from 20 to 40 percent). All rats were exposed at both SAR values, but the sequence of exposures was varied. The task required the rats to obtain saccharin-flavored water reinforcers by pressing a bar when a light flashed, and by not pressing a bar when a sonic stimulus was presented. One of the two stimuli was presented every 5 s, and the light was presented 12.5 percent of the time. Rats exposed at both SARs had an increased number of omission errors (i.e., failures to respond to the light after exposure), but there were no increases in errors of comission (i.e., responding wrongly when the noise was presented). The failure to respond correctly was more frequent at the start of the session, as well as after exposure at the higher SAR.

Schrot *et al.* (1980) experimented with three male albino rats trained to learn a new sequence of pressing three levers for food reinforcers daily in a repeated-acquisition procedure. The rats increased their number of errors and decreased their rate of sequence completions when tested immediately after 30-min exposures to 2800-MHz (PW) fields (500 pulses/s, 2-μs pulse width) at 5 and 10 mW/cm^2 average power density (T_a = 21 ± 1.5°C). No effects were seen at lower average power densities of 0.25, 0.5, and 1 mW/cm^2. Peak powers were 0.25, 0.5, 1, 5, and 10 W/cm^2 in these exposures. The rats were exposed in a sleeve holder with the electric-field vector perpendicular to the long axis of the animal's body. The reported SARs based on temperature measurements were 0.7 and 1.7 W/kg at 5 and 10 mW/cm^2, respectively.

Operant behavior has also been examined during or following the course of chronic microwave exposures in some reports also described in Sec. 5.5.3, Naturalistic Behavior. Mitchell *et al.* (1977) measured performance on two schedules in separate groups of rats pretrained before the start of 22 weeks of 5-h exposures, 5 days/week, to 2450-MHz fields (average SAR at 2.3 W/kg) in a multimodal cavity (T_a = 24 ± 1.5°C, RH = 50 ± 10 percent). Five exposed and five control female Sprague-Dawley rats were tested for 30-min sessions on a schedule of multiple FR5 extinction for 15 s (MULT FR5 EXT 15 s). When a white lamp was on, every fifth response was reinforced by a food pellet, but during periods when the lamp was off, no responses were reinforced. Although the control rats had higher response rates during the FR component, this difference was not significant. Exposed rats had higher response rates than controls during the extinction component, and this difference was statistically significant. The ratio of response rate during the FR5 component to response rate during the EXT15 component was significantly different in exposed as compared with control rats: Exposed rats exhibited a higher ratio, indicating poorer discrimination over the course of exposure, although they had a value like that of the control rats before irradiation began. Another schedule, Sidman avoidance, was used to test escape and avoidance response. Five exposed and four control rats were trained to postpone an unsignaled 2.0-mA foot shock for 15 s (response-shock interval) by pressing a lever. During 30-min sessions, the animals received a shock every 0.5 s (shock-shock interval) until they pressed the lever. No significant effects of microwave exposures were seen with this schedule, although improvement in avoidance was seen in all rats both within and over the course of testing sessions.

Conditioned taste aversion was studied in experiments where rats were exposed chronically to 918-MHz fields in circular waveguides at 10 mW/cm^2 (Moe *et al.* 1976) and 2.5 mW/cm^2 (Lovely *et al.* 1977). Rats were given a saccharin solution to drink in place of water during the microwave exposure period. Presumably, if the saccharin were drunk in conjunction with an agent, such as microwave radiation, which made the rat sick or produced a yet unspecifiable effect, a connection would be learned between the drinking of the agent and the consequences, and the solution would be avoided in the future. The investigators measured preference after exposure by allowing a water-deprived rat to choose between drinking the saccharin solution and water for 20 min. In the experiment at 2.5 mW/cm^2 (Lovely *et al.* 1977), saccharin preference was tested only from the 9th to the 13th week of exposure. No difference between exposed and control rats was seen in amount of saccharin solution consumed either at 2.5 mW/cm^2 (average measured SAR at 1.0 W/kg) or at 10 mW/cm^2 (average measured SAR at 3.9 W/kg).

Several studies have investigated the ability of animals to detect or to take behavioral action to minimize, avoid, or escape from microwaves. In an early paper, King *et al.* (1971) showed that three irradiated and three control male albino rats could respond to 2450-MHz microwaves doubly modulated at 60 and 12 Hz as the conditioned stimulus in a measure of conditional suppression. The microwave radiation was presented in a multimodal exposure cavity (T_a = 24 ± 2°C, RH from 20 to 40 percent). In this experiment, rats were reinforced with sugar water on a random interval schedule for licking at a water tube. At various times during each 2-h session either a 525-Hz tone or the microwaves were presented for 1 min, and an unavoidable 0.5-s electrical foot-shock followed. Conditioned suppression to the tone was reliably indicated by no licks being emitted during the tone. Microwave dose rates of 0.6, 1.2, 2.4, 4.8, and 6.4 W/kg were substituted for the tone in some sessions. During irradiation at SAR = 0.6 W/kg one of three rats suppressed responding, at SAR = 1.2 W/kg

two rats suppressed, and at SAR = 2.4 W/kg all three suppressed reliably.

Johnson *et al.* (1976) trained two male Wistar-derived rats to nose poke in a restraint for food pellets on an FR5 schedule in the presence of an acoustic-pulse stimulus of 7.5 kHz, 10 pulses/s, 3-μs pulse duration for 3-min periods, which alternated with 3-min periods of no stimulation during which nose pokes were not reinforced (extinction). When microwaves at 918 MHz (10 pulses/s, 10-μs pulse durations) were presented for 30-s intervals during an extinction period, or when microwaves were substituted for the auditory stimulus during reinforced periods, response rates were observed that were similar to those seen in periods when the acoustic stimulus was present. The energy density per pulse of microwaves was 150 μJ/cm^2, and the average power density was 15 mW/cm^2. (The SAR would be near 7.5 W/kg if the rats were in the far field.)

Detection of microwaves does not imply that there are affective properties of this stimulus, i.e., that they hurt or feel good. In fact, such detection may be further evidence of the RF hearing phenomenon (Frey and Messenger 1973). Indeed, in several experiments in which PW microwaves are presented during exposure, the alteration in behavior of the exposed animal might be due to effects of acoustic stimulation by the microwave pulses. Such experiments should have as a control the presentation of pulsed auditory stimuli.

Frey *et al.* (1975) experimented with female Sprague-Dawley rats exposed to 1200-MHz (PW) fields at 1000 pulses/s (0.5-s pulse duration) at an average power density of 0.2 mW/cm^2 (SAR estimated at 0.2 W/kg) and a peak power density of 2.1 mW/cm^2. Six rats spent only 30 percent of a 30-min period of exposure in an unshielded half of a Styrofoam shuttle box during the last 2 of 4 successive daily exposures. Six other rats exposed to 1200-MHz (CW) fields at 2.4 mW/cm^2 (SAR estimated at 2.2 W/kg) spent 52 percent of the time in the unshielded half of the box on these days. Six other control rats spent 64 percent of the 30-min period in the unshielded half. Only the rats exposed to PW microwaves could be said to escape from the stimulus or exhibit a modest preference that would decrease their exposure. A similar finding was also reported by Frey and Feld (1975) to occur in male rats during exposures to a 1200-MHz (PW) field at 100 pulses/s at 0.4 or 0.9 mW/cm^2 average power densities (SAR estimated at 0.4 and 0.81 W/kg, respectively) and at 133 or 300 mW/cm^2 peak power densities (T_a = 22°C). These rats spent an average of only 29 percent of their time in the unshielded half during seven 90-min sessions, and this side preference was maintained throughout all 7 days. Sham-irradiated rats spent an average of 57 percent of their time in the unshielded half of the box.

Two groups of eight male Wistar rats spent more than half of each of nine weekly hour periods in the side of a shuttlebox when occupancy of that side kept a PW microwave field turned off (Hjeresen *et al.* 1979). The 2880-MHz field was pulsed at 100 pulses/s (3.0-μs pulse width) with a 9.5-mW/cm^2 average and 33-mW/cm^2 peak power density (SAR calculated at 2.1 W/kg). The exposure was in the far field of an anechoic chamber (T_a from 22 to 24°C, RH from 20 to 50 percent). A group of eight rats that could not extinguish the field and another group that received no microwaves showed no side preferences. Preference for occupancy of the side that extinguished the field increased across each weekly session as judged from the data in Table 1 of Hjeresen *et al.* (1979). Statistically significant preferences for the unexposed side occurred during the hour periods of weeks 2, 4, 6, and 8, during which times the original positions of the exposed and unexposed sides of the shuttlebox were reversed. Substitution of a 37.5-MHz (PW) acoustic stimulus for the microwaves in one session resulted in the rats spending most of the session in the side that kept the acoustic stimulus off. A continuously occurring broadband "pink" noise in the anechoic chamber prevented appearance of side preference in two other groups. In addition to confirming that rats avoid or escape from pulsed microwaves, this experiment suggests that pulsed microwaves may be detected as an auditory stimulus.

Monahan and Ho (1976) showed that male CF1 mice irradiated for 10 or 15 min at 2450-MHz (CW) fields in a waveguide (T_a = 24 ± 0.5°C, RH = 50 ± 1.5 percent) when forward-power levels were stabilized at 0.4, 0.8, 1.6, 2.4, 3.2, 4.0, or 4.8 W exhibited a decline in energy absorption rate at 2.4 W and above. This decline usually occurred within the first 5 min of exposure and stabilized toward the latter part of the period. Monahan and Ho interpreted the results to show that the rats changed their behavior to minimize exposure to the microwaves. However, they did not directly measure any animal behavior. During the first 5 min of exposure the SARs measured in this apparatus ranged from 7.7 to 65.7 W/kg. The lowest SAR at which the mice clearly altered their rates of energy absorption was 28 W/kg. In a second study Monahan and Ho (1977) showed that the SAR associated with reduction of absorption during 20 min of irradiation (RH = 50 ± 1.5 percent) decreased reliably from 43.6 W/kg when ambient temperature was 20°C, to 0.6 W/kg when ambient temperature was 35°C. The reduction in absorption was greater with higher forward-power levels at any given temperature. Forward powers used were 1.62 to 3.84 at 20°C, 1.12 to 3.11 at 24°C, 0.42 to 2.45 at 30°C, and 0.004 to 0.40 at 35°C. The mice did not alter their energy absorption at SARs of 28 W/kg or below until temperature was 30°C or higher.

Videotape observations of rats and mice exposed to 2450-MHz (CW) fields at 15 mW/cm² for 1 h in the far field below a radiating horn in an anechoic chamber did not reveal any preferential behavior that minimized whole-body absorption rates through parallel orientation to the magnetic- as opposed to the electric-field vector (Gage *et al.* 1979). These observations occurred at ambient temperatures of 22 or 28°C (RH = 50 percent) while the animal was held in a cuboid or cylindrical enclosure. Usually, the animals assumed a curled, sleep-like posture in the hour before the microwaves were turned on and maintained that posture throughout most of the exposure period. However,mice exposed at 28°C more often assumed positions that were oriented parallel to either of the two field vectors than positions oriented in other directions. The SAR of the rats without any enclosure was 3.3 W/kg at 15 mW/cm², independent of their orientation. The SAR of the mice when parallel to the electric-field vector was 12.3 W/kg, and the SAR when the mice were parallel to the magnetic-field vector was 6.2 W/kg, without any enclosure. The animals changed positions more frequently when some difference in SAR existed relative to the position assumed.

Rats cannot easily learn to escape from or avoid high-intensity electromagnetic radiation. Carroll *et al.* (1980) reported that 20 female Long-Evans rats did not go to a marked-off floor area in a multimodal cavity to reduce the intensity of 918-MHz microwaves (modulated at 60 Hz with 3-Hz mode stirrer modulation) from 60 W/kg to either 40, 30, 20, or 2 W/kg (T_a = 21.1 ± 2°C; RH = 53 ± 10 percent). The mean number of entries into the marked-off "safe" area and the percentage of time spent there during 22-min sessions were not different when the microwaves were on (for five 2-min periods) or off. SARs > 60 W/kg were associated with lethality within 8 min of continuous exposure in tests of a separate group of rats. However, in the same apparatus 10 rats quickly learned to escape from an 800-μA electric foot shock by going to this marked-off area within a 22-min session. Shocked rats would remain in this area over 90 percent of the session time. A later study (Levinson *et al.* 1982), extending these findings, showed that rats spent significantly more time in the marked "safe" area (which when entered extinguished radiation and light) on the fifth day of repeated light and microwave pairings when microwave radiation was accompanied with the photic stimulus than when the radiation was presented without the light. Groups of four female Long-Evans rats were exposed to a 350-lux stimulus light alone, microwave radiation alone (918 MHz modulated at 60 Hz with a 3-Hz mode stirrer modulation at 60 W/kg in the same multimodal cavity used by Carrol *et al.* [1980]), the microwave radiation in combination with the light, or faradic shock (800 μA_{rms}) to the feet and tail during alternate 2-min periods of five successive 22-min daily sessions. The average time spent in the marked area on the last day (of 1320 s maximum) was about 100 s for rats receiving light, 300 s for rats receiving microwave radiation alone, about 700 s for rats receiving radiation plus light, and about 1200 s for rats receiving shock alone. Additionally, acquisition curves indicated rats were learning to escape from both the microwave radiation presented alone and in combination with light over the course of the sessions, but escape learning occurred sooner in the rats given the multiple stimulus.

Sanza and de Lorge (1977) noted that their rats first tried to jump out of a testing chamber and then assumed a stationary position after failing to escape during exposures to 2450 MHz at 37.5 mW/cm² (SAR = 7.5 W/kg).

5.5.3 Interactions with Other Stimuli

Interactions of microwaves with two other types of stimuli have been reported to affect behavior. One type of stimulus is chemical, specifically, several commonly used psychoactive drugs; the other is physical, e.g., ambient temperature during exposure. Response rates of rats performing on a fixed-interval 1-min schedule of reinforcement beginning 0.5 h after 2.5- to 20-mg/kg dosages of chlordiazepoxide (Librium) (Thomas *et al.* 1979) were increased over control values. These increases were further augmented if an exposure at an average power density of 1 mW/cm² to a 2450-MHz (PW) field (500 pulses/s, 2-μs pulse width, 100-mW/cm² peak power density; T_a = 23 ± 2°C) occurred in the half hour between the injection and behavioral testing. In a second study (Thomas and Maitland 1979), the dose-response function of rats given d-amphetamine sulfate was shifted to a lower range after exposure to microwaves with the same parameters and conditions of exposure as those mentioned above. The shift to a lower range of the dose-response function indicated an increased potency of the drug. After microwave exposure, as opposed to sham exposure, given changes in response rate were produced by lower drug doses. Rats in this second study were reinforced for responses separated by more than 18 s (DRL 18 s). Although the rat was in the near field in these studies, and the exposure field may not have been as uniform as if it were in the far field, the average SAR measured in a Styrofoam-insulated water model was 0.2 W/kg. Thomas and Maitland (1979) also showed that 0.5-h exposure to microwaves, at the parameters indicated above, 4 days/week when amphetamine was not administered, shifted the dose-response function of this drug to a lower range when it was administered on the fifth day of the week when a microwave exposure did not occur. In both of these studies, exposure to microwaves alone or after saline injection had no effect on behavior. The shift to a lower range of a dose-response function indicated

that an exposure to microwaves, which by itself did not affect behavior, acted synergistically with chlordiazepoxide or amphetamine to increase the sensitivity of the organsm to the drug. Similar results have not been seen with chlorpromazine or with diazepam (Valium), an analog of chlordiazepoxide, in experiments in the same laboratory (Thomas *et al.* 1980).

In a related experiment, Monahan and Henton (1979) showed that chlordiazepoxide and, with less consistency, chlorpromazine and d-amphetamine altered response rates of mice trained in an operant-conditioning procedure to escape from or to avoid 2450-MHz (CW) fields at an average dose rate of 46 W/kg (T_a = 24 ± 0.5°C; RH = 50 ± 1.5 percent). Although this experiment showed that drug effects can interact to alter microwave exposure effects, the design of the experiment does not allow any conclusion to be drawn about interactions between drugs and microwaves on performance.

Interactions with ambient temperature and humidity were predicted by Mumford (1969). Monahan and Ho (1977) showed that reduction in the rate of energy absorption by mice exposed in a waveguide to 2450-MHz (CW) fields occurred at a low dose rate of 0.6 W/kg when ambient temperature was 35°C but required higher doses at lower ambient temperatures. Although the mice were not directly observed, the authors presumed the mice reoriented in the microwave field to reduce the amount of absorbed energy.

Gage (1979b) showed that overnight exposures at 5, 10, or 15 mW/cm² to 2450-MHz (CW) fields (SAR = 0.2 mW/g per mW/cm²) at an ambient temperature of 28°C (RH = 50 percent) reduced operant response rates of male Long-Evans rats measured the morning after exposure was terminated. Similar exposures when ambient temperature was 22°C did not result in reduced response rates except after exposure at the highest power density. The rats were reinforced with food on a random interval 1.33-min schedule. Response rates in control sessions that did not follow exposures ranged from about 0.25 to over 2 responses/s for the 12 rats but were consistent over sessions for each rat.

Two reports have indicated that mammals alter thermoregulatory behavior in the presence of as little as 5 mW/cm² of 2450-MHz (CW) microwaves. In one (Stern *et al.* 1979), six male rats were trained to press a lever to switch on an infrared (IR) heat lamp for 2 s in a cold chamber (T_a from 3.9 to 5.3°C). Microwaves at power densities as low as 5 mW/cm² reduced the rate of responding for the heat lamp. The reduced response rate occurring shortly after microwave onset was a direct function of power density in the range of 5 to 20 mW/cm² and returned to base-line values when microwaves were switched off. The rats were exposed in a far field (SAR = 0.2 W/kg per mW/cm²) in which the distribution of power densities varied within 11 percent of the mean value.

Adair and Adams (1980b) showed that thermoregulatory behavior of the squirrel monkey (a New World primate found in equatorial jungle areas) was significantly altered at power densities as low as 6 mW/cm² in the far zone of a 2450-MHz (CW) field within 10 min of onset of exposure. In this study, the monkeys were trained to select a preferred ambient air temperature by making an operant response to obtain 15 s of 55°C air when the air was otherwise 15°C or to obtain 15 s of 15°C air when the air was otherwise 55°C. Preferred air temperatures ranged between 35 and 36°C without microwaves and decreased as a direct function of the microwave power density during exposure. (The SAR in this experiment was determined calorimetrically on saline models to be 0.2 W/kg per 1 mW/cm².) As in the experiment by Stern *et al.* (1979) with rats, preferred temperatures returned to base-line levels when the microwave field was extinguished.

In conclusion, there is ample evidence to suggest that microwaves alter a variety of unlearned and learned behaviors occurring during and after exposures. In most cases the behavior change can be described as a reduction in the level of ongoing activity. However, there are some situations in which increased activity has been seen. When measured, the magnitude of behavioral change seems to be related to the power density or SAR of the exposure. Behavioral changes usually revert to base-line levels after removal of the microwave field. The above studies of behavioral effects caused by microwave exposure are summarized in Table 5-13.

5.5.4 Unresolved Issues

Most unresolved issues regarding behavioral effects of microwaves arise because observed findings have not been verified within the same laboratory or in other laboratories. Repeating a study involves high cost and the risk of failure to confirm a finding due to small unnoticed differences, e.g., between standard procedures in two laboratories. Possibly for these reasons verification has not been often attempted. However, verification and systematic replication would allow determination of the limits of conditions within which a behavioral effect may be expected, as well as definition of the range of conditions adequate to observe a threshold of effect.

There is no unifying hypothesis to explain all the observed behavioral changes. The research on interaction between microwaves and chemicals has not been verified in independent laboratories, and it has not been extended to determine whether the interaction is limited to particular classes of compounds. Delineation of differences between effects of single and multiple exposures would help

Table 5-13. Summary of Studies Concerning RF-Radiation Effects on Behavior

Effects	Species (Weight, g)	Exposure Conditions: Frequency (MHz)	Intensity (mW/cm^2)	Duration (days x min)	SAR* (W/kg)	Reference
Decreased exploratory activity an swimming speed, ΔT increase 2.5°C	Young male rat	2450 (PW, multimodal cavity 120 Hz, AM)	?	1 x 30	6.3	Hunt *et al.* (1975)
No effect on spontaneous activity or activity and forced running	Male rat (160-180)	10700 (CW) 3000 (CW) 3000 (PW) 3000 (PW)	0.6-0.9 0.5-1.0 1.5-2.0 24-26 (av)	7.7 x 1440 7.7 x 1440 7.7 x 1440 17 x 1440	0.2 0.3 0.6 8.3	Roberti *et al.* (1975)
Increased locomotor activity	Female rat (307)	2450 (CW, multi-modal cavity)	10	110 x 300	2.3	Mitchell *et al.* (1977)
Decreased spontaneous activity and food intake	Male rat (360-410)	918 (CW)	10	21 x 600	3.6	Moe *et al.* (1976)
No effect on spontaneous activity or food intake	Male rat (316-388)	918 (CW)	2.5	91 x 600	1.0	Lovely *et al.* (1977)
Decreased activity on stabilimetric platform, no significant increase in wheel running	Male rat (350-375)	2450 (CW)	5	80 x 480	1.2	D'Andrea *et al.* (1979)
Increased activity on stabilimetric platform and in wheel running	Male rat (350-375)	915 (CW)	5	80 x 480	2.5	D'Andrea *et al.* (1980)
Decreased time on treadmill and inclined rod, decreased exploratory activity, increased then decreased shock sensitivity. Decreased activity and shock sensitivity persisted 90 days after exposure	Male rat	2375 (CW)	0.5	30 x 420	0.1	Rudnev *et al.* (1978)
Rectal temperature rise = 0.37°C before start of test, ΔT = 1.5°C with microwaves	Female rat	2450 (PW, multi-modal cavity, 60 and 12 Hz AM)		10 x 0.17 10 x 0.5	420 220	Bermant *et al.* (1979)
Response decreased during exposure on random interval schedule (lowest intensity for effect, ΔT = 1.8°C)	Male rat (350-380)	500 (CW)	25	1 x 11	10	D'Andrea *et al.* (1976)
Response decreased during exposure (maximum effect) on random interval schedule, ΔT = 1.8°C	Male rat (357-382)	600 (CW)	10	1 x 55	7.5	D'Andrea *et al.* (1977)
Decreased observing responses on vigilance task, ΔT = 2°C	Male rhesus monkey (4 kg)	2450 (120 Hz, AM)	72	1 x 60	5.0	de Lorge (1976)
No effect on observing responses			16	1 x 20	1.1	de Lorge (1976)
Decreased observing responses on vigilance task	Male squirrel monkeys (850-950)	2450 (120 H_z, AM)	50	1 x 30 1 x 60	2.8	de Lorge (1979)
No effect on observing responses				1 x 60	0.6-1.7	de Lorge (1979)
Decreased observing responses on vigilance task	Male rat (362-400)	1280 (PW) 5620 (PW)	10 26	1 x 40 1 x 40	2.5 4.9	de Lorge and Ezell (1980)
Response rate decreased on fixed interval schedule in rats with high base-line rates, spending time away from lever	Male rat (290-340)	2450 (120 Hz, AM)	37.5	1 x 60	7.5	Sanza and de Lorge (1977)
No effect on response rate			8.8-18.4	1 x 60	1.8-3.7	Sanza and de Lorge (1977)
No effect on visual tracking task	Male rhesus monkey (6.2-7.9 kg)	1200 (CW)	20	1 x 120	1.6	Scholl and Allen (1979)
Response rate decreased on FR and increased on DRL schedules	Male rat (120 days, 150?)	2450 (CW) 2860 (PW) 9600 (PW)	5 5 5	1 x 30 1 x 30 1 x 30	1.4 1.4 1.5	Thomas *et al.* (1975)
Decreased length of runs and fewer reinforcers on FCN schedule	Male rat (250-300)	2450 (PW)	5	1 x 30	?	Thomas *et al.* (1976)
Decreased response rate on FR operant schedule	Male rat (284-439)	2450 (CW)	10	1 x 900	2.7	Gage (1979a)
Increased rate of missed observing responses on vigilance task	Young male rat	2450 (PW, AM, multimodal cavity)		1 x 30	6.5	Hunt *et al.* (1975)
Decreased rate of responding on repeated acquisition task	Male rat (275)	2800 (PW)	5	1 x 30	0.7	Schrot *et al.* (1980)
Increased response rates in extinction, decreased stimulus control, no effect on Sidman avoidance	Female rat	2450 (CW, multimodal cavity)	10	110 x 300	2.3	Mitchell *et al.* (1977)

Table 5-13. (Continued)

Effects	Species (Weight, g)	Exposure Conditions: Frequency (MHz)	Intensity (mW/cm^2)	Duration (days x min)	SAR* (W/kg)	Reference
No effect on flavor aversion test	Male rat (360-410)	918 (CW)	10	21 x 600	3.9	Moe *et al.* (1976)
No effect on flavor aversion test	Male rat (316-388)	918 (CW)	2.5	91 x 600	1.0	Lovely *et al.* (1977)
Microwaves detected as stimulus	Male rat (409-427)	2450 (PW, 120 Hz, AM, multimodal cavity)		1 x 1	0.6-2.4	King *et al.* (1971)
Microwaves detected as stimulus	Male rat (300-350)	918 (PW)	15	1 x 0.5	7.5	Johnson *et al.* (1976)
Spending more time in shielded vs. unshielded compartment	Female rat	1200 (PW)	0.2	4 x 30	0.2	Frey *et al.* (1975)
Spending equal time in shielded vs. unshielded compartment	Female rat	1200 (CW)	2.4	4 x 30	2.2	Frey *et al.* (1975)
Spending more time in shielded vs. unshielded compartment (occurrred in first of 7 sessions)	Male rat (250)	1200 (PW)	0.4	1 x 90	0.4	Frey and Feld (1975)
Spending more time in unirradiated compartment	Male rat	2880 (PW)	9.5	9 x 60	2.1	Hjeresen *et al.* (1979)
Decrease in SAR at 24°C	Male mouse (30-34)	2450 (CW)		1 x 15	28	Monahan and Ho (1976)
Decrease in SAR when ambient temperature increased from 20°C to 35°C	Male mouse (30-34)	2450 (CW)		1 x 20	43.6-0.6	Monahan and Ho (1977)
No preferential orientation of rats or mice in far field of plane wave	Male rat (200-360)	2450 (CW)	15	1 x 60	3.3	Gage *et al.* (1979)
	Male mouse (25-33)	2450 (CW)	15	1 x 60	6.2-12.3 (depending on orientation)	
Cannot take specific action to reduce intensity of irradiation	Female rat (290)	918 (PW, 60 Hz, AM, multimodal cavity)		5 x 2	60	Carroll *et al.* (1980)
Augmentation of increased response rates produced by chlordiazepoxide	Male rat (325-375)	2450 (PW)	1	1 x 30	0.2	Thomas *et al.* (1979)
Shift to lower doses of d-amphetamine on dose-response curve for DRL schedule	Male rat (250-300)	2450 (PW)	1 1	1 x 30 4 x 30	0.2 0.2	Thomas and Maitland (1979)
No effect on dose response curve for chlorpromazine or diazepam	Male rat (360-380)	3800 (PW)	1	1 x 30	0.2	Thomas *et al.* (1980)
Chlordiazepoxide reduced responses, decreased avoidance responses, and increased escape responses to microwaves	Male mouse (35-44)	2450 (CW)		1 x 30	46	Monahan and Henton (1979)
Response rate decreases were augmented after exposures at higher ambient temperatures	Male rat (315-365)	2450 (CW)	10	1 x 930	2.0	Gage (1979b)
Reduced responding for heat lamp in a cold room	Male rat (325-450)	2450 (CW)	5	1 x 15	1.0	Stern *et al.* (1979)
Selection of a lower ambient air temperature	Squirrel monkey (750-1100)	2450 (CW)	6	1 x 10	1.0	Adair and Adams (1980b)

*If measured SAR was not reported, SAR was estimated when possible.

determine whether effects of chronic exposure are qualitatively different from repeated measurement of effects of each single exposure.

Behavioral experiments have used only a limited sample of microwave exposure conditions. Exploration of frequency spectrum, modulations, waveforms, and interactions between waves of different parameters has hardly begun. Most behavioral work has used rats as subjects. Animals more like humans in physical size and shape have been studied only infrequently to help extrapolate findings to humans. Specific conditions of exposure in addition to the microwave stimulus, such as ambient temperature and humidity, have not been consistently controlled and reported so that their influence on behavior may be determined. There is no information on exposure effects of specific or limited areas of the body in comparison to total-body exposure to evaluate the effects of localized energy absorption.

5.6 Special Senses

Joe A. Elder

5.6.1 Cataractogenic Effects

A cataract is an opacity in the crystalline lens of the eye. These lens defects may be clinically insignificant or may cause partial or total blindness. The following conclusions may be drawn from animal experiments on the cataractogenic potential of RF radiation (Tables 5-14 and 5-15):

1. RF radiation is cataractogenic if exposure is of sufficient intensity and duration.
2. For single acute exposures, the threshold intensity for cataract production exceeds 100 mW/cm^2. Multiple exposures at intensities near threshold values for single acute exposures results in lens opacities.
3. The cataractogenic potential of RF radiation varies with frequency; the most effective frequencies appear to be microwave frequencies in the 1- to 10-GHz range.
4. Similar ocular effects are produced by CW and PW radiation of the same average intensity.
5. In contrast with the above conclusions, which are based on acute, near-field exposures to the eye or head, no cataracts have been reported in unrestrained animals after far-field exposure at power densities near lethal values or in rabbits exposed at 10 mW/cm^2 (2450 MHz) for 180 days. Although the RF power density for cataract induction for long-term exposure of animals (including humans) has not been defined, the threshold is, most probably, significantly higher than that required to induce many other physiological changes.

The review of the literature on human cataracts is in Sec. 5.10, Human Studies.

5.6.1.1 Microwave Radiation in Experimental Cataractogenesis

The rabbit eye has been the experimental model most often used in animal studies because of its similarity in size and anatomy to the human eye (Figure 5-3). Its diameter is ~ 75 percent that of the human eye; the cornea is as large, and although the lens is thicker, its diameter is the same as that of the human eye. In a typical study (Carpenter *et al.* 1960b), one eye of an anesthetized rabbit was exposed to microwave radiation in the near field, and the nonirradiated eye served as the control. The eyes were then examined at various intervals by an ophthalmoscope, slit-lamp biomicroscope, or both instruments. The earliest positive reaction in this type of study, occurring within 24 to 48 h after a cataractogenic exposure, is the appearance of one or two narrow translucent or milky bands in the posterior cortex of the lens, just under the capsule, which extends no further than the lens equator. These bands can be seen only by slit-lamp examination with an angled beam. If the ocular injury is minimal, no further change occurs, and the cortical banding disappears within a few days. Otherwise, in 2 to 4 days after exposure small granules appear in the region of the suture of the posterior lens. If a more intense reaction occurs, larger numbers of granules appear over a larger area within the next few days, and small vesicles may develop. These early changes may develop further and become either well-defined circumscribed or diffuse cataracts. These changes in the lens remain as permanent ocular defects. In general, it has been found that microwave cataracts in rabbits involve only the posterior cortex of the lens, unless the exposure is so intense that the opacity extends throughout the lens.

At exposure levels that cause cataracts, other ocular reactions also occur, but they are transient and differ in severity with the intensity and duration of the exposure. Examples include swelling and chemosis of bulbar and palpebral conjunctivae, pupillary constriction, hyperemia of iris and limbal vessels, and vitreous floaters and filaments (Carpenter 1979).

5.6.1.2 Exposure Threshold Values for Cataracts

Following the publication of reports demonstrating that microwaves can cause cataracts in experimental animals (Richardson *et al.* 1948; Daily *et al.* 1950a,b), three laboratories (Williams *et al.* 1955; Carpenter *et al.* 1960b; Carpenter and Van Ummersen 1968; and Guy *et al.* 1975a) published time vs. power-density threshold curves for cataract induction in rabbits by a single exposure to near-field 2.45-GHz radiation. The time vs. power-density threshold curves originally published by the three laboratories are similar in shape but are quantitatively different. The more recent studies found lower threshold values than those reported by Williams *et al.* (1955). This finding probably reflects differences in the irradiation method and in techniques used to measure power density. In fact, Carpenter (1979) has determined that his power densities were 50 percent higher than originally published. His corrected data are plotted in Figure 5-4 along with the results of Williams *et al.* (1955) for comparison. Guy *et al.* (1975a) replicated Carpenter's work for single acute exposures with essentially the same results, and also quantified the threshold of cataractogenesis in terms of SAR (Figure 5-4). For example, these workers found the cataractogenic threshold for a 100-min exposure, the longest period of irradiation, to be 150 mW/cm^2 (138 W/kg peak absorption) (Figure 5-5).

The cumulative effect of microwave radiation on cataractogenesis in the rabbit has been examined by repeated irradiation of the eye at power densities below the threshold for single acute exposures (Carpenter 1979). For example, daily 1-h exposures at

Table 5-14. Summary of Studies Concerning Ocular Effects of Near-Field Exposures

Effects	Species	Exposure Conditions: Frequency (MHz)	Intensity (mW/cm^2)	Duration (days x min)	SAR (W/kg)	Reference
Cataract	Rabbit	5,500 (CW and PW)	470-785*	1 x 2-100	300-500†	Birenbaum *et al.* (1969a)
Cataract	Rabbit	800 (CW)	785*	1 x 25	500†	Birenbaum *et al.* (1969b)
		4,200 (PW)	785*	1 x 17	500†	
		4,600 (PW)	785*	1 x 15	500†	
		5,200 (PW)	500-785*	1 x 5-12	350-500†	
		5,400 (CW and PW)	500-785*	1 x 3-4	300-500†	
		5,500 (CW and PW)	500-785*	1 x 2-3	300-500†	
		6,300 (PW)	785*	1 x 5	500†	
Cataract and other ocular effects	Rabbit	2,450 (CW)	180*	1 x 240		Carpenter (1979)
			120-180	20 x 60		
No cataract	Rabbit	2,450 (CW)	75	20 x 60		Carpenter (1979)
Cataract	rabbit	2,450 (CW)	150	1 x 100	138††	Guy *et al.* (1975a)
Cataract	Rabbit	2,450 (CW)	295	1 x 30		Hagan and Carpenter (1976)
		10,000 (CW)	375	1 x 30		
Cataract and other ocular effects	Rabbit	2,450 (CW)	180	1 x 140	100††	Kramar *et al.* (1978)
Second- to third-degree nasal burns; no ocular effects	Rhesus Monkey	2,450 (CW)	300	1 x 22	115††	Kramar *et al.* (1978)
No cataract; keratitis (inflammation of cornea)	Rabbit	35,000	40	1 x 60	>175#	Rosenthal *et al.* (1976)
		107,000	40	1 x 60	> 238#	

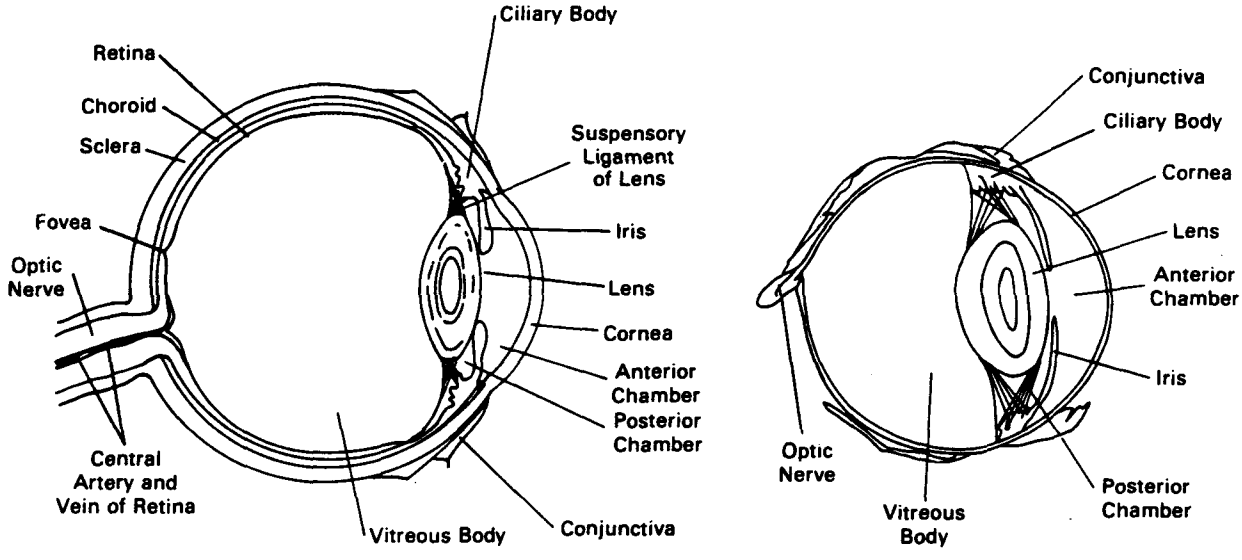
*Estimate of average power density calculated by dividing the microwave power by the irradiated area (d = 1.27 cm) of the eye.
†Estimate based on the assumption that all the incident power was absorbed by the eye (2 g).
††Maximum SAR in the eye.
#Estimated SAR values for the cornea. (See text for discussion of Rosenthal *et al.* studies of frequency specificity.)

Table 5-15. Summary of Studies Concerning Ocular Effects of Far-Field Exposures

Effects	Species	Exposure Conditions: Frequency (MHz)	Intensity (mW/cm^2)	Duration (days x min)	SAR (W/kg)	Reference
No ocular effects, including no lenticular changes	Rabbit	3000 (CW)	100, 200	1 x 15, 30	14, 28*	Appleton *et al.* (1975)
Acute ocular changes, e.g., hyperemia of lids and conjunctiva, meiosis, anterior chamber flare, engorgement of iris vessels, and periorbital cutaneous burns; no lenticular changes			300, 400, 500	1 x 15	42, 56* 70*	
Death			300	1 x 30	42*	
			500	1 x 15	70*	
No catarats	Rabbit	385 (CW)	60	10 x 15	48*	Cogan *et al.* (1958)
		385 (CW)	30	10 x 90	24*	
		468 (CW)	60†	10 x 20	8.1	
No cataracts	Rabbit	2450 (CW)	10	5 x 480 (x 8-17 weeks)	1.5*	Ferri and Hagan (1976)
No ocular effects	Rabbit	2450 (CW)	10	180 x 1380	17#	Guy *et al.* (1980b)
No ocular effects	Monkey *(M. mulatta)*	9310 (PW)	150 (av)	30-40 x 294-665††		McAfee *et al.* (1979)

*Estimated average whole-body SAR values (Durney *et al.* 1978, Figure 31).
†Waveguide average whole-body exposure.
††Total exposure time in minutes for the entire 30- to 40-day experimental period.
#Maximal SAR in head.

Figure 5-3. Cross-sectional sketch of the human (left) and the rabbit (right) eye (from Birenbaum *et al.* 1969a, Figure 1).



180 mW/cm² for 13 to 20 days were found to be cataractogenic in 8 of 10 animals, whereas single exposures at this power density were not effective. At 150 mW/cm², 4 of 10 rabbits gave a positive response after 18 to 32 daily exposures. No cataracts were observed after 20 daily 1-h exposures at 75 mW/cm².

The power densities used in the cumulative-effect experiments were only slightly lower than those that cause cataracts after a single exposure (Figure 5-4). For example, the lowest effective power density (120 mW/cm²) given for 1 h daily for 20 to 24 days produced only one positive response in nine animals (See Table I in Carpenter 1979). But that would be a "thermalizing" level if extended to the whole body. If the entire body of an unanesthesized rabbit is exposed at power densities similar to those that cause cataracts under near-field conditions, the animal exhibits signs of acute stress; Appleton *et al.* (1975) reported that rabbits became heat stressed and struggled out of the field during a 15-min exposure at 100 mW/cm². This report is described in more detail in Sec. 5.6.1.4, along with other experiments in which no evidence of cataracts was observed in animals exposed in the far field. In one of these studies, Guy *et al.* (1980b) found no change in the eyes of rabbits exposed at 10 mW/cm² (2450 MHz) for 23 h/day for 180 days. Although a cumulative effect on the lens of rabbits has been described by Carpenter and his colleagues at high exposure levels, the report by Guy *et al.* (1980b) provides evidence against such an effect at power densities ≤10 mW/cm².

5.6.1.3 Frequency Specificity

As indicated above, most studies of experimental cataractogenesis were conducted at 2.45 GHz, but opacities in rabbit eyes have been reported after near-field exposures at 0.8, 4.2, 4.6, 5.2, 5.4, 5.5, 6.3, and 10 GHz (Birenbaum *et al.* 1969a,b; Hagan and Carpenter 1976). In several studies, the cataractogenic potential of different frequencies was addressed. For example, after Hagan and Carpenter (1976) determined the relative effects of 2.45- and 10-GHz (CW) radiation on the rabbit eye, they concluded that the cataractogenic potential for single acute exposures is greater at the lower frequency. At both frequencies, the opacities were characteristically located in the posterior subcapsular cortex of the lens, although the initial appearance and subsequent development differed. These differences probably reflect differences in the pattern of absorbed microwave energy in the eye due to the different depths of penetration of the radiation at these two frequencies.

Guy *et al.* (1974, 1975a) measured the distribution of absorbed energy in rabbit eyes exposed to 918- and 2450-MHz radiation and found the patterns to be significantly different. At 2450 MHz, energy absorption was maximal in the vitreous body at a point midway between the posterior surface of the lens and the retinal surface (Figure 5-5). The locus of peak absorption thus correlates well with the observation of irreversible changes in the posterior cortical lens. Exposure to 918-MHz fields in a specially devised cavity resulted in relatively uniform absorption in the eye, but maximal absorption was only ~25 percent of the peak absorption at 2450 MHz (Figure 5-6). Therefore, one would expect the threshold for cataractogenesis in rabbits exposed to 918 MHz to be considerably higher than the threshold at 2450 MHz. But more important, at 918 MHz, peak absorption in the rabbit brain was 36 percent higher than in the eye. It is possible that lens effects or ocular

Figure 5-4. Time and power-density threshold for cataractogenesis in rabbits exposed to near-field 2450-MHz radiation; values of maximal SAR are also given (from Guy *et al.* 1975a, Figure 7).

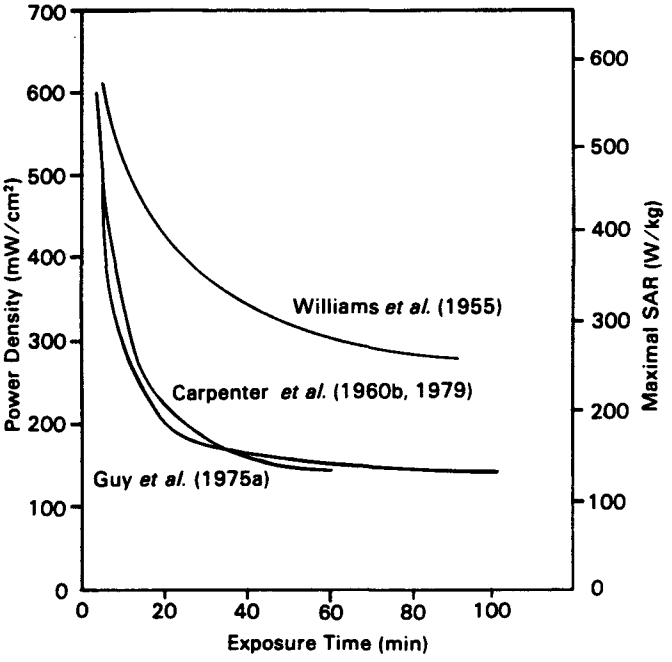
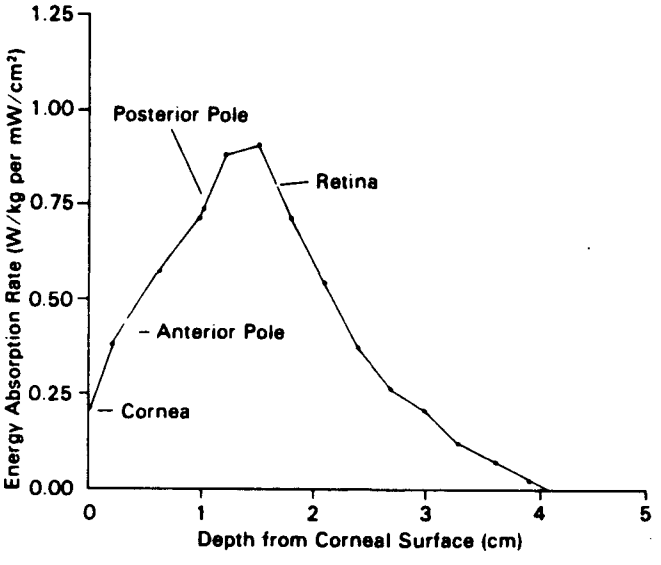


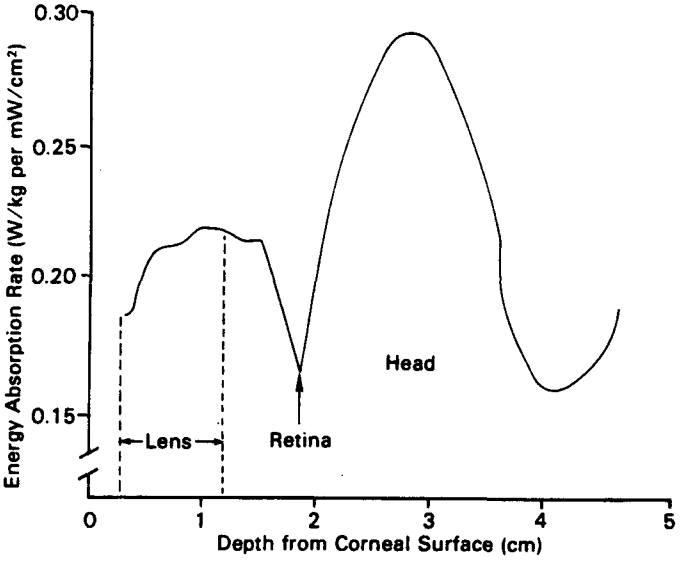
Figure 5-5. Distribution of energy absorption rate (W/kg) per mW/cm² incident power density in the rabbit's eye and head exposed to 2450-MHz radiation (from Guy *et al.* 1974, Figure 3).



changes may not occur before more severe damage occurs in other sensitive tissues, such as the brain, during exposure to 918-MHz fields.

Both Hagan and Carpenter (1976) and Guy *et al.* (1975a) used exposure systems that applied microwave energy across an air space to the eye, and both reported lenticular cataracts in the posterior

Figure 5-6. Distribution of energy absorption rate (W/kg) per mW/cm² incident power density in rabbit's head and eye exposed to 918-MHz radiation (from Guy *et al.* 1974, Figure 27).



subcapsular cortex. Birenbaum *et al.* (1969b) produced cataracts in the anterior cortex of rabbit lens with an exposure system that applied PW microwaves to the corneal surface. Furthermore, as the frequency decreased from 6.3 to 5.2 to 4.6 to 4.2 GHz, longer exposure times at a constant field strength were required to produce lens defects. Under similar experimental conditions, even longer exposure times were required to induce cataracts at a lower frequency, i.e., 0.8-GHz (CW) radiation. Furthermore, Birenbaum *et al.* (1969a) found no substantial difference in the cataractogenic threshold values for CW and PW 5.5-GHz radiation and concluded that the average, not the peak, rate of energy absorption determines whether lens injury will occur. The peak power density of the pulses was 1000 times greater than the estimated average power densities shown in Table 5-14.

Rosenthal *et al.* (1976) examined the effects of 35- and 107-GHz radiation on the rabbit eye. At both frequencies keratitis (inflammation of the cornea) occurred at lower intensities than required to produce any other demonstrable ocular effect, such as lens injury (cataract) or iritis. Irradiation at 107 GHz was more effective in producing immediate corneal damage, but this change was generally gone by the next day. Effects at 35 GHz were persistent, were almost always present the next day, and were associated with marked injury to the corneal epithelium. Effects on the cornea correlate well with the pattern of microwave-energy absorption because most of the energy at these high frequencies is absorbed in the outer regions of the eye. The earliest stage of keratitis or minimal corneal stromal injury occurred after a 30-min exposure at an incident

power of 50 mW or after a 60-min exposure at 25 mW. Estimates of the rate of energy absorption in the eye at the lower incident power (25 mW) are 35 mW at 35 GHz and 47.5 mW at 107 GHz (Rosenthal *et al.* 1976); therefore, the average SARs of a rabbit eye weighing 2 g are 17.5 and 23.8 W/kg, respectively. Since maximal absorption occurs in the outer structures of the eye, the SAR in the cornea is estimated to exceed the average SAR of the eye by more than one order of magnitude.

Although the above data cannot be compared directly because of widely varying experimental procedures, these results indicate that the potential for cataract induction in rabbits is higher in the frequency range between 1 and 10 GHz than at either lower or higher microwave frequencies. Power densities that would cause cataracts at frequencies below 1 GHz and above 10 GHz give rise to insult in other ocular sites and extra-ocular tissues. Rosenthal *et al.* (1976) found that 35- and 107-GHz radiation primarily affected the outer structure of the eye, the cornea for example; and at 918 MHz, Guy *et al.* (1974) showed that maximal energy absorption occurred in the brain, not in the eye.

The effects of near-field microwave exposures on the rabbit eye have been summarized by Cleary (1980) as follows:

> The induction of cataracts in experimental animals, principally New Zealand white rabbits, has been described by a number of investigators using a variety of microwave exposure modalities. Generally microwave field intensities necessary for cataract induction in the rabbit are such that acute whole body exposures would be lethal due to hyperthermia. Most cataract studies have, therefore, employed focused or near-zone fields which limit exposures to the head or eyes. Localized thermal trauma is still of such a magnitude to necessitate the use of general or local anesthesia. Corneal irrigation with physiological saline solutions have also been used to prevent corneal damage due to tissue dehydration during microwave exposure. Anesthesia and corneal irrigation, as well as air temperature and humidity, may significantly affect the temperature of ocular structures.

The experimental results strongly suggest that radiation-induced temperature elevation may be essential for the cataractogenic effect of microwaves. Additional evidence for this position has been provided by Kramar *et al.* (1975), who reported that rabbits kept under general hypothermia during irradiation at known cataractogenic levels of 2.45-GHz (near-field) radiation did not develop cataracts. This study is described more fully in Sec. 5.6.2.

Kramar *et al.* (1978) did a comparative study of the cataractogenic threshold and SAR patterns in the eyes of rabbits and rhesus monkeys exposed in the near field at 2450 MHz. In this experiment, the radiator was designed to simulate a leaky microwave oven door. In rabbits, a time and power-density threshold curve for cataractogenesis was found that was similar to earlier results (see Figure 5-4), and the peak SAR occurred within the lens. These authors reported that the microwave exposure caused immediate effects similar to those described by Carpenter *et al.* (1960b), i.e., constricted pupil, dilated conjunctival and iris vessels, a turbid anterior chamber, and a milky band in the posterior cortex of the lens.

The monkey eye was irradiated at 400 mW/cm^2 for 30 or 60 min or at 500 mW/cm^2 for 60 min with the applicator centered over one eye. Following these exposures at time and power density values that exceeded those required to produce cataracts in rabbits, no lens opacities were observed in three monkeys for a period of 13 months. At the highest exposure, lid edema, contracted pupil, and changes in the anterior chamber were noted. It is interesting that the SAR pattern in the monkey eye revealed that the peak SAR occurred in the anterior chamber and not in the lens. Additional evidence for a marked difference in the pattern of energy absorption in the monkey was the observation that the exposures caused varying degrees of nasal burns in the three animals. A fourth monkey was exposed to an applicator centered between the eyes. An exposure of 300 mW/cm^2 for 22 min caused second- to third-degree burns on the nasal bridge, but the eyes were not affected.

These results show that exposure conditions that cause cataracts in rabbits do not induce cataracts in monkeys. Monkey eyes are better shielded by facial bones and tissues than rabbit eyes. Because of the different anatomical features, the peak SAR, i.e., peak temperature increase, was not observed at the posterior surface of the lens. For example, the peak retrolental temperature following an exposure of 300 mW/cm^2 was only 40.2°C in the monkey but 45.1°C in the rabbit. Kramar *et al.* (1978) stated that an additional factor that helps explain the differential effects on the eyes of rabbits and monkeys might be the relative as well as the absolute size of the lens. The anterio-posterior diameter of the adult rabbit lens is ~ 7 mm, which represents almost one-third of the eye's diameter. In the rhesus monkey and man, the eye is larger but the lens is about 4 mm thick (Figure 5-3). The smaller lens is probably more effectively cooled by the larger pool of surrounding fluid. Since the facial features and eye structure of human beings are more like those of the monkey than those of the rabbit, extrapolation of the results with monkeys is more useful. Based on studies at 2450 MHz, one may conclude that under conditions of acute exposure, the threshold for cataracts in monkeys, and presumably in human beings, is greater than the threshold for rabbits. The reader should note that the report by

Kramar *et al.* (1978) vividly describes a number of other clearly undesirable effects, e.g., facial burns, that occur at subthreshold conditions for cataracts in monkeys.

5.6.1.4 Far-field Exposure Studies

In contrast with the acute, near-field exposures that can cause cataracts and other ocular effects, cataracts have not been produced in rabbits whose entire bodies were exposed to radiation in the far field (Table 5-15). Appleton *et al.* (1975) exposd anesthetized rabbits to far-field radiation at 3000 MHz for 15 or 30 min at 100 or 200 mW/cm^2. No ocular changes were observed during or immediately after exposure. Fourteen daily examinations and four weekly examinations, followed by monthly examinations for 1 year, revealed no lenticular changes. During exposure at higher levels (300, 400, or 500 mW/cm^2 for 15 min) animals exhibited acute ocular changes consisting of hyperemia of lids and conjunctiva, meiosis, anterior chamber flare, engorgement of iris vessels, and periorbital cutaneous burns. Subsequent examinations revealed no morphologic lenticular abnormalities. The authors concluded that "It is noteworthy that one year after a single microwave exposure, sufficient in intensity to cause both thermal cutaneous and acute gross ocular effects, no lens changes or cataracts were observed." It is also noteworthly that these power levels and durations were well above the cutaneous sensation level, because unanesthetized animals became heat stressed and struggled out of the field during a 15-min exposure at 100 mW/cm^2. Exposures at 300 mW/cm^2 for 30 min or 500 mW/cm^2 for 15 min were lethal to some of the rabbits.

Ferri and Hagan (1976) exposed unanesthetized rabbits to 2450-MHz (CW) radiation in the far field at 10 mW/cm^2, 8 h/day, 5 days/week for 8 to 17 weeks. Weekly examinations of the eye showed no abnormal changes during the study, and no post-irradiation changes were observed during the following 3 months. Guy *et al.* (1980b) exposed four rabbits individually (2450 MHz, 10 mW/cm^2) for 23 h/day for 180 days; the peak SAR in the head was 17 W/kg. An equal number of animals were sham-exposed. The authors stated that "Aside from normal aging changes found in the lenses of the 8 animals, no differences were noted in the eyes of the two groups."

Cogan *et al.* (1958) found no cataracts in rabbits 4 weeks after exposure at 385 MHz; the rabbits were irradiated twice weekly for 5 weeks at 60 mW/cm^2 for 15 min or 30 mW/cm^2 for 90 min. Six weeks after exposure in a waveguide, no cataracts were observed in rabbits irradiated at 468 MHz, 60 mW/cm^2 (SAR = 8.1 W/kg), for 10 days (20 min daily). Although the authors reported that the exposure levels at both frequencies were near lethal values, the 8.1-W/kg SAR is considerably lower than the value other investigators have found to be sublethal to rabbits (Table 5-15). The environmental conditions (temperature, airflow, etc.) within the waveguide were not given; therefore, one must assume that the ambient conditions were significantly different from normal values or that the measured SAR is in error.

McAfee *et al.* (1979) trained unfettered monkeys *(Macaca mulatta)* to expose their faces and eyes to 9.31-GHz (PW) radiation at 150 mW/cm^2 average power density (peak power density $\simeq$ 300 W/cm^2). Over a period of about three months, the animals were irradiated for a total of 294 to 665 min during 30 to 40 daily sessions. No cataracts or corneal lesions were observed in these monkeys during a 1-year period following irradiation.

5.6.2 Unresolved Issues

Exposure of the rabbit eye to microwave radiation at sufficient power densities and durations causes an immediate increase in intra-ocular temperature, and after a latent period of a few days, opacities develop in the posterior subcapsular cortex of the lens (Kramar *et al.* 1975). This sequence of events has led to the assumption that microwave-induced lens opacities are thermally caused. Several experiments have been designed to test directly the cause-and-effect relationship between temperature increase and cataract formation. Kramar *et al.* (1975) exposed rabbit eyes to cataractogenic levels of microwave radiation while the animal's body was submerged in cold water. By this means, microwave-induced intra-ocular temperature was limited to $< 41°C$, and no lens opacities developed. In a later experiment, Kramar *et al.* (1976) used heated water to produce ocular and rectal temperatures characteristic of those in rabbits exposed to a cataractogenic level of microwaves. Although the vicinity of the lens was heated to temperatures above those known to be associated with microwave cataracts, no lens opacities were observed; however, the rate of ocular temperature rise was about one-tenth the rate of increase with microwaves. Kramar *et al.* (1976) concluded that a combination of a sharp temperature gradient and rapid rise in temperature following irradiation may be more traumatic to the lens than a critical temperature *per se*.

Carpenter *et al.* (1977) reported no cataracts of the posterior cortex of the lens in rabbits after 6 weeks of treatment in which "the eye was heated at the same rate, to the same extent, and for an equal period of time as it would experience during a cataractogenic microwave exposure, the difference being that the equal heating was provided by other means, namely, direct application of heat to the surface of the eye." In addition, elevating retrolental and rectal temperatures to values characteristic of a cataractogenic microwave exposure, through a combination of restricted body heat loss and irradiation of one eye to power densities

slightly below the cataractogenic threshold, produced cataracts in only 3 of 10 rabbits. According to their hypothesis, if cataracts were solely of thermal origin, all animals given the two treatments should have developed cataracts. Carpenter *et al.* (1977), therefore, concluded that the increase in intra-ocular temperature occurring during microwave irradiation is not the sole causative factor in microwave cataractogenesis.

The reason for the apparent disagreement between the conclusions of Carpenter *et al.* (1977) and Kramar *et al.* (1976) probably rests with the difficulty of duplicating by nonmicrowave heating techniques the temporal and spatial temperature profiles induced by microwave irradiation of the eye. Note that the temperature at a single site in the eye was the basis for evidence of duplicating microwave heating of the eye at the same rate and to the same extent. Furthermore, even though retrolental and rectal temperatures characteristic of cataractogenic microwave exposures were produced, the overall effects on the rabbits were more traumatic than a near-field microwave exposure to one eye. Within 24 h after heated water was applied directly to the eye, almost all the eyes exhibited hemorrhage into the anterior cavity, so that observation of the lens became impossible. Only 21 of 32 rabbits survived the heat treatment. Of these, five developed lenticular cataracts of the anterior cortex, and only three developed cataracts of the posterior cortex of the lens that are characteristic of microwave-induced opacities (Carpenter *et al.* 1977).

As mentioned above, the difficulty of duplicating by nonmicrowave techniques the time-temperature profile of microwave energy absorption in the eye is probably responsible for the unsuccessful attempts to prove that an elevation of temperature is responsible for microwave cataracts (cf. Kramar *et al.* 1976; Carpenter *et al.* 1977). On the other hand, strong evidence for thermalization being the causative factor in microwave cataracts is provided by the experiment of Kramar *et al.* (1975), which showed that cataracts were not produced in hypothermic rabbits receiving a cataractogenic microwave exposure. At present, it is generally understood that intense localized exposure of the eye for substantial durations (i.e., 150 mW/cm^2 for 100 min) is necessary to induce cataracts in laboratory animals, and that such acute exposures cause death by hyperthermia if the entire animal is irradiated.

5.6.3 Auditory Effects

When the human head is exposed to PW RF radiation, an audible sound described as a click, buzz, chirp, or a knocking sensation is perceived by some individuals; the sound appears to originate from within or behind the head. This auditory phenomenon is called "RF sound" or "RF hearing." Our present knowledge of RF hearing is summarized below.

1. The RF sound occurs only upon exposure to PW sources; it appears to originate from within or near the back of the head regardless of orientation of the head in the RF field, and the sound varies with pulse width and pulse repetition rate.
2. RF hearing has been reported at frequencies of 216 to 7500 MHz. The effect has been found to occur at average power densities as low as 0.001 mW/cm^2 with peak power densities in the range of 100 to 300 mW/cm^2. Effective pulse widths vary from 1 to 1000 μs; however, it is the energy in the first 30 μs or so of the pulse that determines the threshold and loudness levels regardless of pulse widths greater than about 30 μs (Table 5-16).
3. The ability to perceive RF pulses has been shown to be related to bone-conduction hearing and to the ability to hear high-frequency acoustic waves above 5 to 8 kHz.
4. The available data support the conclusion that the RF auditory effect is evoked by a mechanism similar to that for conventional acoustic stimuli and that the primary site of interaction is peripheral to the cochlea.
5. The most generally accepted mechanism responsible for the RF auditory sensation is thermoelastic expansion. That is, the absorption of the energy in a brief RF pulse causes a small temperature rise ($\sim 10^{-6}$°C) in a short time ($\sim 10\mu$s), which results in thermoelastic expansion of matter within the head, which then launches a pressure wave that is detected by the hair cells in the cochlea via bone conduction. After stimulation of the auditory nerve in the high-frequency region of the cochlea, transmission of the PW-induced response to the auditory center of the brain follows the same auditory pathways as do all acoustically induced responses.

5.6.3.1 Human Perception of Pulsed RF Radiation

In their recent review article on the RF hearing phenomenon, Chou *et al.* (1982) wrote:

> The earliest report we have found on the auditory perception of pulsed microwaves appeared in 1956 as an advertisement of the Airborne Instruments Laboratory in Vol. 44 of the *Proceedings of the IRE.* The advertisement described observations made in 1947 on the hearing of sounds that occurred at the repetition rate of a radar while the listener stood close to a horn antenna. When the observers first told their coworkers in the Laboratory of their hearing experiences, they encountered skepticism and rather pointed questions about their mental health.

Frey (1961) was the first to study systematically the human auditory response to pulse-modulated

radiation. The subjects, who were more than 30 m from an enclosed antenna, reported hearing a transient buzzing sound upon exposure to the intermittent rotating beam. The apparent location of the sound, which was described as a short distance behind the head, was the same no matter how the people were oriented in the RF field. When an RF shield (aluminum flyscreen) was placed between the subject and the RF source, the subject did not perceive RF sounds (Frey 1973). When earplugs were used, a reduction in the ambient noise level and an increase in the RF sound level were reported. The sensitive area for detecting RF sounds was later described as a region over the temporal lobe of the brain, because the placement of a small piece of metal screen (5 x 5 cm) over this area completely stopped the RF sound (Frey 1962).

Guy *et al.* (1975b) described the effect of PW radiation on two of the coinvestigators. Three pulses, 100 ms apart, were presented each second to keep the average power density below 1 mW/cm^2. Each individual pulse was heard as a distinct and separate click, and short pulse trains were heard as chirps with the tone pitch corresponding to the pulse repetition rate (PRR). The RF sound appeared to originate from within or near the back of the head. This report also included the note that transmitted digital codes could be accurately interpreted by the subject when the pulse generator was keyed manually. Guy *et al.* (1975b) also reported that the threshold for RF hearing was lower when earplugs were used.

In a study by Constant (1967), the RF sound was described as being in the area of the ear on the side opposite to the one that was irradiated. All three of his subjects readily detected 2-μs pulses, whereas 0.5-μs pulses were not perceived. All three experienced a buzzing sensation at PRRs greater than 100/s, whereas individual pulses were heard when subjects were exposed to PRRs below 100/s.

Five of eight human subjects reported hearing distinct clicks either inside the head or behind the head when exposed to 15-μs pulses (Cain and Rissmann 1978). The remaining three people heard faint clicks when the pulse width was increased to 20 μs.

5.6.3.2 Effective Radiation Parameters

In the initial report by Frey (1961), human subjects perceived PW radiation at frequencies of 1310 and 2982 MHz. Although the peak of power-density thresholds for RF hearing was 266 mW/cm^2 for 1310-MHz and 5000 mW/cm^2 for 2982-MHz fields, the average power density thresholds were 0.4 mW/cm^2 and 2 mW/cm^2, respectively. When earplugs were used to attenuate the ambient noise level of 70 to 80 dB, the subjects reported an increase in the RF sound levels.

In the following year, Frey (1962) reported that humans could perceive PW radiation at 425 MHz with an average power density threshold of 1 mW/cm^2; the peak of power density was 263 mW/cm^2. A frequency of 8900 MHz was not effective even at an average power density of 25 mW/cm^2; the peak of power density was 25,000 mW/cm^2. At 216 MHz, the lowest effective frequency reported in the literature, the average power density threshold was 4 mW/cm^2; the peak of power density was 670 mW/cm^2 (Frey 1963).

Table 5-16. Summary of Studies Concerning Auditory Effects of RF-Radiation in Humans

			Exposure Conditions							
Effect	Comment	Number of Subjects	Frequency (MHz)	Pulse Repetition Rates (s^{-1})	Pulse Width (μs)	Peak Intensity (mW/cm^2)	Average Intensity (mW/cm^2)	Energy/ Pulse (μJ/cm^2)	Noise Level (dB)	References
RF hearing "distinct" clicks"	Threshold values	8	3,000	0.5	5 10 15	2500 225-2,000 300-1,000	0.006 0.001-0.01 0.002-0.007	12.5 2.3-20.0 4.5-15.0	45 (+ plastic foam earmuffs)	Cain and Rissmann (1978)
RF hearing: buzz heard at PRR > 100; individual pulses heard at PRR < 100		3	3,000 6,500	<100-1,000 <100-1,000	1-2 1-2	2,500-50,000 2,500-50,000	5 5	40		Constant (1967)
No auditory response			9,500		0.5					
RF hearing "buzzing sound"		4	1,245 1,245	50 50	10 70	370 90	0.19 0.32			Frey and Messenger (1973)
RF hearing "buzz, clicking, hiss, or knocking"	Threshold values	Not given	216 425 425 425 425	— 27 27 27 27	— 125 250 500 1,000	670 263 271 229 254	4.0 1.0 1.9 3.2 7.1		70-90 (+ ear stoppies)	Frey (1962, 1963)
No auditory response			8,900	400	2.5	25,000	25		70-90 (+ ear stoppies)	Frey (1962)
RF hearing "buzzing sound"	Threshold values	8 7	1,310 2,982	244 400	6 1	267 5,000	0.4 2		70-80 (+ earplugs)	Frey (1961)
RF hearing "clicks, chirps"	Threshold values	1	2,450	3	1-32	1,250-40,000	0.1	40*	45	Guy *et al.* (1975b)
RF hearing	Polytonal sound	18	800	1,000-1,200	10-30	>500	—	—	40 (+ ear stoppies)	Tyazhelov *et al.* (1979b)

*Calculated peak-absorbed-energy density per pulse is 16 mJ/kg.

In the study by Constant (1967), three human observers were exposed to PW radiation at 3, 6.5, and 9.5 GHz at an average power density of 5 mW/cm^2 (pulse width was 0.5 to 2.0 μs; PRR was up to 1000/s). Only two of the three observers perceived 3- and 6.5-GHz radiation; none experienced a response to the highest frequency. Cain and Rissmann (1978) reported that all eight of their subjects heard RF pulses at 3 GHz. In this study, plastic foam earmuffs were worn to attenuate the ambient noise, which was 45 dB. The average threshold energy density per pulse was 10.6 μJ/cm^2 (range of values was 3.4 to 17.5 μJ/cm^2). Expression of the peak power threshold (225 mW/cm^2) for the most sensitive individual in units of average incident power density yields 0.001 mW/cm^2, the lowest threshold value for human beings found in the literature. For a given peak power, average power density depends on the pulse repetition rate; the low threshold average power density was a result of a pulse repetition rate of only 0.5/s (Table 5-16).

The range of microwave pulse widths varied from 1 to 32 μs in the study by Guy *et al.* (1975b) on one human subject. The results indicate that regardless of the peak power of the pulse or the pulse width, the threshold for RF hearing of 2450-MHz radiation was related to an energy density of 40 μJ/cm^2 per pulse, or energy absorption per pulse of 16 μJ/g, as caulculated with the aid of a spherical model. The background noise of the exposure chamber was 45 dB. When earplugs were used, the threshold level decreased to 28 μJ/cm^2. The threshold for a second subject, who had a hearing deficit, was approximately 135 μJ/cm^2. Guy *et al.* (1975b) stated that two pulses which occurred within several hundred microseconds of each other were perceived as a single pulse with energy equal to the sum of the two pulses.

The human studies cited above indicate that the highest effective frequency of RF hearing is between 6.5 and 8.9 GHz and that the lowest effective frequency is 216 MHz. Also, the results describe other radiation parameters (peak power density, energy density per pulse, and pulse width) that are important in determining the threshold for RF hearing in humans. Again, the RF hearing phenomenon depends on the energy in a single pulse and not on average power density.

5.6.3.3 Dependence of RF Hearing on Acoustic Hearing

Standard audiograms measure hearing thresholds for air conduction at acoustic frequencies of 250 to 8000 Hz and for bone conduction to 4000 Hz. Cain and Rissmann (1978) measured the hearing ability of eight subjects over the frequency range of 1 to 20 kHz in addition to determining their standard audiograms. They found that, although there was no apparent correlation between the ability to perceive pulsed microwaves at 3000 MHz and hearing ability as measured by standard audiograms, there was a strong correlation between microwave-hearing threshold and hearing thresholds to air-conducted acoustic signals above 8 kHz. For example, three of the subjects who had normal hearing below 4 kHz could not hear microwave pulses of less than 20-μs duration under conditions in which the other subjects could perceive RF sounds. All three had a hearing deficit at frequencies above 8 kHz.

Frey (1961) compared human acoustical hearing and RF hearing and reported that a necessary condition for perceiving the RF sound was the ability to hear audiofrequencies above approximately 5 kHz, although not necessarily by air conduction. This conclusion was based on one subject who had normal air-conduction hearing below 5 kHz but failed to hear the microwave pulses. The person was subsequently found to have a substantial loss in bone-conduction hearing. On the other hand, a subject with good bone-conduction hearing but with poor air-conduction hearing perceived the RF sound at approximately the same power density that induced threshold perception in subjects with normal hearing. The studies by Cain and Rissmann (1978) and by Frey (1961) show RF hearing to depend on high-frequency hearing above 8 kHz and bone-conduction hearing at lower acoustic frequencies. It is interesting that the 1956 report from Airborne Instruments Laboratory stated that two persons with hearing loss above 5 kHz did not perceive RF sounds as well as did observers with normal hearing up to 15 kHz.

5.6.3.4 Similarity of Auditory Response to Microwave and Conventional Acoustic Stimuli

Taylor and Ashleman (1974) measured the electrical response in three successive levels of the cat auditory nervous system (eighth cranial nerve, medial geniculate nucleus, and primary auditory cortex) to both acoustic and pulsed-microwave (2450-MHz) stimuli. They concluded that the microwave-induced auditory effect on the animal is exerted similarly to that of conventional acoustic stimuli. Furthermore, these authors reported that inactivation (perforation of the round window and aspiration of perilymph) of the cochlea, the known first stage of transduction for acoustic stimuli, affected the central nervous system (CNS) response to acoustic and microwave energy in the same way; i.e., the evoked electrical activities of all three sites were abolished by cochlear destrution. These results indicated that the locus of the initial interaction of pulse-modulated microwave energy with the auditory system might reside peripheral to the cochlea.

In an experiment in which the thresholds of evoked electrical responses from the medial-geniculate body in cats were determined as a function of background noise, Guy *et al.* (1975b) found that as the noise level (50- to 15,000-Hz bandwidth) increased from 60 to 80 dB, there was only a negligible increase in the

threshold for the 2450-MHz microwave stimuli, a moderate increase in the threshold for a piezoelectric bone-conduction source, and a large increase in the threshold for loudspeaker-produced stimuli. The finding that the evoked response to microwave stimuli did not increase in relation to background noise, which included acoustic frequencies to 15,000 Hz, indicates that microwaves may interact with the high-frequency portion of the auditory system.

Guy *et al.* (1975b) also demonstrated that potentials evoked by microwave stimuli could be recorded at CNS sites other than those that correspond to the auditory nervous system. This finding indicates that elicited potentials recorded from any CNS location could be misinterpreted as indicating a direct microwave interaction with the particular system in which the recording is made.

Prior to 1970, Frey (1962) had suggested that RF hearing might be a result of direct cortical or neural stimulation. He based this suggestion on (1) his observations that the perception of RF pulses was instantaneous and occurred at low average-incident-power densities and on (2) the failure to record cochlear microphonics at power densities much higher than those required to elicit auditory nerve responses. Cochlear microphonics are electrical potentials that mimic the sonic waveforms of acoustic stimuli; they are the signature of mechanical distortion of cochlear hair cells, the first stage of sound transduction. The failure to observe microwave-induced cochlear microphonics had led to the suggestion that pulsed microwaves, unlike conventional acoustic stimuli, may not act on any sensor prior to acting directly on the inner-ear apparatus (Frey 1967).

In 1975, Chou *et al.* reported their success in overcoming the technical problems that had prevented investigators from recording cochlear microphonics from microwave-irradiated animals. The cochlear microphonics of guinea pigs exposed to 918-MHz (PW) radiation were found to be similar to those evoked by acoustic stimuli.

The results of the above studies of evoked electrical potentials in the auditory system, including the demonstration of pulsed-microwave-evoked cochlear microphonics, strongly indicate that the microwave-induced auditory sensation is detected similarly to conventional sound detection and that the site of conversion from microwave to acoustic energy resides peripheral to the cochlea. However, it is not known what structure(s) in the head transduce(s) the microwave energy to acoustic energy.

5.6.3.5 Mechanism of RF Hearing

As mentioned above, Frey (1967) had suggested that RF hearing might be a result of direct cortical or neural stimulation because of the failure to record cochlear microphonics and because the perception of RF pulses was instantaneous and occurred at low average-incident-power densities. The latter points were evidence against a radiation-pressure/bone-conduction hypothesis. (See also Guy *et al.* 1975b.) Sommer and von Gierke (1964) had suggested that radiation pressure exerted by the RF pulse impinging on the surface of the head could launch an acoustic signal of sufficient amplitude to be detected by the inner ear via bone conduction. Other types of pressure much greater than radiation pressure can be produced in tissue exposed to RF pulses. They include thermal-expansion forces, which are proportional to the square of the electric field in the material. For example, Gournay (1966) has shown that pressures greatly exceeding radiation pressure result when visible light from a laser is converted to acoustic energy by thermal expansion due to absorbed energy in various liquids.

Foster and Finch (1974) extended Gournay's analysis to a physiological solution exposed to microwave pulses similar to those that produce RF hearing in humans. They showed both theoretically and experimentally that radiation-induced pressure changes would result from the absorption of RF pulses and could produce significant acoustic energy in the solution. In fact, audible sounds were produced by rapid thermal expansion, resulting from only a 5×10^{-6}°C temperature rise in the physiological solution, because of the absorption of the energy in the RF pulse.

The following experimental results led Foster and Finch (1974) to propose thermoelastic expansion as the mechanism for RF hearing.

(1) Acoustic transients were recorded with a hydrophone immersed in a 0.15 N KCl solution exposed to 2450-MHz pulses that would elicit RF sounds in a human subject. In addition, they reported the measurement of acoustic transients in blood, muscle, and brain exposed *in vitro* to microwave pulses.

(2) The radiation-induced pressure wave generated in distilled water inverted in phase when the water was cooled below 4°C, and the response vanished at 4°C, in agreement with the temperature dependence of the thermoelastic properties of water.

(3) The thermoelastic theory predicts that the maximal pressure in the medium is proportional to the total energy of the pulse for short pulses and is proportional to the peak power for long pulses. Foster and Finch found the relationship between pulse width and the microwave-generated acoustic transient in the KCl solution to be consistent with the theory.

Based on these findings, they concluded that the RF sounds involve perception, via bone conduction, of

the thermally generated sound transients caused by the absorption of microwave pulses. The pulses must be moderately intense (typically 500 to 5000 mW/cm^2 at the surface of the head). However, they can be sufficiently brief ($\leq$ 50 μs) such that the maximum increase in tissue temperature after each pulse is very small ($<10^{-5}$°C).

A year earlier, Frey and Messenger (1973) published the results of a study of RF hearing in four human subjects. The data in this report are in agreement with the mechanism proposed by Foster and Finch (1974). That is, the loudness of the RF hearing sensation in the human subjects depended upon the incident-peak-power density for pulse widths $<$ 30 μs; for shorter pulses, their data show that loudness is a function of the total energy per pulse.

More recently, Chou and Guy (1979) reported that the threshold for RF hearing in guinea pigs, as measured by auditory brainstem-evoked electrical responses, is related to the incident energy per pulse for pulse widths $>$ 30 μs and is related to the peak power for longer pulses. The threshold dependence on pulse width is in agreement with the predictions of the thermoelastic mechanism as stated above.

The results on threshold and loudness may be summarized as follows. The energy in the first 30 μs or so of the pulse determines the threshold and loudness levels regardless of pulse widths greater than about 30 μs. For wider pulses ($>$ 90 μs), loudness is related to peak power rather than energy because the energy associated with the first 30 μs of the pulse increases directly with peak power. Thus, if sufficient energy is deposited within a 30-μs period, an RF sound will result without regard to pulse width. And, for pulses $>$ 30 μs, loudness increases with an increase in peak power. Thus, the auditory response undergoes a gradual transition from an energy-related effect at pulse widths $<$ 30 μs to an effect dependent on peak power at pulse widths $>$ 90 μs (Frey and Messenger 1973; Chou and Guy 1979).

The hypothesis of Foster and Finch (1974) predicts also that the RF hearing effect is related to thermoelastically induced mechanical vibrations in the head. Vibrations of this type can be produced by other means, such as by a laser pulse or by a pulsed piezoelectric crystal in contact with the skull (Chou *et al.* 1976). Frey and Coren (1979) used a holographic technique to test whether the skull and the tissues of the head of an animal have the predicted vibrations when exposed to a pulsed RF field. No displacements were recorded, but subsequent to this report, Chou *et al.* (1980a) demonstrated that the sensitivity of the holographic technique used by Frey and Coren (1979) was 3 to 4 orders of magnitude too low to detect displacements related to vibrations from microwave-induced thermoelastic expansion in biological tissues.

Tyazhelov *et al.* (1979b) conducted a series of psychophysical experiments with 18 subjects to evaluate the adequacy of the thermoelastic hypothesis and to study the perceptual qualities of RF-induced sounds. Audiofrequency signals were presented alternately to or concurrently with microwave pulses (see Table 5-16) under conditions in which the subject could adjust the amplitude, frequency, and phase of the audio signal. The authors concluded that the thermoelastic hypothesis adequately explained some of their findings for microwave pulses of high peak power and short width ($<$ 50 μs), but other results were interpreted as inconsistent with a thermoelastic mechanism for RF hearing. For example, pulse widths greater than 50 μs, which increased the mean power level, produced increases in loudness that rose more rapidly than predicted by the thermoacoustic model. In addition, suppression of RF sounds by the audio signal was reported to be inconsistent with the model.

Lebovitz and Seaman (1977) compared the response to pulsed microwaves (915 MHz) with the response to acoustic clicks by monitoring single auditory neurons in the cat. A response of these neurons to pulsed microwaves was predicted by earlier studies that demonstrated subjective auditory perception (Frey 1962), auditory evoked potentials (Taylor and Ashleman 1974), and cochlear microphonics (Chou *et al.* 1975). Furthermore, the thermoelastic model predicts that a mechanical wave of pressure stimulates the inner ear via bone conduction. Thus, the response of the neurons in the auditory pathway to pulsed microwaves should be similar to their response to transient mechanical stimuli such as acoustic clicks. The results indicated that mechanical factors within the cochlea are similarly involved in determining both the acoustic and the pulsed microwave response (Lebovitz and Seaman 1977).

Other data in this report (Lebovitz and Seaman 1977) appeared to be inconsistent with the thermoelastic model that predicts a high-frequency component such as the microwave-induced cochlear microphonic recorded by Chou *et al.* (1975). That is, Lebovitz and Seaman (1977) observed a decrease in sensitivity of high-frequency auditory units to microwave pulses. However, they used long pulses of 250 to 300 μs in duration to obtain maximal energy per pulse. More recently, Tyazhelov *et al.* (1979b) reported that long pulses ($\sim$ 100 μs) result in a lower pitch of the RF sound in humans. Two of their observers who had a high-frequency auditory limit of 10 kHz could not hear short RF pulses but could hear long pulses. Thus, the results of single unit recordings in cats are consistent with human perception of RF pulses when the pulse widths are long.

Lin (1977) developed a theoretical model that estimates the characteristics of acoustic signals induced in laboratory animals and humans by

microwave pulses; his model is based on thermal expansion in spherical heads irradiated by pulsed microwave energy. The frequency of the induced sound was found to be a function of head size and of acoustic properties for brain tissues; hence, the acoustic pitch perceived by a given subject is the same regardless of the RF frequency. The calculations of Lin show that the fundamental frequency predicted by the model varies inversely with the radius of the head; i.e., the larger the radius, the lower the frequency of the perceived RF sound. He estimated the fundamental frequency of vibration in guinea pigs, cats, and adult humans to be 45, 38, and 13 kHz, respectively. The frequency for an infant head was estimated to be about 18 kHz. These calculations provide further evidence that a necessary condition for auditory perception by adult humans is the ability to hear sound above 5 to 8 kHz (Frey 1961; Rissmann and Cain 1975).

The results of Lin (1977) appear to be in good agreement with the measurements of Chou *et al.* (1975), who found cochlear microphonics in guinea pigs to be 50 kHz. In a later report, Chou *et al.* (1977) found the frequency of the cochlear microphonic in guinea pigs and cats to correlate well with the longest dimension of the brain cavity. Extrapolation of these results indicates that the frequency of the microwave-induced cochlear microphonic in human beings should be between 7 and 10 kHz. Chou *et al.* (1977) concluded also that the frequency of the cochlear microphonic was independent of microwave frequency (915 or 2450 MHz) and exposure method (horn applicator or cylindrical waveguide).

In summary, evidence from many studies—the measurement of acoustic transients in water, KCl solution, and tissues (Foster and Finch 1974) and in muscle-simulating materials (Olsen and Hammer 1980); the relationship of pulse duration and threshold (Foster and Finch 1974; Frey and Messenger 1973; Chou and Guy 1979); the characteristics of the field-induced cochear microphonics in laboratory animals (Chou *et al.* 1975, 1977) and the theoretical calculations (Lin 1978)—indicates that thermoelastic expansion is the mechanism that explains most of the characteristics of the RF hearing phenomenon.

5.6.4 Unresolved Issues

Several investigators have tried to determine the thresholds for the RF-induced auditory sensation in human beings and in laboratory animals (Table 5-17). Human studies and animal experiments, in general, are few and have used small sample sizes, different frequencies, and different experimental procedures. However, the radiation parameters that are most important in determining the threshold for the auditory response in humans (discussed in Sec. 5.6.3.2, Effective Radiation Parameters) and in laboratory animals (discussed below) are being characterized.

The threshold for an auditory response in cats exposed to 918- and 2450-MHz (PW) radiation was studied by recording of electric potentials from the medial geniculate body (Guy *et al.* 1975b). As the pulse width increased from 0.5 to 32 μs, the threshold value for the peak of power density decreased proportionately for pulse widths below 10 μs. The thresholds of average power density and energy density per pulse also increased with pulse width, but these parameters did not show the strong proportional relationship with pulse width as did the peak of power density. Guy *et al.* (1975b) concluded that the threshold for the evoked auditory response was related to the incident energy density per pulse, at least for pulse widths less than 10 μs. In the cat, the threshold energy density per pulse was found to be about one-half of that which had produced a sensation in one human subject.

In a similar experiment conducted at frequencies between 8670 and 9160 MHz, Guy *et al.* (1975b) found that the threshold values of power density and of energy density per pulse, which include the auditory response of cats, were an order of magnitude higher than those required at 918 and 2450 MHz (Table 5-17). Furthermore, no auditory response was obtained at 8670 to 9160 MHz until the brain was exposed by enlarging the hole in the skull that served as the electrode access port.

Cain and Rissmann (1978) determined the threshold for auditory responses in animals exposed to 3000-MHz (PW) radiation. Although their results are in general agreement with Guy *et al.* (1975b) in that the threshold energy density per pulse was relatively constant for pulse widths of 5, 10, and 15 μs, their results are confounded by the use of scalp electrodes and only few animals of three species (two cats, two chinchillas, and a dog).

In the following year, Chou and Guy (1979) determined the threshold for RF hearing in guinea pigs by measuring auditory brainstem-evoked electrical responses with carbon-loaded Teflon electrodes attached to the skin of the head. In this experiment, the head of the guinea pig was inserted into a 918-MHz circular waveguide exposure system. The threshold dependence on pulse width was found to be in agreement with the predictions of the thermoelastic expansion mechanism; that is, the threshold was related to the incident energy per pulse for short pulse widths (< 30 μs) and was related to the peak power for longer pulses. At the shortest pulse width (10 μs), the threshold absorbed energy density of RF hearing in the guinea pig was about 6 μJ/g.

Wilson *et al.* (1980) described an autoradiographic technique in which [^{14}C]2-deoxy-D-glucose was used

Table 5-17. Summary of Studies Concerning Threshold Values for Auditory-Evoked Potentials in Laboratory Animals

Effect	Species (n)	Frequency (MHz)	Exposure Conditions: Pulse Repetition Rate (s^{-1})	Pulse Width (μs)	Pulse Intensity (mW/cm^2)	Average Intensity (mW/cm^2)	Incident Energy Density Per Pulse ($\mu J/cm^2$)	Peak Absorbed Energy Density Per Pulse ($\mu J/g$)	References
Response obtained with scalp electrodes	Cat (2)	3000	0.5	5 10 15	2,200, 2,800 1,300 580		11, 14 13 8 7		Cain and Rissmann (1978)
Response obtained from round window with carbon lead	Guinea pig (5)	918	100	1-10	*	*		20	Chou *et al.* (1975)
Response obtained with carbon-loaded Teflon electrodes	Guinea pig (not given)	918	30	10-500	62-156	0.05-1.4	1.56-46.8	6-180	Chou and Guy (1979)
Response obtained from medial geniculate with glass electrode	Cat (2)	918 2450 8,670-9,160	1 1 1	3-32 0.5-32 32	800-5,800 600-35,600 14,800-38,800	0.017-0.028 0.015-0.047 0.472-1.24	17.4-28.3 15.2-47.0 472-1,240	12.3-20.0 8.7-26.7	Guy *et al.* (1975b)
Response obtained from individual auditory neurons with glass electrode	Cat (not given)	915	<10	25-250	—	≤1.0	—	4-40	Lebovitz and Seaman (1977)

*Direct comparison of power density in the waveguide exposure system to free-field power density is improper because the efficiency of energy coupling is 10 times higher than for free-field exposure. (See Chou *et al.* 1975, p. 362.)

to map auditory activity in the brain of rats exposed to acoustic stimuli and to PW and CW microwave radiation. With this technique, *in vivo* determination of metabolic activity (i.e., glucose utilization and associated functional activity in the brain) can be visualized. Prior to exposure to the acoustic stimuli or to microwaves, one middle ear was ablated. First, the authors showed the expected bilateral asymmetry of radioactive tracer uptake in the auditory system of rats exposed to acoustic clicks or weak background noise. Second, in contrast, a symmetrical uptake of tracer was found in animals exposed to PW radiation. Thus, the autoradiographic results confirmed the finding that RF hearing does not involve the middle ear (Frey 1961; Chou and Galambos 1979). Unexpectedly, Wilson *et al.* (1980) found similar patterns of radioactive tracer uptake in the auditory system of rats exposed to CW radiation (918 MHz; 2.5 and 10 mW/cm^2) and to PW radiation (2450 MHz).

This result, indicating an auditory response to CW microwaves, was unexpected, because no report of a direct hearing sensation due to exposure to CW microwaves had appeared in the literature. Since the thermoelastic hypothesis of RF hearing is based on the properties of PW radiation, this observation suggests that another mechanism may be involved in the interaction of RF radiation with the auditory system of the brain.

It is well documented that some human beings can hear pulsed RF radiation as a buzz, click, or knock. Furthermore, the thermoelastic expansion mechanism explains how the pulse of RF energy can be transformed to an acoustic impulse in the head. Since a single pulse of RF radiation can be heard, calculation of the threshold energy in terms of the average-incident-power density results in a very small number. Because a very low average-power density can cause an acoustic response in the head and there is the potential for exposure of the public to pulsed fields that induce the effect, an unresolved issue is the need to assess the psychological effects of RF hearing, particularly in populations that may have no knowledge as to the origin of the RF sounds in the head.

5.6.5 Human Cutaneous Perception

Exposure of the human body to microwave radiation can cause heating that is detectable by the temperature-sensitive receptors in the skin. As shown in Table 5-18, several investigators have experimentally determined the microwave intensities that cause sensations of warmth and thermal pain in human subjects.

5.6.5.1 Frequency Specificity

Hendler and colleagues (1963, 1968) exposed a circular area (37 cm^2) of the forehead to 3- and 10-GHz (PW) radiation and to infrared (IR) radiation. The forehead was selected for a study of warmth sensations because the temperature receptors in the skin of the forehead are relatively numerous and are evenly distributed, so that the area constitutes a low-threshold region of uniform temperature sensitivity. The lower-frequency microwaves (3 GHz) had a higher-intensity threshold for warmth sensation. The higher-frequency IR radiation was more effective than either microwave frequency, because the IR energy was absorbed more effectively in the outer skin layers containing the thermal sensors.

The study by Justesen *et al.* (1982) confirmed the earlier work on perception of microwave radiation. Four human adults individually exposed the ventral surface of the forearm for 10 s to 2450-MHz or infrared radiation; two additional subjects experienced

Table 5-18. Summary of Studies Concerning Human Cutaneous Perception of RF-Radiation

Effect	Frequency (MHz)	Intensity (mW/cm^2)	Durtion (s)	SAR* (W/kg)	Reference
Sensation of warmth on forehead	3,000 (PW)	—	1-5	20-40	Hendler (1968)
	10,000 (PW)	—	1-5	25-35	Hendler *et al.* (1963)
Sensation of warmth on forehead	2,880	74 56	15-73 50-180	— —	Schwan *et al.* (1966)
Sensation of warmth on inner forearm	2450 (CW)	26.7	10	—	Justesen *et al.* (1982)
Sensation of warmth on inner forearm	3,000 (PW)	300-2,500	≤6	—	Vendrick and Vos (1958)
Sensation of pain on inner forearm	3,000	2,500 1,000	30 130	2,000	Cook (1952)

*SAR value is estimated.

microwave radiation only. Thresholds of detection of just-noticeable warming were determined to be 26.7 mW/cm^2 for microwave radiation and 1.7 mW/cm^2 for infrared waves. The 15-fold difference between thresholds was attributed to (1) differential scatter (nearly two-thirds of the incident microwave energy is scattered and not absorbed), and (2) the differing depths of penetration of the two forms of energy (a relatively small proportion of the total absorbed microwave energy is absorbed at the skin's surface). The total energy absorbed at threshold values was estimated to be 10.2 joules (9.5 mJ/cm^2) and 1.8 joules (1.7 mJ/cm^2) for microwave and infrared radiation, respectively. Although absorption of microwave energy was more than five times greater at threshold, none of the four observers who experienced both types of radiation could distinguish a difference in sensory quality. The authors concluded that the same set of superficial thermoreceptors was being stimulated, only less efficiently so, by the more deeply penetrating, more diffusely absorbed microwave energy.

5.6.5.2 Temperature Thresholds

For both microwave and IR radiation at intensities producing warmth sensations, a threshold of warmth was experienced when the temperature of a more superficial layer of subcutaneous tissue ~ 0.2 mm below the skin's surface was increased ~ 0.01 to 0.02°C over the temperature of a deeper layer in the skin lying ~ 1 mm below the surface. In this study it was also noted that there was a persistent sensation of warmth for ~ 7 s after cessation of the exposure, which indicated the continued existence of an effective temperature difference between the subcutaneous tissue layers (Hendler 1968).

Schwan *et al.* (1966) exposed a small area of the forehead (7-cm diameter) equivalent to the area exposed in Hendler's studies to 2.88-GHz radiation and measured the length of time that elapsed before the person was aware of a sensation of warmth. The times for four subjects varied from 15 to 73 s at 74 mW/cm^2 and from 50 to 180 s at 56 mW/cm^2. The authors found that the reaction times were not linearly proportional to the reciprocal of the incident power density and concluded that subjective awareness of warmth was not a reliable indication of microwave hazard.

Vendrik and Vos (1958) exposed a 13-cm^2 area of the inner forearm to 3-GHz (PW) radiation (300 to 2500 mW/cm^2) and found the threshold for temperature changes to be 0.4 to 1.0°C. Skin temperature increases that were kept below 1°C were linear with microwave intensity for six exposure durations. In contrast to the regularity of skin temperature changes induced by microwaves, the reports of temperature sensations were variable. Sensations of warmth occurred < 0.5 to 3.5 s after rapid rises in skin temperature. The sensations did not cease when the skin temperature began to drop. In this study, microwave radiation (3 GHz) was found to be a factor of 10 less effective in producing a temperature elevation than was IR radiation at a similar intensity.

Cook (1952) determined the pain threshold in six subjects who were exposed to 3-GHz radiation at five different sites on the body's surface. The initial skin temperature ranged from 31.5 to 33.5°C. Pain resulted when a critical skin temperature (~ 46°C) was reached rather than from a critical temperature rise (ΔT). For an inner forearm area of 9.5 cm^2, the power density pain thresholds varied from 2500 mW/cm^2 for a 30-s exposure to 1000 mW/cm^2 for an exposure of 130 s. The pain threshold was lower for a larger exposed area of 53 cm^2. The skin temperature corresponding to burning pain was found to be

independent of the area of exposure, radiation intensity, exposure time, and anatomical site. At high intensities, the exposure time needed to produce pain was an inverse function of radiation intensity. The author reported that the sensations of warmth and pain with microwave heating differed little from those resulting from IR radiation.

5.6.6 Unresolved Issues

The few studies on thermal pain and warmth sensations in human beings exposed to frequencies in the range of 3 to 10 GHz provide useful data on exposure levels that are clearly undesirable for the general population. Cutaneous perception, however, may be a reliable indicator of an unsafe exposure level only at RF frequencies with wavelengths small in comparison to the length of the exposed body, i.e., wavelengths comparable to or smaller than the thickness of skin. Under these conditions, most of the energy is absorbed in the outer tissue layers containing thermal sensors. At lower frequencies, which have wavelengths approximately equal to or longer than the human body, modeling studies have shown that much of the energy is absorbed within the body below the superficial skin layers. In all mammals tested, the threshold temperature (~42°C) of cellular injury for sustained elevations (seconds to tens of seconds) is *below* the threshold (~ 45°C) of pain (Hardy *et al.* 1967). These results strongly indicate that cutaneous perception of RF energy is not a reliable sensory response that protects against potentially harmful levels of RF radiation over the broad frequency range of 0.5 MHz to 100 GHz.

5.7 Endocrine, Physiological and Biochemical Effects

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5.7.1 Endocrine Effects

The endocrine system in coordination with the nervous system is a major regulatory system in the body. Alterations in the function of the neuroendocrine system often reflect the efforts on the part of the animal to maintain homeostasis when subjected to stressful internal and external stimuli. Detection of changes in the endocrine system is a sensitive means of analyzing the animal's responses either to direct stimulation of the endocrine organs themselves or to stimulation of the CNS.

Animals exposed to a wide variety of stimuli generally respond with a rather specific pattern of physiologic changes, usually referred to as the general adaptation syndrome, and the stimuli that can provoke the syndrome are usually called stressors. An increase in the concentration of corticosteriods in the blood above that which would normally occur at that time of day in the absence of a stimulus is considered by many to be an indicator of an animal's response to stress. Such an increase results when an internal or external stimulus, either chemical, physical, or emotional, excites neurons of the hypothalamus to release corticotropin-releasing hormone, which drives the pituitary to release adrenocorticotropic hormone (ACTH). This hormone then stimulates the adrenal cortex to secrete corticosteroids. Among the strongest stressful stimuli are surgery, anesthesia, cold, narcosis, burning, high environmental temperature, and rough handling or restraint.

The thyroid gland plays a principal role in regulating basal metabolism, as well as in generating metabolic heat in the tissues. Changes in thyroid activity can result from changes in thyroid-stimulating hormone from the hypothalamic-hypophyseal system and/or increased metabolic activity of the thyroid gland due to heating. Direct interaction with the CNS could also produce changes in thyroid activity. Moderate or gradual heating results in a reduction of thyroid hormone; rapid or marked elevation of body temperature results in an increase in thyroid activity. The effects of RF radiation on the endocrine system are discussed below and summarized in Table 5-19.

Thyroid function of rats following exposure to 2450-MHz (CW) microwaves at 10, 20, and 25 mW/cm^2 (SARs estimated at 0.25 W/kg per mW/cm^2) for 4 or 16 h was studied by Parker (1973). No effects on thyroid gland function were found at these exposures. However, at 15 mW/cm^2 (SAR estimated at 3.75 W/kg), exposure for a longer period (60 h) was reported to produce a significant decrease in serum-protein-bound iodine, thyroxine, and thyroid/serum iodine ratio. A significant rectal temperature increase (1.7°C) was reported at 25 mW/cm^2, but not at lower power densities.

Magin *et al.* (1977a,b) irradiated the surgically exposed thyroid gland of anesthetized dogs with 2450-MHz (CW) microwaves using a waveguide applicator at power densities of 72, 162, and 236 mW/cm^2 (SARs from 58 to 190 W/kg) for 2 h. One thyroid was irradiated while the other was used as a control. Tissue temperatures of 39, 41, and 45°C were maintained in the thyroid at the three power densities. They reported an increased release of thyroxine (TH) and triiodothyronine (T3) at all power densities, which showed that the thyroid gland in the dog can be stimulated directly by microwave heating.

Milroy and Michaelson (1972) exposed rats to 2450-MHz microwaves at 1, 10, and 100 mW/cm^2 (SAR = 0.25 W/kg per mW/cm^2) for single exposures of 10, 20, 30, and 45 min and at 1 and 10 mW/cm^2, 8 h/day, for 8 weeks, and reported no effect on T3 levels, thyroxine levels, or on the uptake of radioactive iodine. No rectal temperature increase was observed at 10 mW/cm^2 or less. At 100 mW/cm^2 there was a constant rise in rectal temperature throughout exposure, up to 42°C at the end of the exposure period. Histopathological examination of the thyroid glands also showed no effect from the exposure.

An increased production of thyroid hormone in rabbits as measured by increased incorporation of ^{131}I and increased radioactivity per gram of thyroid (verified by autoradiography) was reported by Barański *et al.* (1972). The animals were exposed for 3 h/day for 4 months to 10-cm (3-GHz, PW) microwaves at an average incident power density of 5 mW/cm^2 (SAR estimated at 0.25 to 0.75 W/kg). They reported no increase in body temperature or thyroid temperature. (The pulse parameters were not given, so peak power density cannot be calculated.)

Lu *et al.* (1977) reported serum thyroxine levels in rats exposed to 2450-MHz microwaves at 1, 5, 10, and 20 mW/cm^2 (0.25, 1.25, 2.5, and 5 W/kg) for 1, 2, 4, or 8 h. Decreased thyroxine levels were observed at 20 mW/cm^2 following 4- and 8-h exposures. The thyroxine values at shorter exposures and lower power densities were not significantly different from the sham values, except for an increase after 4 h at 1 mW/cm^2, which appears to be a chance variation, since at both higher and lower power densities and at longer and shorter periods of exposure no effect was detected. There were small but statistically significant rectal temperature increases at 1 mW/cm^2 after 4 h, at 5 mW/cm^2 after 1 and 2 h, and at 10 mW/cm^2 after 2 and 4 h of exposure. The increases were in the range of 0.2 to 0.56°C. The lack of correlation between power density, exposure time, and rectal temperature increase, along with the small rectal

temperature change, suggests that the effects may not have been due entirely to the microwave exposure but possibly from the stress of confinement. At 20 mW/cm², however, the rectal temperature was significantly elevated at all four exposure times and tended to increase with longer exposures. At 1 and 2 h the changes were small (0.64 and 0.54°C), but larger (1.01 and 1.35°C) increases occurred after 4 and 8 h. Serum corticosteroid levels were decreased at 20 mW/cm² after 8 h only, which the authors report as a shift in the circadian periodicity. Serum growth hormone measurements showed no change at any of the power densities or times reported. They also measured no change in the mass of the thyroid, pituitary, and adrenal glands following irradiation.

In another study on the effects of microwaves on acute endocrine responses in rats, Lu *et al.* (1981) exposed animals to 2450-MHz microwaves (AM at 120 Hz) for 1 and 4 h, and measured colonic temperature, thyrotropin and corticosterone levels immediately after exposure. The 1-h exposures were conducted at power densities of 1, 5, 10, 20, 40, 50, 60, or 70 mW/cm², and the 4-h exposures at 0.1, 1, 5, 10, 20, 25, and 40 mW/cm² (measured SAR = 0.21 W/kg per mW/cm²). The results for the 1-h exposure showed an increase in colonic temperature with increasing power density with a significant increase at 20 mW/cm² and above, but not at 10 mW/cm² or below. Corticosterone also showed an increase with increased power density with evidence of a threshold between 20 and 40 mW/cm². Thyrotropin values showed a decrease with increasing power densities, with significant results at 40 mW/cm² and above, and equivocal results in the 10- to 20-mW/cm² range. (The 10-mW/cm² values were significantly lower; those at 20 mW/cm² were not.) Similar trends were observed following 4-h exposures, with a significant increase in colonic temperatures at 10 mW/cm² and above, and no increases at 5 mW/cm²

Table 5-19. Summary of Studies Concerning RF-Radiation Effects on Endocrinology

		Exposure Conditions					
Effects	Species	Frequency (MHz)	Intensity (mW/cm²)	Duration (days x min)	SAR (W/kg)	ΔT* (°C)	Reference
Increased thyroxine and triiodothyronine	Dog	2450 (CW)	72-236	1 x 120	58-190	2-8 (thyroid temp.)	Magin *et al.* (1977a,b)
No effect on thyroid gland or thyroid hormone	Rat	2450 (CW)	1, 10, 100 1, 10	1 x 10-45 56 x 480	0.25-25 0.25-2.5	≦ 10 mW/cm² = 0 100 mW/cm² ≧ 5	Milroy and Michaelson (1972)
No effect on thyroid function	Rat	2450 (CW)	10, 20, 25	1 x 240-960	2.5, 5, 6.5 (est)	≦ 20 mW/cm² = 0 25 mW/cm² = 1.7	Parker (1973)
Decrease in serum-protein-bound iodine, thyroxine and thyroxine/serum ratio	Rat	2450 (CW)	15	2.5 x 1440	3.8 (est)	0	Parker (1973)
Increase in thyroid hormone	Rabbit	3000 (PW)	5	48 x 180	0.25-0.75 (est)	Not reported	Barański *et al.* (1972)
Decrease in serum thyroxine levels	Rat	2450 (CW)	20 Neg† 1-10	1 x 240-480 1 x 60-480	5 0.25-25	0-0.6 0.6-1.4	Lu *et al.* (1977)
Increase in corticosterone levels	Rat	2450 (120 Hz AM)	40-70 Neg 1-20	1 x 60	8.4-14 Neg 0.21-4.2	1.3-3.0 0-0.6	Lu *et al.* (1981)
Decrease in thyrotropin levels			10, 40-70 Neg 1-5, 20		2.1-14.7 Neg 0.21-4.2	0-3.0 0-0.6	
Increase in corticosterone levels			10-40 Neg 1-5	1 x 240	2.1-8.4 Neg 0.2-1.0	0.3-2.1 0	
Decrease in thyrotropin levels			25, 40 Neg 1-20	5.2, 8.4 0.02-4.2	0.6-2.1 0-1		
No effect on thyroid, pituitary, or adrenal glands weight or growth hormone levels	Rat	2450 (CW)	1-20	1 x 60-480	0.25-25	0-1.4	Lu *et al.* (1977)
No effect on thyroid, anterior pituitary gland, adrenal, prostate or testes weights; no change in follicle-stimulating hormone or gonadotropic hormone levels	Rat	2860-2880 (CW)	10	36 x 360	1-2 (est)	Not reported	Mikolajczyk (1976)
Increase in leutinizing hormone	Rat	2860-2880 (CW)	10	36 x 360	1-2 (est)	Not reported	Mikolajczyk (1976)
Increased adrenal weights and significant adrenal response	Infant Rat	2450 (CW)	40	6 x 5	20-60 (est)	1.5-2.5	Guillett and Michaelson (1977)
Increased plasma corticosterone levels	Rat	2450 (CW)	50, 60 Neg 13-40	1 x 30-60	11.5-13.8 (est) Neg 3.0-9.2	13 mW/cm² = 0.5 20 mW/cm² = 0.7 30 mW/cm² = 0.9-1.4	Lotz and Michaelson (1978)
			20-40 Neg 13	1 x 120	4.6-9.2 es Neg 13 (est)	40 mW/cm² = 1.3-1.4 50 mW/cm² = 1.6-2.4 60 mW/cm² = 2.5-2.9	
Increase in corticosterone	Rat	2450 (AM, 120 Hz)	50, 60	1 x 60	8.3, 9.6	Not reported	Lotz and Michaelson (1979)
No effect on serum corticosterone levels	Rat	918 (CW)	2.5	91 x 600	1.0	0	Lovely *et al.* (1977)

*ΔT = Rectal temperature increase.
†Neg = Effect not found at value indicated.

or below with the exception of one small group at 1 mW/cm^2. The trends for the increase in corticosterone levels and the decrease in thyrotropin levels were not significant; however, the corticosterone level at 40 mW/cm^2 was significantly increased, but not at 25 mW/cm^2 or lower values. Also, the thyrotropin values at 25 mW/cm^2 and 40 mW/cm^2 were significantly decreased, whereas those at 20 mW/cm^2 and below were not. Comparing the effects of 1- and 4-h exposures on the three parameters, the change in colonic temperature was similar for both exposures; however, the stimulatory effect on serum corticosterone levels was less for the 4-h exposures than for the 1-h exposures, but the depression of serum thyrotropin was more pronounced after 4 h than after 1 h. The authors concluded that the hormonal changes probably represented a general nonspecific stress reaction that was related to the intensity and duration of the stressing agent, rather than to the nature of the agent itself.

No change in thyroid weight was seen in a study by Mikolajczyk (1976), where rats were exposed to 2860- to 2880-MHz microwaves at 10 mW/cm^2, 6 h/day, 6 days/week for 6 weeks. The SAR is estimated to be 1 to 2 W/kg for a single animal exposure, but the animals were exposed close together in a box with dividers every 10 cm, which should give a somewhat higher SAR value. The author did find a significant increase in leuteinizing hormone from the anterior pituitary gland but no chance in follicle-stimulating or gonadotropic hormone levels. The weights of the anterior pituitary, adrenal, prostate, or testes were not affected by the exposure.

Lovely *et al.* (1977) exposed rats to 918-MHz microwaves at 2.5 mW/cm^2 (SAR ~ 1.04 W/kg), 10 h/day for 13 weeks, and no changes in serum corticosterone levels were observed. In a study by Guillet and Michaelson (1977), rat pups were exposed to 2450-MHz microwaves at 40 mW/cm^2 (SAR estimated at 20 to 60 W/kg), 5 min/day for 6 days beginning at 1 day postpartum; no change in basal corticosterone levels was found. There was a significant adrenal response to the microwaves, but this response was the same as seen following ACTH administration, which would suggest a stress reaction. Rectal temperatures of the exposed animals averaged 1.5 to 2.5°C higher than those of the sham-exposed animals. Adrenal mass of the irradiated animals was significantly greater than those of the control animals.

In another study, Lotz and Michaelson (1978) irradiated rats with 2450-MHz microwaves at power densities of 13, 20, 30, and 40 mW/cm^2 for 30, 60, or 120 min and at 50 and 60 mW/cm^2 for 30 or 60 min (SAR estimated at 0.21 W/kg per mW/cm^2). Plasma corticosterone levels were increased at power densities at or above 50 mW/cm^2, but not at 40 mW/cm^2 or less, for the 30- and 60-min exposures. At the longest exposure time (120 min), increased levels were seen at or above 20 mW/cm^2 but not at 13 mW/cm^2. Graphs were presented of the rectal temperature taken at the completion of exposures; estimates of the rectal temperature increases taken from the graphs for 50 mW/cm^2 were 1.6 and 2.4°C and for 60 mW/cm^2 were 2.5 and 2.9°C for 30 and 60 min, respectively. The temperature increases for 40 mW/cm^2 were 1.3 and 1.4°C for 30 and 60 min. For the 120-min exposures, rectal temperature increased 0.5°C at 13 mW/cm^2 and 0.7°C at 20 mW/cm^2.

A study by Lotz and Michaelson (1979) suggests that the change in corticosterone levels is due to stimulation of the pituitary gland, probably due to hyperthermia. They exposed hypophysectomized rats to 2.45-GHz microwaves (AM at 120 Hz) at 60 mW/cm^2 (9.6 W/kg) and found significantly lower levels of corticosterone compared to normal and sham-hypophysectomized rats. In another study, dexamethasone effectively suppressed the corticosterone response in rats exposed to 50 mW/cm^2 (8.3 W/kg), but only partial suppression was observed at 70 mW/cm^2 (11.2 W/kg). These results provide further evidence for a stimulatory effect of microwave radiation on the pituitary gland rather than the adrenal gland.

In summary, microwave effects on thyroid function have been reported at SARs as low as 2.1 W/kg, and negative results have been reported at values as high as 25 W/kg. The duration of exposure, as well as the exposure rate, appears to be important, as demonstrated by the study by Parker (1973) where exposures at 6.25 W/kg for 16 h produced no changes, whereas 3.75 W/kg exposures for 60 h resulted in a decrease in serum thyroxine levels. Changes in corticosterone levels have been reported from microwave exposure at SARs as low as 10 W/kg but not at 6.25 W/kg, and adrenal responses have been reported at levels as low as 4.6 W/kg but not at 3 W/kg.

5.7.2 Clinical Chemistry and Metabolism

An individual's response to many stresses manifests itself through changes in some of the clinical chemistry indices. Serum calcium and phosphate levels normally increase initially and then decrease below normal in response to stress; whereas serum glucose, blood urea nitrogen, and uric acid levels increase following stress. These blood chemical responses are consistent with induction of release of adrenocortical hormones in response to stress. Physiological responses, including thermal responses, to RF-radiation exposure may occur at exposure levels too low to produce large changes in thermoregulatory behavior or colonic temperature. In such instances there may be changes in various metabolic parameters. There are few clinical chemistry and

metabolism reports where exposures were sufficiently defined to relate results to the power density or SAR. These studies are described below, and are outlined in Table 5-20.

A study of the effects of microwaves on serum chemistry values was reported by Lovely *et al.* (1977), who exposed rats in circularly polarized waveguides to 918-MHz (CW) radiation. The animals were irradiated 10 h/day for 13 weeks at a power density of 2.5 mW/cm^2 (SAR ~ 1.04 W/kg). They reported no change in Na^+, K^+, ion gap, Cl^-, blood urea nitrogen, or glucose values compared to the sham-irradiated animals. They did report a significant difference in the serum calcium values at the end of the 12-week exposure period. However, this is most probably a spurious result, because the calcium levels in the sham-irradiated animals were decreased from previous values, whereas the levels in the irradiated animals remained unchanged from earlier values. These results, therefore, are interpreted to mean that 918-MHz microwaves at 2.5 mW/cm^2 do not alter the measured clinical chemistry values. Colonic temperature measurements were made on the animals, and no detectable changes were observed.

Somewhat differing from these results, Wangemann and Cleary (1976) reported an increase in serum glucose levels in rabbits exposed for 2 h to 2450-MHz microwaves (CW and PW) at power densities of 5, 10, and 25 mW/cm^2 (SARs estimated at 0.8, 1.6, and 4.0 W/kg, respectively), and an increased blood urea nitrogen value in animals exposed to 25-mW/cm^2 microwaves only. Increased uric acid levels were found at 10 and 25 mW/cm^2, but not at 5 mW/cm^2 (both CW and PW). Levels of calcium, phosphorus, cholesterol, total protein, alkaline phosphatase, lactic dehydrogenase, and serum glutamic oxalic transaminase were unaffected at the three power densities. The authors stated that the PW and CW results could not be compared directly because the exposure conditions were different. The results were those that would be expected from heat stress. Animals exposed at 25 mW/cm^2 for 2 h showed a significant rectal temperature increase of 1.7 and 2.9°C for PW and CW exposures, respectively. Those exposed at 10 mW/cm^2 showed evidence of mild heat stress, such as peripheral vasodilation, but no significant increase in rectal temperature. One possible explanation for the difference between these results and those of Lovely *et al.* is the difference in absorbed energy patterns in rats and rabbits at 2450 MHz.

Brains from rats exposed at 1600 MHz for 10 min at a power density of 80 mW/cm^2 (SAR estimated at 48 W/kg) were analyzed for selected heavy metals by Chamness *et al.* (1976). Iron levels were increased in all the areas of the brain (hypothalamus, corpus striatum, midbrain, hippocampus, cerebellum, medulla, cortex). Manganese was increased in the cortex and medulla, and copper was increased in the cortex; while calcium, zinc, sodium, and potassium levels were unchanged. The observed changes were probably a result of hyperthermia, since most alterations seen were also observed in rats subjected to a hyperthermal environment, and the irradiated animals showed a rectal temperature increase of 4.5°C.

Platelet-rich human plasma was irradiated *in vitro* with 2450-MHz microwaves at power densities from 10 to 280 mW/cm^2 (SARs 1.3 to 38 W/kg) for 0.5 to 24 h by Boggs *et al.* (1972), and effects on blood coagulation were analyzed. They reported no significant changes in platelet count, coagulation time, or clot strength at these power densities. The plasma temperature was maintained below 37°C during the exposures. They also conducted studies on the effect of heating on coagulation time and clot strength. Samples were heated either by microwaves or by radiant heating, and the results were compared to unheated control samples. The relative coagulation time for the microwave-heated samples remained unchanged throughout the temperature range studied (34, 37, 39, and 42°C), and the samples heated by radiant energy showed increases in the relative coagulation time (1.58 and 2.03 times the nonheated samples) at 39 and 42°C, respectively. A similar but reverse effect was seen in the relative clot strength. The samples heated to 42°C by microwaves showed a decrease to 0.74 times the control samples, and the radiant-heated samples showed a decrease to 0.31 times the control values. A possible explanation for these differences is that it is difficult to produce the same heating rate and pattern within a sample with different sources of heat.

Ho and Edwards (1977b) measured the rate of oxygen consumption of mice exposed to 2450-MHz microwaves in a waveguide for 30 min at dose rates from 1.6 to 44.3 W/kg at an environmental temperature of 24°C. They found a significant decrease in the specific metabolic rate (SMR) at 10.4 W/kg or higher, but not at 1.5 or 5.5 W/kg. In measurements taken immediately after exposure, there was no detectable rectal temperature increase at or below 10.4 W/kg, but there was a 0.5°C increase at 23.6 W/kg and a 1.0°C increase at 44.3 W/kg. These results indicate that the mouse compensates for large dose rates of microwave energy by adjusting its metabolic rate downward to compensate for the thermal load.

In a more recent report, Ho and Edwards (1979) reported on a continuation of the previous study. Exposure conditions were identical to those of the previous study except environmental temperatures of 20, 30, and 35°C were also used. At 20°C, they found a significant decrease during exposure in the SMR at 12.1 W/kg and above, but not at 6.0 W/kg or below. A significant decrease was found in the SMR during the 30-min postexposure period at 45.1 W/kg, but not at 27.0 W/kg or less. For the exposures at 30°C there

Table 5-20. Summary of Studies Concerning RF-Radiation Effects on Clinical Chemistry and Metabolism

Effects	Species	Exposure Conditions: Frequency (MHz)	Intensity (mW/cm^2)	Duration (days x min)	SAR (W/kg)	ΔT* (°C)	Reference
No effect on serum chemistry values	Rat	918 (CW)	2.5	91 x 600	1.0	0	Lovely *et al.* (1977)
Increase in serum glucose	Rabbit	2450 (CW and PW)	5, 10, 25	1 x 120	0.8-4.0 (est)	0, 0, 1.7 (PW) 0, 0, 2.9 (CW)	Wangemann and Cleary (1976)
Increase in blood urea nitrogen	Rabbit	2450 (CW)	25	1 x 120	4.0 (est)	2.9	
No increase in blood urea nitrogen	Rabbit	2450 (CW)	5 and 10	1 x 120	0.8, 1.6 (est)	0	
	Rabbit	2450 (PW)	5, 10, 25	1 x 120	0.8-4.0 (est)	0, 0, 1.7	
Increase in uric acid values	Rabbit	2450 (CW and PW)	10, 25	1 x 120	1.6, 4.0 (est)	0, 1.7 (PW) 0, 2.9 (CW)	
			Negt 5		Neg 0.8	0	
No effect on other serum chemistry values	Rabbit	2450 (CW and PW)	5, 10, and 25	1 x 120	0.8-4.0 (est)	0, 0, 1.7 (PW) 0, 0, 2.9 (CW)	
Increased iron and manganese levels in brain	Rat	1600 (CW)	80	1 x 10	48 (est)	4.5	Chamness *et al.* (1976)
Decrease in specific metabolic rate (Ambient T = 24°C)	Mouse	2450 (CW)	—	1 x 30	10.4 (Neg 5.5)		Ho and Edwards (1977b)
Increase in specific metabolic rate (Ambient T = 35°C)	Mouse	2450 (CW)	—	1 x 30	8.6 (Neg 3.6)	0	Ho and Edwards (1979)
Increased NADH fluorescence Decreased ATP Decreased CP	Rat (exposed brain)	591 (CW)	13.8	1 x 0.5	0.36-2.2	0	Sanders *et al.* (1980)
Decreased ATP Decreased CP	Rat (exposed brain)	591 (CW)	5	1 x 0.5	0.13-0.8	0	Sanders *et al.* (1980)
Increase in oxygen consumption	Rat	2450 (120 Hz PW)	—	1 x 30	6.5, 11.1 (Neg 4.5)	0.9, 1.8 0.4	Phillips *et al.* (1975b)
Decreased in metabolic heat production	Monkey	2450 (CW)	6	1 x 10	0.9	0	Adair and Adams (1982a)
No effect on blood coagulation	Human plasma	2450 (CW)	10-280	1 x 30	1.3-38 (est)	Not reported	Boggs *et al.* (1972)

*ΔT = Rectal temperature increase.
†Neg = Effect not found at value indicated.

was no change in the SMR at any of the dose rates used (1.4 to 23.7 W/kg) either during exposure or in the postexposure period. At 35°C there was a significant increase in the SMR at 8.6 W/kg and higher, but not at 3.6 W/kg or lower during exposure, and no changes were observed during the postexposure period. The authors reevaluated their first report (Ho and Edwards 1977b) by comparing the results during exposure with the pre-exposure values, not with those of sham-exposed animals. With this method of evaluation, the SMR values during exposure at 24°C were not significantly different from the pre-exposure values. They reported that this method of comparison accounted for the lack of uniformity among animals at the beginning of each experiment and therefore was a better method of comparison.

The general trends indicated by their studies are that microwave exposure at the lowest ambient temperature resulted in a reduction in the SMR, exposure at the highest ambient temperature resulted in an increase in the SMR, with no significant changes at the intermediate temperatures. A possible interpretation of these trends is that at the lower ambient temperatures the animals are producing heat to maintain thermal neutrality; addition of the microwave heating reduces the animals' demand for additional endogenous heat. At the higher ambient temperatures the animals may be actively trying to dissipate the additional heat from the microwaves as evidenced by spreading saliva, thereby increasing their SMR.

Adult rats were exposed to 2450-MHz microwaves pulsed at 120 Hz in a multimodal cavity for 30 min at SARs of 4.5, 6.5, and 11.1 W/kg; and their metabolic rate was measured beginning within 10 min after the completion of exposure by determining oxygen consumption and carbon dioxide production (Phillips *et al.* 1975b). Room temperature was maintained at 24.2°C. They found no change in metabolic rate at 4.5 W/kg, a decrease at 6.5 W/kg, and a greater

decrease at 11.1 W/kg. Colonic temperature measurements were made at the end of exposure, and the temperatures were elevated 0.4, 0.9, and 1.8°C for the 4.5-, 6.5-, and 11.1-W/kg exposures, respectively. These results tend to confirm those initially reported at 24°C by Ho and Edwards (1977b), where they compared the exposed animals to sham-exposed animals, but not the reanalyzed results (Ho and Edwards 1979), where they compared the exposure values with pre-exposure values on the same animals.

Squirrel monkeys were exposed to 2450-MHz CW microwaves for 10-min periods at 2.5, 4, 6, 8, and 10 mW/cm² (SARs from 0.4 to 1.5 W/kg) at ambient temperatures of 15, 20, and 25°C by Adair and Adams (1982a), and the metabolic heat production was calculated from oxygen consumption measurements. They found that for monkeys restrained at cool temperatures and exposed at power densities of 4 to 6 mW/cm² and above, the metabolic heat production was reduced in direct relationship to the microwave energy absorbed. They also exposed monkeys at 8 mW/cm² (1.2 W/kg) for 90-min (ambient temperature = 20°C) and found that the metabolic heat production initially decreased and then leveled off at ~ 1.2 W/kg below pre-exposure values; i.e., the reduction in metabolic rate was equal to the rate of microwave energy deposition.

A study on the effects of microwaves on energy metabolism of the rat brain was reported by Sanders *et al.* (1980). First, a small area of the brain of anesthetized animals was surgically exposed. Then a horn antenna was positioned so that exposures were in the far field and only the exposed surface of the brain was irradiated with the electric field parallel to the body axis. Animals were exposed at 591-MHz (CW) radiation for 0.5, 1, 2, 3, or 5 min at 13.8 mW/cm² or for 0.5 or 1 min at 5 mW/cm². (Calculated SAR for 5 mW/cm² = 0.13 W/kg using a 2-cm sphere model or 0.8 W/kg using a semi-infinite plane model.) During exposures at 13.8 mW/cm² they found an increase in nicotinamide adenine dinucleotide (NADH) fluorescence to a maximum of 4.0 to 12.5 percent above pre-exposure control levels. In addition, adenosine triphosphate (ATP) levels were significantly decreased at all exposure times, as were creatine phosphate (CP) levels. At 5 mW/cm², ATP and CP levels were also significantly decreased following 0.5- and 1-min exposures. The ATP and CP changes at 5 mW/cm² were not significantly different from those seen at 13.8 mW/cm². There were no changes in rectal temperature at any of the exposures and no significant difference in brain temperature between exposed and sham-exposed animals. The authors concluded that the results (increased NADH fluorescence, decreased ATP and CP levels) support the hypothesis that RF radiation inhibits mitochondrial electron transport chain function and that the changes cannot be attributed to general tissue hyperthermia.

In summary, changes in clinical chemistry values have been reported at dose rates as low as 0.8 W/kg in rabbits, and negative results have been reported at exposures as high as 1 W/kg in rats. The clinical chemistry changes that have been reported are those that would be expected from heat stress. In other studies, effects on the rate of oxygen consumption of mice have been reported at 10.4 W/kg, in rats at 6.5 W/kg, and in squirrel monkeys at 0.9 W/kg; and changes in brain energy metabolism have been found at an SAR estimated to range from 0.13 to 0.8 W/kg (Table 5-20).

5.7.3 Growth and Development

Few investigators have reported the effects of a combination of pre- and postnatal exposure or postnatal exposure only to RF radiation on the growth of laboratory animals (Table 5-21). Smialowicz *et al.* (1979a) exposed rats for 4 h per day, beginning on day 6 of gestation through 40 to 41 days postpartum to 2450-MHz (CW) microwaves at 5 mW/cm² (SARs = 0.7 to 4.7 W/kg), and reported no difference between the weight gains of the exposed and sham-exposed animals.

In another study, Smialowicz *et al.* (1981a) reported the growth and development of rats exposed to 100-MHz (CW) microwaves at an incident power density of 46 mW/cm² (average SAR = 2.8 W/kg) for 4 h/day from day 6 of gestation through 97 days of age. The ambient temperature was maintained at 22°C except for days 1 to 14, when it was maintained at 27°C (RH = 50 percent). There was no consistent difference between the body weights of the exposed and sham-exposed animals, though the exposed animals tended to be larger than the sham-exposed animals. Some of the animals were tested for neurological development, and no differences were observed in the development of a startle response or righting reflex. There was a significant difference in the age of eye opening, with the mean age of eye opening in the sham-irradiated animals occurring almost one day later than the irradiated animals. The authors stated that the change probably did not represent an acceleration of eye opening, as the age of eye opening in the irradiated animals was similar to that normally seen in control animals in other experiments, but that eye opening was delayed in the sham-irradiated animals. Tests for development of motor activity at 35 and 84 days of age showed no difference between exposed and sham-exposed animals. No difference was observed between the exposed and sham-exposed animals for complete blood counts, mitogen-stimulated response of lymphocytes, frequency of T- and B-lymphocytes, or antibody response to *Streptococcus pneumoniae* capsular polysaccharide. No mutagenic effect was observed on the sperm cells after 20 days using the dominant lethal assay. Seven

regions of the brain were weighed at 22, 40, and 97 days of age, and there was a significant increase in the weight of the medulla in the irradiated animals at 40 days of age but not at 22 or 97 days of age, There were no differences in the weights of any other brain region. There were also no differences in the brain protein concentrations for the seven regions. Brain acetylcholinesterase (AChE) activity, however, was reduced in the striatum and medulla at 22 days of age and in the midbrain at 40 days of age. No effects on AChE activity were noted in the other regions at 22 and 40 days of age, and no differences were noted at 97 days of age. The differences were small, and there appeared to be no pattern to the changes; the sample size was small (3 to 5 animals), and out of 21 comparisons made at the 5-percent confidence level, one significantly different result would be expected. Consequently, without replication with a larger sample size, it is difficult to ascribe these changes to the microwave exposure.

The effect of postnatal exposure to microwaves on growth and development was studied by McAfee *et al.* (1973). Weanling mice were exposed to 2450-MHz microwaves at 10 mW/cm^2, 2 min each hour for 24 days; no effect on animal growth was found. There was no elevation of body temperature in the exposed animals. The authors also stated that a previous study, in which a stimulatory effect on growth from microwaves was claimed, was probably in error because of inaccuracies in weighing the animals (Nieset *et al.* 1958).

Guillet and Michaelson (1977) exposed neonatal rats to 2450-MHz microwaves at 40 mW/cm^2 (SARs at 20 to 60 W/kg), 5 min/day for 6 days beginning on day 1 postpartum. No effect on body mass was found, though the authors did report adrenal changes, as discussed in Sec. 5.7.1, Endocrine Effects.

Stavinoha *et al.* (1975) irradiated 4-day-old mice at a field intensity of 5800 V/m (8.92 W/cm^2) for 20 min with 10.5-, 19.27-, or 26.6-MHz radiation, and observed no change in growth rate to 22 days of age compared to the control animals (SARs estimated at 0.9, 1.8, and 3.6 W/kg). Mice were also exposed to 19-MHz microwaves for 40 min/day for 5 days from a near-field synthesizer that delivered an E field of 800 V/m (17 W/cm^2) and an H field of 55 A/m (114 W/cm^2); no change in body mass through 120 days of age was found (SAR estimated at 6.3 W/kg).

In a chronic study, Lin *et al.* (1979a) exposed 4- to 7-day-old mice to 148-MHz microwaves at 0.5 mW/cm^2 (SAR = 0.013 W/kg), 1 h/day, 5 days/week for 10 weeks and reported no significant effect on weight gain.

Albert *et al.* (1981a) reported a significant decrease in the number of Purkinje cells in the cerebellum of rats exposed *in utero* (days 16 to 21 of gestation) and postnatally for 97 days (4 h/day) to 100-MHz (CW) microwaves at 46 mW/cm^2 (SAR = 2.8 W/kg). The animals were from the study by Smialowicz *et al.* (1981a), as reported above. A similar decrease was found in rats exposed 21 h/day *in utero* (days 17 to 21) to 2.45-GHz (CW) microwaves at 10 mW/cm^2 (SAR = 2 W/kg). In rats exposed 7 h/day for 5 days beginning at 6 days of age, a decrease in the number of Purkinje cells was seen in animals immediately after exposure, but after 40 days there was apparent recovery.

In a report by Kaplan *et al.* (1982) squirrel monkeys were exposed to 2.45-GHz microwaves for 3 h/day *in utero* and through 9.5 months of age at 0.034, 0.34, and 3.4 W/kg. The results indicated a possible increase in mortality at 3.4 W/kg. Because of the small number of animals involved, a follow-up study was done with larger number of animals (Kaplan 1981), and this study showed no difference in the mortality between the irradiated (3.4 W/kg) and sham-irradiated animals. Other aspects of these papers are discussed in Sec. 5.3.1.2, Reproductive Effects in Mammalian Models.

Albert *et al.* (1981b) examined the squirrel monkeys described in the preceding paragraph (Kaplan *et al.* 1982) and found no change in the number of Purkinje cells as compared to the sham-irradiated animals.

These studies indicate that RF exposures at SARs $\leq$ 2.8 W/kg have no effect on growth and development of animals exposed pre- and postnatally or postnatally only. Exposures at 20 to 60 W/kg postnatally for short exposure times also did not alter the growth rate of animals even though adrenal changes were seen.

5.7.4 Cardiovascular System

5.7.4.1 Whole-Body Exposures

Some of the initial studies of biological effects of microwave radiation were made on the cardiovascular system. Presman and Levitina (1962) reported that whole-body or ventral exposure to CW microwaves at 2400 MHz, 7 to 12 mW/cm^2, promoted a decreased heart rate (bradycardia) in the rabbit. However, exposing only the head to microwaves at the same power densities resulted in an inceased heart rate (tachycardia). The SAR could not be estimated as the animals were exposed in the near field; therefore, the study is not listed with other cardiac physiology studies in Table 5-22. The report is mentioned here because it provided the impetus for other studies discussed below.

Kaplan *et al.* (1971) attempted to replicate the tachycardia reported by Presman and Levitina by exposing the head of rabbits to 2400-MHz (CW) microwaves at an incident power density of 10 mW/cm^2 (SAR estimated at 2 W/kg) for 20 min. The exposure conditions differed in that Kaplan *et al.* exposed the animals in the far field, whereas Presman and Levitina had used near-field exposures.

Table 5-21. Summary of Studies Concerning RF-Radiation Effects on Growth and Development

Effects	Species	Exposure Conditions: Frequency (MHz)	Intensity (mW/cm^2)	Duration (days x min)	SAR (W/kg)	ΔT* (°C)	Reference
No effect on weight gain	Rat	2450 (CW)	5	55 x 240	0.7-4.7	Not reported	Smialowicz *et al.* (1979a)
No effect on growth, neurological or immunological development or mutagenicity	Rat	100 MHz (CW)	46	112 x 240	2.8	Not reported	Smialowicz *et al.* (1981a)
Possible decrease in brain acetylcholinesterase activity				37, 55 x 240			
Decrease in Purkinje cells	Rat	100 MHz (CW)	46	112 x 240	2.8	Not reported	Albert *et al.* (1981a)
Decrease in Purkinje cells	Rat	2450 MHz (CW)	10	5 x 1260	2	Not reported	Albert *et al.* (1981a)
Decrease, then recovery, in Purkinje cells	Rat	2450 MHz (CW)	10	5 x 240	2	Not reported	Albert *et al.* (1981a)
No change in Purkinje cells	Monkey	2450 MHz (CW)		285 x 180	3.4	Not reported	Albert *et al.* (1981b)
No change in infant mortality	Monkey	2450 MHz (CW)		285 x 180	3.4	Not reported	Kaplan (1981)
No effect on growth	Mouse	2450 (CW)	10	24 x 48	6-8 (est)	Not reported	McAfee *et al.* (1973)
No effect on body weights	Infant rat	2450 (CW)	40	6 x 5	20-60 (est)	1.5-2.5	Guillet and Michaelson (1977)
No effect on growth	Mouse	10.5, 19.27, 26.6 (CW)	8900	1 x 20	0.9, 1.8 3.6 (est)	Not reported	Stavinoha *et al.* (1975)
	Mouse	19	17,000-114,000	5 x 40	6.3 (est)		
No effect on weight gain	Mouse	148 (CW)	0.5	50 x 60	0.013	Not reported	Lin *et al.* (1979a)

*ΔT = Rectal temperature increase.

Kaplan *et al.* reported no change in heart rate. They then exposed rabbits at increasing power densities (20, 40, 60, 80, and 100 mW/cm^2) and measured respiration rate, body temperature, and heart rate. Respiration increased at 40 mW/cm^2 and greater, and body temperature was elevated at 80 and 100 mW/cm^2 (0.5°C at both power densities). Heart rate was increased at 100 mW/cm^2 only.

Birenbaum *et al.* (1975) exposed the heads of unanesthetized rabbits to 2.4-GHz (CW) microwaves for 60 min at 20, 40, 60, and 80 mW/cm^2 (SAR estimated at 3 to 12 W/kg), and found increases in heart rate, respiration rate, and subcutaneous temperature (lower back) at all four power densities, with greater increases at higher exposure levels. They also compared 2.8-GHz (CW and PW, 1000 pulses/s, 1.3 μs) microwaves at 20 mW/cm^2 for the same three parameters and found no differences in the responses to CW or PW irradiation.

Phillips *et al.* (1975b) exposed adult rats to 2450-MHz microwaves pulsed at 120 Hz for 30 min (SARs = 4.5, 6.5, and 11.1 W/kg) and measured colonic and skin temperatures and heart rate after exposure. They reported increases in colonic and skin temperatures with increased exposure levels immediately after irradiation. At the highest exposure, the colonic temperature dropped below normal at 1 h after exposure and remained subnormal for 4 h. There was no postexposure effect on heart rate at 4.5 W/kg; however, there was a mild bradycardia at 6.5 W/kg and the more pronounced decrease in heart rate at 11.1 W/kg. They attributed the effect to the heat stress induced by the microwaves. They also discussed the possibility that heating the regulatory center in the hypothalamus may have stimulated the fall in body temperature.

Hamrick and McRee (1980) assessed the effects of body temperature on the heart rate of embryonic quail. They exposed the embryos to 2450-MHz (CW) microwaves for 5 to 10 min (SARs = 3, 6, 15, and 30 W/kg) at incubation temperatures from 35 to 38°C, and to 2450-MHz (PW) microwaves (10-μs pulses, varied from 10 to 50 pulses/s; SARs at 0.3, 1.5, and 3 W/kg) at incubation temperatures of 35 to 39°C. There were no significant differences between the heart rates of the exposed and control embryos in any of the groups at any of the temperatures used. The authors did observe that the embryonic heart rate increased ~ 23 beats/min for each 1°C rise in incubation temperature in the 36 to 39°C range.

Chou *et al.* (1980b) exposed rabbits both dorsally and ventrally to 2.45-GHz microwaves 20 min/day for 10 days to both continuous and pulsed waves (100 pulses/s, 1-μs pulse width, and 10-μs pulses triggered by the R wave at various delay times). The incident power density for the CW and the PW condition was 5 mW/cm^2, with a calculated local SAR to the heart of 0.093 W/kg for dorsal irradiation and 0.3 W/kg for ventral irradiation. No effect on heart rate was found. Rabbits exposed at 80 mW/cm^2 showed an increase in heart rate, presumably from heat stress.

5.7.4.2 Isolated Heart Preparations

Although the data supporting a microwave-induced bradycardia in the intact animal are equivocal, some researchers have exposed isolated heart preparations and reported an effect of microwaves on heart rate. Tinney *et al.* (1976) attempted to determine the locus of microwave-induced bradycardia in the isolated turtle heart using 960-MHz (CW) microwaves. Although the heart was isolated from the CNS, it was still capable of responding to neurohumoral agents. They found that exposing the isolated heart to microwaves at 8 mW/cm^2 caused bradycardia. When the heart was treated with atropine to block the sympathetic system, tachycardia resulted. However, when the heart was treated with propranolol to block the parasympathetic system, the heart rate decrease was more significant than that following microwave exposure alone, which would show that microwaves may have affected the parasympathetic reflexes. With both blocking agents added to the heart, microwave exposure had only slight effects on the heart rate. Tinney *et al.* postulated that microwave exposure of the isolated heart equally enhances the release of acetylcholine and norepinephrine; however, since the activity of the former usually predominates over the latter (Johansen 1963), the net effect of microwave exposure is a decrease in heart rate.

A similar drug-microwave interaction has been observed in the isolated rat heart by Olsen *et al.* (1977). They exposed the heart to 960-MHz (CW) microwaves for 4 min at 1.3 and 2.1 W/kg and observed a decrease in heart rate. The decrease was greater at 1.3 W/kg than at 2.1 W/kg. They also conducted studies at 2.1 W/kg with drugs to block the sympathetic and parasympathetic nervous system and obtained the same results as Tinney *et al.* (1976).

Table 5-22. Summary of Studies Concerning RF-Radiation Effects on Various Aspects of Cardiac Physiology

		Exposure Conditions				
Effects	Species	Frequency (MHz)	Intensity (mW/cm^2)	Duration (total min)	SAR (W/kg)	Reference
Bradycardia develops after whole-body exposure, along with hyperthermia	Rat	2450 (PW)	28, 48	30	6.5, 11.1	Phillips *et al.* (1975b)
Exposure to head promotes tachycardia; exposure to back raises respiratory rate but not heart rate	Rabbit	2400 (CW and PW)	20	60	3	Birenbaum *et al.* (1975)
Increased respiration	Rabbit	2400	40-100	20	8-20 (est)	Kaplan *et al.* (1971)
Increased heart rate from dorsal exposure of the head	Rabbit	2400	100	20	20 (est)	Kaplan *et al.* (1971)
Alterations in ECG (shortening of QT interval, increased height of T-wave, appearance of U-wave)	72-h Chick heart	24,000 (PW)	74	3	NG*	Paff *et al.* (1963)
No effect on heart rate that cannot be attributed to microwave heating	Quail embryo	2450 (CW and PW)	NA†	5 to 10	0.3-30	Hamrick and McRee (1980)
Pulses synchronized with each R-wave do not affect heart rate	Frog	1420-10,000 (PW)	32 μW/cm^2	100-μs pulses		Liu *et al.* (1976)
Synchronized pulses with QRS complex causes increase in heart rate with some arrhythmias	Frog	1425 (PW)	0.6 μW/cm^2	10-μs pulses	NG	Frey and Seifert (1968)
Increased heart rate	Rabbit	2450 (CW)	80	20 x 10 d	12	Chou *et al.* (1980b)
No effect on heart rate			5	20 x 10 d	0.3 and 0.093	
Low power levels cause bradycardia in the isolated turtle heart	Turtle	960 (CW)	NA	60	2-10	Tinney *et al.* (1976)
Causes slight decrease in the isolated heart	Rat	960 (CW)	NA	5 to 10	1.3 and 2.1	Olsen *et al.* (1977)
Synchronized exposures with ECG have no effect on heart rate	Frog	1420-3000 (PW)	0.0006	2-, 10-, 150-μs pulses	NG	Clapman and Cain (1975)

*NG = Not given.
†NA = Not applicable.

Paff *et al.* (1963), working with the isolated embryonic chicken heart, were unable to detect changes in heart rate during exposure to 24,000-MHz (PW) radar fields. They did, however, detect effects on the electrocardiogram (ECG), including abnormal P and T waves from 3-min exposures at 74 mW/cm^2.

Frey and Seifert (1968) showed that 10-μs pulses at a carrier frequency of 1.425 GHz given at a synchronous period with the ECG (220 ms after the P wave) resulted in tachycardia or heart arrhythmia in the isolated frog heart. The peak power density was 60 mW/cm^2 (average power density ~ 0.6 μW/cm^2). Liu *et al.* (1976) reported no effect on heart rate with isolated frog hearts or in hearts irradiated *in situ* in a similar study. The *in situ* hearts were exposed to 100-μs pulses of either 1.42 or 10 GHz, and the isolated frog hearts were exposed to 100-μs pulses of 1.42 GHz. The pulse was delivered on the rising phase of the R-wave from the ECG, which as somewhat similar to, but not exactly the same as, the 200-ms delay following the P-wave used by Frey and Seifert. (The R-wave follows the P-wave by about 200 ms.) The peak and average power densites of 320 mW and 32 μW were also considerably higher than those used by Frey and Seifert. These factors, plus differences in the manner of preparing the isolated hearts (Liu *et al.* curarized the frogs, whereas Frey and Seifert decapitated the frogs), make it difficult to compare the results of the two studies.

Clapman and Cain (1975), however, tried to replicate the study of Frey and Seifert using similar pulse widths (10 μs), peak and average power densities (60 mW/cm^2 and 0.6 μW/cm^2), carrier frequency (1.42 GHz), and method of isolating the frog heart; they reported no change in heart rate. Also, no heart rate changes were found when they conducted studies with a different peak power (5.5 W/cm^2), frequency (3 GHz), and pulse widths (2 and 150 μs). Clapman and Cain were able to produce an increased heart rate with 20-mA current pulses synchronized 200 ms after the P-wave peak.

The results of microwave exposure on the cardiovascular system (Table 5-22) indicate that whole-body exposure of sufficient intensity to produce heating also produces an increase in heart rate similar to that which would be expected from heating alone. In the isolated heart there appears to be a stimulation of the autonomic nervous system from microwave exposure at levels where very little heating would be expected (1 to 2 W/kg). Low levels of synchronized PW microwaves (0.6 to 32 mW/kg) apparently are ineffective in producing detectable alterations in heart rate.

5.7.5 Biological Effects of Low Frequency Modulation of RF Radiation

Interest in the biological effects of low frequency modulation of RF radiation stems from reports of changes caused by exposure to electric and magnetic fields in the sub-ELF range (0 to 30 Hz). It has been reported that exposure to low-frequency electric fields changes the reaction time in humans (Konig and Ankermuller 1960; Hamer 1968; Konig 1971) and in monkeys (Gavalas; *et al.* 1970; Gavalas-Medici and Day-Magdaleno 1976), and alters circadian activity in human beings (Wever 1973). Friedman *et al.* (1967) observed that magnetic fields modulated at low frequencies also change reaction time in human beings.

Two other studies that provide important background information are reported by Kaczmarek and Adey (1973, 1974). In the first report, they described release of calcium ions and γ-aminobutyric acid (GABA) from the cerebral cortex of cats in response to small changes in the extracellular concentration of calcium. In 1974, they demonstrated release of calcium ions and GABA from the cat cortex in response to low intensity electric currents, pulsed at 200 Hz, applied directly to the cerebral cortex. Thus, extracellular calcium and electric current have similar effects on the release of GABA and calcium ions from brain tissue.

The studies of (1) behavioral changes in animals and human beings induced by low frequency signals and (2) biochemical changes in the cat brain caused by electric currents led to a study of the influence of electric fields on EEG patterns associated with a conditioned behavioral response in cats (Bawin *et al.* 1973). To increase the penetration of the signals into the tissue, they chose an RF carrier wave of 147 MHz, which was amplitude modulated at sub-ELF frequencies (e.g., 3 to 14 Hz). Alterations were observed in the rate of performance, accuracy of reinforced patterns, and resistance to extinction in learned behavior of the exposed animals compared to controls, indicating that the fields were acting as reinforcers. In order to determine whether these effects were mediated via peripheral receptors or occurred as a result of changes induced directly on the CNS, experiments were designed to examine the effects of modulated RF carrier waves on brain tissue *in vitro*.

5.7.5.1 Calcium Ion Efflux *In Vitro*: A Fundamental Finding

The association of calcium ions with brain tissue was selected as the biochemical marker to examine the influence of modulated RF fields because calcium ion efflux has been shown to be sensitive to electric currents applied directly to brain tissue *in vitro*, and because calcium ions have a prominent role in many biochemical and biophysical processes (e.g., cellular membrane integrity and function, enzyme cofactor, putative second messenger for the conduction of extracellular signals to the nucleus of the cell, neural tissue excitation and secretion of transmitter

substances at synapses). The first report of the influence of modulated RF fields on excised brain tissue was Bawin *et al.* (1975), who showed that a 20-min exposure of chick brain tissue *in vitro* to a 147-MHz field at 1 to 2 mW/cm^2 (SAR estimated at 0.002 W/kg) caused enhanced efflux of calcium ions, but only if the field was sinusoidally amplitude modulated at frequencies of 6, 9, 11, 16, or 20 Hz. Maximal efflux was measured at 16 Hz. Modulation frequencies of 0, 0.5, 3, 25, and 35 Hz were ineffective. This frequency-specific response, which occurred while the 147-MHz carrier field was maintained at the same power density, indicates that the field-induced efflux of calcium ions was not due to heating of the samples.

In another report, Bawin *et al.* (1978) exposed chick brain tissue for 20 min to 450-MHz fields, amplitude modulated at 16 Hz, at 0.75 mW/cm^2 (SAR estimated at 0.0035 W/kg) under a variety of chemical conditions. The results demonstrated that (a) the enhanced efflux of calcium ions is not highly sensitive to the external calcium concentration, (b) bicarbonate appears to be important for enhanced efflux, (c) lowering the pH from 7.6 to 6.8 in the presence of bicarbonate may enhance the magnitude of efflux, and (d) lanthanum causes a reversal to field-induced retardation of calcium ion efflux.

Corroboration of the frequency-specific response described by Bawin and co-workers was provided by Blackman *et al.* (1979), who showed that 16-Hz amplitude modulation of 147-MHz carrier waves caused enhanced efflux in chick brain tissue *in vitro*, whereas modulation frequencies of 3, 9, and 30 Hz did not. Although the data had large variances, an unusual intensity response was described, i.e., only 0.83 mW/cm^2 (SAR estimated at 0.0014 W/kg) produced a statistically significant efflux enhancement (intensity values are corrected based on discussion in Blackman *et al.* 1980a); power densities (0.11, 0.55, 1.11 and 1.38 mW/cm^2) below and above the effective value did not cause efflux. In a later report, Blackman *et al.* (1980a) used a revised statistical model and experimental procedure to reduce the influence of the large sample variance. An intensity response identical to their earlier result was found. However, when the distance between samples was halved, the range of intensities that produced enhanced efflux increased to include 0.55, 0.83, 1.11 and 1.38 mW/cm^2, whereas lower and higher values of 0.11 and 1.66 mW/cm^2 were ineffective. In addition, an intensity region from 0.55 to 1.11 mW/cm^2 caused enhanced efflux when 9 Hz was used as the modulation frequency. These data, obtained with a more rigorous experimental protocol, provided additional support for the results of Bawin *et al.* (1975) and Blackman *et al.* (1979); however, the explanation for the dependence on sample spacing awaited further developments.

Joines *et al.* (1981) examined the dependence on sample spacing by calculation of the electrical coupling between the samples; for similicity the samples were modeled as spheres. They found that increased electrical interaction between the more closely packed spheres produced a broader range of internal field strengths within each sphere. Thus, if a given internal field strength were necessary to cause enhanced efflux, the chance would be greater for that internal field strength to occur in closely coupled samples exposed to a specific range of incident intensities. Joines *et al.* (1981) found this result to be consistent with the experimental findings in Blackman *et al.* (1980a). Thus a potential artifact was shown to be a logical result of the experimental procedures.

The intensity response observed by Blackman *et al.* (1979) with modulated 147-MHz carrier waves was confirmed by Sheppard *et al.* (1979) with 450-MHz carrier waves, modulated at 16 Hz; calcium-ion efflux was enhanced at 0.1 and 1.0 mW/cm^2 but not at 0.05, 2.0, or 5.0 mW/cm^2. (The estimated SAR at 1.0 mW/cm^2 is 0.0047 W/kg.) The results of these two reports show that the intensities producing calcium-ion efflux from chick brain tissue *in vitro* are within the range of 0.1 to 1.38 mW/cm^2 for modulated 147-MHz and 450-MHz carrier waves.

The apparent carrier-frequency independence of effective intensities was tested with a 50-MHz carrier wave, amplitude modulated at 16 Hz. Enhanced efflux of calcium ions occurred within two intensity regions (between 1.44 and 1.67, and at 3.64 mW/cm^2; SARs were 0.0013 and 0.0035 W/kg, respectively) separated by intensities of no effect, including 0.72 mW/cm^2 (Blackman *et al.* 1980b). These effective intensity values were different from the corresponding values of 147-MHz radiation; thereby indicating a dependence on carrier frequency. In addition this result revealed the existence of more than one range of effective intensities.

The apparent discrepancy in effective power densities at the three different carrier frequencies (50, 147, and 450 MHz) has been resolved by the finding that efflux is dependent on the electric field strength within the tissue and not on incident intensity (Joines and Blackman 1980). The calculation to transform the incident intensity to internal field strength was based on an empirical model described by Joines *et al.* (1981). With the data available at 50 and 147 MHz, the model was used to predict intensities that would produce both alterations and no alterations in calcium-ion efflux; some predictions were tested and found to be valid (Blackman *et al.* 1981). These reports described two intensity ranges that appear effective for enhanced efflux at both 50 and 147 MHz, identified the internal electric field strength rather than incident intensity as the important exposure parameter, and showed the

importance of frequency-dependent complex permittivity values of brain tissue in the conversion of incident intensity to internal field strength. The exposures at 50 and 147 MHz caused no generalized heating of the sample. The maximum temperature rise was calculated to be <0.0004°C, and SAR calculated at each carrier frequency was <0.0014 W/kg (Blackman *et al.* 1980b).

Subsequent to the critique by Athey (1981) that the simple spherical model used by Joines and Blackman (1980) was too idealized, these authors showed that a layered sphere model produced relationships between incident intensities at 50, 147, and 450 MHz and internal field strengths that were also consistent with the experimental results (Joines and Blackman 1981). The success of the initial, simple models to predict intensity regions of both field-induced efflux enhancement and no enhancement demonstrates the utility of the approach. More refinements in the models are necessary before the experimental situation is realistically described.

Shelton and Merritt (1981), who used different procedures from those described by Bawin *et al.* (1975), Blackman *et al.* (1979, 1980a,b), and Sheppard *et al.* (1979) reported no change in calcium-ion efflux from rat brain. Brain tissue, labeled *in vitro* with radioactive calcium, was irradiated at 1 GHz, pulse-modulated with square waves at 16 or 32 Hz (0.5, 1.0, 2.0, and 15 mW/cm^2). In a second report, Merritt *et al.* (1982) exposed rat brain tissue labeled *in vivo* with radioactive calcium to microwave radiation, pulse modulated at 16 Hz (20-ms pulse width). The intensities for the 1-GHz carrier frequency were 1 mW/cm^2 (SAR = 0.29 W/kg) and 10 mW/cm^2 (SAR = 2.9 W/kg); and for the 2.45-GHz carrier frequency, 1 mW/cm^2 (SAR = 0.3 W/kg). In addition, animals labeled with radioactive calcium were exposed for 20 min to 2.06-GHz radiation at one of 17 different combinations of intensity and pulse repetition rate: 0, 0.5, 1.0, 5.0, 10.0 mW/cm^2 (SAR was 0.24 W/kg per mW/cm^2); and 0, 8, 16, 32 Hz (pulse width was 10 ms). After exposure, brain tissue was analyzed for radioactivity. No statistically significant field-induced enhancement of calcium-ion efflux or change of calcium content in the brain tissue was found. The reason for these negative findings is not known; however, the use of square wave rather than sine wave modulation, the different biological preparation, and different medium composition are factors that may have influenced the outcome.

5.7.5.2 Additional CNS Studies

The reports of field-induced calcium-ion efflux from chick brain tissue *in vitro* have led to other CNS studies. Synaptosomes, prepared from rat cerebra and labelled with radioactive calcium, were exposed for 10 min at 0.5 mW/cm^2 to 450-MHz fields, amplitude modulated at 0, 16, or 60 Hz (Lin-Liu and Adey 1982). Only 16 Hz affected the efflux kinetics of calcium ions. Although the SAR can be estimated as low, an exact value cannot be unequivocally established because the exposure chamber may have been operated in a multimodal condition. (See Weil *et al.* 1981.) Nevertheless, this result is modulation dependent, and it is unlikely that heating is involved as a causative agent.

Similar field-induced efflux enhancement has been reported in a live animal. Adey *et al.* (1982) exposed awake, immobilized cats to 450-MHz fields, amplitude modulated at 16 Hz, at 3.0 mW/cm^2 (SAR = 0.29 W/kg). The release of calcium ions from the cortex was observed as a function of time. Irradiation for 60 min caused episodes of enhanced efflux lasting 20 to 30 min and extending into the postexposure period. Although focusing on a different component of the efflux kinetics than that studied by Lin-Liu and Adey (1982), these results demonstrate that RF fields modulated at 16 Hz can cause changes in both a subcellular membrane system and in the live mammal. Thus, the field-induced phenomenon is not restricted to an avian species nor to *in vitro* preparations.

Recently, Dutta *et al.* (1984) observed field-induced enhancement of calcium ions from cells of human origin. Monolayer cultures of human neuroblastoma cells were exposed for 30 min at ten SARs from 0.01 to 5.0 W/kg to 915-MHz fields, with or without sinusoidal amplitude modulation (80 percent) at frequencies between 3 and 30 Hz. Significant increases in the efflux of calcium ions occurred at two SARs (0.05 and 1.0 W/kg). The increased efflux at 0.05 W/kg was dependent on the presence of 16-Hz modulation but not at the higher value. Exposure at modulation frequencies between 3 and 30 Hz (SAR = 0.05 W/kg) revealed a peak in the response at 16 Hz. Although the effective SAR (0.05 W/kg) for 16-Hz modulation is more than 38 times greater than the SARs for enhanced efflux of calcium ions from chick brain tissue *in vitro,* the low-frequency response pattern was similar to that reported by Bawin *et al.* (1975) and Blackman *et al.* (1979). The relation of enhanced efflux with unmodulated fields at 1.0 W/kg with the effects of modulated fields is not known at this time; however, it is not due to a temperature increase in the sample because enhancement was not found at SARs of 2.0 and 5.0 W/kg.

The effect of modulated RF fields on the EEG was investigated by Takashima *et al.* (1979). Rabbits were exposed 2 h daily for 6 weeks to 1.2 MHz, amplitude modulated at 15 Hz, or 5 MHz amplitude modulated at 14 Hz. Following exposure, the EEG was recorded with scalp electrodes and, when compared to the pretreatment EEG pattern, was found to be altered with enhanced low-frequency components and decreased high-frequency components. The EEG pattern returned to the pretreatment pattern after

several weeks postexposure. Although the electric field intensity was given as 500 V/m, with an error factor as large as 2, the important aspect of the results was that unmodulated fields of similar intensity had no effect on the EEG pattern. The absence of metallic electrodes in the animal during exposure avoids the major criticism of earlier studies that reported field-induced changes in EEG patterns (Gavalas *et al.* 1970; Bawin *et al.* 1973).

Sagan and Medici (1979) studied the influence of 450-MHz fields, sinusoidally amplitude modulated at either 3 or 16 Hz, on locomotor activity in young chickens. The experiments were performed in a plastic, modified Skinner box with light beams to monitor activity; the complete apparatus was placed in an anechoic chamber and exposed in the far field. The authors found no statistically significant change in performance during or immediately after a 23-min exposure at 1 or 5 mW/cm^2 (SAR estimated at 0.2 and 1.0 W/kg). They concluded that the lack of a field-induced response could be due to the use of modulation frequencies not present in the chicken's EEG during performance on the particular (fixed-time schedule) task. An alternative possibility, based on the multiple-intensity ranges observed for field-induced calcium-ion efflux, is that the two intensities used in this study may have been outside the effective ranges.

In summary, four groups (Adey *et al.*; Blackman *et al.*; Dutta *et al.*; Takashima *et al.*) have shown that RF fields, sinusoidally modulated at sub-ELF frequencies, especially 16 Hz, cause CNS changes in different *in vitro* preparations and in the live animal. Many of these studies have been analyzed in reviews (Adey 1981; Blackman *et al.* 1981; Greengard *et al.* 1982; Myers and Ross 1981). It is generally agreed that both the mechanism of interaction and the physiological consequences of these changes are yet to be established.

5.7.5.3 Non-CNS Studies

The effects of exposure of pancreatic tissue and T-lymphocytes to RF fields, sinusoidally amplitude modulated at low frequencies, have been examined. An increase of calcium-ion efflux from rat pancreatic tissue exposed *in vivo* at 2 mW/cm^2 for 1 to 2.5 h at 147 MHz, modulated at 16 Hz (estimated SAR $<$ 0.075 W/kg), has been reported by Albert *et al.* (1980). However, the efflux was not accompanied by a change in protein secretion, which is normally associated with calcium mobilization in the pancreas. The authors attributed the lack of protein secretion to a limitation imposed by the exposure conditions, i.e., a relatively small volume of medium was available to the tissue for normal metabolic activity.

In another *in vitro* assay, the cytotoxic activity of mouse T-lymphocytes was suppressed by a 2-h exposure (1.5 mW/cm^2) to 450-MHz fields, modulated at frequencies between 16 and 100 Hz (Lyle *et al.* 1983). Peak suppression occurred at 60-Hz modulation, with smaller effects at 16, 40, 80, and 100 Hz. The exposed cells recovered full cytotoxic activity 12.5 h after the termination of exposure. This result demonstrated an inhibitory but reversible effect on a cell-mediated immune response by modulation frequencies.

5.7.5.4 Sinusoidal ELF and Sub-ELF Signals

Most of the studies reviewed above demonstrate an absolute requirement for low-frequency sinusoidal modulation of the RF carrier wave in order for the signal to be effective biologically. For completeness, several reports are mentioned that describe biological effects of exposure to low frequencies in the absence of an RF carrier wave. Bawin and Adey (1976, 1977) exposed chick and cat cerebral tissue for 20 min to 1, 6, 16, 32 or 75 Hz at electric field gradients of 5, 10, 56, and 100 V_{p-p}/m in air. Only two frequencies, 6 and 16 Hz, caused a reduction in calcium-ion efflux at 10 and 56 V/m for the chick tissue, and at 56 V/m for the cat tissue. Because all other combinations produced no field-induced responses, the authors described "amplitude and frequency windows" for calcium-ion efflux. Electric field gradients within the tissue were estimated to be 10^{-5} V/m. The field-induced reduction in efflux is in contrast to the enhancement caused by modulated RF carrier waves. Nevertheless, the frequency dependence observed in the two studies was similar, which suggests an interaction with a common substrate as the site of interaction.

Blackman *et al.* (1982) used chick brain to study the influence of 16-Hz signals at 15 intensities between 1 and 70 V_{p-p}/m on the efflux of calcium ions. Two intensity regions that included 5, 6, and 7.5 V/m and 35, 40, 45, and 50 V/m caused enhanced efflux. No field-induced effects were seen below (1, 2, and 3.5 V/m), between (10, 20, and 30 V/m), or above (60 and 70 V/m) the two effective intensity regions. Moreover, 1- and 30-Hz signals at 40 V/m caused no change in efflux. This finding is consistent with the reports of multiple-intensity regions of enhanced efflux caused by modulated RF radiation (Blackman *et al.* 1980b, 1981). In addition to the intensity response, the frequency dependence corroborated reports by Bawin and Adey (1976) for low-frequency signals, and by Bawin *et al.* (1975) and Blackman *et al.* (1979) for modulated RF fields.

In these two low-frequency studies, the cause of the slight difference in effective intensities is unknown. The major disagreement in the results of Bawin and Adey (1976) and Blackman *et al.* (1982) is the direction of the change in efflux; the latter authors state that the "cause may be found in the slightly different preparations and procedures used in the two laboratories."

Several research groups have reported biological changes induced by low-frequency, sinusoidally oscillating magnetic fields. The myxomycete *Physarum polycephalum* has a longer mitotic cycle and reduced respiration rate after chronic exposure to 2.0-gauss magnetic fields at 75 Hz (Goodman *et al.* 1979). Human fibroblasts in culture exposed to sinusoidally varying magnetic fields for a wide range of frequencies (15 Hz to 4 kHz) and amplitudes (0.25 to 5.6 gauss) exhibit enhanced DNA synthesis (Liboff *et al.* 1984). Fruit flies *(Drosophila melanogaster)* preferred not to deposit eggs in a 10-gauss, sinusoidally varying 50-Hz magnetic field; similar exposure during development of the egg produced less viable eggs and pupae in the exposed samples than in controls (Ramirez *et al.* 1983). These results suggest that low-frequency, sinosoidally varying fields may alter fundamental biological processes.

Low-frequency, pulsed magnetic fields have also been reported to produce alterations in diverse biological systems. These systems include the developing chick embryo (Delgado *et al.* 1982; Ubeda *et al.* 1983), *Drosophila* egg laying and mortality (Ramirez *et al.* 1983), the de-differentiating amphibian red blood cell (Chiabrera *et al.* 1979), transcription in the *Dipteran* chromosome (Goodman *et al.* 1983), nerve cells in culture (Dixey and Rein 1982), and mouse bone cells in culture (Luben *et al.* 1982). Many of these studies used an intricate pulsed waveform, which has been used in therapeutic devices for bone nonunions. All the studies used pulse repetition rates below 500 Hz, with most below 100 Hz. Recently, Liboff *et al.* (1984) questioned the need for the particular wave shapes because it appears that the essential element is the low-frequency field.

5.7.5.5 Summary

Many reports of effects of RF fields that are amplitude modulated at very low frequencies have not been independently corroborated. The major exception is calcium-ion efflux from chick brain tissue *in vitro* at intensity levels far below those that cause heating. This exception, combined with the results of studies of brain biochemistry and EEGs in animals and with synaptosomes and human neuroblastoma cells in culture, provides evidence that CNS tissue from several species, including human beings, is affected by low-intensity RF fields sinosuoidally amplitude modulated at specific low frequencies (Table 5-23). The physiological significance of these field-induced effects is not established.

5.7.6 Unresolved Issues

In addition to the CNS-related changes, amplitude-modulated RF fields have been reported to alter an immune response and a pancreatic tissue function. These reports with diverse biological systems are without apparent connection to each other except for the physical agent causing the change. The biological effects of frequency-modulated RF radiation, e.g., FM radio signals, are not known. The reports cited above of Merritt and co-workers indicate that pulsed square-wave modulation may not cause calcium-ion efflux, whereas data from the Bawin *et al.* and Blackman *et al.* studies show that sine wave modulation is effective.

No report has yet described a mechanism of action in sufficient detail to identify the conditions necessary and sufficient to explain unequivocally calcium-ion efflux in the brain or the other biological changes caused by modulated RF fields. The response to specific frequencies and intensities is unusual and at present unexplained. This response to amplitude-modulated RF radiation or to sub-ELF signals alone may be a true field effect at a very low SAR and at biologically relevant frequencies, i.e., in the range of frequencies normally present in the EEG. The frequency-specific nature of the responses provides evidence against heat as the underlying cause. The unusual, multiple-intensity-range response challenges standard dose-response analyses, and by its very nature, may prohibit the invocation of threshold levels.

Other areas of unresolved issues include comparisons of CW vs. PW microwaves under identical exposure conditions. Such studies would help determine if the differences seen by Wangemann and Cleary (1976) were due to different exposure conditions or to the irradiation parameters (CW or PW). There is also a paucity of information on the effects of RF radiation at different frequencies, particularly at frequencies of environmental importance. Studies at different frequencies would help to determine the reasons for differences in effects at similar SARs. Such studies might help explain why Wangemann and Cleary (1976) reported serum chemistry changes in rabbits at 0.8 W/kg (2450 MHz), and why Lovely *et al.* (1977) reported no change in serum chemistry values in rats at 1 W/kg (918 MHz).

There are also data such as those reported by Boggs *et al.* (1972) where the results from microwave heating to a predetermined temperature are different from those resulting from the same temperature produced by other means of heating. Perhaps there are differences in the uniformity of heating or in the rate of heating which would account for these differences. In addition, a study by Deficis *et al.* (1979) reported elevated serum triglyceride and β-lipoprotein levels in mice exposed to 2450 MHz at 1.5, 3.3, or 4 mW/cm^2, but not at 1 mW/cm^2. Because the exposures were conducted in a multimodal cavity, SAR values were not reported and cannot be predicted. If this study is repeated, particular attention should be given to dosimetry. An alternative is to

make or report dosimetric measurements in the exposure system used.

The reported effects on thyroid function at 3.75 W/kg for 60 h contrasted with no effect at 6.25 W/kg for 16 h (Parker 1973) suggests that the total amount of energy absorbed may also be an important consideration. Additional studies could define further the relative importance of dose rate compared with total dose.

Table 5-23. Summary of Studies Concerning Biological Effects of Low Frequency Modulation of RF-Radiation

Effects	Species	RF (MHz)	Modulation (Hz)	Intensity (mW/cm^2)	Time (min)	SAR (W/kg)	Reference
Altered calcium-ion efflux in brain tissue *in vitro*							
frequency specificity	Chicken	147	6-20	1-2	20	0.002*	Bawin *et al.* (1975)
influence of pH and lanthanum	Chicken	450	16	0.75	20	0.0035*	Bawin *et al.* (1978)
frequency and intensity specificity	Chicken	147	16	0.83	20	0.0014*	Blackman *et al.* (1979)
intensity specificity and sample spacing	Chicken	147	9, 16	0.83	20	0.0014*	Blackman *et al.* (1980a)
theoretical analysis of sample spacing	Chicken	147	16	0.83	20	0.0014	Joines *et al.* (1981)
intensity specificity	Chicken	450	16	0.1-1	20	0.0005-0.005*	Sheppard *et al.* (1979)
two intensity ranges	Chicken	50	16	1.5 3.6	20	0.0013 0.0035	Blackman *et al.* (1980b)
theoretical analysis of RF dependence	Chicken	50 147 450	16	—	20	~0.001	Joines and Blackman (1980); Athey (1981); Joines and Blackman (1981)
test of predictions of theoretical analyses	Chicken	147	16	0.37 0.49	20	0.0006 0.0008	Blackman *et al.* (1981)
no effect for pulse modulation	Rat	1000	16*, 32*	0.5-15	20	0.15-4.35	Shelton and Merritt (1981)
no effect for pulse modulation	Rat	1000 2450	16* 8*, 16*, 32*	1, 10 1	20	0.29-2.9 0.3	Merritt *et al.* (1982)
change in calcium efflux kinetics in synaptosomes	Rat	450	16	0.5	10	—	Lin-Liu and Adey (1982)
frequency and intensity specificity in cultured neuroblastoma cells	Human being	915	16	—	30	0.05	Dutta *et al.* (1984)
Altered calcium-ion efflux in brain tissue *in vivo*							
no effect for pulse modulation	Rat	2060	8*, 16*, 32*	0.5-10	20	0.12-2.4	Merritt *et al.* (1982)
change in efflux kinetics from awake animal	Cat	450	16	3	60	0.29	Adey *et al.* (1982)
Changed EEG patterns	Rabbit	1.2 5.0	15 14	500 V/m 500 V/m	120 x 6wk 120 x 6wk	— —	Takashima *et al.* (1979)
No change in behavior	Chicken	450	3, 16	1, 5	23	0.2, 1.0*	Sagan and Medici (1979)
Suppressed T-lymphocyte activity	Mouse	450	16-100	1.5	120	—	Lyle *et al.* (1983)
Altered calcium ion efflux in pancreatic slices *in vitro*	Rat	147	16	2	60-150	<0.075	Albert *et al.* (1980)

*Est. SAR.
*Square wave.

5.8 Genetics and Mutagenesis

Carl F. Blackman

Genetics is the branch of biology that deals with the heredity and variation of organisms. The biochemical basis of heredity lies in the sequence of bases found in the nucleic acids, deoxyribonucleic acid (DNA), and (in a few cases) ribonucleic acid (RNA). All living cells have the biochemical machinery to detect the sequence of bases in the DNA and to transcribe sections of DNA information into similar sequences of bases in RNA. The RNA molecules then move to other locations inside the cell, where their information is translated into various series of amino acids joined together in sequences that were precisely defined in the original DNA molecule. These specifically arranged amino acids form proteins, some of which are enzymes. Enzymes, in turn, catalyze biochemical reactions that ultimately result in the growth and propagation of intact organisms. Hereditary (genetic) material can be either nucleic acids alone, as found in bacteria and viruses, or a nucleic acid in association with proteins, which form the chromosomes found in more complex organisms, including man.

Heat is a physical agent that can disrupt genetic material by causing the temperature to rise above normal physiological range. The effect of heat, or temperature rise, has been studied in many biological systems. As examples, heat has been shown to cause physicochemical damage in isolated DNA preparations (Lindahl and Nyberg 1974; Ginoza *et al.* 1964; Ginoza and Miller 1965) and in bacteria (Pellon *et al.* 1980); chromosome changes in *Drosophila melanogaster* (Grell 1971) and in the *Locusta migratoria* (Buss and Henderson 1971), including a change from diploid to haploid in pollen from maize (Mathur *et al.* 1980); enhanced sensitivity to other agents in mammalian cell cultures (Ben-Hur *et al.* 1974) and in *D. melanogaster* (Mittler 1979); reduced fertility in rats (Bowler 1972; Fahim *et al.* 1975); and mutations in bacteriophages (Bingham *et al.* 1976), in bacteria (Zamenhof and Greer 1958) and in *D. melanogaster* (Muller and Altenburg 1919). Because absorbed RF energy is usually dissipated as heat, all reports of genetic and mutagenic changes caused by exposure to RF radiation must be examined closely to determine whether temperature rise, or some other mechanism, is the causative agent.

Mutations are relatively permanent changes in the hereditary material involving either a physical change in chromosomal relations or a biochemical change in the sequence of nucleic acid bases that make up the genes. These changes can be passed on to future generations of cells. Two different types can be affected: germ cells, which are egg or sperm or their antecedent cells; and somatic cells, which form all other tissues in the body. Mutations in germ cells can be passed on to future generations of the organism, whereas mutations in somatic cells of an organism may lead to impairment of organ function and, in the extreme case, to cancer. Most mutations are considered harmful because they disturb the biochemical processes necessary for the survival of the organism and for the propagation of the species.

Evaluation of the mutagenic potential of RF radiation has generally followed the procedures established for testing the mutagenic activity of chemicals (Hollaender 1971). This evaluative scheme utilizes

- molecular systems, to detect changes in the hereditary material;
- single-cell organisms, to detect changes in structure and function that are transmissible to the next generation;
- multicellular systems, including plants and animals, to detect changes in reproductive potential;
- infra-human primates, to detect changes in reproductive potential.

The evaluation scheme starts with simple, well-defined genetic systems that enable rapid analysis and identification of suspected agents meriting further evaluation. The more complex biological systems used in further testing require substantially larger investments of time and resources.

In summary, the following conclusions may be drawn from the review of the literature on the genetic and mutagenic effects of RF radiation. Experiments designed to examine the genetic consequences of exposure to RF radiation have been conducted with a variety of test systems, including isolated DNA, prokaryotic and eukaryotic cells, and whole animal systems. Radiation-induced effects on biochemical properties of DNA, on chromosomal structure, on mutation induction, and on reproductive capabilities have been investigated. The reports demonstrate that

(1) RF irradiation of low-to-moderate intensity does not cause mutations in biological systems in which temperature is adequately controlled, and

(2) the only exposures that are potentially mutagenic are those at high power densities of CW or PW radiation, i.e., exposures that result in substantial thermal loading at sensitive sites or result in extremely high electric-field forces.

These conclusions must be qualified because (a) only specific frequencies or small regions of the RF spectrum have been experimentally examined, (b) few detailed dose-response analyses have been performed, (c) the influence of modulated radiation has not been sufficiently examined, an (d) potential synergistic reactions with other environmental stresses have not been adequately studied.

5.8.1 Effects on Genetic Material of Cellular and Subcellular Systems

5.8.1.1 Physical and Chemical DNA and Chromosome Studies

Mechanisms for the absorption of RF radiation by DNA molecules are treated elsewhere in this document (Sec. 3.2, RF-Field Interactions with Biological Systems, and Sec. 5.1, Cellular and Subcellular Effects). This section addresses the experimental studies that have examined changes in genetic material induced by RF radiation. Purified DNA or DNA extracted from the testes of exposed mice has been examined to determine whether the physical properties of the molecule can be altered by the exposure to RF radiation. Hamrick (1973) examined the thermal-denaturation profiles of aqueous solutions of isolated DNA exposed *in vitro* at 37°C to 2450-MHz (CW) radiation (SAR = 67 W/kg). No changes were found. Even elevated temperatures (to 50°C) produced by microwaves (1 h at an SAR estimated to be 160 W/kg) did not cause a difference in the thermal denaturation profile. (See Sec. 5.1 for details.)

Varma and Traboulay (1976) reported radiation-induced changes in thermal denaturation profiles (i.e., shift to lower temperature in the midpoint of the transition curve [T_m] and reduction in the maximum hyperchromicity) as well as changes in the base composition of testicular DNA extracted from anesthetized mice whose testes were irradiated in the near field. Ten animals were exposed individually either to 1.7-GHz radiation at 50 mW/cm^2 for 30 min (SAR estimated at 2.4 W/kg for testes alone) or at 10 mW/cm^2 for 80 min (SAR estimated at 0.48 W/kg for testes alone), or to 0.985-GHz radiation at 10 mW/cm^2 for 80 min (SAR estimated at 0.26 W/kg for testes alone). The animals exposed to 1.7-GHz fields at 50 mW/cm^2 or to 0.985-GHz fields at 10 mW/cm^2 were given a 1-day recovery period before they were subjected to euthanasia, and the DNA was extracted. The animals exposed to 1.7-GHz fields at 10 mW/cm^2 were used in another test for 8 weeks before euthanasia, and the DNA was extracted. Identical results are reported for the 1.7-GHz exposure at 50 mW/cm^2 in another publication (Varma and Traboulay 1977). They conclude "that biological damage may be due to the combined effect of thermal and nonionizing radiation."

To evaluate the relative contributions of the thermal effects versus nonionizing radiation *per se*, the results reported by Varma and Traboulay must be examined with careful attention to the control experiments and to the potential size of the thermal insult. A critical examination of the base composition and hyperchromicity data reveals that the authors' explanations are not supported by the data. Although the higher percent adenine/thymine in the DNA extracted from exposed animals could be responsible for the drop in T_m, the variability normally inherent in the extraction procedures and in the base composition measurements is not given. Without an explicit indication of this variability, one cannot conclude that the differences between control and exposed samples are significant; nor can it be concluded that the differences result from the radiation exposure directly, rather than from the extraction procedures. Similarly, the potential size of the thermal insult must be examined. The SAR values for testicular exposures were crude estimates based on incomplete information and appear too low to produce the types of damage described in the report. For example, in an anesthetized animal exposed in the near field to 1.7-GHz radiation at 50 mW/cm^2 (SAR estimated at 2.4 W/kg) and shielded with Eccosorb except for the testes, a 1 to 2°C rectal-temperature rise was recorded following exposure (Varma and Traboulay 1977). Since no description of the exact shielding technique was provided, it is possible that more than just the testes of the animal was exposed, thus accounting for the rectal temperature increase. In another report (Varma and Traboulay 1975), animals were exposed under the same conditions as described above, except that the exposure time varied between 30 and 40 min, and the testes were examined histologically. The authors report that "the lumens were empty with complete disintegration of spermatids, Sertoli cells and the delicate connective tissue which surrounds the seminiferous tubules." This type of damage can be caused by abnormal temperature elevation of the tissue (Muraca *et al.* 1976). Since anesthesia has been shown to impair thermoregulation (Cairnie *et al.* 1980b), it is possible that sufficient energy was deposited in the anesthetized animals to cause the temperature elevation responsible for many of the changes that are attributed to microwave-specific effects. (See Sec. 5.3.3, Reproductive Effects—Testes, for further discussion of the influence of abnormal temperature rise on radiation-induced damage in the testes.) Thus, an alternative explanation for the results described by these authors is that the causative agent is elevated temperatures, produced at sensitive sites in the tissue by the radiation exposures. This explanation is consistent with the available data, and there is no need to advocate an unknown mechanism for radiation-induced damage.

Thus, an evaluation of the existing evidence from physical studies on DNA indicates that RF irradiation at low-to-moderate intensities not accompanied by temperature rise causes no changes in DNA bases, the fundamental unit of the genetic code. However, if substantial elevations of temperature occur during exposure, disruptions in the pairing of the two complementary strands, as well as other damage, may result.

Other researchers have used cytogenetic techniques to examine some physical and chemical properties of

chromosomes in intact cells to determine if the relationship of various parts of the genetic material is altered by RF-radiation exposure. Huang *et al.* (1977) stated that no RF-induced chromosomal aberrations were found in white blood cells from Chinese hamsters exposed to 2450-MHz radiation at power densities up to 45 mW/cm^2 (SAR = 20.7 W/kg) for 15 min/day on 5 consecutive days; however, the data are presented in a manner which does not permit independent statistical analysis. McRee *et al.* (1978) in a preliminary report found no sister chromatid exchanges in bone-marrow cells of mice exposed to 2450-MHz fields at 20 mW/cm^2 (SAR = 15.4 W/kg), for 8 h daily, 28 days total. Alam *et al.* (1978) showed, in great detail, that chromosomal aberrations occurred in a Chinese-hamster-cell line (CHO-K1) exposed 30 min to 2450-MHz radiation from a diathermy applicator, but only if the temperature of the culture was allowed to rise to 49°C during exposure. These authors demonstrated that irradiation of cell lines at high (> 200 mW/cm^2) power densities (SAR estimated at 360 W/kg) would cause no detectable cytogenetic effects, provided proper temperature control was maintained. Thus, heating seems to account for the observed cytological changes.

Authors of one detailed study used a frequency well below the 1.7- to 2.45-GHz range. McLees *et al.* (1972) exposed rats treated to undergo liver regeneration either to 13.12-MHz CW (4.45 kV_{p-p}/m) fields or to PW (44.1 kV_{p-p}/m, 200-μs pulse width, 50-Hz pulse repetition rate [PRR]) radiation for 28 to 44 h. They examined the effects of radiation on liver cell mitotic activity (i.e., the percentage of cells in mitosis and the number of chromosomal aberrations). Rat liver cells may be very sensitive to exogenous stresses during this regenerative process because they are normally nondividing cells in an intact animal unless challenged to divide *in situ*. However, the authors found no RF-induced alterations in chromosomal morphology (SAR estimated at 1.2 to 1.3 W/kg). Their results indicate that no cytogenetic changes would be expected in the range of frequencies studied for low-intensity exposures. Thus, although there are reports indicating that exposure to RF radiation can cause cytogenetic changes, these changes appear to result from radiation-induced elevations of temperature.

McRee *et al.* (1981) have recently published the paper that was reviewed when in preliminary format (McRee *et al.* 1978). Twelve 10-week-old female mice (CD-1 strain) were exposed to 2450-MHz CW fields at 20 mW/cm^2 (SAR = 21 W/kg) for 8 h daily (4 h in morning, 1 h delay, 4 h in afternoon) each day for 28 days. Exposure was dorsal. Immediately after the last exposure, procedures were initiated that produced, 19 h later, labeled bone marrow cells that were processed to give a measure of sister chromatid exchanges. Upon analysis, no statistical differences were detected in the mean number of sister chromatid exchanges per cell between the exposed and either of the unexposed control groups (sham and cage control). Based on the percentage of mitotic cells in each group, the microwave treatment did not have an effect on the rate of cell proliferation in bone marrow of mice. These results are consistent with those given in the preliminary report.

5.8.1.2 Biological Studies of DNA and Chromosomes

Bacteria have been used to study the mutagenic potential of RF radiation, because the single-cell system is simple, easy to culture, quick to test, and relatively sensitive to the action of mutagenic agents. By using the bacterial system and the biological amplification it provides for any DNA change, molecular biologists have been able to decipher the genetic code and to identify a change in as few as one DNA subunit out of 10^{10} to 10^{12} subunits. In contrast, biologists using standard physical techniques such as DNA melting curves usually can detect changes in no better than 0.1 percent of the DNA. Blackman *et al.* (1976) exposed growing cultures of the bacterium *Escherichia coli* either to 1.7- or to 2.45-GHz (CW) radiation for 3 to 4 h. Exposure at 1.7 GHz was in the near field at 88 V_{rms}/m or ~ 250 V_{p-p}/m (SAR = 3 W/kg). The 2.45-GHz exposures were in the far field at either 10 or 50 mW/cm^2 (SAR = 15 or 70 W/kg, respectively). Although exposure of growing cells provided enhanced sensitivity to mutagenic agents, no mutagenic activity was detected. A positive control, ultraviolet (UV) light, caused mutations and was used to demonstrate the sensitivity of the assay method. Dutta *et al.* (1979a) exposed growing cultures of various bacterial strains of *Salmonella typhimurium,* commonly used in the Ames testing procedures to detect chemical mutagens (Ames *et al.* 1975), to 2.45-GHz (CW) radiation for 90 min at 20 mW/cm^2 (SAR = 40 W/kg) and to 8.6-, 8.8-, 9.0-, 9.2-, 9.4-, and 9.6-GHz (PW) radiation (1-μs pulse width, 1-kHz PRR) at 10 and 45 mW/cm^2 average power densities, and 10,000 and 45,000 mW/cm^2 peak power densities. (The SAR at 45 mW/cm^2 was estimated at 80 W/kg.) No mutagenic activity was observed under any of these exposure conditions.

Another approach with bacterial systems is to test for radiation-induced alterations in genetic processes, including cell death. Since most mutations are detrimental, they might be detected indirectly by this method. Corelli *et al.* (1977) exposed cultures of *E. coli* to microwaves at frequencies swept between 2.6 and 4.0 GHz for 8 h (SAR = 19 W/kg). Although at 26°C these cultures were probably growing slowly, no change was noted in the number of colony-forming units (CFUs) in the cultures following irradiation, indicating no detectable lethal events because of the exposure. These workers also examined the infrared (IR) spectrum of these cells

when exposed to 3.2-GHz radiation for 11 to 12 h (SAR is either 21 or 16 W/kg). There was no observable effect on the molecular or conformational structure of these cells, in contrast to results obtained with a positive control, ionizing radiation. Two strains of *E. coli,* one deficient in an enzyme needed to repair damaged DNA, were tested for survival following microwave exposure (Dutta *et al.* 1979b). The exposure conditions were 8.6-GHz (PW) radiation (1-μs pulse width, 1-kHz PRR, SAR = 12 W/kg) for 1, 2, 4, or 7 h. There was no significant change in the relative growth patterns of these strains that could be attributed to microwave-induced DNA damage that was repaired in one strain, but not in the other. Blackman *et al.* (1975) exposed a different strain of *E. coli* in log phase (actively dividing) and in lag phase (undergoing metabolic activities preparatory to division) at 32°C for 4 h to 2.45-GHz radiation at 0.005, 0.5, 5.0, or 50 mW/cm^2. (At 50 mW/cm^2 power density the SAR = 75 W/kg.) Additional experiments were conducted at 5 mW/cm^2 and 25°C to test for the influence of cold stress, and in two-culture media at 30 and 35°C to compare the relative influence of a rich medium with a minimal medium; the latter required greater utilization of the genetic apparatus of the cell for growth to occur. Except for enhanced growth at 50 mW/cm^2, which was attributed to slight temperature rises in the exposed cultures, no change was found in the colony-forming ability of the cultures due to the exposure.

Few researchers have used single-cell systems more complex than bacteria specifically to look for RF-radiation-induced mutagenesis. Dutta *et al.* (1979a) exposed a diploid strain of the yeast *Saccharomyces cerevisiae,* a primitive eukaryote, to 2.45-GHz (CW) radiation for 2 h at 20 mW/cm^2 (SAR = 40 W/kg). They found essentially no change in the number of mutations at either of two loci affecting the nutritional requirements for adenine or tryptophan. These investigators conducted additional tests at 8.5-, 8.6-, 8.8-, 9.0-, 9.2-, 9.4-, and 9.6-GHz (PW) radiation (1-μs pulse width, 1-kHz PRR) for 2 h at average power densities of 1, 5, 8.9, 10, 15, 30, 35, 40, or 45 mW/cm^2. Although no measurements of SAR are cited, so that comparisons with CW exposures are difficult, the highest power density was reported to raise the temperature of the culture by 12°C, which would mean substantial absorption of the radiation. (At 45-mW/cm^2 power density the estimated SAR = 80 W/kg.) In no case did the exposures cause a change in the frequency of genetic events, altering the requirements for either adenine or tryptophan, in the treated population as compared with the control population. *Saccharomyces cerevisiae* was also used in two studies by Dardalhon and co-workers. In the first report, Dardalhon *et al.* (1979) exposed two haploid and one diploid strain of the yeast at 20°C in the near field to either 70.5- or 73-GHz CW fields at power densities up to 60 mW/cm^2 (SAR estimated at 17 W/kg) for durations up to 3 h. In the second report, Dardalhon *et al.* (1980) exposed a diploid strain of *S. cerevisiae* at 20°C in the near field of 9.4-GHz (CW) radiation (SAR estimated at < 2 W/kg) for 1 to 5 h, or in the near field of 17-GHz (CW) radiation at either of two power densities (SARs estimated at 28 or < 6 W/kg, respectively) for various times to 24 h. No significant changes attributable to the irradiation were observed in the percent survival, in the induction of cytoplasmic "petite" mutations, in the induction of mitotic recombinations, or in sporulation. Thus, no changes were detected in complex single-cell systems used to examine directly the mutagenic potential of microwaves at frequencies of 9.4, 17, 70.5, or 73 GHz (CW) and SARs of < 2 to 28 W/kg.

Some work has been done with bacteria and yeast cultures that compares the lethal and mutagenic effects of microwaves with those induced by conventional heating. Dutta *et al.* (1980) examined the responses of various strains of the bacteria *S. typhimurium* and *E. coli* and those of a diploid strain of the yeast *S. cerevisiae,* exposed to 8.6-, 8.8-, or 9.0-GHz (PW) radiation (1-kHz PRR, 1-μs pulse width) at average power densities to 45 mW/cm^2 (SAR estimated maximum at 80 W/kg). The bacteria were exposed 90 min at an ambient temperature of 37°C, whereas the yeast were exposed 2 h at 30°C. The comparison of these irradiation treatments with those obtained from treatments at elevated temperatures produced by conventional heating indicated that conventional heating could produce cellular damage leading to reduced survival in a manner similar to the changes caused by microwave-induced elevations of temperature (to 10°C above normal growth temperatures). No mutational events occurred in bacteria to 42°C, or in the yeast to 40°C, however, at 45°C, a slight increase in mutational events occurred in the yeast, and at 47°C, in *S. typhimurium.* To obtain some indication of the temperature rise associated with exposure to RF radiation, Dardalhon *et al.* (1979) developed a response curve for zygote formation, the production of a diploid cell from the union of two haploid cells, as a function of temperature. Exposure to 70.5-GHz CW fields at 60 mW/cm^2 (SAR estimated at 17 W/kg) produced a response in zygote formation that could result from a 3°C temperature rise. This result demonstrated that biological systems could be used as sensitive indicators of temperature change under exposure conditions in which temperature can not be readily measured. In another study, Dardalhon *et al.* (1980) exposed a diploid strain of *S. cerevisiae* for 3 h at 52°C. (Normal growth temperature is 30°C.) Large changes were observed in the percent survival, in the induction of cytoplasmic mutations, and in the induction of mitotic recombinations after 3 h, compared to no changes in these end points during microwave exposure at 20°C to 9.4-GHz or 17-GHz fields (SAR estimated at < 28 W/kg), described above. Both groups of authors conclude that care

must be exercised in evaluating genetic changes in microbial assay systems when elevated temperatures accompany microwave exposure.

Since 1980, three groups have published reports in this subject area. Dutta extended his previous work (Dutta *et al.* 1979b, 1980) with two strains of *E. coli,* one deficient in an enzyme needed to repair damaged DNA, to compare bacterial growth under high-intensity microwaves and conventional heating (Hossain and Dutta 1982). Both bacterial strains were grown for 2, 5, 10, or 15 h either at 35.2°C or 42.2°C, or exposed to 8.8-GHz (PW) radiation (1-μs pulse width, 1-kHz PRR, SAR = 12 W/kg) at 35.2°C (final temperature of the sample was 42.2°C) and assayed for growth, as colony-forming units. The results demonstrated that although the microwave exposure caused a change in the bacterial growth when compared with the 35.2°C control, it had no effect on the growth of *E. coli* beyond that associated with the radiation-induced temperature increase.

Dardalhon and co-workers (1981) exposed the yeast *S. cerevisiae,* and both normal and repair-deficient strains of the bacterium *E. coli,* to microwave fields and tested for survival and induction of mutations. In diploid yeast, they tested for sporulation capacity and gene segregation during meiosis. They found no evidence for altered survival in any of the bacterial strains following near-field exposure for 30 min to 9.4-GHz CW fields (SAR = 23 W/kg), 17-GHz CW fields (up to SAR = 28 W/kg), or 70- to 75-GHz CW fields (SAR = 9 W/kg), nor any evidence of mutation induction following exposure for 30 min to 70- to 75-GHz CW fields (SAR = 28 W/kg) or 17-GHz CW fields (SAR = 6 W/kg). Exposure of haploid yeast strains to 70- to 75-GHz CW fields (SAR = 28 W/kg), 17-GHz CW fields (up to SAR = 28 W/kg), or 9.4-GHz CW fields (SAR = 23 W/kg) produced no detectable changes in survival, induction of cytoplasmic mutations, induction of reversions, or genetically altered colonies. Similarly, exposure of diploid yeast to 9.5-GHz CW (SAR = 23 W/kg) or 17-GHz CW (SAR = 28 W/kg) fields for 48 h produced no significant alterations in the sporulation capacity nor in meiotic gene segregation. Thus with both prokaryotic and eukaryotic cells these investigators did not detect any significant genetic effects from exposure to microwave radiation at selected frequencies between 9.4 and 75 GHz.

In a series of three detailed papers, Swedish researchers studied the possible genetic effects in bacteria of exposure to high-frequency RF fields (Anderstam *et al.* 1983; Ehrenberg *et al.* 1983; Hamnerius 1983). Tests for forward mutations were performed in two *E. coli* strains and three *S. typhimurium* strains, for backward mutations in three *E. coli* strains and two *S. typhimurium* strains, and for prophage induction in three *E. coli* strains. The bacterial samples were exposed in the far field at 37°C to either 3.07-GHz pulsed fields (500 Hz PRR, 2-μs pulse width) at average power densities up to 210 mW/cm² (SAR = 100 W/kg), or 2.45-GHz CW fields (which were essentially 100-percent amplitude modulated at 100 Hz) at power densities up to 170 mW/cm² (SAR = 80 W/kg). Bacterial samples were exposed similarly to 27.12-MHz CW field components: electric fields at 72 V/m in the sample generated between two parallel plates (SAR = 3 W/kg), and magnetic fields at 20 A/m in the sample generated by a Helmholtz coil (SAR = 20 W/kg). Exposures were conducted for 1 to 7 h, followed by measurements of cellular growth for viability, mutation or prophage induction, or RNA synthesis. The battery of bacterial test systems used in this detailed study was designed to provide a measure of resolving power and thus to place an upper confidence limit on the number of mutagenic events that would be probable for a given result. The authors state that the pooled mutation frequency did not differ from that of the controls, although a weak prophage-induction capability and an ability to modify the response to UV-radiation (DNA repair) were noted. The most prevalent finding was a stimulation of growth, especially for certain strains and as the cultures were entering stationary phase. This result was also exhibited in the RNA synthesis studies. Although the authors discounted at length the influence of temperature difference as the underlying cause of the growth stimulation, because of the high SARs that were used, a 1°C temperature gradient was known to exist between the bacterial samples and the cooling bath. Other workers, notably Livingston *et al.* (1979), have emphasized the extreme caution that must be exercised in interpreting data obtained under conditons where local hot spots could occur. To support their contention that temperature change contributed in only a minor way to the observed growth stimulation, the authors could have conducted exposures at temperatures below and above the optimum growth temperature. If temperature increases were a major factor in the field-induced growth-rate changes, one would expect a reversal in the response between the lower and higher temperatures. The complex biochemical changes that occur as the cells transfer from exponential to stationary growth phase adds further uncertainty to any evaluation of altered growth patterns. Nevertheless, with a comprehensive battery of test systems, the authors were unable to demonstrate any mutagenic activity due to exposures to 27.12-MHz CW, 2.45-GHz CW, or 3.07-GHz pulsed fields.

In another study to determine temperature change during RF exposure, Dardalhon *et al.* (1979) exposed one diploid and two haploid strains of the yeast *S. cerevisiae,* at 20°C in the near field to either 70.5 or 73-GHz CW fields at power densities up to 60 mW/cm² (est. SAR = 17 W/kg) for up to 3 h. No changes were observed in cell survival, or in induction

of mitotic recombination or of cytoplasmic mutations. To obtain some indication of the temperature rise associated with these exposures, the authors developed a biological indicator, namely a response curve for zygote formation as a function of temperature. Exposure to 70.5-GHz CW fields at 60 mW/cm^2 (est. SAR = 17 W/kg) produced a response that could result from a 3°C temperature rise. This result demonstrates the usefulness of biological systems as sensitive indicators of temperature change under exposure conditions where temperature can not be readily measured.

All these reports are consistent with the conclusion reached above that no well-defined genetic effects have been reported occurring from exposure to microwave radiation that could not be attributed to temperature rise. However, the work of Grundler and Keilmann (1983) identifies possible frequency-specific alterations in the growth of yeast (Sec. 5.8.3). The mechanism for this response has not been identified.

5.8.2 Effects on Genetic Material of Higher-Order Biological Systems

5.8.2.1 Plants

Plant systems are sensitive to mutagenic agents and thus can serve to identify conditions that should be examined more carefully in mammalian systems. Although several studies are reported in the literature, none has sufficiently described experimental conditions to allow independent evaluation of the work. Thus, useful mutagenic testing of RF radiation with respect to plant systems has yet to be accomplished and documented.

5.8.2.2 Invertebrates

Several investigators have studied *D. melanogaster*, a standard model for testing mutations induced by RF radiation. No mutagenic effects were reported by Hamnerius *et al.* (1979) in embryos exposed 6 h in water at 24.5°C to 2450-MHz (CW) fields at 100 W/kg. Similar negative effects were reported by Pay *et al.* (1972), who exposed adult males to 2450-MHz fields for 45 min at 4600, 5900, or 6500 mW/cm^2 (SARs estimated at 140, 190, and 210 W/kg, respectively) and mated each of the surviving males individually with two virgin females during 15 consecutive days. No changes were observed in the generation time or sex-ratio pattern of the offspring. These offspring were then mated and observed for possible sex-linked lethal mutations in their offspring. No such mutations were found at frequencies > 1 percent, a detection limit based on the small number of chromosomes (< 800) actually evaluated. An additional caveat by the authors was that the most sensitive stages to detect recessive sex-linked lethal mutations (late spermatocytes and early meiosis) were not tested in their study, because few sperm were still in meiosis at the time of exposure. Mittler (1976), who exposed adult males from various strains of *D. melanogaster* to 29-MHz (CW) fields at 600 V_{rms}/m (SAR roughly estimated at 0.024 W/kg and to 146-MHz (CW) fields at 62.5 V_{rms}/m (SAR roughly estimated at 0.015 W/kg) for 12 h, mated them with virgin females for 12 h every 2 days in production of 4 or 5 broods. In these experiments, brood 4 was produced from sperm irradiated "in or about meiosis." No mutations were induced by these treatments as evidenced by the lack of chromosome loss, nondisjunction, or sex-linked recessive lethals. In addition, Mittler (1977) observed no mutagenic effects (recessive lethals) when exposing adult females to 98.5-MHz frequency-modulated fields (composed of standard commercial broadcast audio frequencies) at 0.3 V_{rms}/m (SAR estimated at 0.0004 W/kg), 134 h per week for 32 weeks. Although the results with *D. melanogaster* are difficult to extrapolate to the human condition, this test system as a qualitative index could not detect any mutagenic alterations by RF radiation over a wide range of frequencies.

5.8.2.3 Vertebrates

Experiments with vertebrates address the impact of the genetic effects of RF radiation most directly because of the general biological similarities between man and other vertebrates. However, there are very few such experiments directed at this subject. Three studies have been reported that are directly focused on the mutagenic potential of microwaves in mice and rats. Varma *et al.* (1976) used the dominant-lethal test to investigate the effects of 2.45-GHz (CW) radiation. The testes of anesthetized mice were treated either by a single 10-min exposure at 100 mW/cm^2 (SAR estimated at 11.4 W/kg), or by three exposures of 10 min each at 2-h intervals on the same day at 50 mW/cm^2 (SAR estimated at 5.7 W/kg), or by four exposures of 10 min each at 3-day intervals over 2 weeks at 50 mW/cm^2 (SAR estimated at 5.7 W/kg). Varma and Traboulay (1976) in a similar study exposed the testes of anesthetized mice to a single dose of 1.7-GHz radiation, at 10 mW/cm^2 for 80 min (SAR estimated at 0.48 W/kg) or at 50 mW/cm^2 for 30 min (SAR estimated at 2.4 W/kg). Following a 24-h recovery period, the males were bred with virgin females—one group of females per week for 6 to 8 weeks. In the 2.45-GHz study, the authors used the week-6-group results for comparison; they found a higher mutagenicity index in the results of the 100-mW/cm^2 group bred at week 1, and in results of the 50-mW/cm^2 group exposed three times in one day and bred at week 4. The authors concluded that a single intense exposure or multiple exposures during one day induced a number of significant mutations in the mice. The results of the 1.7-GHz studies at 50 mW/cm^2 for 30 min indicated a radiation-induced increase in infertility, in pre-implantation losses, and in the mutagenicity index of the

groups bred at 3, 4, 5, and 6 weeks. In addition, for the group exposed to 1.7-GHz fields at 10 mW/cm^2 for 80 min, an increase was seen in the mutagenicity index of the groups bred at 1, 2, 3, and 6 weeks. The authors concluded that the "biological damage may be due to the combined effect of thermal and nonionizing radiation." Both these reports should be evaluated on the basis described in Sec. 5.8.1.1, Physical and Chemical DNA and Chromosome Studies, for the physical and chemical studies reported by these authors. Basically, the reports do not describe the exposure conditions in sufficient detail to allow an unequivocal evaluation of the results. Also, it is not possible to determine the extent of the biological damage caused by elevated temperature in either of these reports, especially because anesthetized mice lack an effective temperature-regulatuion capability (Cairnie *et al.* 1980). However, if the histological damage found in the testes of animals exposed under similar conditions (Varma and Traboulay 1975) is reflected in damage to sperm, it could account for many if not all changes in the mutagenic index, fertility, and pre-implantation loss reported by those authors in later studies.

The conclusion that radiation in the frequency range of 1.7 to 2.45 GHz could cause mutagenic changes in mice was challenged in a detailed study by Berman *et al.* (1980). Unanesthetized male rats were exposed to 2.45-GHz (CW) radiation under three treatment regimens: 4 h/day from day 6 of gestation to 90 days of age at 5 mW/cm^2 (SAR varied from 4.7 W/kg to somewhat less than 0.9 W/kg at day 90, because growth of the animals changed their energy absorption efficiencies); 5 h/day for 5 days beginning on day 90 at 10 mW/cm^2 (SAR estimated at 2 W/kg); and 4 h/day, 5 days/week, for 4 weeks beginning on day 90 at 28 mW/cm^2 (SAR estimated at 5.6 W/kg). During selected weekly periods after treatment, the exposed males were bred to untreated females that were examined in late pregnancy by the dominant-lethal assay. No significant germ-cell mutagenesis was detected under any treatment condition, even though significant increases in rectal and testicular temperature were observed during the 28-mW/cm^2 exposure and were associated with a concomitant decrease in incidence of pregnancy during some of the breeding periods, which indicates temporary sterility. In addition, these authors reexamined the data of Varma and concluded they had been interpreted incorrectly because the effects of litter size on fetal mortality had been ignored and the differences between treated and control groups had been overemphasized when the control values were not representative of normal values. Berman *et al.* (1980) concluded that "it still remains to be demonstrated that microwaves, even at near-lethal doses, can cause a dominant lethal mutagenic effect in the mouse or the rat." Thus, well-designed experiments with biological systems having complex genomes similar to man's have demonstrated no mutagenic effects from low- to moderate-intensity RF radiation when the temperature of the biological system is maintained in the physiological range. Most of the reported changes are consistent with the effects expected from elevations in temperature, caused by CW exposure to high-intensity RF radiation. The other purported changes cited in this section may have resulted from incomplete experimental design.

Recently, dominant lethality was tested by Saunders *et al.* (1983), who exposed the lower half of adult male C3H mice one time for 30 min in a waveguide at 2450-MHz CW fields (average SAR = 43 W/kg). The exposed males were then mated with pairs of virgin females each week for 10 weeks. The uterine contents of the females were examined either on day 14 or day 18. The post-implantation survival, defined as the number of living implants divided by the total number of implants, was used as a measure of the dominant lethality. There were no significant changes in the dominant lethal test for any of the 10 mating periods, which indicated that no stage of spermatogenesis was preferentially sensitive to the RF treatment. This result is in agreement with the other results cited in this section. Other measures made by Saunders *et al.* are discussed in Sec. 5.3.3.

5.8.3 Unresolved Issues

Heating, which raises the temperature of biological samples above normal physiological ranges and may result in genetic and mutagenic changes, is a well-known result of exposure to high-intensity RF radiation. The choice of exposure conditions to study the genetic and mutagenic effects of moderate to low intensity radiation is arbitrary because no well-defined mechanism of RF interaction other than heating has been developed to address this biological problem. The experimenter must select the frequency, intensity, and duration of exposure, as well as the type and characteristics of modulation. To compound the problem further, the number of biological systems that could be selected for study is limitless. Several guides can be developed from recent experimental findings to help delineate a future experimental plan.

Although the conclusion has been stated above that no strong evidence exists in the cited reports to demonstrate activity for low-intensity RF radiation *per se,* it should be qualified by the following observations:

1. These experiments are limited to small portions of the RF region of interest, i.e., 0.5 MHz to 100 GHz. This 10^6-Hz frequency range is so large that if detrimental effects occurred over very narrow frequency ranges, they might have gone undetected.
2. Many of the experiments were conducted with CW radiation. If effects exist, they may occur with

amplitude-, frequency-, or PW-modulated radiation at frequencies associated with ongoing biological or biochemical processes. An exposure to a short-duration, high-intensity PW radiation (radar-like) may not produce the same biological response as a CW exposure of the same average power density. Thus, the concept of averaging the intensity of PW radiation over time to determine an effective intensity may not be generally valid.

3. The general approach in most experimental studies has been to assume that the higher the radiation intensity, the more pronounced the biological effect. It is possible that several mechanisms are operative during radiation exposure and that mechanisms with thresholds at relatively high intensities (e.g., heating) mask the effects, which may be caused by the more subtle mechanisms.
4. RF radiation may enhance the effects of known mutagenic agents as a co-stressor. In environmentally relevant situations, biological systems are exposed simultaneously to many agents, both chemical and physical.
5. Standard test procedures that have been optimized to identify ionizing and chemical mutagens are not necessarily applicable to examining the interaction of RF radiation with complex biological structures and genetic material. No test system should be overlooked as potentially sensitive for detection of mutagenic activity. For example, plant systems have been shown to be extremely sensitive indicators of environmental pollution.

Recent experimental developments support some of the suggestions made above. Possible frequency-specific responses were reported by Smolyanskaya and Vilenskaya (1973), who described the induction of colicin in *E. coli* by extremely high-frequency radiation, near 37 GHz, at power densities of 0.001, 0.01, 0.1, or 1.0 mW/cm^2 for 0.5, 1, and 2 h. Colicin is a protein usually not made by the cell. Its induction, *though not well understood, requires the transcription* of a new portion of the DNA molecule. This induction demonstrates that specific microwave frequencies can induce changes in the genetic processes of cells. More recently, Grundler *et al.* (1977) described frequency-dependent growth responses in the yeast *S. cerevisiae* exposed for periods to 11 h to microwave frequencies between 41 and 42 GHz at 1 to 3 mW/cm^2 (average SAR estimated at 4 to 11 W/kg). (See Sec. 5.1, Cellular and Subcellular Effects, for details.) Although this work is controversial, it does support the frequency-specific-response concept.

The importance of examining the effects of RF radiation as a co-stressor with other agents is emphasized in the report by Dardalhon *et al.* (1980) that was discussed earlier with respect to exposure either to heat or to microwave radiation. These authors exposed haploid and diploid strains of *S. cerevisiae* for 1 h to 17-GHz (CW) radiation, near field, at 50 mW/cm^2 (SAR estimated at < 6 W/kg) and 20°C, followed by exposure to various doses of UV light (254 nm), which is known to cause damage directly to the DNA. Both haploid and diploid strains were affected. The exposure combination caused a tendency—but apparently not a statistically significant change—toward diminished survival, increased mitotic recombination, and increased cytoplasmic "petite" mutations, when compared with the effects caused by exposure to the same doses of UV light alone. This possible microwave-radiation enhancement of effects due to UV-light exposure would be unusual, because it was observed only at high doses of UV light, where additional repair systems are presumably operative. The authors found similar trends by replacing microwave-radiation exposure with temperature elevation to 46°C before treatment with UV light. No influence from exposure to microwave radiation, followed by UV light, was observed for 17-GHz fields at 2.5 mW/cm^2, or for 9.4-GHz fields at 5 mW/cm^2. Because the microwave-radiation treatment caused only a 1°C global temperature rise in the sample that was 10°C below its normal growth temperature, the authors reasoned *that if temperature rise is the basic agent enhancing* the UV-light-induced response, it must be occurring selectively at specific sites within the biological system other than on the DNA itself, so that change is perhaps caused in metabolic processes or in the structural integrity of cytoplasm, or of membranes. In this case, a differential sensitivity among the various repair systems may be induced by the UV light. Similar investigations might reveal biological processes, including repair of damage or detoxification of chemicals, that may be particularly sensitive to microwave-radiation exposure.

In another area, radiation-induced efflux of calcium ions from *in vitro* brain tissues has been shown to *depend on the modulation frequency of a carrier wave* (Bawin *et al.* 1975; Blackman *et al.* 1979). The effective modulation frequencies were in the same frequency range as the natural biological rhythms associated with the EEG in the intact animal, and thus the radiation may have coupled with an existing oscillatory system. Further studies by Blackman *et al.* (1979; 1980a,b) and Sheppard *et al.* (1979) indicated that higher and lower intensities of radiation can lead to the disappearance of the effect. This result suggests that examining biological processes only at a single power density may provide misleading information.

Three additional, incomplete reports have been *included in this section. These studies are included* either because they present positive findings at

frequency ranges or intensities seldom studied or because of a strong claim by the authors. Heller (1970) and Mickey and Koerting (1970) reported chromosomal aberrations in cultured Chinese-hamster lung cells exposed for 30 min to 19- or 21-MHz fields, although no changes were observed after exposure to 15- or 25-MHz (PW) fields (100-Hz PRR, 50-μs pulse width) at field intensities to 300 kV_{p-p}/m. It is very likely either that the extremely high peak voltages (up to 300 kV_{p-p}/m) were producing intense, rapid heating within the cells, or that the field *per se* was causing major stresses within the system. These reports provide insufficient descriptions to allow an estimate of the SAR values, and thus these results cannot be compared with those found by others. It is possible that fields at extremely high intensities can account for some cytogenetic changes. Manikowska *et al.* (1979) reported a dose-independent increase in chromosomal translocations and in chromosomal pairs remaining as univalents at Metaphase I in the sperm cells of mice exposed 1 h/day, 5 days/week, for 2 weeks to 9.4-GHz (PW) radiation at 200-, 1000-, 2000-, or 20,000-mW/cm^2 peak power densities (0.5-μs pulse width; 1-kHz PRR; 0.1-, 0.5-, 1-, and 10-mW/cm^2 average power densities, respectively). (Average SAR is roughly estimated at 5 W/kg, and peak SAR roughly at 9000 W/kg for the highest power density used.) The authors do not describe the relation of the animals' testes to the incident field, which thus raises the question of the actual quantities of energy coupled to the target cells at 9.4 GHz, where tissues exhibit large attenuation coefficients. A description of the environmental conditions during exposure is also absent. These omissions prevent any critical assessment of the results. Furthermore, because of the small number of animals used in the study, the authors themselves state that "the findings... obviously need confirmation on larger numbers of animals."

In another study, based on bacteria exposed to extremely high temperatures, an incomplete analysis of the distribution of temperatures within the samples led to an unjustified conclusion. Blevins *et al.* (1980), who exposed several strains of *S. typhimurium* commonly used in the Ames testing procedures (Ames *et al.* 1975) to 2.45-GHz radiation in a microwave oven at a calculated power density of 5100 mW/cm^2 for periods of 2 to 23 s, examined the cultures for lethality and for mutation induction. These exposures caused extremely large elevations of temperature. Corollary heating experiments were performed in high-temperature water baths to determine the extent to which temperature change alone contributed to lethality and mutations. Their conclusion that microwave radiation is a potent mutagen, because it caused mutations in excess of those expected from the radiation-induced temperature rise, is not supported by their data. The authors failed to demonstrate that the uniformity of microwave heating was duplicated by the water bath experiments. The authors acknowledge that "differences in the kinetics of water bath and microwave heating are possible" but do not evaluate this possibility further. Because of the larger temperature increases in their culture systems—apparently as large as 46°C in 14 s—more definitive temperature distribution work must be done to establish accurately the contribution that temperature change makes to induction of mutations before additional mutagenic properties are assigned to microwaves. Blevins *et al.* (1980) reported using a power density 500 times greater than the current U.S. occupational guidelines. Because the apparent mechanism (i.e., heating) is based on such high, nonphysiologic temperatures, the authors' conclusions are not applicable to the other cited studies, which have used 2.45-GHz radiation. However, the study may support a reevaluation of the concept that brief, high-intensity exposures can be averaged over a longer time period to define the average intensity. For example, an exposure to 5100 mW/cm^2 for 2 s is 28 mW/cm^2 if averaged over 6 min, and an exposure for 14 s becomes 200 mW/cm^2 if averaged over 6 min. The Blevins *et al.* study would also support the concept that high-intensity pulses of microwaves may affect biological systems differently from convection or conduction heating.

Although no solid evidence exists (i.e., there are no independently verified reports) to indicate that low-intensity RF radiation is mutagenic, sophisticated concepts and designs are just beginning to appear in experiments concerning the biological effects of RF radiation. Thus, although it is premature to proclaim unequivocally that RF radiation is not mutagenic, the majority of evidence at present indicates, in the absence of temperature elevation, that is the case. The above studies of the biological effects of RF radiation that relate to genetics and mutagenesis are summarized in Table 5-24.

Since 1980, several recent reports at scientific meetings have supported or extended the concerns raised in this section. Kremer *et al.* (1983) examined the puffing pattern of giant chromosomes from the salivary gland of the midge *Acricotopus lucidus* following a 2-h exposure to fields swept between 64 and 69 GHz CW, or at single, stabilized frequencies of 67.2 or 68.2 GHz CW. Power densities were less than or equal to 5 mW/cm^2 and resulted in temperature rises of less than 0.03°C. There was up to a 10 times reduction in the Balbiani ring BR2 in chromosome II; that is, the normal mass of DNA fibers usually seen at one chromosome locus was dramatically retarded following microwave exposure. No change in the normal puffing pattern was observed in either the sham treated samples or the sham plus heat treated samples (2.5°C temperature increase). This result

Table 5-24. Summary of Studies Concerning Genetic and Mutagenic Effects of RF-Radiation Exposure

Effects	Species	Exposure Conditions: Frequency (MHz)	Intensity (mW/cm^2)	Duration (days x min)	SAR* (W/kg)	Reference
No change in thermal denaturation profile, except at elevated temperature	DNA	2,450 (CW)	134	1 x 960	67 (est)	Hamrick (1973)
Change in thermal denaturation profile and hyperchromicity of DNA extracted from testes following exposure	Mouse	1,700 (CW) 985 (CW)	≤50 10	1 x 80	≤2.4 (est-testes) ≤0.26 (est-testes)	Varma and Traboulay (1976, 1977)
No chromosome aberrations in white blood cells	Chinese hamster	2,450 (CW)	5-45	5 x 15	21	Huang *et al.* (1977)
No sister chromatid exchange in bone marrow cells	Mouse	2,450 (CW)	20	28 x 480	21	McRee *et al.* (1981)
No chromosome aberrations in CHO-K1 cell line if temperature maintained	Chinese hamster	2,450 (CW)	≤200	1 x 30	≤360 (est)	Alam *et al.* (1978)
No chromosome aberrations or change in mitotic activity in regenerating liver cells in rat	Rat	13.12 (CW) 13.12 (PW)	4.45 kV_{p-p}/m 44.1 kV_{p-p}/m	1 x 1,680-2,640	1.3 (est)	McLees *et al.* (1972)
No mutation induction	*E. coli* *E. coli*	2,450 (CW) 1,700 (CW)	10 or 50 250 V_{p-p}/m	1 x 180-240 1 x 210	15 or 70 3	Blackman *et al.* (1976)
No mutation induction observed in Ames tester strains	*S. typhimurium*	2,450 (CW) 8,600-9,600 (PW)	20 10, 45	1 x 90 1 x 90	40 18, 80 (est)	Dutta *et al.* (1979a)
Reduction in survival concomitant with rise in sample temperature	*E. coli*	8,600-9,000 (PW)	1-20	1 x 90	≥50	Dutta *et al.* (1980)
	S. typhimurium *S. cerevisiae*	8,600-9,000 (PW) 8,600-9,000 (PW)	≤45 ≤45	1 x 90 1 x 120	≤80 ≤80	
No reduction in survival or mutational events	*S. cerevisiae*	70,500 (CW) 73,000 (CW)	60	1 x 180	≤17 (est)	Dardalhon *et al.* (1979)
No reduction in survival or mutational events	*S. cerevisiae*	9,400 (CW) 17,000 (CW)		1 x 300 1 x 1,440	≤28 (est)	Dardalhon *et al.* (1980)
No detectable lethal events due to no change in CFUs	*E. coli*	2,600-4,000 (CW)		1 x 480	19	Corelli *et al.* (1977)
No observable change in molecular structures because no change in IR spectrum	*E. coli*	3,200 (CW)		1 x 660-720	21 or 16	Corelli *et al.* (1977)
No repairable DNA damage	*E. coli*	8,600 (PW)		1 x 60-420	12	Dutta *et al.* (1979b)
No change in growth pattern; enhanced colony-forming activity	*E. coli*	2,450 (CW)	0.005-50	1 x 240	0.008-75	Blackman *et al.* (1975)
No change in mutation frequencies at either of two loci controlling requirements for adenine and tryptophan	*S. cerevisiae*	2,450 (CW) 8,500-9,600 (PW)	20 1-45	1 x 120 1 x 120	40 ≤80 (est)	Dutta *et al.* (1979a)
No mutagenic effects in exposed embryos	*D. melanogaster*	2,450 (CW)	—	1 x 360	100	Hamnerius *et al.* (1979)
No changes in generation time, sex ratio, or sex-linked lethal mutations in offspring	*D. melanogaster*	2,450 (CW)	4,600-6,500	1 x 45	150-210 (est)	Pay *et al.* (1972)
No mutations in adult males as evidenced by chromosome loss; nondisjunction; or sex-linked recessive lethals	*D. melanogaster*	29 (CW) 146 (CW)	600 V_{rms}/m 62.5 V_{rms}/m	1 x 720 1 x 720	0.024 (est) 0.015 (est)	Mittler (1976)

Table 5-24. (Continued)

Effects	Species	Exposure Conditions: Frequency (MHz)	Intensity (mW/cm^2)	Duration (days x min)	SAR* (W kg)	Reference
No mutagenic changes (recessive lethals) in adult females	*D. melanogaster*	98.5 (CW)	0.3 V_{rms}/m, (FM) at audio	224 x 1,140	0.0004 (est)	Mittler (1977)
No significant germ-cell mutagenesis in weekly breedings	Rat	2,450 (CW)	5	106 x 240	4.7-0.9	Berman *et al.* (1980)
No significant germ-cell mutagenesis in weekly breedings	Rat	2,450 (CW)	10	5 x 300	2	Berman *et al.* (1980)
Same, except decrease in pregnancies, indicating temporary sterility caused by elevated testicular temperatures	Rat	2,450 (CW)	28	20 x 240	5.6	Berman *et al.* (1980)
Induction of a repressed protein, colicin, indicating a change in the genetic processes	*E. coli*	37,000 (CW)	0.001-1	1 x 30-120		Smolyanskaya & Vilenskaya (1973)
Change in growth rate that was very frequency specific, indicating an alteration in the processes of the cell	*S. cerevisiae*	41,000-42,000 (CW)	1-3	1 x 660	4-11 (est, av)*	Grundler *et al.* (1977)
	S. cerevisiae	41,650-41,825 (CW)	≤10	1 x 180		Grundler and Keilmann (1983)
Chromosome aberrations in lung cells *in vitro* at two frequencies but not at two closely related frequencies, 15 or 25 MHz	Chinese hamster	19 (PW) 21 (PW)	up to 300 kV_{p-p}/m	1 x 30		Heller (1970) and Mickey and Koerting (1970)
Increase in chromosome translocations in sperm cells	Mouse	9,400 (PW)	0.1-10	10 x 60	0.05-5 (est)	Manikowska *et al.* (1979)
Increased mutations and lethality	*S. typhimurium*	2,450 (CW)	5,100	1 x 0.03-0.48		Blevins *et al.* (1980)
No change in growth when compared to temperature controls	*E. coli*	8,800 (PW)		1 x 900	12	Hossain and Dutta (1982)
No change in survival or mutation induction	*E. coli*	9,400 (CW) 17,000 (CW) 70,000-75,000 (CW)		1 x 30 1 x 30 1 x 30	23 ≤28 9	Dardalhon *et al.* (1981)
	S. cerevisiae	9,400 (CW) 17,000 (CW) 70,000-75,000 (CW)		1 x 30-2,880 1 x 30-2,880 1 x 30	23 28 28	
No change in dominant lethality	Mouse	2,450 (CW)		1 x 30	43	Saunders *et al.* (1983)
No change in mutation induction	*E. coli*	27.12 (CW) 2,450 (CW) 3,070 (PW)		1 x 60-400 1 x 60-400 1 x 60-400	≤4 35-100 35-100	Anderstam *et al* (1983)
	S. typhimurium	27.12 (CW) 2,450 (CW) 3,070 (PW)		1 x 60-400 1 x 60-400 1 x 60-400	≤4 35-100 35-100	
Higher mutagencity index perhaps due to heating and RF	Mouse	2,450 (CW) 2,450 (CW) 1,700 (CW)	100 50 10	1 x 10 3 x 10 1 x 80	11.4 (est-testes) 5 7 (est-testes) 0.5 (est-testes)	Varma *et al* (1976)

*est = estimated, est-testes = estimated for testes only; av = average.

reinforced the concerns expressed above that specific interactions may occur in unexamined frequency domains. Edwards *et al.* (1983) reported microwave absorption in isolated DNA molecules in salt solution when exposed over the 8- to 12-GHz range. This absorption was strongly dependent on the number of single strand breaks in each molecule. Since these breaks occur naturally, as during DNA replication or repair, this result provides a basis for assuming that certain biochemical states of DNA could be highly susceptible to change by exposure to microwaves. (For example, see discussion of co-stressors, above.)

Manikowska-Czerska *et al.* (1983a,b) reported, in abstract form, further work with unanesthetized male IRC mice exposed to 9.4-GHz pulsed, 2450-MHz CW, and 915-MHz CW fields (Manikowska *et al.* 1979). Exposures were 30 min/day, 6 days/week, for 2 weeks at SARs between 0.05 and 20 W/kg. Two studies were performed. In one, increased chromosomal translocations were observed in meiotic cells from the testes of exposed mice. The numbers of translocations followed the same unusual dose-response profile described in the earlier preliminary report (Manikowska *et al.* 1979). In the other study, exposed and sham treated males were mated with unexposed females each week for 3 weeks. Post-implantation loss was assayed on day 13-14 of gestation. Significantly increased loss was reported for the group mated to the exposed males. This result is different from that obtained by Saunders *et al.* (1983), who exposed at a higher SAR, 43 W/kg (reviewed in Sec. 5.8.3.3), and found no change in post-implantation survival. The incompletely described exposure conditions and analyses in the Manikowska-Czerska abstracts, which did not receive peer review, preclude rigorous evaluation of the reports; however, the occurrence of intensity-specific effects is consistent with qualification 3, stated above. Conversely, if the animal restraint produced additional stress in the exposed animals (Justesen *et al.* 1971), the results may address qualification 4. Nevertheless, because the procedures and exposure levels employed by these two research groups differed, additional experiments are needed to resolve the influences of particular exposure geometries, SAR, stress produced by animal restraint, ambient temperature and cooling capacity, and animal species to determine the general nature of this response.

A recent publication by Grundler and Keilmann (1983) has corroborated their earlier report (Grundler *et al.* 1977) of frequency-specific alterations in growth rates of the yeast *S. cerevisiae*. In this new study, the growth rate of yeast was monitored spectrophotometrically during exposure by either one of two different antenna systems. Numerous narrow frequency ranges between 41.650 and 41.825 GHz (CW) caused up to 10 percent change in either growth enhancement or retardation compared to control samples. There was substantial agreement in results observed from the two exposure systems. The emphasis on improved frequency resolution also revealed that a residual modulation up to 0.5 MHz was present. No SAR was given by the authors nor could one be estimated from the data presented; however, the authors stated that this effect occurred and saturated above a threshold intensity that is much less than 10 mW/cm^2. Because the exposure increased the sample temperature from 0.16 to 0.4°C for the power (10 to 25 mW) usually applied, results of a small thermal increment on the growth rate were established separately and displayed along with the results of exposure at different powers. These results reinforce the concern expressed above that low-intensity, frequency-specific effects may exist but have not been widely detected because of inadequacies either in the experimental design or in the stability of the exposure sources. Although there are theoretical models that are consistent with these results, no mechanism of action has yet been established.

5.9 Life Span and Carcinogenesis

William P. Kirk

The generalizations that can be drawn from the literature on the effects of RF radiation on life span and carcinogenesis are:

- There is no convincing evidence that exposure to RF radiation shortens the life span of human beings or experimental animals or that RF radiation is a primary carcinogen (cancer inducer); however, (1) few studies have used longevity or cancer incidence as end points, and (2) human studies have lacked statistical power to exclude life shortening or cancer.

- There is evidence from one group of investigators that chronic exposure to RF radiation (SAR = 2 to 3 W/kg) resulted in cancer promotion or co-carcinogenesis in three different tumor systems in mice.

5.9.1 Life Span

5.9.1.1 Human Studies

There are few data and no definitive studies on which to judge the long-term effects of RF-radiation exposure on human survival. Two studies have evaluated cause of death several years after exposure of the study populations (Table 5-25). First, information has been developed on the mortality experience of U.S. Government employees assigned to the Moscow Embassy during the period 1953 to 1976, when microwave irradiation of the embassy by the Soviets was taking place. Comparisons were made with a group of employees who had been stationed at other U.S. embassies in Soviet Bloc cities (Budapest, Leningrad, Prague, Warsaw, Belgrade, Sophia, and Zagreb). The comparison was chosen to be as similar as possible to the 1800 employees in the Moscow group for selection, i.e., posting, criteria, and environmental influences, except that the posts were not subject to microwave exposure (Lilienfeld *et al.* 1978). No evidence was found that the Moscow group had experienced any higher mortality or any differences in specific causes of death up to the time of the report. Investigators noted that because the population was relatively young it was too early to detect long-term mortality effects except for those serving in the earliest period of the study. The methods and other results of this study are detailed in Sec. 5.10, Human Studies.

Robinette *et al.* (1980) examined the records of a group of 40,000 U.S. Navy personnel who enlisted during the period 1950 to 1954. Approximately 20,000 had job classifications with maximum potential exposure to radar; a similar number of employees, believed to have minimum potential for exposure, were used as a comparison group. The authors found no apparent difference in mortality patterns between the two exposure groups more than 20 years post-exposure. This study is also described in more detail in Sec. 5.10, Human Studies. Exposure data for both of these studies are given in Table 5-25.

5.9.1.2 Animal Studies

Although there have been many median-lethality experiments to determine the lethal effects in animals exposed to RF radiation, data on life span effects of experimental animals exposed to low power levels are scarce. Only one report is known of a study in which animals were exposed to microwave radiation as the sole stressor and observed throughout their life span. Spalding *et al.* (1971) exposed 24 adult female mice to 800-MHz fields at a power density of 43 mW/cm^2 for 2 h/day, 5 days/week for 35 weeks. A waveguide apparatus was used to irradiate the animals, which were cooled by forced air. No temperature or relative humidity data are reported. The whole-body-averaged SAR is estimated to be 12.9 W/kg. Four exposed mice died of "thermal effects" during the experiment, and a fifth is reported to have died during exposure because it became too obese for the exposure chamber. The mean life span of the remaining 19 exposed mice was 664 ± 32.2 (SEM) days, and that of the 24 sham-irradiated mice was 645 ± 32.2 (SEM) days, differences that are not statistically significant.

Prausnitz and Süsskind (1962) studied pathological and longevity effects on male Swiss mice exposed to 9270-MHz (PW) radiation (duty cycle = 0.001) at an average power density of 100 mW/cm^2 for 4.5 min daily, 5 days/week for 59 weeks. The daily exposure produced an average body temperature rise of 3.3°C. This daily dose is stated to be half the LD_{50} for the mice. Originally, there were 200 irradiated mice and 100 control mice. Five percent of each group was killed for pathological and hematological examination 7 months after the beginning of irradiation, and an additional 10 percent of each group was killed at 16 months, within a month of the final irradiation. Because of a partial contradiction in pathological findings in the animals killed at 7 and 16 months, all surviving mice (19 controls and 67 irradiates) were killed 19 months after the beginning of irradiation (4 months after final irradiation). The data from this experiment are summarized in Table 5-26. The authors state that the longevity of the mice did not appear to be affected under the prevailing conditions and suggested that "conceivably microwave irradiation in this modality, with periodically induced slight artificial fevers, is of some benefit to the animal in combating disease." The data generally appear to support this statement—and perhaps even the stronger statement that significantly more irradiated mice than controls survived until the termination of the experiment. If simple 2 x 2 contingency tables are

Table 5-25. Summary of Studies Concerning RF-Radiation Exposure Effects on Life Span/Carcinogenesis

Effects	Species	Exposure Conditions: Frequency (MHz)	Intensity (mW/cm^2)	Duration (days x min.)	SAR (W/kg)	References
No effect on life span or cause of death	Human adult male & female	2560-4100 600-9500	0.005 (max) 0.018 (max)	8030* x 600 180 x 1200	2×10^{-4} (max) 7×10^{-4} (max)	Lilienfeld *et al.* (1978)
No effect on mortality in a military population followed for 20 years	Human adult male	200-5000 (est) (PW)	~ 1 (routine) 100 (occasional)	730 x 480 (est)	<0.05 (est) ≤5 (est)	Robinette *et al.* (1980)
Slight increase in mean life span	Adult mouse	800	43	175 x 120	12.9 (est)	Spalding *et al.* (1971)
Increased mean and maximum life span for "irradiated mice with tumors." Increased mean life span but no change in maximum life span of non-tumor-bearing mice. Delay in development of tumors in irradiated mice but no change in ultimate number of tumors	Infant mouse	2450		4 x 20 *(in utero)*	35	Preskorn *et al.* (1978)
Increased mean life span in irradiated mice (concurrent infection-pneumonia)	Adult mouse	9270 (PW)	100	4.5 min/day 5 days/week 59 weeks	40 (est)	Prausnitz and Süsskind (1962)

*The duration of 8030 days equals the number of years (22) of irradiation of the embassy and length of the study period, but the average exposure of individuals is estimated to be 2 to 4 years.

used with data from Prausnitz and Süsskind (1962, Figure 3) and from Table 5-26, ignoring all animals in sacrifice series #1 and #2, the difference in survival is not significant at 14 months into the experiment ($\chi^2 \simeq 2.2$) but is significant at 19 months ($\chi^2 = 4.9$, $0.05 > p > 0.025$). The data provided are not sufficiently detailed to permit application of the subsequently developed, more refined methods of analyzing survival (Peto *et al.* 1976, 1977). The calculation would be perturbed slightly by the fact that sacrifice series #1 and #2 were not predesignated prior to the beginning of exposure but rather selected randomly from survivors at that point in the experiment. This procedure would have the effect of decreasing the proportion of survivors in both control and irradiated groups.

There have been some reports of altered and possibly enhanced immunological competence after microwave exposure. These reports are discussed in detail in Sec. 5.2, Hematologic and Immunologic Effects. In a relevant study, Preskorn *et al.* (1978) compared tumor development and longevity in female mice prenatally exposed to 2450-MHz microwaves with sham-irradiated controls. The irradiated mice were offspring of dams exposed for 20 min/day on days 11,

Table 5-26. Summary of Prausnitz and Süsskind Data (1962)

Series	When Sacrificed (months)	Controls (100 Total): No. Animals	% of Total	No. with "Leucosis"	% This Series with "Leucosis"	Irradiates (200 total): No. Animals	% of Total	No. with "Leucosis"	% This Series with "Leucosis"	Comment
Sacrifice Series #1	7	5	5	None apparently given	—	10	5	None apparently given	—	Reported as negative for "leucosis"
Sacrifice Series #2	16 (1 month post-irradiation)	10	10	1	10	20	10	6	30	Reported as positive for "leucosis"; not statistically significant χ^2 (1 df) = 1.49
Sacrifice Series #3 (all animals surviving at 19 months)	19 (4 months post-irradiation)	19	19	4	21	67	33.5	12	18	Reported as negative for "leucosis"
Longevity Series	As occurred	40	40	4	10	60	30	21	35	See text
Spontaneous Deaths	No data given	26	26	—	—	43	22	—	—	Autolysis too advanced for diagnosis of cause of death

12, 13, and 14 of gestation in a multimodal cavity (SAR = 35 W/kg). Both groups were injected with sarcoma cells at age 16 days. Both the mean and maximum survival time of "irradiated mice with tumors" exceeded those of "non-irradiated mice with tumors" ($p < 0.05$). The mean survival time of "irradiates without tumors" was also greater than "non-irradiated mice without tumors." When 50 percent of the controls had died, 67 percent of the irradiates were alive. The difference was not significant ($0.05 < p < 0.1$), however, and maximum life span did not differ.

Rotkovska and Vacek (1972, 1977) reported increased survival and increased LD_{50-30} in mice for sublethal (600 to 750 R) acute exposures to 200-kV X rays if the X-ray exposures were preceded (1, 3, 14 days) or followed (30 min) by a 5-min exposure to 2450-MHz microwaves at 100 mW/cm^2. In their initial experiment, the 30-day survival after an X-ray exposure of 600 R was increased from 14 percent (controls) to 53, 88, or 90 percent when such exposure followed the microwave irradiation by 1, 3, or 14 days, respectively. In their second experiment, the LD_{50-30} was increased by 100 R with all microwave-irradiated groups having significantly higher survival at 30 days than their control counterparts. These data, together with the interaction with psychoactive drugs, are illustrative of the potentially confounding variables that may have to be considered in determining RF-radiation exposure limits.

5.9.2 Carcinogenesis

5.9.2.1 General

Carcinogenesis is the process of inducing cancer or malignant neoplasia. Neoplasia is uncontrolled growth or cell division in a tissue; a malignant neoplasm or cancer is a group of cells that replicate uncontrollably and has the capacity to shed cells which enter the blood and travel to other parts of the body to colonize and form new tumors (metastases). Metastasis is characteristic of malignancy but is not required for diagnosis which is done histologically. A tumor that does not metastasize is considered benign, although it may well grow to sufficient size to be life threatening. Consideration of the various theories of carcinogenesis is beyond the scope of this discussion, except that most authorities believe that the initiating event(s) on the cellular level involves physical or chemical alterations of a cell such that its descendant cells are abnormal and may override the body's cellular proliferation control processes. In recent years carcinogenesis has come to be viewed as a multistaged process that for simplicity can be divided into two major stages, i.e., induction (actual induction of malignant transformation by genetic damage) and promotion (enhanced growth and/or survival of malignantly transformed cells). Promotion is increasingly seen as an essential phase in the carcinogenic process since it is assumed that many cells capable of resulting in malignant tumors simply die, or remain dormant unless stimulated to divide, or are somehow protected from potentially lethal DNA damage. Promoters are substances that result in enhanced progression to malignant tumors when applied in close proximity to transforming events. A given moiety, chemical or physical, may act as an inducer, promoter, or both. (Ionizing radiation, for example, is both a weak inducer and promoter.) The role that the immune system plays in primary carcinogenesis has not been well documented and is somewhat controversial. However, it is thought that neoplasia may arise through an epigenetic mechanism in which immunosuppression allows the development of tumors initiated by a genetic event.

Potential carcinogenicity has been periodically discussed in connection with RF-radiation exposure since 1953 when J.R. McLaughlin, a medical consultant to the Hughes Aircraft Corporation, submitted a report to the military, listing leukemia as one of the possible effects of radar exposure (McLaughlin 1953). The relevant literature, which is sparse, has been reviewed by Barański and Czerski (1976), Justesen *et al.* (1978), and Dwyer and Leeper (1978), with little supportable evidence that RF exposures are likely to be carcinogenic. However, the subject remains controversial for many reasons, including:

(1) the failure of the public and the media to distinguish between ionizing radiation, a proven carcinogen, and nonionizing radiation (specifically, RF radiation);

(2) the existence of several anecdotal and/or case reports associating cancer in humans with RF-radiation exposure;

(3) report of studies indicating that RF exposure may cause leukemia (Prausnitz and Süsskind 1962; Susskind 1962) or promote the development of several types of cancer in mice (Szmigielski *et al.* 1980, 1982);

(4) the lack of well-designed human or animal studies that have adequate exposure data that are free from artifact and are statistically adequate to draw reliable conclusions.

5.9.2.2 Human Studies

The two relevant and acceptable studies in this area deal with the health status of (1) U.S. Government employees stationed at the U.S. Embassy in Moscow (Lilienfeld *et al.* 1978) and (2) U.S. Navy personnel exposed to radar during the Korean War (Robinette *et al.* 1980). For these two studies, only those aspects dealing with carcinogenesis are discussed here.

In the Moscow Embassy study, the Moscow group experienced less overall mortality from all causes of

death than did the comparison group; however, the death rate in Moscow group females from malignant neoplasms was slightly, but not significantly, higher than expected, and when exposure to microwaves was considered, it was found that the death rate was highest for those having the least exposure to microwaves. The incidence of malignant neoplasms, other than of the skin, was significantly higher in the Moscow female group. In both cases, the numbers were very small. In the former case, 7 different cancer sites were involved in 8 cases, which according to the authors, virtually eliminates a single causal factor; in the latter case, there were 10 cases involving 7 different sites.

One of the end points examined in the U.S. Navy study (Robinette *et al.* 1980) was the effect of exposure from 1950 to 1954 on the relative incidence of cancer during 1950 to 1976. No statistically significant differences between the high- and low-exposure groups were evident for malignant neoplasms as a cause of death from 1950 to 1974, or as a cause of hospitalization in Navy or VA hospitals. Within the high exposure group, three subgroups were developed to provide a gradient of potential exposure. (Sec. 5.10, Human Studies, gives details.) There were significantly more malignant neoplasms of the respiratory tract in the subgroup rated as highly exposed. A significant trend for increased death from increased exposure was also noted when these subgroups were used. However, information relevant to the development of lung cancer, such as smoking histories, was not available because the study used death certificates to obtain data on cause of death. Also, when many statistical comparisons are made, as was done in this study, with a $p = 0.05$ criterion, one or two positive findings would be expected by chance.

5.9.2.3 Animal Studies

The only animal study reported to date that was of sufficient duration and employed end points appropriate to detect the induction of cancer by RF exposure was that of Prausnitz and Süsskind (1962). They conducted an experiment to determine the pathological and life-shortening effects of chronic microwave exposure of mice. Two hundred male Swiss mice were irradiated with 9270 MHz (PW) at an average power density of 100 mW/cm^2 for 4.5 min daily. This exposure produced an average body temperature increase of 3.3°C. Exposures were conducted 5 days/week for 59 weeks; and survival, body mass, blood parameters, and certain postmortem pathological findings were compared with those of a concurrently sham-irradiated group of 100 animals. Tissues taken for histopathology included liver, spleen, lymph nodes, kidneys, adrenals, gut, lungs, and testes. No data were given regarding ambient temperature during exposure. Between exposures, the mice were housed 10 to the cage in a cabinet maintained between 21 and 24°C. Animals were sacrificed at 7, 17, and 19 months after the beginning of irradiation. In addition, 23 percent of the animals were lost to the study by spontaneous death and autolysis prior to necropsy. The remaining 100 animals (40 controls, 60 irradiates) formed a "longevity" study group. One of the findings reported in this group was "cancer of the white cells," defined as monocytic or lymphocytic leucosis, or lymphatic or myeloid leukemia. Leucosis was defined as a noncirculating neoplasm of the white cells, whereas leukemia was defined as a circulating leucosis. Data were grouped and reported as "leucosis." A contemporary medical dictionary (Taber 1953) defines leucosis as (1) unnatural pallor, (2) presence of an abnormal number of leukocytes in blood, (3) increase in leukocyte-forming tissue; however, it is not a usual pathological term. Although the liver, spleen, and lymph nodes were removed for examination at necropsy, they were not considered in determining lymphoid infiltration, even though these organs are usually involved in this kind of reaction. Data describing the differential composition of the blood cell types are not given. A summary of the fate of the 200 irradiates and 100 controls is shown in Table 5-26.

The results as reported are confusing. The authors performed a third sacrifice series at 19 months to resolve a perceived contradiction in the "leucosis" findings from the first and second sacrifice series, even though a 2 x 2 contingency table analysis to test the prevalence of leucosis in the control and irradiated animals sacrificed in the second series yields a χ^2 of only 1.49 (uncorrected for continuity) with one degree of freedom ($p > 0.20$). Thus, the prevalence of leucosis in irradiated animals was not significantly different from that in the control animals for any of the "sacrifice" groups.

Although leucosis in the "longevity" series is highly significant ($p < 0.005$, $\chi^2 > 8.0$), these data are severely compromised by (1) the marked loss due to autolysis of animals that would have fallen in this group, (2) the differential loss of control animals due to infection, and (3) the premature sacrifice of all remaining animals to resolve an apparent paradox. Comparing data from two groups of animals that selected themselves (by dying prior to 19 months and being found in time for necropsy) is not an acceptable statistical analysis of experimental data. An acceptable method would be to compare the prevalence rates of leucosis in the controls and irradiates in combined groups that include all the animals at risk in the original longevity group (longevity and third sacrifice series). If that is done, the following results are obtained:

Group	With Leucosis	Without Leucosis	Total
Control	8 (a)	51 (b)	59 (a+b)
Irradiated	33 (c)	94 (d)	127 (c+d)
Total	41 (a+c)	145 (b+d)	186 (n)

To test whether the leucosis rates are different in controls and irradiates, the following statistic may be used:

$$S = n(ad - bc)^2/[(a + b)(c + d)(a + c)(b + d)]$$

If the animals comprising the table represent a random sample from a larger population, S approximately follows a χ^2 distribution with one degree of freedom. Upon substitution, the value of 3.62 ($p \sim 0.06$) is obtained. Since $\chi^2 < 3.84$ ($p = 0.05$), the rates would not be declared different at the 5-percent significance level. Furthermore, if a continuity correction were used in computing this statistic, the resultant $\chi^2 = 2.93$, with a probability of 0.09 (not significant).

There are now better statistical methods available to analyze survival data (Peto *et al.* 1976, 1977), but they require detailed documentation of the fate of each animal during the course of the experiment. Given (a) the loss of histopathological data on animals because of autolysis and infection, (b) the further complication that different pathologists were used for different sacrifice series, and (c) the absence of historical data on the incidence of leucosis in the mouse strain used, it is not feasible to apply these methods retroactively. In summary, because of the previously described problems with the biological protocol, the lack of sound statistical methodology in experimental design and data analyses, and the questionable significance of what was reported, the 1962 study of Prausnitz and Süsskind is of limited value in defining the pathological effects of chronic wholebody microwave radiation. As noted previously, the data on survival times (Sec. 5.9.1.2) are of considerable interest due to similar findings by Spalding *et al.* (1971) and Preskorn *et al.* (1978).

There have been several acceptable reports dealing with the effects of RF exposure in the development of experimental, spontaneous, or chemically induced tumors in mice (Preskorn *et al.* 1978; Szmigielski *et al.* 1980, 1982). In their paper, discussed in Sec. 5.9.1, Life Span, Preskorn *et al.* (1978) reported that the development of tumors following injection of sarcoma cells into 16-day-old CFW mice was significantly delayed if the mice had been exposed to 2450-MHz radiation *in utero* on day 11, 12, 13, and 14 of gestation (20 min/day, SAR = 35 W/kg). However, there was no difference in the ultimate number of tumors.

Szmigielski *et al.* (1980, 1982) demonstrated that repeated exposure of mice to 2450-MHz radiation (far field) at 5 or 15 mW/cm² (SAR = 2 to 3 or 6 to 8 W/kg), 2 h per day, 6 days per week for varying times up to 10 months accelerates the appearance of spontaneous mammary cancer (female C3H/HeA mice) and of skin cancer in male Balb/c mice treated with 3,4-benzopyrene during or after microwave treatment. Animals were exposed in plastic cages containing 10 mice per cage. The chamber temperature was maintained at 22 to 23°C with humidity of 60 to 70 percent. Stress produced by chronic confinement in compartments 5 x 6 x 10 cm, 1 animal per compartment, 20 compartments/cage produced approximately the same effect as the 5-mW/cm² exposure. An additional finding is that this exposure regimen increases the number of neoplastic nodules developing in the lungs of Balb/c mice injected with L_1 sarcoma cells (2×10^5 cells) and examined 14 days later. Challenge with the sarcoma cells after a 3-month exposure to 5 or 15 mW/cm² or confinement produced the following results.

Dose Groups	Nodules ($\bar{X} \pm SD$)
Cage Controls	2.8 ± 1.6
Sham Irradiates	3.6 ± 2.2
5 mW/cm²	6.1 ± 1.8
15 mW/cm²	10.8 ± 2.1
Chronic Confinement	7.7 ± 2.0

It seems clear that exposure of mice to RF radiation in these experiments resulted in the acceleraction, or promotion, of three completely different tumors. Whether the effect is by direct action of RF radiation at the cellular or subcellular level, a nonspecific stress reaction (caused by RF radiation, crowding, or thermal stress), or a general effect on immune response cannot be said with any confidence. Exposure of 10 animals in a cage is certainly open to criticism on grounds of nonuniformity of energy absorption and resulting thermal load.

Comparison of the Preskorn *et al.* (1978) data with the Szmigielski *et al.* (1980, 1982) data is difficult since the biological models and exposure conditions were substantially different (offspring of pregnant female mice exposed at 35 W/kg, 20 min daily for 4 days, resulting in elevation in body temperature by several degrees, as compared with months of exposure for 2 h daily at 2 to 3 or 6 to 8 W/kg, levels that do not produce noticeable heating). The Preskorn *et al.* conditions resulted in slower development of experimental sarcomas in mature offspring irradiated *in utero*, whereas the Szmigielski *et al.* work resulted in increased incidence of cancer, and/or accelerated growth of experimental, chemically induced, or spontaneous tumors.

5.9.2.4 Anecdotal and Other Unsupported Reports

Much of the impetus for public and media belief in the carcinogenicity of RF radiation can be traced to the popularization of anecdotal and other unsupportable reports by Brodeur (1977), Zaret (1976, 1977), Dwyer and Leeper (1978), and others. Most of these reports deal with a perceived increase in cancer incidence in one of several groups of defense contract personnel working in RF-radiation research and development, usually in situations having the potential for substantial X-ray exposure from the RF generators

being used. No reliable reports on these incidents have appeared in the scientific or medical literature.

A good illustration of the kind of misunderstanding/misinterpretation that has occurred is the so-called North Karelia Connection. In the early to mid-1970's, the Finnish government, with the World Health Organization, conducted a program known as the North Karelia Project, designed to decrease morbidity and mortality from the high levels of cardiovascular disease (CVD) in eastern Finland by identifying causative factors, devising means for primary prevention, and strengthening treatment and secondary prevention (Puska *et al.* 1978; Keys 1970). The proximity of North Karelia to the Soviet border prompted Dr. Milton Zaret, who is known for his investigations into causation of cataracts and lens opacities from radiation, to speculate in a presentation (at the 1973 Warsaw Symposium on the Biologic Effects and Health Hazards of Microwave Radiation) that microwave radiation from Soviet communications or radar might be contributing to the incidence of CVD. His remarks do not appear in the Symposium record. This CVD hypothesis was restated, however, in a published article (Zaret 1976) and letter to the editor (Zaret 1977), both of which include allegations, without data or reference other than a newspaper article, of the emergence of an increased incidence of cancer in North Karelia. The Zaret article (1976) was later misinterpreted by Dwyer and Leeper (1978), who presented the North Karelia project as being designed to test the hypothesis that RF radiation caused or contributed to heart attacks or cancer. The Finnish government (K. Jokela, personal communication to M. Hattunen, Scientific Counselor of Embassy of Finland, 2133 Wisconsin Avenue N.W., Washington, DC 20007, November 22, 1978) specifically denies the existence of an abnormal cancer incidence in eastern Finland and knowledge of any possible linkage to microwave fields.

5.9.3 Unresolved Issues

Because few RF radiation studies in man or animals have employed life span or cancer as end points and none has had sufficient statistical power and adequate quality control to place an upper limit of risk at less than twice control incidences, the questions of RF-radiation carcinogenesis or life shortening are still open. None of the complete reports in the literature presents a convincing case for the existence of a significantly increased risk of cancer induction or life shortening in exposed populations. Neither theory nor the existing data on RF-radiation mutagenesis support the notion of a role for RF radiation in cancer induction except, very remotely, at exposures causing substantial tissue heating. The data of Szmigielski *et al.* (1980, 1982), however, raise the possibility that RF radiation may act as a cancer promoter even at levels within the physiologic limits of thermal regulation of the animal. In a different system with higher exposures, Preskorn *et al.* (1978) observed a delay in development of experimental sarcomas. The existence of either promotion or inhibition is yet to be confirmed in other systems and laboratories and the mechanisms of action determined.

Two letters to the editor have appeared recently in the *New England Journal of Medicine* suggesting an association of polycythemia vera with occupational microwave exposure (Friedman 1981) and of leukemia with occupational exposure to a variety of electric and magentic fields, including radio, TV, and other electronic devices (Milham 1982). Neither of these letters meets the literature selection criteria established for this review but should lead to more elaborate studies to resolve the questions raised. A critical issue is the difficulty of developing exposure data or information in human population studies.

The relationships of RF radiation to other physical and chemical moieties in carcinogenesis or other physiologic interactions having the potential to affect survival have not been characterized sufficiently. For example, (1) microwave-induced hyperthermia has been demonstrated to increase the effectiveness of X-ray treatment of various cancers and to increase the LD_{50} for mice exposed to X rays; (2) in nontherapeutic situations, as noted above, both inhibition and promotion of growth of experimental and chemically induced tumors in mice have been reported; (3) Riddle *et al.* (1982) demonstrated that exposure (2450 MHz, CW) at 20 or 30 mW/cm^2 (SAR = 12 to 18 W/kg) after the injection of *Salmonella typhimurium* lipopolysaccharide (LPS) in male mice significantly decreased the LPS dose required to kill 50 percent of the mice. Irradiation prior to the LPS injection did not affect the LD_{50}; (4) Chang *et al.* (1981) found that exposure to 5 mW/cm^2 of 1-GHz radiation for 20 min significantly inhibited the ability of methotrexate (MTX) to delay the development of CNS leukemia in mice when irradiation occurred after MTX treatment.

It is easy to postulate feasible scenarios where interactions of RF radiation with neurologically active drugs (tranquilizers, medication for treatment of various cardiovascular problems, etc.) or synergistic effects with increased temperature, both noted in Sec. 5.5.5 (Interactions with Other Stimuli), result in life-threatening situations. In view of the relatively few multiple-agent-effects studies involving RF radiation as one of the agents, the foregoing reports could well be the harbingers of future developments in the study of the biological effects of RF radiation.

5.10 Human Studies

Doreen Hill

The general approach used in this document for the evaluation of the health-effects literature is stated in Sec. 2. Rigorous criteria were established and applied to the reports of experimental results in order to establish what is believed to be a credible data base. However, it is difficult to apply these selection and review criteria uncompromisingly to the human studies or epidemiological literature, largely because the research method is population based and observational rather than experimental. The papers included here were selected because they were judged to present relatively more information on exposure parameters and/or more rigorous or analytical study designs. The amount of detail in reporting and the degree of specification of study methods and procedures (use of controls, statistics, control of confounding variables, and so forth) were considered important. Case reports are not reviewed.

From this review, the following general conclusions can be drawn:

- The currently available epidemiological data on RF radiation are very limited and not useful for deriving environmental exposure limits. This conclusion is based on various problems in the data on human beings, as discussed in Sec. 5.10.5, Unresolved Issues.
- Two recent exploratory studies of physiotherapists who use RF equipment in their occupation describe potentially significant findings of heart disease, primarily ischemic heart disease, in adult males and poor pregnancy outcome in female physiotherapists. However, neither study provided quantitative information on radiation levels in the work environment.
- Although some studies have associated ocular-lens defects with microwave radiation exposure, no data would at present support a conclusion that low-level, chronic exposure to microwave radiation induces cataracts in human beings.

Table 5-27 summarizes those studies on human beings for which SAR values could be estimated.

5.10.1 Occupational Surveys/Clinical Studies

The majority of reports in the literature concern people occupationally exposed in military or industrial settings. A wide variety of conditions, symptoms, and clinical measurements are usually evaluated. The health conditions investigated usually are pre- or subclinical instead of overt or diagnosed disease. Studies of this type that focused on single rather than multiple end points are described later.

Barron *et al.* (1955) presented results of a study conducted to evaluate changes in various physical characteristics of radar personnel employed by an airframe manufacturer. A total of 226 exposed workers were initially included in the medical surveillance program. The radar workers were characterized by their duration of exposure, as shown in Table 5-28. Controls totaling 88 subjects, stated to have had no industrial radar exposure, were also examined. Methods of selection of cases or controls were not specified. The age distribution of all subjects ranged from 20 to more than 50 years, with the majority under 40 years of age. However, the controls were older (Table 5-29).

A decrease in the number of polymorphonuclear cells below 55 percent was observed in 25 percent of the radar workers vs. 12 percent of the controls, but this change did not occur in a second study (Barron and Baraff 1958). An increase in monocytes and eosinophils was also observed for the exposed group, but in the 1958 report these effects were attributed to a technical error. Platelet counts and urinalyses were similar in the two groups. Ophthalmological examinations revealed ocular anomalies of several diverse types among 12 exposed persons vs. 1 case in the control group. The medical surveillance program was extended to permit periodic reexaminations (Barron and Baraff 1958). No significant changes in physical health status were noted.

The radar bands of exposure included S-band (2880 MHz) and X-band (9375 MHz); the majority of personnel worked with or around APS-45 and AN/APS-20-B and E radars. Exposure times and power densities for individuals could not be developed, but zones at various distances from the antenna were specified and used to estimate three ranges of power densities. The minimal average power density in Zone A was 13.1 mW/cm^2. The field strength in Zone B ranged from 3.9 to 13.1 mW/cm^2, and in Zone C the levels were <3.9 mW/cm^2. The authors stated that because of the relatively low power densities, personnel working in Zone C were eliminated from the study. By establishing these zones of potential exposure, steps were taken to limit entry of personnel to Zone A. Zone B was judged to be safe for occasional but not constant exposure. As a result, most subjects continuing in or added to the examination program are believed to have had incidental exposures to power densities less than 13.1 mW/cm^2.

The strengths of this study are the attempts to estimate potential exposures and to reexamine the workers periodically. But there are some major problems with study methods and analyses. For example, there were fewer control subjects than radar workers. Also, the comparability of the two groups is questionable because of age differences (Table 5-29). None of the observed results was tested statistically.

Table 5-27. Summary of Selected Human Studies Concerning Effects of RF-Radiation Exposure

		Exposure Conditions				
Effects	Species	Frequency (MHz)	Intensity (mW/cm^2)	Duration (Years)	SAR (W/kg) (est)	Reference
No significant change in health status of exposed personnel	Human adult male	400 (PW) 2880 (PW) 9375 (PW)	~4 (avg) ~4 (avg) ~4 (avg)	0-13	~0.16 ~0.12 ~0.12	Barron and Baraff (1958) (See also Barron *et al.* 1955)
No differences in three major diagnostic categories between the two groups of microwave workers	Human adult male	Radar	<0.2 (avg) >0.2 (avg) 6.0 (max)	1-10	$<8 \times 10^{-3}$ $>8 \times 10^{-3}$ 0.24 (max)	Czerski *et al.* (1974); Siekierzynski *et al.* (1974a,b)
No differences observed in clinical evaluations; more subjective complaints in exposed group	Human adult male	Radar	<5	5-10	<0.2	Djordjevic *et al.* (1979)
No effect on life span or cause of death	Human adult male and female	2560-4100 600-9500	0.005 (max) 0.018 (max)	22* 0.5	2×10^{-4} (max) 7×10^{-4} (max)	Lilienfeld *et al.* (1978)
No effect on mortality in a military population followed for more than 20 years	Human adult male	200-5000 (est, PW)	~1 (routine) 100 (occasional)	2	≤0.05 ≤5	Robinette *et al.* (1980)
Decreased number of sperm/ml of ejaculate; reduced percentages of normal and motile sperm in ejaculate	Human adult male	3600-10,000	Tens to hundreds $\mu W/cm^2$	1-17 8 (avg)	$0.3\text{-}4 \times 10^{-2}$	Lancranjan *et al.* (1975)

*Number of years of irradiation of the embassy and length of the study period, but the average exposure of individuals is estimated to be 2 to 4 years.

Table 5-28. Distribution of Years of Exposure for 226 Radar Workers*

Years of Exposure	No. of Workers	Percent of 226
0 to 2	106	47
2 to 5	83	37
5 to 13	37	16

*Data from Barron *et al.* 1955.

Table 5-29. Age Distribution of 226 Microwave Workers and 88 Controls*

	Radar		Controls	
Age	% of 226	Cumulative %	% of 88	Cumulative %
20 to 29	34	34	14	14
30 to 39	49	83	40	54
40 to 49	13	96	27	81
50+	4	100	19	100

*Data from Barron *et al.* 1955.

It is in occupational surveys and industrial health surveillance programs that the potential for neurological and behavioral changes has been investigated. The Soviet and Eastern European literature frequently describes a collection of symptoms reported to occur in personnel industrially exposed to microwaves. These collective symptoms, which have been variously called the "neurasthenic syndrome," the "chronic overexposure syndrome," or "microwave sickness," are based on subjective complaints that include headaches, sleep disturbances, weakness, decrease of sexual activity (lessened libido), impotence, pains in the chest, and general poorly defined feelings of non-well-being (Barański and Czerski 1976, p. 157). Also described are labile functional cardiovascular changes including bradycardia (or occasional tachycardia), arterial hypertension (or hypotension), and changes in cardiac conduction; this form of neurocirculatory asthenia is also attributed to nervous system influence (Silverman 1980).

Czerski, Sierkierzynski, and co-workers in Poland evaluated 841 men occupationally exposed to pulse-modulated microwave radiation (Czerski *et al.* 1974; Sierkierzynski *et al.* 1974a,b). The radiation frequencies were not explicitly stated, but one can infer from the references to pulse modulation and radiolocation that the working environment dealt with radar frequencies. The age distribution of the men ranged from 20 to 45 years. The men had worked various periods of time, with some employed over 10 years. An unexposed control population comparable in general working conditions and socioeconomic status could not be established; therefore, the study group was subdivided into two groups on the basis of level of microwave exposure. One group consisted of 507 men exposed to mean power densities greater than 0.2 mW/cm^2, with short-term exposures estimated to reach 6 mW/cm^2 The other group was 334 men exposed to mean power density levels less than 0.2 mW/cm^2.

The health end points evaluated covered three major categories: neurotic syndrome, digestive-tract functional disturbances, and cardiocirculatory disturbances with abnormal electrocardiogram (ECG)

findings. According to Polish occupational exposure criteria, these conditions are considered contraindications for work in a microwave environment. The neurotic syndrome was defined by a variety of symptoms such as fatigue, headaches, sleep disturbances, and difficulties in memorizing and concentrating. Psychologic examinations were given. Comparisons were made between and within exposure groups according to age and duration of occupational exposure. The two groups were found to be similar with respect to the distribution of these symptoms and conditions. There was no dependence on the duration of exposure.

In 1979, Djordjevic *et al.* reported on medical evaluations of radar workers, aged 25 to 40 years, with a work history of 5 to 10 years. Specific frequencies of exposure were not cited but were stated to be within the whole range used in radar operations. Evaluation of the working environment was undertaken, including power-density measurements. Although the environmental analyses are not given in the paper, it was concluded that the workers were exposed to pulsed microwaves within a wide range of intensities but generally at levels less than 5 mW/cm^2. The lower limit of this exposure may have been 1 mW/cm^2, but the discussion does not clarify whether this estimate refers to the workers included in this study or to radar station personnel in general. The control group consisted of 220 persons reported to be similar in age, character of work regime, and socioeconomic status. The controls did not have work experience with microwave sources. Selection criteria or further descriptive information was not given for either the cases or controls.

Ten major end points or diagnoses were covered in the clinical evaluation, including ophthalmologic examinations. The medical evaluations were conducted by clinical specialists who followed the same scheme for classification of abnormalities. The two groups did not differ with respect to the 10 diagnostic categories. Functioning of the nervous and cardiovascular system was analyzed in greater detail. Electrocardiogram results, multiple biochemical and hematologic indicators, frequency of sleep disturbance, inhibition of sexual activity, and impairment of memory were not different between the groups. Radar workers reported more subjective complaints of headache, fatigue, and irritability. Based on their survey of working conditions, the authors attribute the latter result to specific problems such as poor lighting, poor ventilation, and high noise levels in the environment of the radar workers as well as the need to concentrate on the radar screen. If that is true, the working environments for the two groups were evidently not similar in all respects, even though the authors stated that the controls had been matched on the basis of comparable work regimes. Other factors could also have been operating to produce more subjective complaints. One possibility is reporting bias on the part of the radar workers, e.g., enhanced awareness of the possible "microwave sickness" syndrome. Another environmental factor may have been present that may not have been measurable in the type of environmental survey conducted or detectable through these clinical evaluations; however, microwave exposure cannot be clearly excluded.

An exploratory study was published recently of male physical therapists who use RF, infrared, and ultrasound diathermy equipment in their occupation (Hamburger *et al.* 1983). The study population consisted of 3004 men who responded to a mail questionnaire survey. The cohort was divided into subgroups according to the types of exposures they had experienced, that is, by their use of the various types of diathermy equipment and treatment modalities—ultrasound, microwave, shortwave, and infrared. High and low exposures were approximated by considering length of employment, frequency of treatments per week, and combinations thereof. An association between heart disease (primarily ischemic heart disease) and exposure to shortwave (27-MHz) radiation was the only consistently significant finding in comparisons between high and low exposure groups. In general, the prevalence rates for heart disease were lower than rates in a general population comparable with respect to sex, age, and race. The lower prevalence rates were attributed to higher socioeconomic status in the study group, to a health care occupation in a medical setting, and to a "healthy worker effect." The authors considered their report to be an exploratory analysis because the response rate to the questionnaire was low (58 percent), the nonresponderits could not be characterized, and individual exposures could not be estimated.

5.10.2 Mortality Studies

Lilienfeld and associates (1978) completed a broad survey of the mortality and morbidity experience of Foreign Service employees and their dependents to assess the potential health consequences of microwave irradiation of the U.S. Embassy in Moscow. The health status of Foreign Service employees and those from other agencies who had served in the Moscow Embassy during 1943 to 1976 was compared with that of employees at eight other embassies or consulates in Eastern Europe over the same time period.

The microwave irradiation of the Moscow Embassy was first detected in 1953 and subsequently varied in intensity, direction, and frequency over time. The frequencies ranged from 0.6 to 9.5 GHz (U.S. Senate, Committee on Commerce, Science, and Transportation 1979; Pollack 1979). The measured average power densities over time are given in Table 5-30.

Table 5-30. Microwave Exposure Levels at the U.S. Embassy in Moscow*

Time Period	Exposed Area of Chancery	Power Density and Exposure Duration
1953 to May 1975	West Facade	Max of 5 $\mu W/cm^2$ 9 h/day
June 1975 to Feb. 1976	South and East Facade	18 $\mu W/cm^2$ 18 h/day
Since Feb. 7, 1976	South and East Facade	Fractions of a $\mu W/cm^2$ 18 h/day

*Data from Lilienfeld *et al.* 1978.

Extensive efforts were launched to identify and trace the populations. Information on illnesses, conditions, or symptoms were sought from two major sources: (1) employment medical records, which were fairly extensive, given examination requirements for foreign duty, and (2) a self-administered health history questionnaire. Questionnaire responses were validated for a stratified sample by review of hospital, physician, and clinic records. Death certificates were also sought, although other sources also were used to ascertain mortality status.

Standardized mortality ratios for various subgroups were calculated for each cause of death, were standardized for age and calendar period, and were specific for sex. Similar procedures were used to develop summary indices of morbidity.

A total of 4388 employees and 8283 dependents were studied. More than 1800 with 3000 dependents were employed at the Moscow Embassy and 2500 with more than 5000 dependents worked at the comparison posts. Ninety-five percent of the employees were traced. Receipt of completed questionnaires was less successful, with an overall response rate of 52 percent for State Department personnel.

Based on information in medical records, various health problems were generally similar, with two exceptions. Moscow employees had a threefold greater risk of acquiring protozoal infections than comparison-post employees. In general, both sexes in the Moscow group had somewhat higher frequencies of most of the common kinds of health conditions reported. Lilienfeld *et al.* (1978) stated, "However, these most common conditions represented a very heterogeneous collection and it is difficult to conclude that they could have been related to exposure to microwave radiation since no consistent pattern of increased frequency in the exposed group could be found."

Some excesses were reported by Moscow employees in the health history questionnaire. Both sexes reported more eye problems due to correctable refractive errors. More psoriasis was reported by men and anemia by women. The Moscow employees, especially males, reported more symptoms such as irritability, depression, difficulties in concentration, and loss of memory. It is possible, however, that a bias due to awareness of potential adverse effects is operating, since the strongest differences were present in the subgroup with the least exposure.

The observed mortality was less in both male and female employees than expected, based on U.S. mortality rates; the male employees had more favorable experience than female employees. In both sexes, cancer was the predominant cause of death. The Moscow and comparison groups did not differ appreciably in overall and specific mortality. However, the population was relatively young; it may have been too early to detect long-term mortality effects.

The authors concluded that no convincing evidence was discovered to implicate microwaves in the development of adverse health effects at the time of the analysis. But they also carefully discussed the limitations inherent in the study: uncertainties associated with the reconstruction of the employee populations and dependents, difficulties of obtaining death certificates, the low percentage of responses for the questionnaire, and the statistical power of the study. The limitation most critical for consideration in a document such as this relates to ascertainment of exposure. Problems relative to individual mobility within the embassy and variation of field intensities within the building are present in this study as in any other. No records were available on where employees lived or worked, so one had to rely on questionnaire responses to estimate an individual's potential for exposure. The highest exposure level (18 $\mu W/cm^2$) was recorded for only 6 months in 1975-76; thus, the group exposed to the most intense fields had the shortest cumulative time of exposure and of observation in the study.

Robinette and Silverman (1977) and Robinette *et al.* (1980) examined mortality and morbidity among U.S. naval personnel occupationally exposed to radar. Records of service technical schools were used to select subjects for the study; the men graduated from technical schools during the period from 1950 through 1954. Exposure categorizations were made on the basis of occupational specialty. The exposure group (probably highly exposed) consisted of technicians involved in repair and maintenance of radar equipment. The controls (probably minimally exposed) were involved in the operation of radar or radio equipment. It was estimated from shipboard monitoring that radiomen and radar operators (in the low-exposure group) were generally exposed at less than 1 mW/cm^2, and gunfire control and electronics technicians (in the high-exposure group) were exposed to higher levels during their duties. Over 40,000 veterans were included in the study, with about equal numbers in these two major exposure classifications. The mean age in 1952 of the low-exposure group was 20.7 years and of the high-exposure group, 22.1 years. In conjunction with naval

personnel, an effort was also made to develop an index of potential exposure, termed Hazard Number, for a limited portion of the population. This number was based on the duty months multiplied by the sum of the power ratings (equipment output power of gunfire-control radars (ship) or search radars (aircraft)) where technicians were assigned.

Medical information was obtained through Navy and Veterans Administration records. Records were searched for information on four major end points: (1) mortality, (2) morbidity via in-service hospitalizations, (3) morbidity via VA hospitalizations, and (4) disability compensation.

Mortality was ascertained through the VA beneficiary system. Strokes, cancers of the digestive tract and respiratory system, and leukemias were elevated for the high exposure group, but none of the increases was statistically significant. The authors noted that the differences in mortality from malignant neoplasms of the lymphatic and hematopoietic system were not statistically significant. As seen in Table 5-31, comparisons were also made within the high exposure group across Hazard Number categories. In this case, only two comparisons were statistically significant: (1) the difference in respiratory tract cancer between those with a Hazard Number smaller than 5000 vs. larger than 5000 and (2) the test for trend for all diseases combined. These results may be fortuitous since one or two positive findings might be expected when many statistical comparisons are made. Furthermore, additional information relative to the development of lung cancer, e.g., smoking histories, could not be obtained; the mortality data were obtained from death certificates, and obtaining background information from next of kin was not feasible. Differential health risks with respect to hospitalized illness around the period of exposure were not apparent. Subsequent VA hospitalizations and disability awards provided incomplete information.

Because the study focused largely on the use of automated VA record systems, it was not possible to determine non-Navy or non-VA hospitalizations, nonhospitalized conditions, reproductive histories, or subsequent employment histories. Since actual individual exposure could not be reconstructed retrospectively, only an estimate of the potential exposure of the individuals was possible.

5.10.3 Ocular Effects

The potential of RF radiation to induce cataracts and less significant lens defects and opacities has been cited in both U.S. and foreign literatures. Ocular effects have, in fact, been the major end point of study in U.S. research, primarily in military populations. For this health end point more than others, much attention has been devoted to careful, detailed clinical examinations and to use of standard procedures or protocols. However, population selection criteria are not well elaborated; therefore, the possibility of selection bias cannot be excluded for most of these surveys. Ocular studies have largely taken the form of cross-sectional clinical surveys in actively working

Table 5-31. Number of Deaths from Disease and Mortality Ratios* by Hazard Number: U.S. Enlisted Naval Personnel Exposed to Microwave Radiation During the Korean War Period†

Cause of Death	International Classification of Diseases (8th Rev.)	Number of Deaths				
			High Exposure			
				Hazard Number		
		Low Exposure	Total	0	1-5000	5000+
All diseases	000-796	325 (1.04)	309 (0.96)	63 (0.82)	160 (0.91)	86 (1.23)
Malignant neoplasms	140-209	87 (0.96)	96 (1.04)	22 (0.99)	45 (0.90)	29 (1.44)
Digestive organs	150-159	14 (0.85)	20 (1.14)	6 (1.49)	11 (1.14)	3 (0.78)
Respiratory tract	160-163	16 (0.85)	24 (1.14)	4 (0.82)	10 (0.86)	10 (2.20)
Lymphatic and hematopoietic system	200-209	29 (0.83)	26 (1.18)	6 (1.09)	12 (1.04)	8 (1.64)
Other malignant neoplasms	Residue	37 (1.19)	26 (0.82)	6 (0.78)	12 (0.70)	8 (1.17)
Diseases of circulatory system	390-458	167 (1.07)	150 (0.93)	36 (0.94)	73 (0.83)	41 (1.17)
Other diseases	Residue	71 (1.08)	63 (0.92)	5 (0.30)	42 (1.13)	16 (1.08)

*Mortality ratio (in parentheses) standardized for year of birth; the combined experience of the low and high exposure groups is taken as the standard.
†Table from Robinette *et al.* 1980.

populations and, as such, have focused on minor lens changes. Longitudinal studies of populations with known exposure, with follow-up of either a prospective or retrospective nature, are nonexistent despite the identification of potential cohorts from the cross-sectional surveys. The research to date has not determined whether lens changes lead to overt clinical eye disease or conditions, e.g., the functional and clinical significance of minor lens changes in general and over time. Thus, although it appears reasonable that RF radiation at high levels could influence cataractogenesis, it cannot be confirmed without more rigorous follow-up studies in already identified exposed populations. This would be a reasonable line of future research if such epidemiological studies prove feasible.

More than 50 cases of cataract development have been attributed to microwave exposure (Zaret 1974). These instances have generally been related to acute exposure to high-intensity fields in the workplace. For most cases, work history information sufficient to estimate dose rates or exposure conditions is lacking (Zaret 1970).

Utilizing Veterans Administration hospital records and military personnel records, Cleary *et al.* (1965) conducted a case-control study to examine cataract formation among U.S. Army and Air Force veterans. This is the only case-control study of clinically diagnosed cataracts. Cases were defined as white males born after 1910 who were treated for cataracts between 1950 and 1962, based on diagnoses given in VA hospital records. The restriction on year of birth resulted in a study population under 55 years of age. According to the authors, this was done to minimize dilution of the sample with senile cataracts. Also, cases with certain specific cataract diagnoses were not included in the study because the diagnoses are unrelated to microwave exposure. These cases were congenital cataracts, cataracts in Down's Syndrome, traumatic cataracts, and diabetic cataracts. Controls, also born after 1910, were drawn from the same sources by selection of men with adjacent hospital register numbers; therefore, the control group had a sample of diagnoses made in the same hospitals at the same time the cataract cases were diagnosed. Military occupational specialties, as abstracted from service records, were used to denote radar or nonradar workers. Job classification was then used as an indicator of potential exposure. The distribution of cases and controls according to radar exposure is seen in Table 5-32. The frequency of microwave exposure as denoted by radar work history was similar between cases and controls; the odds ratio was less than one (0.67) and was not statistically significant. The distribution in different age groups is shown in Table 5-33. Excess risk was noted for U.S. Air Force veterans, but the numbers were small. Only 40 radar workers were found in over 5000 cases and controls.

Table 5-32. Classification by Military Occupation of World War II and Korean War Veterans With and Without Cataracts, Based on Discharges from VA Hospitals*

	Veterans' Cataract Status		
Military Occupation†	Yes	No	Total
Radar Workers	19	21	40
Nonradar Workers	2625	1935	4560
TOTAL	2644	1956	4600

$$\text{Odds Ratio} = OR = \frac{(19)(1935)}{(21)(2625)} = 0.67$$

*Data are from Cleary *et al.* 1965.
†Based on Military Occupational Specialties.

Table 5-33. Estimated Relative Risk of Cataracts Among Army and Air Force Veterans by Age Group and Occupation*

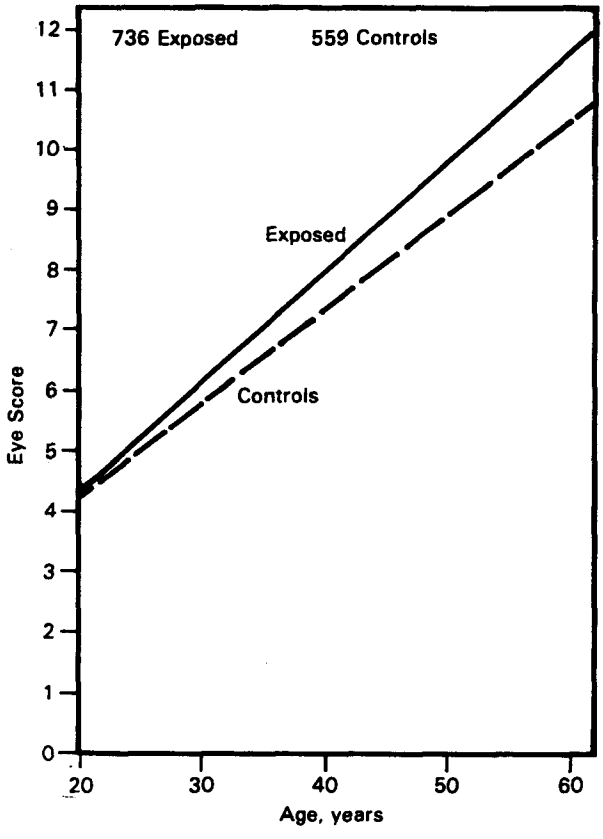
Age Group	Cataracts	Radar Workers	Nonradar Workers	Odds Ratio	χ^2
Total	Yes	19	2625		
	No	21	1935	0.67	1.26 NS
20-39	Yes	3	418		
	No	4	522	0.94	0.08 NS
40-49	Yes	7	1517		
	No	13	1101	0.39	3.39 NS
50-59	Yes	9	699		
	No	4	316	1.02	0.09 NS

*Data are from Cleary *et al.* 1965.

Cleary and Pasternack (1966) examined and scored subclinical or minor lens changes in 736 microwave workers and 559 controls. The population was drawn from 16 microwave installations of various types at different locations. Sampling constraints did not permit matching on age. The mean age of each group was very similar (32.8 years for microwave workers and 33.2 for controls), but the age distributions were different. The age frequency distribution for controls was broader than for the exposed group, with more younger and older individuals, whereas more of the exposed group were 26 to 30 years of age. Slit lamp examinations were performed, and a grading procedure revised by Zaret and Eisenbud (1961) was used to provide a relative measure (eye score) of minor types of lens changes. Detailed occupational histories were taken. The work environment in terms of microwave exposure parameters was not reported; that is perhaps the greatest drawback of the study. However, a relative microwave exposure index or score was developed by use of various parameters such as power output and distance from the microwave-generating source. The exposure score was used to compare lens findings with occupational microwave exposure.

By linear regression techniques, the number of defects was found to increase significantly in both groups with increasing age, and microwave workers were found to have more lens changes than controls (Figure 5-7). The authors suggested that the

Figure 5-7. **Linear regressions of eye score on age for workers exposed to microwave radiation and controls (from Cleary and Pasternack 1966, Figure 3).**



subclinical lens changes observed with greater frequency in the microwave workers may indicate accelerated aging of lens tissue. The types of lens defects that accounted for the differences in eye scores between the two groups were posterior polar defects and opacification. In an expanded analysis, the increase in lens defects was correlated with duration of microwave work, exposure score, and duration of exposure interaction. The group of microwave workers was further characterized by the identification and evaluation of five occupational subgroups. The subgroups were found to differ with respect to the average values for age, duration of work, exposure score, and eye score. The subgroup involved in research and development of microwave equipment had the greatest mean eye score. The authors concluded that certain types of microwave work environments may result in different modes of exposure and increased frequency of lens defects.

The authors also examined the possibility that another agent, ionizing radiation, was responsible for the observed differences in lens defects rather than microwave radiation. After evaluating mean eye score in two subgroups that presented the highest and lowest potential for ionizing radiation exposure, the authors concluded that no evidence indicated ionizing radiation exposure was responsible for the increase in lens defects in these microwave workers.

Majewska (1968) examined the eyes of 200 Polish workers employed from 6 months to 12 years at installations with microwave-generating equipment that operated from 600 MHz to 10.7 GHz (2.8 to 50 cm). Although cited as "high intensity" by the author, intensity levels were not specified. Two hundred controls, stated to be matched on age, were also examined. The methods of subject selection were not reported. The group of workers included eight women; the distribution of the control group by sex was not stipulated. After dilation of the subjects' pupils, lenses were examined with an ophthalmoscope and a slit lamp. It was not stated whether the examinations were conducted so as to mask the group assignment of the subjects for the examiners. Lens changes were noted in 168 of the microwave workers vs. 148 controls. The differences between the two groups were noted by the author as being statistically significant. This result was presented as a summary measure over all ages; age-specific differences were not presented.

In the same study, the effects of longer-term exposure were evaluated by comparison of 100 controls with 102 employees, drawn from the original group, who had worked with high-frequency electromagnetic-wave generators for more than 4 years. Subjects were graded on a five-point scale for degree of lens opacity. The mean grade of opacities in the exposed group was greater than in controls in each 5-year age-group interval for ages ranging from 20 to 50 years. Among microwave workers, the mean grade of lens changes, uncontrolled for age, also showed an increase with length of employment. Although this part of the study was stated to be focused on employees with 4 or more years of work experience, the data on lens scores and duration of employment list results for persons with less than 4 years of employment. This evaluation also suffers from lack of quantitative measures of exposure.

In 1972 Appleton and McCrossan reported a clinical survey conducted among 226 military personnel stationed at Fort Monmouth, N.J. Microwave-exposed workers (91) were defined as those who worked with U.S. Army Signal Corps electronic communication, detection, guidance, and weather equipment. The 135 controls did not report such a work history. Likely intensities or frequencies were not specified. Personnel were drawn from the post's Occupational Vision Program, but sampling or selection procedures were not documented. Ophthalmologists based diagnoses on slit-lamp examination of dilated pupils. The presence or absence of opacities, vacuoles, and posterior subcapsular iridescence was noted. The examination results were similar in the two groups over all age groupings, although no statistical tests were applied.

The survey was later extended to six other installations with results reported by Appleton in 1973. The exposure of military personnel was classified as "likely" vs. "unlikely"; the latter group served as controls. Masking procedures were used for the examining ophthalmologists; that is, they were not aware of the exposure classification of subjects. The same team of examiners performed all tests, except at one location, to minimize interobserver variation. The same three end points used in the 1972 study were also used in the 1973 study. Older age groups demonstrated a trend of greater opacities among exposed personnel, but since the numbers in some groups were small, the validity of this result is questionable.

Odland (1973) reported results of a survey of ocular anomalies in personnel from eight military installations. The population consisted of 377 exposed individuals and 320 controls. Exposure conditions were not specified. Exposed personnel were defined as individuals whose primary duties involved the operation or maintenance of radar equipment. The selection criterion for controls was duty that did not permit actual or potential exposure to radar, although the actual work assignments were not stated. Medical histories were taken, and ophthalmic examinations were performed in a manner which masked the exposure classification of the individuals. The frequency of occurrence of lens anomalies was similar in the two groups; however, the frequency of anomalies between control and exposed groups was different for individuals who had a family history of diabetes, nontraumatic cataract, glaucoma, or defective vision. Lens changes were noted in 29 percent of the exposed individuals with such a history vs 17 percent in the controls with a family history of eye problems. No statistical tests were applied to any of the reported frequency distributions.

Shacklett *et al.* (1975) reported eye examinations of 817 military and civilian personnel. There were 477 persons with a history of microwave exposure and 340 controls without exposure drawn from eight U.S. Air Force bases between November 1971 and December 1974. The authors stated that detailed work histories were recorded (including time spent with different types of equipment), but information on typical exposure settings was not given. Local unit commanders selected the subjects by using criteria established by the examining team. Standard diagnostic criteria were established. The same ophthalmologists performed all examinations and were not aware whether a subject was considered as exposed or a control. No differences were noted between the two groups in the frequency of opacities, vacuoles, and posterior subcapsular iridescence. Differences in results were reported as not being statistically significant, but the type of statistical test was not stated. An age-dependent increase in lens changes was noted in both groups.

The study by Siekierzynski *et al.* (1974b) discussed earlier also compared lens opacities in the two exposure groups (< 0.2 mW/cm^2 and 0.2 to 6 mW/cm^2). Ophthalmologic examinations were performed. Lens translucency was assessed with a slit lamp after pupil dilatation and according to criteria established for five grades. No differences were reported between the exposure groups nor within the groups for duration of exposure.

5.10.4 Congenital Anomalies and Reproductive Effects

In 1965 Sigler *et al.* reported a history of occupational exposure to radar and more military service among fathers of children with Down's Syndrome. The association with radar exposure was an ancillary observation; this study was specifically directed toward examination of the relationship between ionizing radiation exposure and Down's Syndrome. A case-control approach was used, and 288 children born with Down's Syndrome in Baltimore between January 1946 and October 1962 were identified for inclusion in the study. The investigators selected controls by matching each case of Down's Syndrome with another normal birth for (1) hospital of birth, (2) sex, (3) date of birth, and (4) maternal age at birth of child. Of the original 288, 216 matched pairs were available for final analysis. Eliminations occurred for various reasons such as non-cooperation or equivocal diagnoses. Occupational histories and other data were obtained by interview of the parents. The fathers of the children with Down's Syndrome had more military service experience than control fathers, but the difference was not statistically significant. A more frequent history of radar exposure was reported by case fathers; this difference was statistically significant. Exposure to radar occurred primarily in job assignments as radar operators or technicians. (Some radar operators may be exposed to only low levels if the place of operation is distant from the power-generating equipment or the microwave source.)

Cohen *et al.* (1977) extended the study. The case series was expanded to include 128 additional verified cases and their matched pairs born through 1968. To serve as an independent replication, essentially the same procedures were applied along with the following expansions: (1) more extensive questions on microwave/radar exposure and military service, (2) validation of exposure histories by searching of armed service records, and (3) chromosomal studies. The previously noted differences disappeared in the extended analysis (Table 5-34). Results of the cytogenetic analyses are not yet available.

The authors stated that although the extended study did not confirm excess radar exposure among Down's case fathers, the possible relationship of such

Table 5-34. Paternal Radar Exposure Before Conception of Index Child (from Interview and/or NAS)*

Case Series†		Down's Cases No.	Down's Cases %	Controls No.	Controls %
1. Current	Exposed	20	15.7	27	21.3
	Exposure Known	127	100.0	127	100.1
2. Original	Exposed	36	18.6	30	15.2
	Exposure Known	194	100.1	198	100.0
3. Combined	Exposure	56	17.4	57	17.5
	Exposure Known	321	99.9	325	100.0

*Data are from Cohen *et al.* 1977.
†1, 128 pairs; 2, 216 pairs; 3, 344 total pairs.

exposure to increased risk of Down's offspring cannot completely be ruled out. They added further that the most challenging aspect of the investigtion was the definition of radar "exposure." In discussing explantions for lack of confirmation of a radar exposure factor (if one does exist), the authors offer several possibilities. As mentioned above, inaccurate exposure estimates could distort results. The role of maternal factors in Down's Syndrome is so important that paternal factors could be masked. It was also suggested that detecting a paternal relationship in a retrospective study of Down's cases may be difficult. If radar exposure does pose some increased health risk to the fathers, the most highly exposed males may have poor survivorship or an increased risk of germinal tissue damage. This factor could result in elimination of such men from reproductive experience. It was further suggested that a prospective approach might then prove more fruitful. Although not discussed by the authors, radar equipment and military occupational specialties could have changed over time in such a way as to lower risk. It has also been suggested that since microwave-generating equipment, especially of an older vintage, may have emitted more ionizing radiation than modern equipment, the ionizing radiation presents the actual risk factor, with microwave radiation possibly operating as a covariable.

Lancranjan *et al.* (1975) studied 31 adult males with a mean age of 33 years and a mean exposure of 8 years (a range of 1 to 17 years) to electromagnetic fields that "frequently were in the range of tens to hundreds of $\mu W/cm^2$." The frequencies were defined as microwaves of wavelengths between 3 and 12 cm and frequencies between 10,000 and 3,600 MHz. No details on the RF source(s) were provided. A group of 30 men of similar mean age and no known exposure to microwaves served as a control group for the analysis of spermatic fluids and hormones. Statistical analysis of the results showed no differences in urinary content of 17 ketosteroids (as an indirect measure of Leydig cell function) or total gonadotropin between the exposed and controls. Slight but statistically significant decreases were reported for exposed personnel in the number of sperm per milliliter of semen, percent of motile sperm in the ejaculate, and the percent of normal sperm.

The goal of this study was application of objective measures to assess the subjective reports of decreases in libido or of other sexual disturbances. This goal was accomplished, but the exposures are poorly defined, and the number of men evaluated was very small. Spermatogenesis improved in two-thirds of the subjects after cessation of exposure. The investigators felt this supported an argument for microwave influence on the observed alterations. But the values obtained by the semen analyses for both exposed and control groups might be considered to be low-normal or below normal values.

Källen *et al.* (1982) examined the pregnancy outcome of 2018 Swedish women who were certified physiotherapists at the time of pregnancy during 1973 to 1978. There were 2043 infants born, including 25 pairs of twins. To identify the mothers and the births, the investigators linked data from computerized national registers of certified physiotherapists, of deliveries, and of major congenital malformations. It is likely that use of these record systems resulted in reasonably complete ascertainment of the study population.

Overall, this cohort had a better than expected delivery outcome as measured by eight different end points. All measures of infant health were near or below the expected national values, which were adjusted for age and parity distribution, as well as hospital of delivery, to control for diagnostic variability.

To examine whether a "healthy worker" effect may have been operating in this group and to obtain more detailed work histories, a nested case-control study was also conducted. The cases were defined as infants with a major malformation plus all perinatal deaths. Two controls per case were selected, matched for maternal age, parity, and date of delivery. After elimination of ineligible women, 33 cases and 63 controls remained. A work history questionnaire was mailed to the study group, and the response rate was 93 percent.

Of several end points explored, the only positive finding was a higher frequency of shortwave equipment use among the women with a dead or malformed infant than among the control physiotherapists. This difference was statistically significant in both unmatched and matched pair analyses. Use of ultrasound equipment followed a similar pattern but was not statistically significant. The authors stressed that exposure to the two types of equipment was heavily associated. Information on work with X rays was not reported, although questions on X rays were included in the questionnaire. Measurement of the radiation fields in the work environment was not performed in conjunction with the health study. Furthermore, no information was presented on

shortwave radiation levels typical of the various physiotherapy work environments or on the types of equipment most commonly used in Sweden.

5.10.5 Unresolved Issues

There are some general issues surrounding the use and applicability of epidemiological research methods to study the effects of environmental agents, including RF radiation. Examples of such issues include the ability of epidemiological studies to detect low-level risks, to separate the effects of multiple causes, and to identify and control confounding factors. Moreover, specific problems are common in the current epidemiologic literature on RF radiation that limit the ability to draw inferences from this body of data and its usefulness in establishing environmental exposure limits for the general population. These problems are briefly discussed below.

5.10.5.1 Exposure Assessment

It is difficult to determine actual exposure and dose for individuals, and even for groups; that is perhaps the largest single problem in epidemiological studies on RF radiation. In general, there are no continuous surveillance programs in the workplace that could yield data for use in epidemiological studies. It is a formidable task to reconstruct RF-radiation exposure data for health studies that are begun after exposure has taken place. The study by Robinette and Silverman (1980) is a good example of attempts to deal with the difficulties of retrospective exposure assessment, e.g., two approaches (job type vs. Hazard Number) were used, and an exposure gradient was obtained with the Hazard Number which simultaneously considered the RF sources and the length of service assignment. Despite these efforts, the estimates remain those of potential rather than actual exposures. In many of the other studies, the levels and frequencies of exposure are not known, not estimated, or not reported. Also, in studies of military populations, information relevant to exposure conditions might be classified. When well-developed exposure data are not available, it is difficult to analyze possible dose-response relationships, to interpret the significance of the findings, and to use the data in establishing protective exposure limits.

5.10.5.2 Documentation and Methods

Another problem in the RF radiation literature on human beings relates to documentation of methods and procedures. Degree of detail in reporting seems to be a major difference between studies done in the U.S. and those conducted in other countries. The paper "Guidelines for Documentation of Epidemiologic Studies" (Epidemiology Work Group 1981) suggests the types of topics that are useful to document when reporting an epidemiologic study, especially one used to support regulatory decisions. These major elements include a statement of background and objectives, methods of selection and characterization of study and comparison subjects, data collection procedures, and analysis. Few reports on human beings exposed to RF radiation adequately include such necessary information. It is frequently difficult to tell whether certain research methods were not applied or simply not reported. For example, the criteria for selecting controls are frequently not stated, but controls are often said to be comparable in all respects except exposure; analyses or data to support such statements may not be supplied. Also, common practices such as development of standardized rates or use of procedures to control confounding variables, e.g., age ajdustment, are usually not reported. Statistical power is rarely evaluated or discussed, but it is difficult to estimate power if the underlying prevalence or incidence of the disease under study is not well known, especially for some of the conditions and symptoms, e.g., functional disturbances, studied in relation to RF radiation exposure.

5.10.5.3 Health End Points: Design and Populations

Another issue is the medical significance of any changes that may be induced by exposure to RF radiation. For example, the studies on ocular effects usually have examined a subclinical end point, e.g., lens opacities, which may not necessarily be an early marker or risk factor for cataractogenesis and visual problems (Silverman 1979). Further, most studies present only single measures at one point in time; the study populations have not been followed long enough to permit development of longitudinal data upon which to base a determination of whether symptoms and subtle changes lead to disability or disease. A similar concern surrounds the problematic information on functional changes and nervous system effects reported in some of the Eastern European literature. The potential for neurological or behavioral effects has not been thoroughly and rigorously evaluated, and standardized questionnaires and more objective medical measurements need to be used in studies on these effects.

Most studies concern occupational groups of relatively young healthy males. It cannot be presumed that sensitivity, or lack thereof, to RF-radiation exposure would be the same in the general population as in working groups. The general population is more diverse, with the full range of ages, sexes, races, and other factors that could influence health status or the development of disease. To resolve this issue, specific exposed populations could be identified and evaluated if such research appeared feasible.

5.10.5.4 Summary

Serious methodological problems in the human studies literature make results equivocal. These problems are not necessarily insurmountable. But at present, the data on human beings exposed to RF radiation are not adequate nor sufficiently developed to be very useful in determining exposure limits for the general population.

Section 6
Summary and Conclusions

Joe A. Elder

This document presents a critical review of the literature on the biological effects of RF radiation with the objective of determining the relation between biological effects and exposure to RF radiation in terms of (1) absorbed dose rate (SAR) and (2) increased body temperature. In Sec. 3, the interaction of RF radiation with biological systems is discussed, and in Secs. 4 and 5, research reports are reviewed for the presence or absence of biological effects of RF radiation. The major conclusions or generalizations that can be drawn from these three sections are now presented. In addition, the biological effects of RF radiation are discussed in relation to SAR and to increased body temperature in an attempt to analyze, synthesize, and consolidate the available information from this multidisciplinary field into a coherent picture.

6.1 Major Conclusions and Generalizations

1. RF radiation is a form of nonionizing electromagnetic radiation of very low photon energies and frequencies (0-3000 GHz), as distinguished from the very high photon energies and frequencies associated with ionizing electromagnetic radiation, e.g., X and gamma rays. Included in the RF-radiation spectrum are AM and FM radio, UHF and VHF TV, radar, and microwave communication frequencies. The frequency range of concern in this document is 0.5 MHz to 100 GHz, which includes nearly all the significant sources of population exposure except 60-Hz electrical power systems. However, there is very little information on effects in human beings at any of these frequencies and limited data on responses of animals exposed at frequencies above 10 GHz and below 10 MHz; most of the animal research is concentrated in the range of 900 MHz to 3 GHz.

2. RF-energy absorption by biological systems is a complex function of frequency and the dimensions, orientation, and dielectric properties of the absorber and the complexity of the incident radiation fields. Resonant frequencies (and their related wavelengths) for an absorber are those at which maximum RF energy is coupled into the absorbing system. Resonance occurs when the long dimension of the absorber is approximately 0.4 times the wavelength of the incident RF radiation, if the object is located in free space. Under these conditions, the whole-body resonant frequency range for humans (from adults to infants) is approximately 30 to 300 MHz. In this document, whole-body average specific absorption rate (SAR) is used to normalize the rate of energy absorption across the frequency range, 0.5 MHz to 100 GHz, and to quantitate the relation between biological effect and dose rate of RF radiation. SAR is the mass-normalized rate at which the energy of an electromagnetic field is coupled into an absorbing body; the units of SAR are watts per kilogram (W/kg).

3. High level RF radiation is a source of thermal energy (e.g., microwave ovens) that carries all of the known implications of heating for biological systems. At a given incident field strength, maximal heating occurs at the resonant frequency (D'Andrea *et al.* 1977). In general, the data are consistent with the hypothesis that the SAR required to raise body temperature of laboratory animals decreases as body mass increases.

4. In most of the animal studies that report a biological effect of RF radiation, exposures occurred at ambient temperatures of 20 to 25°C and relative humidities of 50 to 70 percent. At more thermally stressful conditions, e.g., higher ambient temperature and the same or higher relative humidity, the experimental results show that lower SARs cause a similar biological effect. For example, Rugh *et al.* (1974) found that the lethal dose of 2450-MHz radiation for mice was inversely related to the temperature-humidity index (Figure 4-22). Gage (1979b) showed that a 2450-MHz exposure at 22°C resulted in a reduced behavioral response rate in rats at 3 W/kg, but that similar exposures at 28°C caused reduced rates at 1, 2 and 3 W/kg.

5. No consistent biological effect has yet been found with molecular and subcellular systems exposed *in vitro* to RF radiation other than effects occurring at SARs that cause general temperature increases. Conclusions regarding effects of *in vitro* exposure of higher-order biological systems, such as single cells and brain tissue, are given below.

6. The electrophysiological properties of single cells, especially the firing rates of neurons in isolated preparations, may be affected by RF radiation at SARs

as low as 1 W/kg in a manner different from generalized heating.

7. In general, no changes in chromosomes, DNA, or reproductive potential of RF-exposed animals have been reported and corroborated in the absence of significant rises of temperature. Similarly, RF radiation does not appear to cause mutations or genetic changes in bacterial test systems unless temperatures well above the normal physiological range are produced.

8. Effects on the hematologic and immunologic systems have been reported at SARs $\geq$ 0.5 W/kg; however, there is a lack of convincing evidence for RF-radiation effects on these systems without some form of thermal involvement. Some of the reported effects of RF radiation on the hematologic and immune systems are similar to those resulting from a stress response involving the hypothalamic-hypophyseal-adrenal axis or following administration of glucocorticoids. In those few cases where the reversibility of RF radiation effects on the hematologic and immunologic systems has been examined, the effects have proved to be transient.

9. RF radiation is teratogenic at high SARs ($>$ 15 W/kg) that approach lethal levels for the pregnant animal. High maternal body temperatures are known to be associated with birth defects. There appears to be a threshold for the induction of experimental birth defects when a maternal rectal temperature of 41 to 42°C is reached. Any agent capable of producing elevated internal temperatures in this range, including RF radiation, is a potential teratogen.

10. Reduced fetal mass seems to occur consistently in rodents exposed during gestation to teratogenic levels of RF radiation, or at SARs somewhat less than those which cause death or malformation.

11. There is evidence that exposure of rodents during gestation to RF radiation may cause functional changes later in life. For example, Johnson *et al.* (1978) observed lower body weight at weaning and in young adult rats exposed at 2.5 W/kg for 20 h/day during 19 days of gestation, and Chernovetz *et al.* (1975) found increased postnatal survival of mice exposed at 38 W/kg for 10 min during gestation.

12. Permanent changes in reproductive efficiency have been directly associated with RF-radiation exposures that caused temperatures in animal testes greater than 45°C. At temperatures of 37 to 42°C mature sperm may be killed with a temporary loss of spermatogenic epithelium. Irradiation of rats at an SAR of 5.6 W/kg, which produced a core temperature of 41°C, resulted in temporary infertility.

13. Neurons in the central nervous system (CNS) of experimental animals have been reported to be altered by acute high-level and by chronic low-level exposures ($\geq$ 2 W/kg). Pulsed RF radiation may have a potentiating effect on drugs that affect nervous system function. Some of the early reports of RF-radiation effects on the blood-brain barrier (BBB) at SARs $\leq$ 2 W/kg have not been substantiated by later investigations.

14. An increased mobilization of calcium ions occurs in brain tissue exposed *in vitro* to RF radiation, amplitude modulated at frequencies recorded in the electroencephalogram (EEG) of awake animals. The response appears to be based on the intensity of the electric field within the tissue, which can be related to SAR; the lowest effective SAR in *in vitro* samples is estimated to be 0.0013 W/kg. Calcium-ion efflux is a nonlinear effect in terms of both AM frequency and field intensity; that is, the response occurs at specific frequencies and electric field strengths. The physiological significance of this effect has not been established.

15. Some types of animal behavior are disrupted at SARs that are approximately 25 to 50 percent of the resting metabolic rates of many species. For example, changes in locomotor behavior in rats occur at an SAR of 1.2 W/kg, and alterations in thermoregulatory behavior in squirrel monkeys occur at an SAR of 1 W/kg. Decreases in other operant or learned behavioral responses during exposure have been found at an SAR of 2.5 W/kg in the rat and at 5.0 W/kg in the rhesus monkey. The reported behavioral alterations appear to be reversible with time.

16. Changes reported in endocrine gland function and blood chemistry are similar to those observed during increased thermoregulatory activity and heat stress, and are generally associated with SARs $>$ 1 W/kg. Exposures of sufficient intensity to produce whole-body heating produce an increase in heart rate similar to that caused by heating from other sources. Changes in whole-body metabolism have been reported following exposures at thermal levels ($\sim$ 10 W/kg), and brain energy metabolism is altered at levels as low as 0.1 W/kg following irradiation of the exposed surface of the brain of anesthesized animals.

17. A single acute exposure of the eye to high-intensity RF radiation, if applied for a sufficient time, is cataractogenic in some experimental animals. In the rabbit, the animal most often used in ocular studies, the cataractogenic threshold for a 100-min exposure is 150 mW/cm^2 (138 W/kg peak absorption in the lens). The cataractogenic potential of microwave radiation varies with frequency; the most effective frequencies for cataracts in the rabbit eye appear to be in the 1- to 10 GHz range. Cataracts were not produced in primates exposed acutely to RF-radiation conditions that caused cataracts in lower mammals such as the rabbit. The absence of cataracts in the primate is attributed to the different facial structure that caused a different pattern of absorbed energy in the eye. No cataracts have been reported in rabbits after whole-body, far-field RF-

radiation exposures, even at near-lethal levels (SAR = 42 W/kg for 15 min). No data at present support a conclusion that low-level, chronic exposure to microwave radiation induces cataracts in human beings, although some studies have associated ocular-lens defects with microwave radiation exposure.

18. Pulsed RF radiation in the range 216 to 6500 MHz can be heard by some human beings. The sound associated with the "RF hearing" varies with pulse width and pulse-repetition rate and is described as a click, buzz, or chirp. The threshold for human perception of this effect is approximately 40 $\mu J/cm^2$ (incident energy density per pulse). The most generally accepted mechanism for the RF-auditory sensation is that the incident pulse induces a minuscule but rapid thermoelastic expansion within the skull, which results in a pressure wave that is conducted by the bone to the cochlear region of the ear.

19. For the broad range of frequencies between 0.5 MHz and 100 GHz, cutaneous perception of heat and thermal pain may be an unreliable sensory mechanism for protection against potentially harmful RF-radiation exposure levels. Many frequencies deposit most of their energy at depths below the cutaneous thermal receptors.

20. There is no convincing evidence that exposure to RF radiation shortens the life span of human beings or experimental animals or that RF radiation is a primary carcinogen (cancer inducer); however, (1) few studies have used longevity or cancer incidence as end points, and (2) human studies have lacked statistical power to exclude life shortening or cancer. There is evidence from one group of investigators that chronic exposure to RF radiation (SAR = 2 to 3 W/kg) resulted in cancer promotion or co-carcinogenesis in three different tumor systems in mice; the incidence of cancer was comparable to that observed in mice exposed to chronic stress conditions only.

21. Human data are currently limited and incomplete but do not indicate any obvious relationship between prolonged low-level RF-radiation exposure and increased mortality or morbidity, including cancer incidence.

The prospects for revision and refinement of the major conclusions and generalizations stated above are considerable because of our limited knowledge of (1) effects of most frequencies in the range 0.5 MHz to 100 GHz; (2) effects of chronic low-level exposures on human beings and laboratory animals; (3) which segments of the population are most sensitive; (4) the influence of ambient environmental conditions and of potential synergistic interaction with other agents; (5) the implication of nonhomogeneous RF-energy deposition; (6) the existence and significance of frequency-specific effects and power-density windows; and (7) the physical mechanisms of interaction at low exposure levels, including field-specific phenomena.

6.2 Specific Absorption Rate

Reports on the biological effects of RF radiation usually specify the frequency and power density of the field applied to the biological system. Individually or together, these parameters do not provide a reasonable correlate with biological effects because RF-energy absorption is known to depend on the relation between wavelength and absorber size and orientation. However, when frequency and power density are combined with a knowledge of absorber size and dielectric property, an estimate of SAR can be made. The whole-body average SAR is currently of limited use because it is an estimate of absorbed energy averaged over the whole-body mass. It does not address the existence of localized areas of increased energy deposition in exposed biological systems, nor the considerable differences between species in their capacity to regulate a given energy burden. However, work is currently under way to extend the usefulness of this concept in both areas. The SAR is currently the parameter used most frequently to describe the energy absorbed by a biological system exposed to RF radiation. In the discussion below, whole-body average SAR is used as a correlate for the observed biological responses.

The data cited in the preceding sections show that acute whole-body exposure of laboratory animals at SAR values $>$ 30 W/kg is lethal. For example, Chernovetz *et al.* (1977) reported that a 20-min exposure (2450-MHz) at 31 W/kg was lethal to 23 percent of the rats. Appleton *et al.* (1975) found that 3000-MHz exposures at 42 W/kg for 30 min or 70 W/kg for 15 min were lethal to rabbits. A shorter exposure (15 min) at 42 W/kg caused acute ocular changes, but no cataracts, and cutaneous burns around the eye (see Table 5-15). During a 15-min exposure at 14 W/kg, rabbits showed signs of acute heat stress and struggled out of the field. Localized exposure to very high intensity RF radiation can result in burns, as shown by Kramar *et al.* (1978), who reported second- to third-degree burns on the face of rhesus monkeys exposed for 22 min to 2450-MHz radiation that produced an SAR in the eye of $\sim$ 115 W/kg.

Brief exposures ($<$ 5 min) of the whole body to high intensities result in significant biological damage, as shown by Rugh (1976a) and Rugh *et al.* (1975), who irradiated pregnant mice at SAR values near 100 W/kg and found birth defects, increased embryonic and fetal resorptions, postnatal weight decrements, and reduced survival upon re-irradiation of the offspring of mice exposed during pregnancy.

Laboratory animals have generally been found to be affected by SARs in the 10- to 30-W/kg range, even

when the exposures have been short (minutes to hours). Fetotoxic effects in mice exposed at 22 W/kg have been reported by Berman *et al.* (1978). Some components of the immune system appear to react with an increased response, whereas others demonstrate diminished responses. Components reported to increase are PMN levels (Kitsovskaya 1964; Michaelson *et al.* 1964; Lappenbusch *et al.* 1973; Liburdy 1977), splenic lymphocytes (Wiktor-Jedrzejczak *et al.* 1977a,b,c; Sulek *et al.* 1980), lymphocyte response to mitogen stimulation (Huang and Mold 1980; Wiktor-Jedrzejczak *et al.* 1977a,b,c), and lymphocyte transformation to the lymphoblast stage (Huang *et al.* 1977). Decreases are reported in the primary antibody response to sheep red blood cell (SRBC) (Wiktor-Jedrzejczak *et al.* 1977a,b,c), the CFU for the erythroid granulocyte-macrophage series in bone marrow (Huang and Mold 1980), lymphocyte traffic from lung to spleen (Liburdy 1980), and circulating lymphocyte levels (Lappenbusch *et al.* 1973; Liburdy 1977). Roszkowski *et al.* (1980) reported a general immunosuppressive effect at 35 W/kg; they found an increase in lung cancer colonies and an inhibition of contact sensitivity to oxazlone in mice.

Some biological end points appear to be unaffected even at 10 to 30 W/kg. Examples are postnatal survival, adult body weight, and longevity (Guillet and Michaelson 1977; Spalding *et al.* 1971).

In contrast to the results of animal studies, *in vitro* studies at 10 to 30 W/kg have shown few effects on the irradiated systems if temperature is properly controlled, e.g., no mutation induction in bacteria (Blackman *et al.* 1976; Corelli *et al.* 1977; Dutta *et al.* 1979a, 1980), no effects on enzyme activities (Ward *et al.* 1975; Bini *et al.* 1978; Allis and Fromme 1979), no effects on the physical characteristics and structure of biomolecules such as nucleic acids and proteins (Allis 1975; Allis *et al.* 1976; Corelli *et al.* 1977), and no change in lymphocyte transformation (Smialowicz 1976). Notable exceptions are Ismailov's (1971, 1977, 1978) reports that the human RBC exhibits increased electrophoretic mobility, K^+ efflux, Na^+ influx, and hydrogen exchange at SARs between 5 and 45 W/kg; and Seaman and Wachtel's (1978) observation of a decreased firing rate of Aplysia pacemaker neurons at SARs as low as 1 W/kg.

The majority of the experimental studies that met the criteria for inclusion in this document employed SARs $\leq$ 10 W/kg. Many of these studies are differentiated by observed "effects" (without regard to biological significance) or "no effects," and arranged within these two groupings by decreasing SAR values in Tables 6-1 and 6-2.

Biological variables that do not appear to be sensitive to RF radiation at $\leq$ 10 W/kg include organ weight, litter size, teratology and growth (Table 6-1). Physiological systems and parameters that appear to be sensitive include behavior, the central nervous system, and hematology and immunology (Table 6-2).

In Table 6-2, several positive findings at SARs $\leq$ 10 W/kg are listed for a number of biological variables. A comparison of Table 6-1 with Table 6-2 reveals that many reports of "no effects" occur in the same biological systems (e.g., behavior and hematology/immunology) over a similar SAR range. Negative findings are important to define the lower exposure limits of biological effects and the sensitivity of specific biological end points; however, in general, they cannot displace the reports of positive findings that are the principal concern in a review of the biological effects of RF radiation.

It seems appropriate at this point to cite the conclusions of the subcommittee that developed the rationale for the recently published ANSI RF-radiation (0.3 MHz to 100 GHz) exposure guidelines (ANSI 1982). The subcommittee completed its review of the literature in February 1979. Note that about half of the reports on behavior shown in Tables 6-1 and 6-2 were published prior to 1979. The ANSI subcommittee concluded the following:

> The most sensitive measures of biological effects were found to be based on behavior.
>
> The whole-body-averaged SARs associated with thresholds of reversible behavioral disruption were found to range normally between 4 and 8 W/kg in spite of considerable differences in carrier frequency (600 MHz to 2.45 GHz), species (rodents versus primates), and mode of irradiation (cavity, waveguide, and plane wave).
>
> Because of the paucity of reliable data on chronic exposures, the subcommittee focused on evidence of behavioral disruption under acute exposures, even that of a transient and fully reversible character. The assumption is that reversible disruption during an acute exposure is tantamount to irreversible injury during chronic exposure.
>
> The concensus remained that reliable evidence of hazardous effects is associated with whole-body-averaged SARs above 4 W/kg.

Other significant effects in laboratory animals which occur at SARs of 4 to 8 W/kg are:

1. Temporary sterility in male rats exposed at an SAR = 5.6 W/kg for 4 h/day for 20 days (Berman *et al.* 1980).
2. Bradycardia in rats after whole-body exposure (SAR = 6.5 W/kg) (Phillips *et al.* 1975b). Exposure of the head of the rabbit at an SAR of 3 W/kg caused tachycardia (Birenbaum *et al.* 1975).

Potentially significant biological effects that have been reported at SARs $<$ 4 W/kg include the following:

Table 6-1. Selected Studies Reporting "No Effects" at SARs ≤ 10 W/kg Grouped by Biological Variable

Biological Variable	Relevant Studies	SARs
Growth (Food, Water Intake)	Stavinoha *et al.* (1975)	6.3
	McAfee *et al.* (1973)	6.0-8.0
	Kaplan (1981)	3.4
	Michaelson *et al.* (1978)	2.5-10.0
	Johnson *et al.* (1978)	2.5
	Lovely *et al.* (1977)	1.0-2.5
	D'Andrea *et al.* (1979)	1.0-2.5
Behavior	D'Andrea *et al.* (1976)	5.0-6.0
	Moe *et al.* (1976)	3.9
	Mitchell *et al.* (1977)	2.3
	Sanza and de Lorge (1977)	2.1-4.7
	Gage (1979a)	0.3
	Scholl and Allen (1979)	1.6
	de Lorge (1976)	1.1-1.4
	Lovely *et al.* (1977)	1.0
	Roberti *et al.* (1975)	0.2-8.3
	Schrot *et al.* (1980)	0.2
	Thomas *et al.* (1979)	0.2
Mortality/Life Span	Kaplan (1981)	3.4
	Johnson *et al.* (1978)	2.5
	Spalding *et al.* (1971)	1.7
Hematology/Immunology	Smialowicz *et al.* (1981a)	10
	Smialowicz *et al.* (1979b)	>4.0
	Liburdy (1980)	3.8
	Smialowicz (1981a)	2.0-3.0
	Spalding *et al.* (1971)	1.7
	Djordjevic *et al.* (1977)	1.0
Mutations/Chromosomal Aberrations	Blackman *et al.* (1975, 1976)	0.08-7.5
	McLees *et al.* (1972)	1.3
	Berman *et al.* (1980)	0.9
Teratology	Johnson *et al.* (1978)	2.5
	Berman *et al.* (1978)	2.0-8.1
Litter Size	Michaelson *et al.* (1978)	2.5-10.0
	Johnson *et al.* (1978)	2.5
Organ Weight	Michaelson *et al.* (1978)	2.5-10.0
	Mikolajczyk (1976)	1.0-2.0
Blood Chemistry	Wangemann and Cleary (1976)	0.8
Fertility	Berman *et al.* (1980)	1.0-2.0
Hormones	Mikolajczyk (1976)	1.0-2.0
	Parker (1973)	2.0-6.5
	Lu *et al.* (1977)	2.5
	Milroy and Michaelson (1972)	0.25-2.5
Neurotransmitter Levels	Merritt *et al.* (1976)	3.0
Metabolic Rate	Ho and Edwards (1977a,b)	5.5
Cardiovascular System	Phillips *et al.* (1975b)	4.5

1. The decrease in behavioral response rates cited in ANSI (1982) were based on studies done at ambient temperatures of 20 to 25°C. Gage (1979b) has shown that similar changes in behavior occur at lower SARs when exposures are conducted at higher ambient temperature; that is, at 22°C the effective SAR was 3 W/kg, whereas at 28°C SARs of 1 and 2 W/kg were effective.

2. Although RF radiation does not appear to be a primary carcinogenic agent (cancer inducer), there is evidence from one laboratory that RF radiation acts as a cancer promoter or co-carcinogen in three different tumor systems in mice at an SAR of 2 to 3 W/kg (Szmigielski *et al.* 1980, 1982).

3. A decrease in the number of Purkinje cells in the brain of rats exposed at an SAR of 2 W/kg was reported by Albert *et al.* (1981a).

4. Endocrine gland function and blood chemistry changes are similar to those observed during heat stress and are generally associated with SARs > 1 W/kg (Sec. 5.7.1).

Table 6-2. Selected Studies with Reported "Effects" at SARs ≤ 10 W/kg Grouped by Biological Variable

Biological Variable	Relevant Studies	SARs
Behavior	Gordon (1983a)	7.0
	Gordon (1983b)	5.3
	de Lorge (1976)	5.0
	Moe *et al.* (1976)	3.6
	Gage (1979a)	2.7
	de Lorge and Ezell (1980)	2.5-4.9
	D'Andrea *et al.* (1980)	2.5
	Mitchell *et al.* (1977)	2.3
	Gage (1979b)	2.0
	Thomas *et al.* (1975)	1.4-1.5
	D'Andrea *et al.* (1979)	1.2
	Stern *et al.* (1979)	1.1
	Thomas *et al.* (1976)	1.1
	Rudnev *et al.* (1978)	1.0
	Adair and Adams (1980a,b)	1.0
	Schrot *et al.* (1980)	0.7
	Frey and Feld (1975)	0.4
Central Nervous System	Albert and DeSantis (1975, 1976)	5.0-12.5
	Switzer and Mitchell (1977)	2.3
	Albert (1979b)	2.0
	Albert *et al.* (1981a)	2.0
	Seaman and Wachtel (1978)	1.0
	Albert and Kerns (1981)	0.9-2.0
	Sanders *et al.* (1980)	0.1
	Goldstein and Sisko (1974)	0.1-0.3
	Barański (1972b)	0.4-2.5
	Blackman *et al.* (1979, 1980a,b)	0.0013
	Takashima *et al.* (1979)	0.0001
Hematology/Immunology	Sulek *et al.* (1980)	5.0-11.8
	Smialowicz *et al.* (1979a, 1982)	5.0-7.0
	Liburdy (1979)	4.6
	Michaelson *et al.* (1964)	4.0-6.0
	Huang and Mold (1980)	3.6-10.0
	Huang *et al.* (1977)	2.3-30.7
	Djordjevic and Kolak (1973)	2.0
	Deichmann *et al.* (1963)	1.5-2.2
	McRee *et al.* (1980a)	1.5
	Czerski (1975)	0.5-0.8
	Szmigielski *et al.* (1975)	0.5
	Barański (1971)	0.5
	Prince *et al.* (1972)	0.4-2.0
Hormones	Lu *et al.* (1977)	5.0
	Lotz and Michaelson (1978)	3.0-12.8
	Mikolajczyk (1976)	1.0-2.0
Drug Potentiation	Edelwejn (1968)	1.0
	Thomas and Maitland (1979)	0.2
Mutations/Chromosome Aberrations	Manikowska *et al.* (1979)	0.05-5.0
Neurotransmitter Levels	Merritt *et al.* (1977)	6.0
Fertility	Berman *et al.* (1980)	5.6
Clinical Chemistry	Wangemann and Cleary (1976)	1.6-4.0
Cardiovascular System	Kaplan *et al.* (1971)	8.0
	Phillips *et al.* (1975b)	6.5
	Birenbaum *et al.* (1975)	3.0

5. Effects on the hematologic and immunologic systems occur at SARs ≥ 0.5 W/kg and appear to result from some form of thermal involvement due to absorbed RF energy (Sec. 5.2).
6. Changes in cellular energy metabolism in the rat brain have been reported at an SAR ≃ 0.1 W/kg; the data support the conclusion that the effect is frequency specific (Sanders *et al.* 1980).
7. Results of studies of amplitude-modulated (AM) radio-waves, particularly AM frequencies near or at 16 Hz, have shown changes in calcium-ion efflux from chick brain tissues *in vitro*. The effect

has been shown to be frequency and intensity specific and to occur at SARs as low as 0.0013 W/kg (Blackman *et al.* 1979, 1980a,b). In 1984 Dutta *et al.* reported that 16-Hz AM microwave radiation caused changes in calcium-ion efflux from human brain cells in culture at an SAR of 0.5 W/kg.

Human data are limited and not useful for developing a quantitative relation between effect and SAR; however, two recent studies of physiotherapists suggest two potentially significant health effects associated with work with RF equipment. The first is heart disease (primarily ischemic) in males; (Hamburger *et al.* 1983) the second is pregnancy outcomes in female physiotherapists (Källén *et al.* 1982). Both studies are considered to be exploratory, and neither provides quantitative data on the RF radiation levels in the work environment, so that SAR values cannot be estimated.

In summary, the data currently available on the relation of SAR to biological effect show evidence for biological effects at an SAR of about 1 W/kg. This value is lower by a factor of 4 than 4 W/kg, the value above which reliable evidence of hazardous effects was found by ANSI (1982) following a review of the literature in February 1979. The above conclusion is based on:

1. the findings that more thermally stressful conditions result in lower threshold SARs for behavioral changes similar to those changes determined by ANSI (1982) to be the most sensitive measures of biological effects
2. the effects on endocrine gland function, blood chemistry, hematology, and immunology that appear to result from some form of thermal involvement due to absorbed RF energy
3. data from one laboratory showing that RF radiation can act as a cancer promoter or co-carcinogen and results from another laboratory describing changes in brain cellularity.

The experimental evidence suggests that the central nervous system is particularly sensitive to RF radiation. Two other areas of research that may prove to be highly significant are calcium-ion efflux and brain energy metabolism.

6.3 Core Temperature

Heating is the least controversial explanation for most RF-radiation effects, and it is appropriate to examine the biological effects in relation to an increase in body temperature in the range of 0 to 6°C above normal. The average rectal (core) temperature is approximately 37.0°C (98.6°F) for human beings and ranges from 36 to 38°C for most mammals (Schmidt-Nielsen 1979). In general, the lethal temperature is approximately 6°C above the average core temperature (cf. Table 4-2). Prolonged elevation of core temprature at 5°C above normal (42°C = 107°F) is associated with heat stroke and brain lesions; the temperature 41.2°C (106.2°F) occurs in only 1 of 1000 humans during fever (Folk 1974). With RF-radiation exposures, even brief periods (15 to 20 min) at core temperatures of 41.5 to 42.5°C in rats can result in increased fetal resorptions, decreased fetal body weights (Chernovetz *et al.* 1977), and significant hemolysis and K^+ efflux in red blood cells of adult rats (Peterson *et al.* 1979). In healthy young men whose mean body temperature was increased to 41°C by RF-radiation exposure for up to 3 h, sperm numbers had decreased by 60 percent by 40 to 60 days after treatment (MacLeod and Hotchkiss 1941). At this core temperature, temporary infertility in male rats has also been reported (Berman *et al.* 1980).

Berman *et al.* (1981) showed that when RF-radiation exposure produced a maternal colonic temperature of <41°C in the pregnant rat, no effects were detectable in the fetus; O'Connor (1980) reached a similar conclusion. The mouse fetus is apparently more sensitive to increased maternal body temperature than is the fetal rat. Berman *et al.* (1978) reported that a 0.8°C temperature differential between exposed and sham-irradiated dams produced a 10-percent decrease in the body mass of the exposed mouse fetus.

Several RF-radiation-induced effects have been reported for other stages of life in various animal species at core temperature increases of 1 to 3°C. These effects include an increased response of the adrenal glands in irradiated infant rats (Guillet and Michaelson 1977); increased serum glucose and blood urea nitrogen (BUN) levels in adult rabbits (Wangemann and Cleary 1976); increases in circulating neutrophils and T and B lymphocytes in spleens of mice, along with a decrease in circulating lymphocytes (Liburdy 1977, 1979); changes in lymphocyte circulation between bone marrow, spleen, liver, and lung similar to that produced by stress-related steroids (Liburdy 1980); increased responsiveness of lymphocytes to mitogen stimulation in monkeys (Prince *et al.* 1972); increased white blood cell (WBC) count and decreased ^{59}Fe uptake in mice (Rotkovska and Vacek 1975); decreased exploratory activity of rats (Hunt *et al.* 1975); decreased vigilance in monkeys (de Lorge 1976); and work stoppage in rats (D'Andrea *et al.* 1977).

RF-radiation exposures that produced core temperature increases of 1 to 2°C are reported to be associated with decreased serum thyroxine and increased corticosteroid levels (Lu *et al.* 1977). Michaelson *et al.* (1964) found decreased lymphocyte, neutrophil, and eosinophil levels and hemoconcentration at temperatures of 1.0 to 1.7°C above normal in dogs. In association with a temperature rise of 1.0°C in irradiated rats, Djordjevic and Kolak (1973) observed

increases in RBC, hematocrit, and hemoglobin which may also be a case of hemoconcentration. Pazderová-Vejlupková and Josifko (1979) reported decreases in the hematocrit, WBC, and lymphocyte numbers in rats at a temperature change of only +0.5°C.

As a general rule, exposures that produce a core-temperature rise of ≤ 0.5°C do not cause detectable effects on reproduction, fetal weight, growth, development, hematological and immunological end points, hormonal levels, and clinical blood chemistry (Berman *et al.* 1978, 1980; Johnson *et al.* 1978; Michaelson *et al.* 1978; Guillet and Michaelson 1977; Djordjevic *et al.* 1977; Smialowicz *et al.* 1979b; Milroy and Michaelson 1972; Lovely *et al.* 1977; Wangemann and Cleary 1976).

In most of the animal studies that report a biological effect of RF radiation, the exposures occurred at ambient temperatures of 20 to 25°C and relative humidities of 50 to 70 percent. At more thermally stressful conditions, e.g., higher ambient temperature and the same or higher relative humidity, the experimental results show that lower SARs will cause a similar biological effect. In other words, it is reasonable to expect that all the above biological effects described in Sec. 6.3 that are associated with an increase of core temperature ≥ 0.5°C will occur also at lower SARs if the combination of RF radiation exposure and ambient conditions result in a similar core-temperature increase.

In Sec. 6.2, the biological effects relative to SAR were presented, and the important conclusions from ANSI (1982) relative to hazardous levels of RF radiation were discussed. In this section, it is instructive to use the threshold limit value (TLV) for deep-body temperature of workers as an introduction to a discussion of temperature changes in human beings exposed to RF radiation. The TLV of the American Conference of Governmental Industrial Hygienists (1983) states that workers should not be permitted to continue their work when their deep-body temperature exceeds 38°C , that is, 1°C above the average normal temperature for adult human beings. One may conclude therefore that exposure to an environmental agent such as RF radiation that may cause a 1°C rise in core temperature should be considered hazardous to relatively healthy individuals. The application of this reasoning to the general public, which varies in health status, age, etc., is discussed below.

There are few data on the RF-radiation exposure conditions that cause core temperature changes of 0 to 1°C in human beings. One of the first attempts to consider the addition of RF energy as a thermal load in a model of man was done by Guy *et al.* (1973), who later used a thermodynamic model of the human body to determine increase in temperature (Guy *et al.* 1978). They reported that an exposure of 4 W/kg at 79 MHz (resonant frequency for an adult human being in free space) for about two hours caused the hypothalamic temperature to rise 1°C. If no unusual hot spot occurred in the hypothalamic area, one could assume that the temperature within the head was a good estimate of core temperature, that is, the core temperature rose about 1°C also. Using a mathematical model of the human body, Spiegel *et al.* (1980a) predicted than an 80-MHz exposure (T_a = 30°C, RH = 30 percent) at an SAR = 2.3 W/kg would produce a 1°C rise in core temperature; and SAR of 1.4 W/kg resulted in a 0.5°C rise in core temperature. In their report, in which they examined the relation of biological effects to increase in body temperature, Tell and Harlen (1979) concluded that whole-body exposure of human beings to 3 W/kg at resonant frequencies would raise a resting individual's rectal temperature by about 1°C for exposure durations of the order of 1 h or more. In summary, the results of Guy *et al.* (1978), Spiegel *et al.* (1980a), and Tell and Harlen (1979) show that SARs of 1 to 4 W/kg for short durations (1 h) produce significant increases in human body temperature at ambient temperatures of 25 to 30°C. It is reasonable to conclude that increases in body temperature are likely to occur at lower SARs if exposure takes place under more thermally stressful conditions, e.g., higher ambient temperature and/or higher relative humidity.

Data from experimental studies with primates are in good agreement with the results of the modeling experiments described above. In 1976, de Lorge found that a 2450-MHz exposure of the rhesus monkey for 1 h (T_a = 21 to 24°C; RH = 70 percent) at an SAR of 2.2 to 2.9 produced a temperature rise of 0.5°C; an SAR of 4.3 W/kg caused an increase of 1°C. Exposure of the rhesus monkey to 225 MHz, a frequency close to resonance, at only 1.2 W/kg (T_a = 24°C) caused a 0.5 to 0.6°C rise in rectal temperature; at 1290 MHz, an SAR of 3 W/kg caused a similar temperature rise (Lotz 1982; Lotz and Podgorski 1982). In these two studies, the ability of the animals to dissipate heat may have been compromised because of various factors in the experimental design.

Two additional points must be given serious consideration.

1. **When a measurable increase in body temperature occurs, it can be interpreted as an indication that the body is under some stress. Exposure to RF radiation at SARs below those that cause an increase in core temperature may activate the heat-dissipating thermoregulatory mechanisms of the body to maintain core temperature within the normal range.**
2. **Under many conditions of RF exposure, some regions of the body will probably experience an increase in temperature due to localized RF-energy absorption while the core temperature**

remains near normal (Guy *et al.* 1978; Spiegel *et al.* 1980a). For example, Spiegel *et al.* (1980a) showed that an SAR of 1.4 W/kg produced a 3.6°C rise in temperature of the thigh while the core temperature rose only 0.5°C.

Consideration is now given to the health impact of the thermal extremes that can exist in the U.S. during summer months. During the period 1952-67, heat waves occurred in five different years. Ellis (1972) examined the Vital Statistics Reports of the U.S. Public Health Service for these years and drew the following conclusions:

1. During the five heat-wave years 1952-55 and 1966, excess deaths due to heat-aggravated or heat-precipitated illness during the heat wave were conservatively estimated to be at least 10 times those to be expected in this category in the General Mortality Tables.
2. In either June or July there were excess numbers of deaths due to vascular accidents of the central nervous system in 1952-55 and 1966, and similar but smaller excess numbers of diabetic deaths in 1952, 1954, 1955, and 1966.
3. Excess deaths from arteriosclerotic and degenerative heart disease, including coronary disease, were observed in 1955 and 1966, and there was an excess of deaths from hypertensive heart disease in May, June, or July in each of the heat-wave years but not in 10 of the other 11 years.
4. Infants below 1 year of age are the most heat-illness-prone age group below 50 years of age; adults above 50 years are more heat-illness-prone than infants and become progressively more so with advancing age.

The evidence indicates that exposure of human beings at frequencies in the resonant region at an SAR of approximately 1 W/kg produces significant changes in body temperature under some environmental conditions. This conclusion should not be interpreted as conservative because, as stated above:

1. when an increase in body temperature occurs, it can be interpreted as an indication that the body is under some stress;
2. under many conditions of RF exposure, it is very likely that some regions of the body increase in temperature due to localized RF-energy absorption while the core temperature remains near normal;
3. the general population has groups of individuals particularly susceptible to heat.

6.4 Summary

The review of the currently available literature on RF radiation provides evidence that biological effects occur at an SAR of about 1 W/kg; some of them may be significant under certain environmental conditions. This value was derived from two perspectives; (1) the relation of biological effects to SAR (dose rate) and (2) the relation of biological effects to increased body temperature caused by absorption of RF energy.

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Glossary

ABSORPTION The irreversible conversion of electromagnetic energy into other forms of energy as a result of interaction with matter. See SPECIFIC ABSORPTION and SPECIFIC ABSORPTION RATE.

ACCLIMATION A physiological change, occurring within the lifetime of an organism, which reduces the strain caused by experimentally induced stressful changes in particular climatic factors.

α-HELIX A conformation found in protein molecules where the amino acid chain turns in a helical pattern with weak chemical bonds (hydrogen bonds) forming between successive turns in the helix.

AMES TEST A standard test for mutagenic potential of various agents performed with specialized strains of bacteria.

ANECHOIC CHAMBER A chamber lined with material that absorbs RF radiation; an RF-exposure system free of scattered and reflected radiation.

ANGULAR MOMENTUM The quantity of motion of a rotating body - directly proportional to the angular velocity of the rotating body.

ANTENNA A device for radiating or receiving radio waves.

ANTENNA REGIONS The distinction between electromagnetic fields far from and those near to the antenna. The regions are usually classified into three zones: near (static) zone, intermediate (induction) zone, and far (radiation) zone. The zones are spatially located by drawing spheres of different radii around the antenna. The radii are approximately $r < \lambda$ for the near zone, $\lambda < r(\lambda)$ for the intermediate zone, and $r > \lambda$ for the far zone. Note that λ is the wavelength of the electromagnetic field produced by the antenna. In the far zone the field components (E and H) lie transverse to the direction of the propagation, and the shape of the field pattern is independent of the radius at which it is taken. In the near and intermediate zones the field patterns are quite complicated, and the shape is, in general, a function of the radius and angular position (azimuth and elevation) in front of the antenna.

ATHERMAL EFFECT (NONTHERMAL EFFECT) Any effect of electromagnetic energy on a body that is not a heat-related effect.

ATTENUATION A general term used to denote a decrease in magnitude of RF transmission from one point to another.

AUTOLYSIS The decomposition of an organ or tissue by its own enzymes.

AVERAGE POWER $\overline{W}$ The time-average rate of energy transfer:

$$\overline{W} = 1/(t_2 - t_1) \int_{t_1}^{t_2} \overline{W}(t)dt$$

For radar calculations, average power $\overline{W}$ = peak power x pulse width x pulse repetition frequency.

BASES Biochemcial compounds, either purine or pyrimidines, that are ring structures containing carbon and nitrogen and which are capable of weak bonding to each other.

β-SHEET A conformation found in protein molecules where two or more portions of amino acid chains line up side-to-side, with weak hydrogen bonds forming between adjacent chains.

BIOPOLYMER A polymeric substance formed in a biological system, e.g., DNA, proteins.

BLASTOGENIC RESPONSE The transformation of small lymphocytes into large morphologically primitive blast-like cells capable of undergoing mitosis; this phenomenon can be induced in cultured cells by a variety of agents, including mitogens as well as antigens, to which the cell donor has been previously immunized.

BLOOD-BRAIN BARRIER A functional concept to explain the observation that many substances transported by blood readily enter other tissues but do not enter the brain. The barrier functions as if it were a continuous membrane lining the brain vasculature.

BURSA OF FABRICUS A lymphoidal organ in the hindgut of birds that influences B cell development.

CALCIUM EFFLUX The release of calcium ions from a sample into a surrounding solution.

CALORIE The amount of heat necessary to raise the temperature of one gram of water 1 °C. One calorie equals 4.184 joules.

CARCINOMA Any of the various types of malignant neoplasm derived from epithelial tissue, occurring more frequently in the skin, bronchi, stomach, and prostate gland in men, and in the breast, cervix, and skin in women.

CATARACTOGENIC Giving rise to the formation of a cataract, an opacity in the crystalline lens of the eye.

CHEMOSIS Excessive edema of the ocular conjunctiva.

CHROMOSOMES Large complex biochemical structures, containing nucleic acid (DNA) and proteins, which can be visualized in some cells by certain light microscopy techniques.

CIRCULARLY POLARIZED If the electric field is viewed as a point in space, the locus of the end point of the vector will rotate and trace out an ellipse once each cyle.

COLONY-FORMING UNIT (CFU) Colonies of bone marrow or blood cells arising from a single progenitor cell when grown *in vitro* or *in vivo.*

COMPLEX DIELECTRIC PERMITTIVITY The characterization of electrical parameters of materials at the macroscopic level.

CONFORMATION The spatial distribution of the parts of a macromolecule in relation to each other, i.e., how a chain of amino acids folds on itself to form a protein.

CONTINUOUS WAVE (CW) Electromagnetic fields that vary sinusoidally in time; that is, those fields which oscillate at a single frequency.

COUNTER-CURRENT HEAT EXCHANGE The heat exchange between blood flowing in opposite directions at different temperatures, e.g., adjacent arteries and veins.

CORE TEMPERATURE The temperature near the center of the body; usually measured through the rectum.

CRITICAL TEMPERATURE, LOWER The ambient temperature below which the rate of metabolic heat production of a resting thermoregulating animal increases by shivering and/or nonshivering thermogenic processes to maintain thermal balance.

CRITICAL TEMPERATURE, UPPER 1. The ambient temperature above which thermoregulatory evaporative heat loss processes of a resting thermoregulating animal are recruited. 2. The ambient temperature above which there is an increase in metabolic rate due to a rise in the core temperature of a resting thermoregulating animal.

CYTOSIS Increase in number of cells, e.g., leukocytosis, increase in the total number of circulating leukocytes.

DEBYE A unit for dipole moment equal to the dipole moment of a charge distribution of one positive and one negative charge, each equal in magnitude to the charge of an electron separated by 1 A (10^{-10}m).

DECIBEL (dB) A unit expressing the logarithmic ratio of two powers or voltages. One tenth of a Bel.

DENSITOMETRY The measurement of exposure to an RF field; usually expressed in units of milliwatts per square centimeter.

DEPTH OF PENETRATION For a plane wave electromagnetic field incident on the boundary of a good conductor, the depth of penetration of the wave is that depth at which the field strength of the wave has been reduced to 1/e or approximately 37% of its original value.

DIELECTRIC MATERIAL A class of materials that act as electric insulators. For this class the conductivity is presumed to be zero, or very small. The positive and negative charges in dielectrics are tightly bound together so that there is no actual transport of charge under the influence of a field. Such material alters electromagnetic fields because of induced charges formed by the interaction of the dielectric with the incident field.

DIPOLE A molecule (or other structure) having the effective centers of positive and negative charges separated.

DIPOLE MOMENT A quantity describing the strength of a particular dipole:

$$\vec{d} = \int_v \rho(\vec{r})\,\vec{r}\,d\vec{r}$$

where the dipole $(\vec{d})$ is the integral of the charge distribution $(\rho(\vec{r}))$ times the vector distance $(\vec{r})$ from a designated origin over the entire space containing the charge distribution (v).

DNA Deoxyribonucleic acid; the chemical which makes up the genes, the basic unit of heredity.

DNA MELTING CURVE Characteristic loss of helical structure and separation of the strands of a DNA molecule when temperature is raised.

DOSIMETRY The measurement of the absorbed dose or dose rate by an object in a radiofrequency field; usually expressed as watts per kilogram or joules per kilogram.

DUTY FACTOR (CYCLE) The product of the pulse duration and the pulse repetition frequency.

ELECTRIC FIELD STRENGTH The force on a stationary unit positive charge at a point in an electric field. This force may be measured in volts per meter (V/m).

ELECTROMAGNETIC RADIATION (EMR) Energy in the form of electric and magnetic fields.

ELECTROMAGNETIC WAVE A wave characterized by variations of electric and magnetic fields. Electromagnetic waves are categorized as radio waves, light rays, etc., depending on the frequency.

ELECTROPHORETIC MOBILITY The ability of a cell or macromolecule to move in response to a constant electric field.

ELECTROSTRICTIVE FORCE Force exerted by an electrostatic field that causes the elastic deformation of a dielectric.

ELLIPSOID SHAPE A surface, all plane sections of which are ellipses or circles.

ENZYME KINETICS (ACTIVITY) Measure of how rapidly an enzyme catalyzes a chemical reaction.

EPITHELIOMA Carcinoma derived from squamous cells (scale-like cells) or from the basal and adnexal cells (accessory cells) of the skin.

ERYTHROPOIESIS The production of red blood cells.

EUKARYOTE An organism composed of one or more complex cells containing chromosomes that are segregated from the rest of the cell by a nuclear membrane. This distinction is in contrast to bacteria, which have less complex DNA structure distributed throughout the cell volume.

EXCITATION The absorption of energy by a molecule or other structure.

FAR FIELD REGION See antenna regions.

FEVER A pathological condition in which there is an abnormal rise in core temperature. The extent of the rise is variable. The temperature rise in an individual may be considered as fever when it is greater than the mean standard deviation for the species in basal conditions.

FIELD-INDUCED MIGRATION The physical movement of charged bodies under the influence of an electromagnetic field.

50TH PERCENTILE For a large set of measurements arranged in order of magnitude, the 50% percentile is the value such that 50% of the measurements are less than that value and 50% are greater.

FINITE DIFFERENCE TECHNIQUE The approximation of differentials by their finite difference; e.g., $dy/dx \sim \Delta y/\Delta x$.

FIRST-ORDER DIFFERENTIAL EQUATION A differential equation of order one (only single-order derivatives are included in the equation).

FREQUENCY The number of sinusoidal cycles made by electromagnetic radiation in one second; usually expressed in units of hertz.

GIGAHERTZ (GHz) One billion cycles per second.

HERTZ (Hz) One cycle per second.

HISTOPATHOLOGY The department of pathology concerned with minute structure, composition, and function of diseased tissues; microscopic pathology.

HOMEOTHERMY The pattern of temperature regulation in a warm-blooded species in which the cyclic variation in core temperature, either nychthemerally or seasonally, is maintained within arbitrarily defined limits ($\pm 2°C$) despite much larger variations in ambient temperature.

HUMORAL Relating to the extracellular fluids of the body, i.e., blood and lymph. In immunology, the name ascribed to immune mechanisms leading to antibody products.

HYPERTHERMIA The condition of a temperature-regulating animal when the core temperature is more than one standard deviation above the mean core temperature of the species in resting conditions in a thermoneutral environment.

HYPOTHERMIA The condition of a temperature-regulating animal when the core temperature is more than one standard deviation below the mean core temperature of the species in resting conditions in a thermoneutral environment.

INSENSIBLE WATER LOSS The sum of the water lost by diffusion through the skin and water lost in breathing, and excluding any water excreted.

IN UTERO Within the uterus or womb.

IN VITRO Within glass; observable in a test tube.

IN VIVO Within the living body.

INFINITE SLAB A piece of material that has an infinite cross section but finite thickness.

IONIZING ELECTROMAGNETIC RADIATION Electromagnetic radiation of high frequency, short wavelengths, and high photon energy which, when it interacts with matter, causes the removal of electrons from atoms, e.g., x-rays and gamma rays.

KILOHERTZ (kHz) One thousand cycles per second.

LATENT HEAT OF VAPORIZATION The quantity of heat released (or absorbed) in the reversible process of evaporation (or condensation) of unit mass of liquid (or vapor) under isobaric and isothermal equilibrium conditions.

LOSSY CAPACITOR A capacitor containing a dielectric material with a loss tangent above 0.1.

MACROMOLECULE A molecule, such as a protein or a nucleic acid, that has a molecular weight greater than a few thousand.

MEGAHERTZ (MHz) One million cycles per second.

METABOLIC RATE See resting metabolic rate.

METASTABLE A state that is not stable but will exist for a long period of time.

MICROWAVES A particular segment of the RF radiation spectrum with a frequency range of 300 MHz to 300 GHz.

MITOGEN A substance that stimulates lymphocytes to proliferate independently of any specific antigen.

MODULATION The process of varying the amplitude, frequency, or phase of an RF carrier wave.

MULTILAMELLAR VESICLES Phospholipid bilayers that form a series of concentric closed spherical structures somewhat analogous to the layers of an onion; these structures are commonly used as models for studying membrane properties.

MYELOPOIESIS The formation of bone marrow and the cells that arise from it.

NEUROTRANSMITTER A chemical substance that transmits nerve impulses across a synapse.

NEAR FIELD REGION See antenna regions.

NONIONIZING RADIATION (NIR) Electromagnetic radiation of low frequency, long wavelength, and low photon energy, unable to cause ionization (i.e., to remove an electron from an atom); e.g., RF radiation.

NONTHERMAL Not related to heat.

NUCLEIC ACIDS Biochemical compounds, consisting of one or more subrings of a base, a sugar, and a phosphate group. When subrings are covalently bonded to each other, forming a chain, the bond occurs between the sugar and the phosphate, with the base off to the side. In DNA (q.v.), two such chains are weakly attached to each other through contact of their bases, which form the rungs of a ladder, while the sugar and phosphate groups form the sides of the ladder. The bases associate with each other only if their chemical structure is compatible, i.e., complementary. There are four such bases commonly found in DNA. The sequence of these bases provides the information necessary to make other biochemical molecules.

OPERANT CONDITIONING The process of rewards and reinforcements by which specific behaviors are learned.

ORGANOGENESIS The development or growth of organs, especially embryologic.

OSMOTIC FRAGILITY The tendency of a cell membrane to break because of a large imbalance of ion concentration inside and outside the cell.

PARABOLIC REFLECTOR One of the most widely used microwave antennas, consisting of a metal disk whose surface forms a circular parabola.

PARAMETER Any of a set of physical properties whose values determine the characteristics or behavior of something.

PHAGOCYTOSIS The engulfing of microorganisms, other cells, or foreign bodies by phagocytes.

PENIA Reduction in the number of cells; e.g., neutropenia, reduction in the number of polymorphonuclear neutrophiles.

PERITONEAL Relating to the peritoneum, which is the serous sac lining the abdominal cavity and covering most of the viscera therein contained.

PHILIA Increase in number of cells; e.g., neutrophilia, increase in number of neutrophiles.

PHONON A particle of mechanical vibrational (sound) energy.

PHOTON A particle of electromagnetic energy.

PHOSPHOLIPID BILAYER A double-layered sheet of phospholipid molecules arranged so that the hydrophilic (water-liking) part of the molecules associate with water and the hydropholic (water-disliking) part of the molecules associate with each other and avoid contact with water; this structure is the basis for biological membranes.

PLASMID Short piece of DNA that normally codes for one of a few proteins and can often be transferred to another cell; it is usually separate from the cell's major DNA, which carries the information for reproducing the cell.

PLANE WAVE An electromagnetic wave in which the electric and magnetic field vectors lie in a plane perpendicular to the direction of wave propagation.

POIKILOTHERM A cold-blooded animal; an ectotherm; an animal with little or no control of its body temperature.

POIKILOTHERMY The pattern of thermoregulation of a species exhibiting a large variability of core temperature as a proportional function of ambient temperature.

POLARIZABILITY A linear coefficient that quantitates the change in the magnitude of the dipole moment (q.v.) of a molecule or any other structure in response to an electric field, i.e.,

$$\vec{d} = \alpha\vec{E} + \vec{d}_o$$

where α is the polarizability, $\vec{E}$ is the applied electric field, and $\vec{d_o}$ is the dipole moment when there is no applied field.

POWER DENSITY Magnitude of the Poynting vector at a point in space, in power per unit area (watts per square meter). For plane waves E^2 is simply related to power density, and it is the quantity measured by a survey meter when the sensing element is sensitive to the square of the magnitude of the electric fields; i.e., $P = E^2/3770$, in mW/cm^2.

PROLATE SHPEROID An approximately spherical object that is elongated in the direction of a line joining the poles; similar to a football.

PUPA The second stage in the development of an insect, between the larva and the imago.

Q_{10} The ratio of the rate of a physiological process at a particular temperature to the rate at a temperature 10°C lower, when the logarithm of the rate is an approximately linear function of temperature.

RADIATION The transfer of energy from one body to another through an intervening medium.

RADIOFREQUENCY RADIATION See RF radiation.

RESONANCE A small electrical stimulus at a given frequency that produces a large amplitude response in the system at the same frequency.

RESONANT FREQUENCY That frequency which produces resonance in a system; typically those frequencies whose wavelengths are integral multiples of the body's length.

RESPIRATORY CONTROL RATIO. A measure of mitochondrial activity and integrity; the rate of utilization of oxygen in the presence of adenosinediphosphate (ADP) divided by the rate of utilization of oxygen in the absence of ADP.

RESTING METABOLIC RATE (RMR) The metabolic rate of an animal which is resting in a thermoneutral environment but not in the postabsorptive state. The relationship of RMR (W/kg) to body mass, M (kg), is $RMR = 3.86M^{-0.24}$ Basal metabolic rate (BMR) is the rate of energy production of an animal in a rested, awake, fasting, and thermoneutral state.

RF RADIATION Radiofrequency radiation; nonionizing electromagnetic radiation in the frequency range 0 to 3000 GHz.

ROOT MEAN SQUARE (RMS) Certain electrical effects are proportional to the square root of the mean value of the square of a periodic function (over one period). This value is known as the effective value or the root-mean-square (RMS) value since it is derived by first squaring the function, determining the mean value of this squared value, and extracting the square root of the mean value to determine the end result.

SARCOMA A tumor, usually highly malignant, formed by proliferation of poorly differentiated cells; a malignant connective tissue neoplasm.

SCHEDULE OF REINFORCEMENT Also called reinforcer schedule. The specification of the way in which reinforcers are assigned to particular responses within an operant-class or classes. Examples include: the fixed ratio schedule, in which the last of a constant, specified number of responses is reinforced; the fixed interval schedule, in which a constant, specified period of time must elapse before a response is reinforced; the differential reinforcement of low rate schedule, in which a response is reinforced only if at least a specified period of time has elapsed since the last response.

"SILK" Polyester material used in the silk-screen graphic process.

SPECIFIC ABSORPTION The absorbed energy in the tissue, in joules per kilogram (J/kg). See also SPECIFIC ABSORPTION RATE.

SPECIFIC ABSORPTION RATE (SAR) The rate at which energy is absorbed in the tissue, in watts per kilogram: $SAR = \sigma E_t^2/\rho$, where σ = tissue conductivity at irradiation frequency, E_t = rms electric field strength in the tissue, and ρ = tissue density (kg/m^3).

SPECIFIC HEAT (c) The quantity of heat required to raise the temperature of unit mass of a substance by 1 °C.

SPONTANEOUS BEHAVIOR Unlearned or natural responses to a stimulus.

SQUARE LAW The output of a device is proportional to the square of the input to the device.

SUBSTRATE The molecule upon which an enzyme catalyzes a chemical reaction.

SURVEY INSTRUMENT A portable instrument capable of measuring the strength of electric and magnetic fields.

SYNGENEIC Individuals of a species that are genetically identical at all relevant transplantation loci.

TEMPERATURE, AMBIENT (T_a) The average temperature of a gaseous or liquid environment (usually air or water) surrounding a body, as measured outside the thermal and hydrodynamic boundary layers that overlay the body.

TEMPERATURE, CORE The mean temperature of the tissues at a depth below that which is affected directly by a change in the temperature gradient through peripheral tissues. Mean core temperature cannot be measured accurately, and is generally represented by a specific core temperature, e.g., that of the rectum (Synonym: TEMPERATURE, DEEP BODY.)

TEMPERATURE-HUMIDITY INDEX A means of estimating the heat stress caused by variations in temperature and humidity.

TEMPERATURE REGULATION The maintenance of the temperature or temperatures of a body within a restricted range under conditions involving variable internal and/or external heat loads. Biologically, the existence of some degree of body temperature regulation by autonomic or behavioral means.

TEMPERATURE REGULATION, AUTONOMIC The regulation of body temperature by autonomic (i.e., involuntary) responses to heat and cold which modify the rates of heat production and heat loss (i.e., by sweating, thermal tachypnea, shivering, and variations in peripheral vasomotor tone and basal metabolism).

TEMPERATURE REGULATION, BEHAVIORAL The regulation of body temperature by complex patterns of responses of the skeletal musculature to heat and cold which modify the rates of heat production and/or heat loss (e.g., by exercise, change in body conformation, and in the thermal insulation of bedding and (in man) of clothing, and by the selection of an environment which reduces thermal stress).

TERATOLOGY That division of embryology and pathology which deals with abnormal development and congenital malformations.

THERMAL EFFECT In the biological tissue or system, an effect that is related to heating of the tissue through the application of electromagnetic fields, and that can occur through other forms of heating.

THERMOGRAM A recording of temperature distribution over a surface or in a material as measured at the surface.

THERMOGENIC LEVELS Power densities of RF radiation which produce measurable temperature increase in the exposed object.

THERMOGRAPHY A technique for detecting and measuring variations in heat emitted by various regions of the body.

THERMONEUTRAL ZONE (TNZ) The range of ambient temperature within which metabolic rate is at a minimum, and within which temperature regulation is achieved by nonevaporative physical processes alone.

THERMOREGULATION See temperature regulation.

TRANSDUCE To convert one form of energy into another form, e.g., from heat to electrical current in a thermocouple.

TWIN-WELL CALORIMETRY The technique used to determine the absorbed RF dose or dose rate by comparing the excess heat in an RF-exposed system to an identical unexposed system in a comparison well.

VIGILANCE The degree of attentiveness or watchfulness. Vigilance is often investigated by measuring the number of times the occurrence of an infrequent event is correctly detected. In some experiments objective measurements are made of the times the subject looks for occurrence of the infrequent event. Called observing responses, these responses may be required to allow observation of the infrequent event.

WAVE A disturbance that moves through a medium.

WAVEGUIDE A transmission line comprised of a hollow conducting tube within which electromagnetic waves may be propagated.

WAVE, TRANSVERSE ELECTRIC (TE) In a homogeneous, isotropic medium, an electromagnetic wave in which the electric field vector is everywhere perpendicular to the direction of the propagation.

WAVE, TRANSVERSE ELECTROMAGNETIC (TEM) In a homogeneous isotropic medium, an electromagnetic wave in which the electric and the magnetic field vectors are everywhere perpendicular to the direction of propagation.

WAVE, TRANSVERSE MAGNETIC (TM) In a homogeneous isotropic medium, an electromagnetic wave in which the magnetic field vector is everywhere perpendicular to the direction of the propagation.

WAVELENGTH The distance between points of corresponding phase of a periodic wave of two constant cycles. The wavelength λ is related to the phase velocity v and the frequency by $\lambda = v/f$.

WHOLE-BODY IRRADIATION Pertains to the case in which the entire body is exposed to the incident electromagnetic energy or the case in which the cross section (physical area) of the body is smaller than the cross section of the incident radiation beam.

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